National Institute for Health and Care Excellence

Final

# Attention deficit hyperactivity disorder (update)

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

*NICE guideline NG87*

*Intervention evidence review*

*March 2018*

*Final*

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

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# 1Pharmacological treatment

## Introduction

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

This picture is further complicated in that few drugs are licensed in the UK for the initiation of treatment in adults that have received a new diagnosis of ADHD. One lisdexamfetamine preparation (Elvanse adult ®) is licensed for use in newly diagnosed adults and one methylphenidate preparation (Medikinet XL®)is in the final stages of having a license to treat adults with diagnosed and newly diagnosed ADHD, atomoxetine is licensed for use in adults if the presence of symptoms of ADHD in childhood are confirmed and some methylphenidate preparations (Concerta XL®, Delmosart ®, Matoride XL ®, Medikinet XL®, Xiggitin XL®, Xenidate XL®) are licensed for continuation of treatment from childhood or adolescence.

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

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

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

The aim of this review, is to evaluate the evidence for the clinical and cost effectiveness of the pharmacological management of children, young people and adults with ADHD. There are two reviews; the first, evaluating the most clinically and cost effective pharmacological treatment for people with ADHD and the second explores the most clinically and cost-effective sequence of pharmacological treatment for children and young people and adults with ADHD. This review should be read alongside the evidence report E on adverse events and evidence report F: combination treatment, for the detail on when to decide on which treatment approach to take (pharmacological or non-pharmacological).

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

### 1.1.1 PICO table

For full details see the review protocol in appendix A.

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

| | |
|---|---|
| **Population** | Children, young people and adults with ADHD<br><br>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:<br><br>• Methylphenidate<br>• Methylphenidate modified release<br>• Dexamfetamine<br>• Lisdexamfetamine dimesylate<br>• Atomoxetine<br>• Guanfacine<br>• Clonidine<br>• Tricyclic antidepressants<br>• SSRIs<br>• SNRIs<br>• MAOIs<br>• Risperidone<br>• Olanzapine<br>• Clozapine<br>• Haloperidol<br>• Quetiapine<br>• Aripiprazole<br>• Carbamazepine<br>• Valproate<br>• Lamotrigine<br>• Lithium<br>• Asenapine<br>• Buspirone<br>• Bupropion<br>• Nicotine<br>• Modafinil<br>• Melatonin<br>• Sativex<br>• Acetylycholinesterase inhibitors<br>• Antiparkinson medication<br>• Combinations of the above<br><br>Not all of these medicines have a license for the treatment of ADHD, see individual summary of product characteristics for more information. |
| **Comparisons** | Placebo<br>Compared against each other<br>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.<br><br>**Critical**<br><br>• Quality of life [continuous]<br>• ADHD symptoms [continuous]<br>• Clinical Global Impressions scale (improved or much improved) [dichotomous]<br><br>**Important**<br><br>• Serious adverse events (all) [dichotomous]<br>• Behavioural (children)/Functional (adults) measures [continuous]<br>• Emotional dysregulation [continuous]<br>• Academic outcomes (children) [continuous]<br>• Substance use (alcohol and drug use) [dichotomous]<br>• Self-harm [dichotomous] |
| **Study design** | Blinded RCTs and systematic reviews of RCTs |

### 1.1.2 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[474] Methods specific to this review question are described in the review protocol in appendix A.

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

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

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

A number of Cochrane reviews were identified which evaluated the effectiveness of pharmacological treatments for people with ADHD[144, 512, 513, 520, 627, 628]. As all of the reviews included some studies that did not match the review protocol (for example, treatments not on the protocol, studies that included only known responders), no review was fully included. Rather, the references of each review were checked, and the data from relevant studies were independently extracted and assessed for quality.

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

### 1.1.3 Clinical evidence

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

Four RCTs were included in the review[41, 275, 291, 540] that evaluated the effectiveness of pharmacological treatments in pre-school age children (under 5 years of age); these are summarised in Table 2 below.

Two studies compared the effectiveness of methylphenidate versus placebo[275, 291], one study compared risperidone versus placebo[41], while the other compared risperidone versus standard treatment [540]. One of these studies[41] did not state whether any children included in the sample had previously received medication. The other studies included both stimulant naïve children and children that had previously received psychotropic medication[146, 275, 291]. The last study compared risperidone to standard treatment had both groups receiving methylphenidate [540]. Evidence from these studies is summarised in the clinical evidence summary tables below (Table 5, Table 6 and Table 7)

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.

#### 1.1.3.2 Excluded studies

See the excluded studies list in appendix I.

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

**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)<br><br>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<br>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[275] | Intervention 1: CNS stimulants – Methylphenidate initiated at 1.25mg t.i.d. and titrated based on response and tolerance<br><br>Intervention 2: placebo<br>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<br>Behaviour outcomes at 4 weeks | Mixed line. 8 children were drug naïve and 6 had received previous psychotropic medication.<br>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[291](PATS study) | Methylphenidate multiple doses (n=165)<br><br>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[540] | 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)<br><br>Comparison: Methyphenidate alone (n=21) | Children aged 3 – 6 years that met the DSM-IV criteria for ADHD | ADHD symptoms – total, inattention, hyperactivity<br>CGI-I<br>Behaviour outcomes<br>Discontinuation due to adverse events<br>Serious adverse events<br>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. |

See appendix D for full evidence tables.

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

Seventy 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, 202, 208, 235, 260, 267, 272, 293, 309, 316, 341, 346, 347, 351, 362, 367, 379, 390, 391, 430, 450, 452, 456, 457, 460, 469, 471, 476, 479, 491, 503, 539, 546, 553, 554, 576, 577, 590, 592, 598, 615, 631, 633, 639, 647, 657, 658, 672, 695, 702, 712] that evaluated the effectiveness of pharmacological treatments in children and young people (5-18 years of age); these are summarised in Table 3 below. The following comparisons were included in the review:

- eight RCTs compared immediate release methylphenidate versus placebo[172, 178, 293, 491, 503, 576, 633, 702],
- four RCTs compared osmotic-release oral system methylphenidate versus placebo [3, 167, 235, 476]

- one RCT compared immediate release methylphenidate versus extended release methylphenidate [702]
- one RCT compared lisdexamfetamine versus placebo [167]
- one RCT compared methylphenidate versus lisdexamfetamine [167]
- 26 RCTs compared atomoxetine with placebo [25, 45, 62, 100, 118, 200, 202, 208, 267, 272, 309, 316, 341, 367, 391, 430, 450, 452, 460, 476, 592, 598, 615, 657, 658, 672]
- two RCTs compared atomoxetine versus methylphenidate [476, 647]
- one compared atomoxetine versus guanfacine extended release [341]
- one RCT compared guanfacine versus placebo [553]
- eight RCTs compared guanfacine extended release versus placebo [89, 181, 341, 379, 479, 546, 554, 695].
- four RCTs compared clonidine versus placebo[351, 491, 577, 633]
- one RCT compared clonidine versus methylphenidate [491]
- one RCT compared clonidine versus desipramine [577]
- one RCT compared clonidine versus carbamazepine [471]
- two RCTs compared desipramine versus placebo [577, 590]
- one RCT compared venlafaxine versus methylphenidate [712]
- three RCTs compared risperidone versus placebo [129, 347, 469]
- one RCT compared aripiprazole versus placebo [631]
- one RCT compared buspirone versus placebo [198]
- two RCTs compared buspirone versus methylphenidate [198, 459]
- two RCTs compared bupropion with placebo [142, 177]
- two RCTs compared buproprion versus methylphenidate [67, 346]
- three RCTs compared modafinil versus placebo [95, 362, 539]
- one RCT compared modafinil versus methylphenidate [35]
- one RCT compared melatonin versus placebo [639]
- one RCT compared amantadine versus methylphenidate [457]
- two RCTs compared clonidine and methylphenidate combined versus methylphenidate monotherapy, clonidine monotherapy and placebo monotherapy[491, 633]
- one RCT compared atomoxetine versus fluoxetine versus atomoxetine.[390]

Evidence from these studies is summarised in the clinical evidence summary tables below.

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

**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)<br><br>Comparison: Placebo<br><br>Crossover trial (n=19) | 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<br><br>ADHD-RS scores 1.5SDs above gender and age norms<br><br>58% inattentive subtype; the rest unspecified |
| Allen 2005[25] | Intervention: Atomoxetine 0.5mg/kg per day to | Children aged 7 to 17 years that met DSM-IV criteria for | ADHD symptoms (ADHD Rating Scale) at 18 weeks | 68.2% had previous stimulant |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | 1.5mg/kg per day (n=76)<br><br>Comparison: Placebo (n=72) | ADHD and had concurrent Tourette's syndrome or chronic motor tic disorder. (n=148) | Discontinuation due to adverse events at 18 weeks | exposure<br><br>ADHD-RS scores 1.5SDs above gender and age norms.<br><br>60.8% combined subtype, 35.5% inattentive and 3.4% hyperactive/impulsive. Baseline scores of CGI-S show the majority of the population had moderate ADHD. |
| Amiri 2008[35] | Intervention: Modafinil 200-300mg/day (n=30)<br><br>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<br>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 [633] | Intervention: Methylphenidate; mean dose 25.7mg/day (n=37)<br><br>Intervention 2: Clonidine; mean dose 0.25mg per day (n=34)<br><br>Intervention 3: Clonidine and methylphenidate combination; mean doses 0.25mg/day and 26.1mg/day (n=33)<br><br>Comparison: Placebo (n=32) | 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<br>Discontinuation due to adverse events at 16 weeks | 28% combined type; 70% inattentive; 2% hyperactivity subtype<br><br>ADHD symptoms scores indicate the majority of participants had moderate ADHD.<br><br>58% of participants had previously used stimulants and 36% had prior use of clonidine |
| Arnold 2006[45] | Intervention: Atomoxetine 0.3- | Children aged 5-15 years who met | ADHD symptoms (DSM-IV) at 6 | Subjects also had autism |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | 0.4mg/kg/day<br><br>Comparison: Placebo<br><br>Crossover trial (n=16) | DSM-IV criteria for ADHD. | weeks<br>Behavioural outcomes at 6 weeks | 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)<br><br>Comparison: Placebo (N=70) | Children and adolescents aged 12-18 who met DSM-IV criteria for ADHD<br>(n=142) | ADHD symptoms (ADHD Rating Scale) at 9 weeks<br>Dropped out due to adverse events at 9 weeks | 79% had prior exposure to stimulants<br>All subtypes (43% combined, 47% inattentive, 10% is hyperactive-impulsive) with severity over 1.5 SDs above ADHD-RS norms.<br><br>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<br><br>Comparison: Methylphenidate 20-60mg/day<br><br>Crossover trial (N = 18) | 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<br>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 "severe" in 12 and "moderate" in three. |
| Block | Intervention: | Children aged 6 to | ADHD symptoms | 75% combined |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| 2009[100] | Atomoxetine (mean dose 1.25mg/kg per day) (n=195)<br><br>Comparison: placebo (n=93) | 12 years who met the DSM-IV criteria for ADHD (n=288) | (ADHD-RS) at 6 weeks | subtype<br><br>Severity: ADHD-RS score 1.5SDs above age and gender norms.<br><br>Previous non-responders to atomoxetine or those with intolerable adverse effects were excluded. 30% had previously received stimulant treatment. |
| Biederman 2006[95] | Modafinil. Titrated from 85mg to 425mg per day (n=197)<br><br>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<br>Serious adverse events at 9 weeks<br>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<br><br>76% combined subtype, 20.6% inattentive subtype, 3.4% hyperactive-impulsive subtype<br><br>Participants were stimulant naïve or had manifested an unsatisfactory response to stimulant therapy |
| Biederman 2007[87] (Childress 2014[155], Lopez | Intervention: Lisdexamfetamine dimesylate 30-70mg/day (n=218) | Children aged 6 to 12 years who met the DSM-IV criteria for ADHD (n=290) | ADHD symptoms at 4 weeks<br>Discontinuation due to adverse events at 4 weeks | 96% combined subtype<br><br>ADHD-RS-IV scores of 28 or |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| 2008[418]) | Comparison: Placebo (n=72) | | | more<br><br>Unclear line of treatment: previous non-responders were excluded |
| Biederman 2008[89] | Interventions:<br>Extended release guanfacine 2mg/d (n=87)<br>Extended release guanfacine 3mg/d (n=86)<br>Extended release guanfacine 4mg/d (n=86)<br><br>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<br>Clinical Global Impressions - Improvement scale at 5 weeks<br>Behavioural outcomes at 5 weeks<br>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)<br><br>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<br>Serious adverse events at 6 weeks | 70% naïve to psychotropics.<br>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]; Weiss 2005[663] | Intervention: Atomoxetine 0.8-1.8mg/kg/day (n=101) | Children aged 8-12 with diagnosis of ADHD confirmed by DSM-IV (n=153) | ADHD symptoms (ADHD Rating Scale) at 7 weeks<br>Quality of life at 7 weeks | Allowed previous use of stimulant (60%) up to one week before enrolling. |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | Comparison: Placebo (n=52) | | | 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)<br><br>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<br>Clinical Global Impressions - Improvement Scale at 6 weeks<br>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)<br><br>Comparison: Placebo<br><br>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<br>Clinical global impressions (improvement) at 4 weeks | All participants drug naïve<br>All participants combined subtype |
| NCT00763971 trial: Coghill | Intervention: Lisdexamfetamine dimesylate 30- | Children 6 to 16 years with ADHD according to DSM- | ADHD symptoms (ADHD-RS) at 7 weeks | ADHD-RS-IV score of 28 or higher |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| 2013[167] (Coghill 2014[171], Banaschewski 2013[61], Coghill 2014[170]) | 70mg/day (n=111)<br><br>Comparison: Methylphenidate 18-54mg per day (n=111)<br><br>Comparison: placebo (n-110) | IV-TR criteria (n=336) | Discontinuation due to adverse events at 7 weeks<br>Clinical global impressions (improvement) at 7 weeks<br>Academic outcomes at 7 weeks | 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.<br><br>68.7% combined subtype |
| Conners 1980[178] | Intervention: Methylphenidate, max dose 60mg/day (n=20)<br><br>Comparison: Placebo (n=21) | Children aged 6-11 years with physician diagnosed hyperkinesis (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)<br><br>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<br>Discontinuation due to adverse events at 6 weeks | Unclear line of treatment.<br>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)<br><br>Comparison: Placebo (n=79) | Children aged 6-12 years who met DSM-IV criteria for ADHD and oppositional symptoms. (n=217) | Discontinuation due to adverse events at 8 weeks | Unclear line of treatment.<br>All subtypes (Inattentive (12.6%), Hyperactive (3.3%), and Combined |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | | (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)<br><br>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<br>Serious adverse events at 6 weeks<br>Discontinuation due to adverse events at 6 weeks | Drug naïve.<br>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<br><br>Comparison: Placebo<br><br>Crossover trial:<br>ADHD alone (n=16)<br>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<br>Clinical global impressions – Improvement scale at 4 weeks | Unclear line<br><br>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 severe ADHD. |
| Dell'agnello 2009[202] | Intervention: Atomoxetine | Children aged 6-15 years who met | ADHD symptoms (CARS ADHD | 20% of the atomoxetine |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | 1.2mg/kg/d(n=105)<br><br>Comparison: Placebo (n=32) | DSM-IV diagnostic criteria for ADHD and oppositional defiant disorder. (n=137) | index) at 8 weeks<br>Discontinuation due to adverse events at 8 weeks | group and 12.5% of the placebo group had previous therapy.<br><br>89% of the population diagnosed with combined subtype. |
| Dittmann 2011[208]; Wehmeier 2011[656] | Intervention: Atomoxetine max dose 1.2mg/kg (n=121)<br><br>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<br>Quality of life at 9 weeks | 44% previously treated with a stimulant.<br><br>75% of the population diagnosed with combined subtype. |
| Findling 2008[235] | Intervention: OROS methylphenidate, max dose 54mg/day (n=91)<br><br>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.<br>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[260](262 Gadow 2007 [261]) | Intervention: IR Methylphenidate 0.1-0.5mg/kg per day<br><br>Comparison: Placebo<br><br>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<br>37% had previous history of medication for ADHD<br>Mean score of 20.7 on Child Symptom Inventory (parent rated) |
| Gau 2007[267] | Intervention: Atomoxetine 1.2-1.8mg/kg/day, mean daily dose 43.12mg (n=72)<br><br>Comparison: placebo (n=34) | Children aged 6-16 years diagnosed with ADHD according to the DSM-IV. (n=106) | ADHD symptoms (ADHD - Rating Scale) at 6 weeks<br>Discontinuation due to adverse events at 6 weeks | 64% drug naïve.<br><br>Baseline scores of CGI-S show the majority of the population had moderate ADHD. 73% combined |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | | subtype, 27% combined subtype, and no participants had the predominantly hyperactive subtype. |
| Geller 2007[272] | Intervention: Atomoxetine, max dose 120 mg/day (n=87)<br><br>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<br>Discontinuation due to adverse events at 12 weeks | 37.5% were stimulant naïve<br>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[293] | (n=155) Intervention 1: CNS stimulants – Methylphenidate (maximum 60mg/day)<br><br>(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<br>64% had been previously treated for ADHD |
| Handen 2015 [309] | Intervention 1: Atomoxetine (n=32), mean dose 49.8 (23.3) mg/ day.<br><br>Intervention 2: Atomoxetine and parent training (n=32)<br><br>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<br>CGI-I at 10 weeks<br>behaviour outcomes at 10 weeks | Severity: mixed |
| Harfterkamp 2012[316]; Harfterkamp 2014[315] | Intervention:<br>Atomoxetine, fixed dose of 1.2mg/kg/day (n=48) | Children aged 6 to 17 diagnosed with ADHD and ASD according to the DSM-IV. (n=97) | ADHD symptoms (ADHD - Rating Scale) at 8 weeks<br>Clinical global impressions - | 37% received no previous drug treatment<br>All subjects scored over 1.5 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | Comparison: Placebo (n=49) | | Improvement) at 8 weeks<br>Discontinuation due to adverse events at 8 weeks | 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 [341] | Intervention 1: Guanfacine 4-7mg/day (n=115)<br><br>Intervention 2: Atomoxetine 1.2mg/kg per day; mean dose 42.1(20.1)mg per day mean (n=112)<br><br>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<br>ADHD symptoms (ADHD Rating Scale) at 10 to 13 weeks<br>Discontinuation due to adverse events at 13 weeks | 85% combined, 12% inattentive and 3% hyperactive impulsive<br><br>Moderate severity (ADHD-RS score of 32 or higher at baseline)<br><br>Unclear line of treatment |
| Jahangard 2017 [347] | Intervention: Risperidone 0.5 mg/d (=42)<br><br>Comparison: placebo (n=42) | Children aged 7 to 10 years who met the DSM-IV criteria for ADHD (n=84) | ADHD symptoms – inattention, hyperactivity<br>Behaviour outcomes<br>Emotional dysregulation<br>All reported PT at 8 weeks | All participants were on methylphenidate (1 mg/kg/d), Ritalin, sustained. |
| Jain 2011[351] | Intervention: Clonidine (0.2mg/kg per day and 0.4mg/kg per day) (n=158)<br>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<br>Serious adverse events at 8 weeks<br>Discontinuation due to adverse events at 8 weeks | Minimum score of 26 on ADHD-RS |
| Jafarinia 2012[346] | Intervention: Bupropion 100mg/d if <30kg, 150mg/d if >30kg(n=20)<br><br>Comparison: Methylphenidate 20mg if <30kg, 30mg is >30kg (n=20) | 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<br>Serious adverse events at 6 weeks<br>Discontinuation due to adverse events at 6 weeks | All patients were drug naïve.<br>All subjects scored over 1.5 SD above age-standard norms for ADHD-RS. Subtype diagnosis not stated. Baseline scores of ADHD-RS show the |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | | majority of the population had severe ADHD. |
| Kahbazi 2009[362] | Intervention: Modafinil 200mg is <30kg, 300mg if >30kg (n=23)<br><br>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.<br>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[367] | Intervention: Atomoxetine. Maximum of 1.8mg/kg per day (n=133)<br><br>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<br>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[390] | Intervention: Atomoxetine 1.2mg/kg per day and fluoxetine 20mg/day (n=127) | Children aged 7-17 years old who met ADHD diagnostic criteria as defined by DSM-IV and comorbid | ADHD symptoms (ADHD-RS) at 8 weeks<br>Discontinuation due to adverse events at 8 weeks | All/mixed subtypes (77.3% combined, 20.7% inattentive and 2% hyperactive). |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | Comparison: Atomoxetine 1.2mg/kg per day and placebo; (n=46) | depressive or anxiety symptoms (n=173)<br><br>45.7% of participants had major depression and 31.85% generalised anxiety disorders | | Line of treatment unclear.<br>ADHD-RS scores at least 1.5SDs above age and gender norms. |
| Kratochvil 2011[391] | Intervention: Atomoxetine 0-8-1.8mg/kg/d (n=51)<br><br>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<br>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[379] | Intervention 1: Extended release guanfacine 1-3 mg/ day (n=121)<br><br>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<br>Discontinued due to adverse effects at 6 weeks | Previous treatment allowed, proportion not stated.<br>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[430] | Intervention: Atomoxetine, titrated to a max dose of 1.8mg/kg/day (n=72)<br><br>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<br>Serious adverse events at 6 weeks<br>Discontinuation due to adverse events at 6 weeks | All participants were stimulant naive, however 40% were on nootropics (n=30) or psychotropics (n=14) before the trial, and 10% continued another medication during the trial. All ADHD |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | | 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[452](Newcorn 2005)[478] | Intervention: Atomoxetine 0.5mg/kg/d - 1.8mg/kg/d (n=213)<br><br>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<br>ADHD symptoms (ADHD - Rating Scale) at 13 weeks<br>Clinical Global Impressions - Improvement scale at 13 weeks<br>Behavioural outcomes at 13 weeks<br>Discontinuation due to adverse events at 13 weeks | Unclear line of therapy.<br><br>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[450] | Intervention Atomoxetine. Maximum 1.5mg/kg per day. (n=85)<br><br>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<br>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 |
| Mohammadi 2010[457] | Intervention: Amantadine 100mg/d if <30kg, 150mg/d if >30kg (n=20)<br><br>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.<br><br>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 of ADHD-RS show the majority of the |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | | population had moderate ADHD. |
| Mohammadi 2012[456] | Intervention: Buspirone 20mg if <30kg, 30mg if >30kg (n=23)<br><br>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 naïve.<br>All patients had combined subtype of ADHD. Baseline scores of ADHD-RS show the majority of the population had severe ADHD. |
| Montoya 2009[460] | Intervention: Atomoxetine 1.2mg/kg/d(n=100)<br><br>Comparison: Placebo (n=51) | Children and adolescents aged 6-15 years who were newly diagnosed (≤ 3 months) with ADHD according to DSM-IV-TR (n=151) | ADHD symptoms (ADHD - Rating Scale) at 12 weeks | All patients drug naïve.<br>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[469] | Intervention: Risperidone. No dosage details provided. (n=20)<br><br>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.<br><br>All/mixed subtypes were included. |
| Nair 2009[471] | Intervention: Clonidine 8 µg/kg (n=25)<br><br>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.<br>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 scores on Vanderbilt rating scale were |

| Study | Intervention and comparison | Population | Outcomes | Comments |
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| | | | | approximately 45 at baseline. |
| Newcorn 2008[476] | Interventions:<br>Atomoxetine, 0.8-1.8 mg/kg per day (n=82)<br>OROS methylphenidate, 18-54 mg/day (n=82)<br><br>Comparison:<br>Placebo (n=27) | Children aged 6-16 diagnosed with ADHD as per the DSM-IV criteria (n=191) | Quality of life at 6 weeks<br>ADHD symptoms (CPRS) at 6 weeks | Subpopulation of stimulant naïve subjects |
| Newcorn 2013[479] (Stein 2015[599]) | Intervention:<br>Extended release guanfacine maximum dose 4mg/d (n=227)<br><br>Comparison:<br>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<br>Academic outcomes at 8 weeks | Unclear line.<br>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[491] (Cannon 2009[136], Daviss 2008[199]) | Interventions:<br>Clonidine, maximum dose 0.6mg/day (n=31)<br>Methylphenidate, maximum dose 60mg/day (n=29)<br>Methylphenidate and clonidine combination (maximum doses 60mg/day and 0.6mg/day respectively) (n=32)<br><br>Comparison:<br>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<br>Behavioural outcomes at 16 weeks<br>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<br><br>75% combined subtype, 18.8% inattentive, 6.2% hyperactive/impulsive. Approximately half of the population had comorbid ODD suggesting moderate ADHD. |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Pliszka 2000[503] | Intervention: Methylphenidate, 5-10mg BD-TDS (n = 20)<br><br>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.<br>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 2003898 | Intervention: Modafinil, 200-300mg/day (n=11)<br><br>Comparison: Placebo (n=11) | Children aged 5-15 who met DSM-IV for ADHD (n=22) | ADHD symptoms (ADHD - Rating Scale) at 6 weeks<br>Discontinuation due to adverse events at 6 weeks | Unclear line<br>All subjects had an average percentile score for the ADHD Rating Scale IV of 70 or higher |
| Sallee 2009 [546] | Intervention: Guanfacine (n=258) All doses – 1, 2, 3 and 4mg/day.<br>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<br>Clinical global impressions – improvement at 6 weeks<br>Discontinuation due to adverse events at 6 weeks | 73% combined, 26% inattentive, 2% hyperactive/impulse<br>Severity: Mixed (Mean ADHD-RS-IV score of 40.1 (SD 8.65))<br>Unclear line of treatment |
| Scahill 2001[553] | Intervention: Guanfacine 0.5mg TDS (n=17)<br><br>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<br>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[554] | Intervention: Extended release guanfacine. Maximum 3mg (<25kg) and 4mg (>25kg). (n=30)<br><br>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<br>Behavioural outcomes at 8 weeks<br>Serious adverse events at 8 weeks<br>Discontinuation due to adverse events at 8 weeks | Mixed line of treatment.<br>A minimum score of 24 on the parent-rated Aberrant behaviour Checklist-hyperactivity subscale, a CGI-S score of moderate or greater and an |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | | 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 2013385 | Intervention: Methylphenidate 0.5mg, 1mg and 1.5mg/kg TDS (n=61)<br><br>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<br>Discontinuation due to adverse events at 16 weeks | Unclear line |
| Singer 1995[577] | Interventions:<br>Desipramine 25mg QDS<br>Clonidine 0.05mg QDS<br><br>Comparison: Placebo<br><br>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 naïve. Comorbidities tic disorder and Tourette's. Baseline scores of the child behaviour checklist show the majority of the population had severe ADHD. |
| Spencer 2002 [592] | Intervention: Atomoxetine. Maximum 2mg/kg per day (n=127)<br><br>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<br><br>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 [590] | Intervention: desipramine. 3.5mg/kg per day (n=21)<br><br>Comparison: Placebo (n=20) | Children diagnosed with ADHD as per the DSM-IV criteria. All subjects had a history of Tourette disorder or non-Tourette disorder chronic tic | ADHD symptoms (ADHD - Rating Scale) at 6 weeks | 53.6% had received previous stimulants. Baseline scores of ADHD-RS show the majority of the |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | disorders. (n=41) | | population had severe ADHD. |
| Spencer 2008 [598] | Intervention: Atomoxetine 0.5-1.5mg/kg per day (n=61)<br><br>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<br>Discontinuation due to adverse events at 8 weeks | 65.9% combined type; 31% inattentive; 4.1% hyperactivity subtype<br><br>ADHD-RS scores 1.5SDs above age and gender norms<br><br>68.4% of participants had previously used stimulants. |
| Takahashi 2009[615] | Intervention 1: Atomoxetine 0.5mg/kg per day (n=62)<br><br>Intervention 2 Atomoxetine 1.2mg/kg per day (n=60)<br><br>Intervention 3 Atomoxetine 1.8mg/kg per day (n=61)<br><br>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<br>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[631] | Intervention: Aripiprazole 5 – 20mg/day (n=18)<br><br>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.<br>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 = 0-3. Baseline scores of CGI-S |

| Study | Intervention and comparison | Population | Outcomes | Comments |
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| | | | | show the majority of the population had moderate ADHD. |
| Van der heijden 2007[639] | Intervention: Melatonin 3mg if <40kg, 6mg if > 40kg (n=54)<br><br>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<br>Behavioural outcomes at 4 weeks<br>Discontinuation due to adverse events at 4 weeks | Unclear line of treatment.<br><br>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 2007131 | Intervention: Atomoxetine 0.8-1.8 mg/kg/day (n = 164)<br><br>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<br>Behavioural outcomes at 8 weeks<br>Discontinuation due to adverse events at 8 weeks | 24% had had previous exposure to stimulant treatment.<br>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[657] (Wehmeier 2015[655], | Intervention: Atomoxetine. Target dose 1.2mg/kg/day (n=63) | Children aged between 6-12, diagnosis of ADHD according to DSM- | ADHD symptoms (ADHD Rating Scale) at 8 weeks | 75.2% of the study population were stimulant naive, previous |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Wehmeier 2014[653]) | Comparison: Placebo (n=62) | IV criteria (n=125) | | treatment with atomoxetine was an exclusion criteria.<br>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.<br>Baseline scores of CGI-S show the majority of the population had moderate ADHD. |
| Wehmeier 2011[658] | (n=64) Intervention 1: CNS stimulants – Atomoxetine (1.2mg/kg per day)<br><br>(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[670] (Saylor 2010[552] Wietecha 2009[672]) | Intervention: Atomoxetine 1.2mg/kg per day (n=120)<br><br>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.<br>48% combined subtype, 49.8% inattentive subtype.<br><br>Baseline scores of ADHD-RS show the majority of the population had severe ADHD. |
| Wilens 2015[695] | Intervention: Extended release guanfacine, max dose 4-7mg depending on weight (n=157)<br><br>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<br>Academic achievement at 13 weeks<br>Discontinuation due to adverse events at 13 weeks | Around 75% of the population had previously used stimulant medication<br>Baseline scores of CGI-S show the majority of the population had moderate ADHD. 68% |

| Study | Intervention and comparison | Population | Outcomes | Comments |
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| | | | | combined subtype, 29% inattentive subtype, 3% hyperactive subtype. |
| Wolraich 2001[702] | Intervention: IR-Methylphenidate 18-54mg/day(n=94)<br>Intervention 2: OROS-MPH 18-54mg/day (n=95)<br>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<br>Clinical global impressions – improvement at 4 weeks<br>Discontinuation due to adverse events at 4 weeks | 73.4% combined, 19.5% inattentive and 7.1% hyperactive/impulsive<br><br>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<br><br>Severity not stated |
| Zarinara 2010[712] | Intervention: Venlafaxine 50mg if <30kg, 75mg if >30kg (n=19)<br><br>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<br>All participants combined subtype.<br>Baseline ADHD-RS-IV scores were ~ 30 (teacher) |

See appendix D for full evidence tables.

### 1.1.3.5 Included studies (adults)

Thirty nine RCTs were included in the review[8, 11, 12, 16, 21, 34, 50, 84, 90, 91, 110, 117, 140, 162, 216, 282, 287, 288, 306, 386, 393, 401, 446, 449, 494, 522, 524, 527, 533, 591, 593, 608, 620, 621, 625, 666, 667, 689, 711] that evaluated the effectiveness of pharmacological treatments in adults these are summarised in Table 4 below. The following comparisons were included in this review:

- eight RCTs compared immediate release methylphenidate versus placebo[21, 110, 386, 393, 591, 593, 625, 666]
- twelve RCTs compared controlled release methylphenidate versus placebo[21, 90, 91, 117, 140, 162, 282, 287, 446, 524, 533, 593]

- three RCTs compared dexamfetamine versus placebo [494, 620, 621]
- three RCTs compared lisdexamfetamine versus placebo[8, 11, 84]
- ten RCTs compared atomoxetine versus placebo[12, 16, 216, 288, 401, 449, 608, 667, 689, 711]
- one RCT compared guanfacine versus placebo [621]
- one RCT compared guanfacine versus dexamfetamine [621]
- one RCT compared reboxetine versus placebo [527]
- one RCT compared venlafaxine versus placebo [34]
- two RCTs compared bupropion versus placebo [306, 393]
- one RCT compared bupropion versus methylphenidate [393]
- two RCTs compared modafinil versus placebo [50, 620]
- one RCT compared modafinil versus dexamfetamine [620]
- one RCT compared atomoxetine and buspirone versus placebo [608]

Evidence from these studies is summarised in the clinical evidence summary below.

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

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

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Adler 2008[11] (Mattingly 2013[436], Adler 2009[10], Kollins 2011[381]) | Interventions: Lisdexamfetamine dimesylate 30mg/d (n=119), lisdexamfetamine dimesylate 50mg/d (n=117), lisdexamfetamine 70mg/d (n=122)<br><br>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<br>Discontinuation due to adverse events at 4 weeks | Unclear line of treatment.<br><br>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)<br><br>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<br>ADHD symptoms (Conners Adult ADHD Rating scale) at 16 weeks<br>CGI-I at 16 weeks<br>Discontinuation due to adverse events at 16 weeks | Unclear line of treatment.<br><br>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)<br><br>Comparison: Placebo (n=112) | Adults aged 18 to 54 years who met the DSM-IV criteria for ADHD (n=206) | Quality of life at 6 months<br>ADHD symptoms (Adult ADHD Self Report; Adult ADHD Investigator Symptom Rating | 72% combined subtype<br><br>Unclear line of treatment; exclusion criteria: failure to respond to an adequate trial of |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | Scale; Conners Adult ADHD Rating Scale) at 6 months<br>Discontinuation due to adverse events (6 months) | ADHD stimulant medication, buproprion or other non-stimulant medications. |
| Adler 2009[21] | Intervention: Methylphenidate 36-108mg/day (mean dose 67.7mg/day) (n=113)<br><br>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<br>Discontinuation due to adverse events at 7 weeks | Severity: AISRS score of 24 or higher<br><br>Unclear line of treatment; known non-responders were excluded from the study<br><br>80% combined subtype |
| Adler 2013[8](Adler 2013[9] | Intervention: Lisdexamfetamine dimesylate (30-70mg/day) (n=80)<br><br>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<br>Quality of life at 10 weeks<br>Discontinuation due to adverse events at 10 weeks | 81.11% combined, 18.24% inattentive, 0.63% hyperactive-impulsive<br><br>Severity: baseline score of 39.9 on ADHD-RS<br><br>Line of treatment unclear |
| Amiri 2012[34] | Intervention: Venlafaxine 75mg TDS (n=22)<br><br>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<br>Serious adverse events at 6 weeks<br>Discontinuation due to adverse events at 6 weeks | All participants were drug naïve.<br>The participants were parents or siblings of children diagnosed to have ADHD. |
| Arnold 2014[50] | Intervention 1: Modafinil 255mg/day (n = 73)<br><br>Intervention 2: Modafinil 340mg/day (n = 73)<br><br>Intervention 3: Modafinil 425mg/day (n=74)<br><br>Intervention 4: Modafinil 510mg/day (n=44)<br><br>Comparison: | Adults aged 18 and over diagnosed with ADHD according to DSM-IV criteria. (n = 338) | Quality of life at 9 weeks<br>ADHD symptoms (Adult ADHD Self Report Scores) at 9 weeks<br>Behavioural outcomes at 9 weeks<br>Discontinuation due to adverse events at 9 weeks | 37% of the population had received ADHD medication within the last 5 years.<br>Baseline CGI-S scores show the majority of the population had moderate ADHD. |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | Placebo (n = 74) | | | |
| Biederman 2006[90] | Intervention: Methylphenidate CR, maximum dose of 1.3mg/kg (n=72)<br><br>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.<br>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)<br><br>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<br>Discontinuation due to adverse events at 6 weeks | Unclear line of treatment |
| Biederman 2012[85] | Intervention: Lisdexamfetamine, max dose 70mg/day (n=35)<br><br>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<br>Behavioural outcomes at 6 weeks<br>Discontinuation due to adverse events at 6 weeks | Unclear line of treatment. |
| Bouffard 2003[110] | Intervention: IR methylphenidate, max dose 15 mg TDS<br><br>Comparison: Placebo<br><br>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<br>Behavioural outcomes at 4 weeks | Unclear line of treatment.<br>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<br><br>Comparison: Placebo<br><br>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.<br>All participants had combined subtype of ADHD. Baseline scores of ADHD-RS show the majority of the population had moderate ADHD. |
| Casas | Intervention: | Adults aged 18-65 | ADHD symptoms | 70% combined |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| 2013[140] (Kooij 2013[387]) | OROS Methylphenidate 54-72mg/day (n=182)<br><br>Comparison: Placebo (n=97) | years who met the DSM-IV criteria for ADHD (n=279) | (Conners self-reported and investigator reported scales) at 13 weeks<br>Discontinuation due to adverse events at 13 weeks | subtype; 26% inattentive; 4% hyperactive-impulsive<br><br>CAARS-O:SV score of 36<br><br>Unclear line of treatment; known non-responders to methylphenidate were excluded. |
| Chronis-tuscano 2008[162] | Intervention: Methylphenidate, max dose 90 mg (n=9)<br><br>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.<br>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)<br><br>Comparison: Placebo (n=225) | Adults aged 18-30 years that met DSM-IV criteria for ADHD (n=445) | Quality of life at 12 weeks<br>ADHD symptoms (Conners Adult ADHD Rating Scale) at 12 weeks<br>Behavioural outcomes at 12 weeks<br>Discontinuation due to adverse events at 12 weeks | 64% of subjects were drug naïve.<br>Baseline scores of CGI-S show the majority of the population had moderate ADHD.<br><br>78% had combined subtype, 21.6% had the inattentive subtype and 0.45% had the hyperactive/impulsive subtype. |
| Ginsberg 2012[282] | Intervention: Methylphenidate OROS 72mg/d (n=15)<br><br>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<br>Behavioural outcomes at 5 weeks | 14% had previously received pharmacological treatment.<br>93% were of the combined subtype of ADHD, 7% were predominantly inattentive subtype. 23.3% of the study |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | | 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 |
| Goodman 2016[287] | Intervention: Methylphenidate OROS 72mg/d (n=178)<br><br>Comparison: Placebo (n=179) | Adult male prison inmates aged 18-65 years with ADHD according to DSM-IV criteria. (n=357) | ADHD symptoms (Adult ADHD symptom rating scale) at 6 weeks<br>Discontinuation due to adverse events at 6 weeks | Unclear line of treatment<br>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 |
| Goto 2013 [288] | Intervention: Atomoxetine (n=195) | Adults aged 18 and over who met DSM-IV criteria for ADHD (n=391) | ADHD symptoms (Conners Adult ADHD Rating Scale) at 10 | 22% had prior stimulant exposure<br>All participants were required to have a |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | Placebo (n=196) | | weeks<br>Quality of life at 10 weeks<br>Discontinuation due to adverse events at 10 weeks | CGI-S score of 4 or more. |
| Hamedi 2014 [306] | Intervention: Buproprion 150mg/day (n=21)<br><br>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[386] | Intervention 1: Methylphenidate IR, titrated up to 1mg/kg/day<br><br>Comparison: Placebo<br><br>Crossover trial: (n=45) | Adults aged 20-56 who met DSM-IV criteria for ADHD | ADHD symptoms (DSM-IV) at 3 weeks<br>Discontinuation due to adverse events at 3 weeks | Stimulant naïve population.<br>All subtypes were included. Baseline scores of CGI-S show the majority of the population had moderate ADHD. |
| Kuperman 2001[393] | Intervention 1: Bupropion SR, maximum dose 300mg/day (n=11)<br><br>Intervention 2: Methylphenidate IR, max dose 0.9mg/kg/day (n=8)<br><br>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<br>Discontinuation due to adverse events at 7 weeks | Unclear line of treatment.<br>Baseline scores of CGI-S show the majority of the population had mild ADHD. |
| Lee 2014[401] | Intervention: Atomoxetine, maximum dose 120mg daily (n=37)<br><br>Comparison: Placebo (n=37) | Adults aged 18 and over who met DSM-IV criteria for ADHD (n=74) | Quality of life at 10 weeks<br>ADHD symptoms (Conners Adult ADHD Rating Scale) at 10 weeks<br>Discontinuation due to adverse events at 10 weeks | 19.2% had previous treatment with stimulants.<br>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, CGI-ADHD-S score of 4 or more at baseline. Baseline |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | | scores of CGI-S show the majority of the population had moderate ADHD. |
| Medori 2008[446] | Intervention: Methylphenidate 18-72mg/day (n=305)<br><br>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<br>Discontinuation due to adverse events at 5 weeks | 70.8% combined subtype; 24.2% inattentive subtype; 4% hyperactive-impulsive subtype (1% unspecified)<br><br>Severity: Conners Adult ADHD score of >24.<br><br>Unclear line of treatment: non-responders to methylphenidate were excluded |
| Michelson 2003 [449] | Intervention: Atomoxetine 80-120mg/d (n=270)<br><br>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<br>Discontinuation due to adverse events at 8 weeks | 66.4% combined, 31% inattentive, 2.6% hyperactive/impulsive<br><br>Unclear line of treatment; patients responding to initial placebo trial were excluded<br><br>Baseline scores of CGI-S score show the majority of the population had moderate ADHD |
| Paterson 1999[494] | Intervention: Dexamfetamine, up to six tablets per day (n=24)<br><br>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.<br>All subtypes were included. Baseline scores of CGI-S show the majority of the population had moderate ADHD. |
| Retz 2012[524] | Intervention: Methyphenidate CR, maximum daily dose 1mg/kg (n=84)<br><br>Comparison: Placebo (n=78) | 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<br>Clinical Global Impressions - Improvement at 8 | Unclear line of treatment.<br>Baseline scores of CGI-S show the majority of the population had moderate ADHD. |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | weeks<br>Discontinuation due to adverse events at 8 weeks | |
| Reimherr 2007[522] (Robison 2010[530]) | Intervention: Methylphenidate 18-90mg/day<br><br>Comparison: placebo<br>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<br>Clinical global impressions (improvement) at 4 weeks<br>Emotional dysregulation at 4 weeks | Line of treatment not specified<br>Subtype not specified<br>Baseline ADHD-RS scores of 36.2 |
| Riahi 2010[527] | Intervention: Reboxetine, 4 mg BD (n=23)<br><br>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<br>Behavioural outcomes at 6 weeks<br>Discontinuation due to adverse events at 6 weeks | Unclear line of treatment. |
| Rosler 2009[533] (Rosler 2010[535]) | Intervention: Methylphenidate CR, maximum dose 60mg/day (n=241)<br><br>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[593] | Intervention: Methylphenidate average dose 0.92mg/kg per day<br><br>Comparison: placebo<br><br>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<br>Unclear subtype<br>Unclear severity |
| Spencer 2005[591](Biederman 2006[90] | Intervention: Methylphenidate IR, maximum dose of 1.3mg/kg (n=104)<br><br>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.<br>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. |
| Sutherland | Intervention: | Adults aged 18-60 | ADHD symptoms | Unclear line of |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| 2012[608] | Atomoxetine 80-100mg/d (n=97)<br>Intervention 2: Combination atomoxetine (80mg/d) and buspirone (40mg/d) (n=97)<br><br>Placebo (n=47) | years with ADHD according to DSM-IV-TR criteria and AISRS (n=241) | (Adult ADHD Investigator Symptom Report Scale) at 8 weeks | treatment.<br>All subjects had to have a score of 24 or more on the AISRS scale, Mean scores AISRS = 36 |
| Takahashi 2014[616] | Intervention: OROS Methylphenidate (n=143)<br><br>Placebo (n=141) | Adults aged 18-60 years with ADHD according to DSM-IV-TR criteria and AISRS (n=284) | ADHD symptoms (Conners Adult ADHD Investigator and Self Symptom Report Scale) at 8 weeks<br>Quality of life at 8 weeks<br>Discontinuation due to adverse events at 8 weeks | Unclear line of treatment.<br>All subjects had to have a score of 24 or more on the CAARS-O:IR scale, mean score 31.75 |
| Taylor 2000[620] | Interventions:<br>Dexamfetamine, max dose 40 mg/day<br>Modafinil, max dose 400 mg/day<br>Comparison: Placebo<br><br>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.<br>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[621] | Interventions:<br>Dexamfetamine, max dose 20 mg/day<br>Guanfacine, max dose 2 mg/day<br><br>Comparison: Placebo<br>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.<br>Subjects had to meet full DSM-IV criteria for the disorder by the age of 7 years as well as currently. |
| Tenenbaum 2002[625] | Intervention: Methylphenidate IR, gradually titrated up to 15mg TDS<br><br>Comparison: | 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.<br>All subjects were diagnosed with the combined subtype of ADHD. |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | Placebo<br><br>Crossover trial: (n=24) | | | |
| Wender 1985[666] | Intervention: Methylphenidate IR<br><br>Comparison: Placebo<br><br>Crossover trial: (n=37) | Adults who met DSM III criteria for ADHD | Behavioural outcomes at 2 weeks | Unclear line of treatment.<br>All subjects had ADHD, residual type |
| Wernicke 2004[667] | Intervention: Atomoxetine 2mg/kg/d (n=102)<br><br>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[689] | Intervention: Atomoxetine 25-100mg/d (n=72)<br><br>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<br>ADHD symptoms (Adult ADHD Investigator Symptom Report Scale) at 13 weeks<br>Behavioural outcomes at 13 weeks<br>Discontinued due to adverse events at 13 weeks | Unclear line of treatment.<br>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[711] (Wietecha 2012[671]) | Intervention: Atomoxetine 60-100mg/d (n=268)<br><br>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<br>Discontinuation due to adverse events at 24 weeks | 84% of the subjects were stimulant naïve.<br>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 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | | were excluded from the trial. Baseline scores of CGI-S show the majority of the population had moderate ADHD. |

See appendix D for full evidence tables.

### 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[a,b] 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[a,b] 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[a,b] 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) |

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

**Table 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 | 33 (1 study) 6 weeks | VERY LOW[a,b] due to risk of bias, | | 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 |

| 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) |
| are beneficial | | imprecision | | | (4.21 lower to 6.89 higher) |
| ADHD symptoms (ADHD-RS inattentive subscale scores) parent rated; 0-27; lower values are beneficial | 33 (1 study) 6 weeks | VERY LOW[a,b] 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[a,b] 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[a,2b] 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) |

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

**Table 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[a,b] due to risk of bias, imprecision | | The mean ADHD symptoms parent rated score in the control groups | The mean parent rated ADHD symptoms score in the intervention groups was 3.33 lower (12.72 lower to 6.06 higher) |

| 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) |
| | | | | was 33.85 | |
| ADHD Inattention symptoms (parent rated; CPRS inattention subscale; 0-18, low scores are beneficial) | 42 (1 study) 6 weeks | VERY LOW[a,b] due to risk of bias, imprecision | | The mean ADHD symptoms parent rated score in the control groups was 6.67 | The mean parent rated ADHD inattention symptoms score in the intervention groups 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[a,b] 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 benefical) | 42 (1 study) 6 weeks | VERY LOW[a,b] 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[a,2b] 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[a] due to risk of bias | OR 9.17 (1.45 to 58.07) | | 240 more per 1000 (from 50 to 530 more) |

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

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

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

**Table 8: 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) |
| ADHD total symptoms parent rated (Abbreviated parent rating scale and Conners ADHD index; lower values are beneficial) | 62 (2 studies) 4-7 weeks | MODERATE[a] 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[a,b] 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[a] 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[a] 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- | 128 (2 studies) | LOW[a,b] due to risk of | | The mean ADHD symptoms teacher rated score in the control groups | The mean parent 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 Immediate release methylphenidate versus placebo (95% CI) |
| 20; low values are beneficial; change scores reported) | 16 weeks | bias, imprecision | | was -3.2 | 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[a] 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 (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[a] 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[a,c] 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[a,b] 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, | 122 (1 study) 16 weeks | LOW[a,c] 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) |

| 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) |
| lower values are beneficial) | | | | | |
| ADHD inattention symptoms parent rated; (SNAP-IV inattention subscale; 0-3; lower values are beneficial) | 183 (1 study) 4 weeks | MODERATE[a] 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 symptoms teacher rated; (SNAP-IV inattention subscale; 0-3; lower values are beneficial) | 183 (1 study) 4 weeks | MODERATE[a] due to risk of bias | | The mean SNAP-IV inattention subscale score in the control groups was 1.97 | The mean SNAP-IV inattention 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[a] 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[a,b] 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[a] 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[c] 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[a] due to risk of bias | RD 0 (-0.01 to 0.01) | 0 events in control arm | 0 events in both arms |

*(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.*
*(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.*
*(c) 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[a,b] 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[a] 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[a] 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[a] 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- | 116 (1 study) | MODERATE[a] due to risk of | | The mean investigator rated ADHD symptom score was -5.7 | The mean investigator rated ADHD symptom 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 OROS Methylphenidate versus placebo (95% CI) |
| RS total scores); 0-54; lower values are beneficial | 7 weeks | bias | | | groups was<br>13 lower<br>(16.05 to 9.95 lower) |
| ADHD inattention symptoms investigator rated (ADHD-RS Inattentive subscale); 0-27, lower values are beneficial | 109<br>(1 study)<br>6 weeks | VERY LOW[a,b] due to risk of bias, imprecision | | 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<br>5.8 lower<br>(9 to 2.6 lower) |
| ADHD inattention symptoms teacher rated (SNAP-IV Inattentive subscale); 0-3 Lower values are beneficial | 221<br>(2 studies)<br>4 weeks | LOW[a,b] 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<br>(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<br>(2 studies)<br>4 weeks | MODERATE[a] 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<br>(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<br>(1 study)<br>6 weeks | VERY LOW[a,b] due to risk of bias, imprecision | | The mean ADHD-RS hyperactive subscale score in the control groups was<br>-3.8 | The mean ADHD-RS hyperactive subscale score in the intervention groups was<br>4.9 lower<br>(7.47 to 2.33 lower) |
| ADHD hyperactivity symptoms teacher rated (SNAP-IV hyperactivity | 221<br>(2 studies)<br>4 weeks | MODERATE[a] 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 |

| 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); 0-3 Lower values are beneficial, change scores reported | | | | | (0.87 to 0.47 lower) |
| ADHD hyperactivity symptoms parent rated (SNAP-IV hyperactivity subscale); 0-3 Lower values are beneficial, change scores reported | 221 (2 studies) 4 weeks | MODERATE[a] 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) |
| Clinical global impressions – improvement (score of 1 or 2) | 396 (2 studies) 4-7 weeks | MODERATE[a] 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[a,b] 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[a] 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[2b]due to imprecision | RR 0.81 (0.25 to 2.62) | 21 per 1000 | 4 fewer per 1000 (from 16 fewer to 34 more) |

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

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

**Table 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) |
| ADHD inattention symptoms teacher rated (SNAP-IV inattention subscale; 0-3; lower values are beneficial) | 194 (1 study) 4 weeks | MODERATE[a] 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[a] 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[a] 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[a] 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[b] 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[b] due to imprecision | RR 0.95 (0.06 to 14.91) | 11 per 1000 | 1 fewer per 1000 (from 11 fewer to 156 more) |

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

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

**Table 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[a] 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[a] 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[a] 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[b] 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[b,c] 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) |

*(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.*
*(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.*
*(c) 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[a] 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[a,b] 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[a,b] 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[a] 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[b] due to imprecision | RR 0.44 (0.09 to 2.22) | 44 per 1000 | 27 fewer per 1000 (from 41 fewer to 46 more) |

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

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

**Table 13: Clinical evidence summary: Atomoxetine versus placebo**

| Outcomes | No of | Quality of the | Relative | Anticipated absolute effects |
|---|---|---|---|---|

| | 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[a] 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[a] 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[a,c] 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[a,c] 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[b] 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[b] 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[a,b] 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[a] 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[a,b] 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[a,b] 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[b] | | 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[a,b] 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[a] 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[a] 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[a] 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[c] 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[b] 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[a] 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[a,c] 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[a] 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[a] 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[a,b] 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[a] 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[a,b] 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[b] 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[b] 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[b] 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) |

*(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.*
*(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.*
*(c) 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 beneficial, final values | 147 (1 study) 6 weeks | MODERATE[a] 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 (3.67 lower to 3.87 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) |
| reported | | | | | |
| ADHD total symptoms parent rated (ADHD symptoms – CRPS, ADHD-RS); lower values are beneficial | 480 (2 studies) 6-8 weeks | MODERATE[a] 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[a] 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[a] 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[a] 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[a] 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) |

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

**Table 15: Clinical evidence: Atomoxetine versus guanfacine extended release**

| Outcomes | No of | Quality of the | Relative | Anticipated absolute effects |
|---|---|---|---|---|

| | 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[a] 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[a,b] 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[b] due to imprecision | RR 0.57 (0.2 to 1.65) | 78 per 1000 | 34 fewer per 1000 (from 63 fewer to 51 more) |

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

**Table 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[a] 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[a] 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 hyperactive subscale); | 34 (1 study) | MODERATE[a] due to | | The mean ADHD-RS hyperactive subscale score in the control groups was | The mean ADHD-RS hyperactive 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 Guanfacine versus placebo (95% CI) |
| 0-27, lower values are beneficial | 8 weeks | imprecision | | 16.3 | 5.5 lower<br>(10.95 lower to 0.05 lower) |
| CGI-I (score of 1 or 2; much improved or very much improved) | 34<br>(1 study)<br>8 weeks | HIGH | OR 14.01 (3.12 – 62.88) | 0 events in control arm | 530 more per 1000<br>(from 290 more to 770 more) |

*(a) 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<br>(6 studies)<br>5-13 weeks | LOW[a,b]<br>due to risk of bias, imprecision | | The mean ADHD-RS in the control group was<br>-10.6 | The mean ADHD-RS in the intervention groups was<br>6.6 lower<br>(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<br>(4 studies)<br>6-8 weeks | LOW[a,b]<br>due to risk of bias, imprecision | | The mean ADHD-RS inattentive subscale - change scores in the control groups was<br>-6.97 | The mean ADHD-RS inattentive subscale score in the intervention groups was<br>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<br>(3 studies)<br>6-8 weeks | HIGH | | The mean ADHD-RS hyperactivity/impulsivity subscale - change scores in the control groups was<br>-6.9 | The mean ADHD-RS hyperactive subscale scores in the intervention groups was<br>3.87 lower<br>(5.32 to 2.85 lower) |
| ADHD hyperactivity symptoms investigator rated | 62<br>(1 study) | MODERATE[a]<br>due to risk of | | The mean ADHD-RS hyperactivity/impulsivity subscale | The mean ADHD-RS hyperactivity/impulsivity 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 ER Guanfacine versus placebo (95% CI) |
| (Aberrant Behaviour Checklist – Hyperactivity); 0-100, Lower values are beneficial, final values reported | 8 weeks | bias | | - final values in the control groups was 18.7 | 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[a] 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[d] | 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[a,b] 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) |

*(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.*
*(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.*
*(c) Downgraded by 1 increment because of heterogeneity, unexplained by subgroup analysis.*
*(d) Control group risk not reported.*

**Table 18: Clinical evidence summary: 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 Clonidine versus placebo (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 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[a,b] 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[a,b] 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[a,b] due to risk of bias, imprecision | | See comment[c] | 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[b] 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 |

*(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.*
*(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.*
*(c) 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[a,b] 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 beneficial, change scores | 60 (1 study) 16 weeks | VERY LOW[a,b] due to risk of bias, imprecision | | See comment[c] | 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) |
| reported | | | | | |
| Behavioural outcomes (Children's Global Assessment Scale) 0-100, higher values are beneficial | 60 (1 study) 16 weeks | LOW[a] due to risk of bias | | See comment[c] | 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[a,b] 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) |

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

| | 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<br>(1 study)<br>4 weeks | VERY LOW[a,b]<br>due to risk of bias, imprecision | RR 2.17<br>(0.45 to 10.46) | 154 per 1000 | 180 more per 1000<br>(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<br>(1 study)<br>4 weeks | LOW[a]<br>due to risk of bias | RR 5.43<br>(1.89 to 15.56) | 158 per 1000 | 699 more per 1000<br>(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<br>(1 study)<br>4 weeks | LOW[a]<br>due to risk of bias | RR 3.54<br>(1.47 to 8.55) | 235 per 1000 | 598 more per 1000<br>(from 111 more to 1000 more) |

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

**Table 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<br>(1 study)<br>6 weeks | HIGH | | The mean ADHD-RS score in the control groups was 42 | The mean ADHD-RS score in the intervention groups was<br>18 lower<br>(24.05 to 11.95 lower) |
| ADHD hyperactivity symptoms (Mother/Teacher CBCL Hyperactivity subscale); 0-100, lower | 68<br>(1 study)<br>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<br>7 lower<br>(7.58 to 6.42 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 Desipramine versus placebo (95% CI) |
| values are beneficial | | | | | |

**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<br>(1 study)<br>6 weeks | MODERATE[a] due to imprecision | | The mean ADHD-RS - parent rated in the control groups was<br>-16.63 | The mean ADHD-RS - parent rated in the intervention groups was<br>2.48 higher<br>(2.51 lower to 7.47 higher) |
| ADHD total symptoms (ADHD-RS total scores teacher rated); 0-54, Lower values are beneficial | 38<br>(1 study)<br>6 weeks | MODERATE[a] due to imprecision | | The mean ADHD-RS - teacher rated in the control groups was<br>-15.31 | The mean ADHD-RS - teacher rated in the intervention groups was<br>2.26 higher<br>(1.98 lower to 6.5 higher) |

*(a) 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 subscale; 0-3; high is | 84<br>(1 study)<br>8 weeks | MODERATE[a] due to imprecision | | The mean ADHD inattention symptoms score in the control groups was<br>2.02 | The mean ADHD inattention score in the intervention groups was<br>0.23 lower<br>(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) |
| poor) | | | | | |
| ADHD hyperactivity symptoms (8 weeks PT; parent rated; CPRS hyperactivity subscale; 0-3; high is poor) | 84 (1 study) 8 weeks | MODERATE[a] 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[a] 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[a] 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[a] due to imprecision | OR 0.14 (0.00 to 6.82) | 53 per 1000 | 45 fewer per 1000 (from 53 fewer to 222 more) |

*(a) 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 parent rated | 41 (1 study) 6 weeks | LOW[a,b] due to risk of bias, imprecision | | The mean SNAP-IV in the control groups was 0.55 | The mean SNAP-IV in the intervention groups was 0.24 higher (0.3 lower to 0.78 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) |
| (SNAP-IV); 0-3, lower values are beneficial | | | | | |

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

**Table 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[a,b] 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[a,b] 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[a] 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) 6 weeks | VERY LOW[a,b] due to risk of bias, imprecision | OR 6.61 (0.13 to 335.5) | 0 events in control arm | 60 more per 1000 (from 90 fewer to 200 more) |
| Serious adverse events | 34 (1 study) 6 weeks | LOW[a] due to risk of bias | RD 0.00 (-0.11 to 0.11) | 0 events in control arm | 0 events in both arms |

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

**Table 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[a] 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[a] 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[b] 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) |

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

**Table 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; | 40 | LOW[a,b] | | The mean ADHD symptoms parent | The mean ADHD symptoms parent |

| 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-RS Parent rated); 0-54, lower values are beneficial | (1 study)<br>6 weeks | due to risk of bias, imprecision | | rated score in the control groups was<br>-26.2 | rated score in the intervention groups was<br>1.4 higher<br>(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<br>(1 study)<br>6 weeks | LOW[a,b]<br>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<br>3 higher<br>(0.76 lower to 6.76 higher) |
| ADHD total symptoms (ADHD-RS Teacher rated); 0-54, lower values are beneficial, change scores PT | 40<br>(1 study)<br>6 weeks | LOW[a,b]<br>due to risk of bias, imprecision | | The mean ADHD symptoms teacher rated score in the control groups was<br>-7.3 | The mean ADHD symptoms parent rated score in the intervention groups was<br>0.5 lower<br>(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<br>(1 study)<br>6 weeks | LOW[a,b]<br>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<br>3 higher<br>(1.37 lower to 7.37 higher) |
| ADHD inattention symptoms (ADHD-RS Inattention subscale - Parent rated); 0-27, lower values are beneficial; change score PT | 40<br>(1 study)<br>6 weeks | LOW[a,b]<br>due to risk of bias, imprecision | | The mean ADHD symptoms inattention subscale parent rated score in the control groups was<br>-12.4 | The mean ADHD symptoms inattention subscale parent rated score in the intervention groups was<br>1 higher<br>(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 | 30<br>(1 study)<br>6 weeks | LOW[a,b]<br>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<br>2.4 higher<br>(0.75 to 4.05 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 Bupropion versus methylphenidate (95% CI) |
| beneficial) | | | | | |
| ADHD inattention symptoms (ADHD-RS Inattention subscale - Teacher rated); 0-27, lower values are beneficial, change scores PT | 40<br>(1 study)<br>6 weeks | LOW[a,b]<br>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<br>0.4 lower<br>(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<br>(1 study)<br>6 weeks | LOW[a,b]<br>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<br>1.9 higher<br>(0.75 lower to 4.55 higher) |
| ADHD hyperactivity symptoms (ADHD-RS Hyperactivity subscale - Parent rated); 0-27, lower values are beneficial | 40<br>(1 study)<br>6 weeks | VERY LOW[a,b]<br>due to risk of bias, imprecision | | The mean hyperactivity subscale - parent rated score in the control groups was<br>-13.9 | The mean hyperactivity subscale - parent rated score in the intervention groups was<br>0.6 higher<br>(2.58 lower to 3.78 higher) |
| ADHD hyperactivity symptoms (ADHD-RS Hyperactivity subscale - Teacher rated); 0-27, lower values are beneficial | 40<br>(1 study)<br>6 weeks | LOW[b]<br>due to imprecision | | The mean hyperactivity subscale - teacher rated score in the control groups was<br>-3.8 | The mean hyperactivity subscale - teacher rated score in the intervention groups was<br>0.1 lower<br>(3.17 lower to 2.97 higher) |
| Discontinuation due to adverse events | 40<br>(1 study)<br>6 weeks | LOW[b] due to imprecision | RD 0.00<br>(-0.09 to 0.09) | 0 events in control arm | 0 events in both arms |

| 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) |
| Serious adverse events | 40<br>(1 study)<br>6 weeks | LOW[b] due to imprecision | RD 0.00<br>(-0.09 to 0.09) | 0 events in control arm | 0 events in both arms |

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

**Table 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<br>(1 study)<br>5 weeks | LOW[a] 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<br>(18.69 to 9.83 lower) |
| ADHD total symptoms (ADHD-RS Teacher rated); 0-54, lower values are beneficial, final values reported | 68<br>(2 studies)<br>5-6 weeks | VERY LOW[a,c] 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<br>(22.74 lower to 6.4 higher) |
| Clinical global impressions – improvement (score of 1 or 2) | 198<br>(1 study)<br>4 weeks | LOW[a,c] 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<br>(1 study)<br>4 weeks | LOW[a,b] 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 | 248 | VERY | OR 3.67 | 0 events in control arm | 50 more per 1000 (from 10 more to 90 |

| 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) |
| adverse events | (1 study)<br>4 weeks | LOW[a,b]<br>due to risk of bias, imprecision | (0.71 – 19.00) | | more) |

*(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.*
*(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.*
*(c) 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<br>(1 study)<br>6 weeks | LOW[a,b]<br>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<br>(8.46 lower to 5.06 higher) |
| ADHD total symptoms (ADHD-RS total scores Teacher rated); 0-54, lower values are beneficial | 60<br>(1 study)<br>6 weeks | LOW[a,b]<br>due to risk of bias, imprecision | | The mean ADHD-RS - teacher rated score in the control groups was -21.33 | The mean ADHD-RS - teacher rated score in the intervention groups was 0.8 higher<br>(4.23 lower to 5.83 higher) |

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

**Table 31: Clinical evidence summary: Melatonin versus placebo**

| Outcomes | No of | Quality of the | Relative | Anticipated absolute effects |
|---|---|---|---|---|

| | Participants (studies) Follow up | evidence (GRADE) | effect (95% CI) | Risk with Control | Risk difference with Melatonin verses 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[a] 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[a] due to imprecision | RD 0.00 (-0.04 to 0.04) | 0 events in control arm | 0 events in both arms |

*(a) 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 Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | 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[a] 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[a] 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) |

| 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 Amantadine versus methylphenidate (95% CI) |
| | | | | | |
| ADHD hyperactivity symptoms (ADHD-RS Hyperactivity subscale - Parent rated); 0-27, lower values are beneficial | 38<br>(1 study)<br>6 weeks | LOW[a]<br>due to imprecision | | The mean ADHD-RS hyperactivity subscale - parent rated score in the control groups was<br>8.8 | The mean ADHD-RS hyperactivity subscale - parent rated score in the intervention groups was<br>0.6 higher<br>(3.36 lower to 4.56 higher) |
| ADHD hyperactivity symptoms (ADHD-RS Hyperactivity subscale - Teacher rated); 0-27, lower values are beneficial | 38<br>(1 study)<br>6 weeks | LOW[a]<br>due to imprecision | | The mean ADHD-RS hyperactivity subscale - teacher rated score in the control groups was<br>10.35 | The mean ADHD-RS hyperactivity subscale - teacher rated score in the intervention groups was<br>0.2 lower<br>(3.54 lower to 3.14 higher) |

*(a) 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) |
| ADHD total symptoms; teacher rated (Conners ASQ-T total scores; 0-20; low values are beneficial) | 61<br>(1 study)<br>16 weeks | LOW[a]<br>due to risk of bias | | The mean conners asq-t in the control groups was<br>-5.07 | The mean conners asq-t in the intervention groups was<br>2.21 lower<br>(5.9 lower to 1.48 higher) |
| ADHD total symptoms; parent rated (Conners ASQ-P total scores; 0-20; low values are beneficial) | 61<br>(1 study)<br>16 weeks | VERY LOW[a,b]<br>due to risk of bias, imprecision | | See comment[c] | The mean ADHD symptoms score the intervention groups was<br>3 lower<br>(6.4 to 0.4 lower) |
| Behaviour (CGAS; 0-100; higher scores are beneficial) | 61<br>(1 study)<br>16 weeks | VERY LOW[a,b]<br>due to risk of bias, | | See comment[c] | The mean ADHD symptoms score the intervention groups was<br>2.7 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 Methylphenidate and clonidine versus methylphenidate (95% CI) |
| | | imprecision | | | (2.6 lower to 8 higher) |
| Discontinued due to adverse events | 61 (1 study) 16 weeks | LOW[b] due to imprecision | RR 2.72 (0.3 to 24.7) | 34 per 1000 | 59 more per 1000 (from 24 fewer to 817 more) |

*(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.*
*(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.*
*(c) 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 values are beneficial) | 62 (1 study) 16 weeks | VERY LOW[a,b] 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 (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[a,b] due to risk of bias, imprecision | | See comment[c] | 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[a,b] due to risk of bias, imprecision | | See comment[c] | 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[a,b] 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) |

*(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.*
*(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.*
*(c) 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 beneficial) | 127 (2 studies) 16 weeks | VERY LOW[a,b] due to risk of bias, imprecision | | 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 (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[a,b] due to risk of bias, imprecision | | See comment[c] | 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[a,b] due to risk of bias, imprecision | | See comment[c] | 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[1ab] 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) |

*(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.*
*(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.*
*(c) 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[a,b] 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) |
| ADHD inattention symptoms; investigator rated (ADHD-RS inattention subscale); 0-27; low values are beneficial | 157 (1 study) 8 weeks | VERY LOW[a,b] 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[a,b] 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[a,b] 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) |

### 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 | Quality of the | Relative | Anticipated absolute effects |
|---|---|---|---|---|

| | Participants (studies) Follow up | evidence (GRADE) | effect (95% CI) | Risk with Control | Risk difference with Immediate release methylphenidate versus placebo (95% CI) |
|---|---|---|---|---|---|
| Treatment response (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) | 200<br>(2 studies)<br>3-6 weeks | MODERATE[a] due to risk of bias | RR 4.45<br>(2.4 to 8.25) | 117 per 1000 | 403 more per 1000<br>(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<br>(2 studies)<br>3-4 weeks | LOW[a,c] due to risk of bias, inconsistency | | The mean ADHD symptoms - final values in the control groups was<br>2.1 | The mean ADHD symptoms - final values in the intervention groups was<br>0.34 standard deviations lower<br>(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<br>(1 study)<br>7 weeks | VERY LOW[a,b] due to risk of bias, imprecision | | The mean ADHD symptoms - change scores in the control groups was<br>-12.4 | The mean ADHD symptoms - change scores in the intervention groups was<br>2.3 higher<br>(6.2 lower to 10.8 higher) |
| CGI-I score of 1 or 2 (much improved or very much improved) | 65<br>(2 studies)<br>7 weeks | MODERATE[a] due to risk of bias | RR 6.42<br>(2.31 to 17.85) | 118 per 1000 | 638 more per 1000<br>(from 154 more to 1000 more) |
| Behavioural outcomes (Global Assessment of Functioning and Problem Behaviour scale); higher values are beneficial, final values reported | 134<br>(2 studies)<br>2-4 weeks | MODERATE[a] due to risk of bias | | The mean behavioural outcomes in the control groups was<br>31.08 | The mean behavioural outcomes in the intervention groups was<br>1.01 standard deviations higher<br>(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) |

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

**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) |
| Quality of life (Q-LES-Q, 0-80, high scores are good) | 282 (1 study) 8 weeks | HIGH | | The mean Q-LES-Q score in the control group was 0.8 | The mean quality of life score in the intervention group was 1.6 higher (1.52 lower to 4.72 higher) |
| 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[a] 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 | 1537 (5 studies) 5-13 weeks | LOW[a,b] 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 0.4 standard deviations lower (0.50 to 0.29 lower) |
| ADHD total symptoms(AISRS/ADHD-RS total scores); | 124 (2 studies) 5-8 weeks | MODERATE[a] 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 |

| 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) |
| lower values are beneficial, final values reported | | | | | 0.91 standard deviations lower (1.28 to 0.53 lower) |
| 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[c] 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 | 1038 (3 studies) 5-8 weeks | LOW[a,d] 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 6.37 lower (8.25 lower to 4.49 lower) |
| ADHD total symptoms self-rated (CAARS total scores); 0-54, lower values are beneficial, change scores reported | 279 (1 study) 13 weeks | LOW[a,d] 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 self rated (CAARS inattention subscale at 8 weeks; 0-27, low values are beneficial) | 281 (1 study) 8 weeks | MODERATE due to imprecision[b] | | The mean ADHD inattention subscale in the control group was -3.4 | The mean ADHD symptoms inattention subscale in the intervention groups was 3.1 lower (4.54 to 1.66 lower) |
| ADHD inattention symptoms investigator rated (CAARS Inattention subscale); | 681 (2 studies) 5 to 8 weeks | LOW[a,d] 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 4 lower (4.9 lower to 3.1 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 Controlled release methylphenidate versus placebo (95% CI) |
| 0-27, lower values are beneficial, change scores reported | | | | | |
| ADHD inattention symptoms investigator rated (CAARS Inattention subscale, ADHD-RS inattention subscale); lower values are beneficial, final values reported | 114<br>(2 studies)<br>3-8 weeks | MODERATE[b] due to imprecision | | The mean ADHD symptoms inattention subscale in the control groups was<br>65.55 | The mean ADHD symptoms inattention subscale in the intervention groups was 0.66 standard deviations lower<br>(1.04 lower to 0.28 higher) |
| ADHD inattention symptoms investigator rated (CAARS Inattention subscale); 0-27, lower values are beneficial | 279<br>(1 study)<br>13 weeks | LOW[a,b] due to risk of bias, imprecision | | The mean ADHD symptoms inattention subscale in the control groups was<br>-5.5 | The mean ADHD symptoms inattention subscale in the intervention groups was 2.46 lower<br>(4.03 lower to 0.89 lower) |
| ADHD hyperactivity symptoms self rated (CAARS hyperactivity subscale at 8 weeks; 0-27, low values are beneficial) | 281<br>(1 study)<br>8 weeks | MODERATE due to imprecision[b] | | The mean ADHD inattention subscale in the control group was<br>-3.2 | The mean ADHD symptoms hyperactivity subscale in the intervention groups was 1 lower (2.14 to 0.14 lower) |
| ADHD hyperactivity symptoms investigator rated (CAARS Hyperactive subscale); 0-27; lower values are beneficial, change scores reported | 683<br>(2 studies)<br>5-8 weeks | LOW[a,b] due to risk of bias, imprecision | | The mean ADHD symptoms hyperactivity score in the control groups was<br>-3.4 | The mean hyperactivity subscale score in the intervention groups was<br>1.46 lower<br>(2.35 lower to 0.57 higher) |
| ADHD hyperactivity symptoms investigator | 114<br>(2 studies) | LOW[a] due to | | The mean ADHD symptoms hyperactivity score in the control | The mean hyperactivity 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 Controlled release methylphenidate versus placebo (95% CI) |
| rated (CAARS and ADHD-RS hyperactivity subscales); lower values are beneficial, final values reported | 2-8 weeks | imprecision, inconsistency | | groups was 48.27 | 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[a,b] 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 (much improved or very much improved) | 474 (3 studies) 7-13 weeks | MODERATE[a] due to risk of bias | RR 2.02 (1.52 to 2.67) | 217 per 1000 | 220 more per 1000 (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[a,b] 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; | 94 (1 study) | MODERATE[b] 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 |

| 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) |
| WRAADS emotional dysregulation subscale); 0-28; lower values are beneficial | 4 weeks | | | | (9.68 to 3.32 lower) |
| Discontinued due to adverse events | 2138 (9 studies) 6-13 weeks | HIGH | OR 3.33 (2.29 to 4.85) | 23 per 1000 | 72 more per 1000 (from 51 more to 101 more) |

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

**Table 39: Clinical evidence summary: Dexamfetamine 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 Dexamfetamine 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[a] 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 | 76 (2 studies) 2 weeks | MODERATE[a] 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) |

| 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 Dexamfetamine versus placebo (95% CI) |
| values reported | | | | | |
| ADHD hyperactive symptoms investigator rated (DSM-IV RS Hyperactive subscale); 0-27; lower values are beneficial, final values reported | 76<br>(2 studies)<br>2 weeks | MODERATE[a] due to imprecision | | The mean investigator rated hyperactive subscale score in the control groups was<br>12.7 | The mean investigator rated hyperactive subscale score in the intervention groups was<br>3.11 lower<br>(5.93 to 0.3 lower) |
| CGI-I score of 1 or 2 (much improved or very much improved) | 45<br>(1 study)<br>6 weeks | MODERATE[b] due to risk of bias | OR 14.31<br>(4.1 to 50.01) | 0 events in control arm | 583 more per 1000<br>(from 380 more to 787 more) |

*(a) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.*
*(b) 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 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<br>(1 study)<br>10 weeks | VERY LOW[a,c] due to risk of bias, imprecision | | See comment[d] | The mean quality of life score in the intervention groups was<br>14,70 higher<br>(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<br>(3 studies)<br>4-10 weeks | MODERATE[a] due to risk of bias | | The mean investigator rated ADHD-RS score in the control groups was<br>7.5 | The mean ADHD-RS score in the intervention groups was<br>10.51 lower<br>(12.71 to 8.31 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 placebo (95% CI) |
| ADHD inattention symptoms investigator rated;(ADHD-RS inattention subscale); 0-27, lower values are beneficial | 153<br>(1 study)<br>10 weeks | LOW[a]<br>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<br>6.1 lower<br>(8.26 to 3.94 lower) |
| ADHD hyperactivity symptoms investigator rated (ADHD-RS hyperactivity subscale); 0-27, lower values are beneficial | 153<br>(1 study)<br>10 weeks | LOW[a]<br>due to risk of bias | | The mean ADHD-RS score in the control groups was<br>-4.2 | The mean hyperactivity/impulsivity subscale score in the intervention groups was<br>5 lower<br>(6.8 to 3.2 lower) |
| CGI-I score of 1 or 2 (much improved or very much improved) | 420<br>(1 study)<br>4 weeks | MODERATE[a]<br>due to risk of bias | RR 1.99<br>(1.34 to 2.97) | 290 per 1000 | 287 more per 1000<br>(from 99 more to 572 more) |
| Behavioural outcomes (global assessment of functioning); 0-100, high values are beneficial | 61<br>(1 study)<br>6 weeks | LOW[a,c]<br>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<br>(3 studies)<br>4-10 weeks | VERY LOW[a,c]<br>due to risk of bias, imprecision | RR 2.19<br>(0.72 to 6.66) | 24 per 1000 | 24 more per 1000<br>(from 6 fewer to 97 more) |

*(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.*
*(b) The majority of the evidence included an indirect population (downgrade by 1 increment) or a very indirect population (downgrade by 2 increments).*
*(c) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.*
*(d) Control group risk not reported.*

**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) |

| 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[a] 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[a] 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[a,b,c] 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 (CAARS and AISRS total scores; Investigator rated); lower values are beneficial, final values reported | 530 (2 studies) 8-12 weeks | VERY LOW[a,b,c] due to risk of bias, imprecision, inconsistency | | The mean investigated rated ADHD symptom score in the control groups was 22.9 | The mean ADHD symptoms 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[a,b] 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 | 831 (2 studies) 10-12 weeks | LOW[a,b] due to risk of bias, | | The mean self-rated ADHD symptoms score in the control groups was | The mean self-rated ADHD symptoms 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) |
| beneficial, change scores reported | | imprecision | | -8.3 | 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[a,b,c] 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[a,b,c] 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 - Investigator rated); lower values are beneficial | 1044 (3 studies) 16-24 weeks | LOW[a,b] due to risk of bias, imprecision | | 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 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[a,b] 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, | 831 (2 studies) 10-12 weeks | MODERATE[a] 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) |

| 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) |
| change scores reported | | | | | |
| ADHD hyperactivity symptoms (AISRS and CAARS Hyperactivity/impulsivity subscale - Investigator rated); lower values are beneficial | 1044 (3 studies) 16-24 weeks | VERY LOW[a,b] 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[a] 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[a] 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 events | 502 (1 study) 24 weeks | MODERATE[a] due to risk of bias | RR 2.26 (1.43 to 3.58) | 94 per 1000 | 118 more per 1000 (from 40 more to 243 more) |

*(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.*
*(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.*
*(c) Downgraded by 1 increment because of heterogeneity, unexplained by subgroup analysis.*
*(d) 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 | 34 | MODERATE[a] | | The mean investigator rated ADHD | The mean investigator rated ADHD |

| 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) |
| investigator rated (DSM-IV RS); 0-54; lower values are beneficial | (1 study)<br>6 weeks | due to imprecision | | symptoms score in the control groups was<br>30.4 | symptoms score in the intervention groups was<br>8.1 lower<br>(14.47 to 1.73 lower) |
| ADHD inattention symptoms investigator rated (DSM-IV RS Inattentive subscale); 0-27; lower values are beneficial | 34<br>(1 study)<br>6 weeks | MODERATE[a] due to imprecision | | The mean investigator rated symptoms inattentive score in the control groups was<br>17.2 | The mean investigator rated inattentive score in the intervention groups was<br>4.4 lower<br>(7.55 to 1.25 lower) |
| ADHD hyperactivity symptoms investigator rated (DSM-IV RS Hyperactive subscale); 0-27; lower values are beneficial | 34<br>(1 study)<br>6 weeks | MODERATE[a] due to imprecision | | The mean investigator rated hyperactive score in the control groups was<br>13.2 | The mean investigator rated hyperactive score in the intervention groups was<br>3.7 lower<br>(7.56 lower to 0.16 higher) |

*(a) 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 dexamfetamine**

| 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 dexamfetamine (95% CI) |
| ADHD total symptoms investigator rated(DSM-IV RS total scores); 0-54; lower values are beneficial | 34<br>(1 study)<br>6 weeks | MODERATE[a] due to imprecision | | The mean investigator rated ADHD symptoms score in the control groups was<br>24.2 | The mean investigator rated ADHD symptoms score in the intervention groups was<br>1.9 lower<br>(8.81 lower to 5.01 higher) |
| ADHD inattention symptoms investigator | 34<br>(1 study) | MODERATE[a] due to | | The mean investigator rated inattentive score in the control groups | The mean investigator rated inattentive 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 Guanfacine versus dexamfetamine (95% CI) |
| rated (DSM-IV RS Inattentive subscale); 0-27; lower values are beneficial | 6 weeks | imprecision | | was<br>14 | 1.2 lower<br>(4.69 lower to 2.29 higher) |
| ADHD hyperactivity symptoms investigator rated (DSM-IV RS Hyperactive subscale); 0-27; lower values are beneficial | 34<br>(1 study)<br>6 weeks | LOW[a]<br>due to imprecision | | The mean investigator rated hyperactive score in the control groups was<br>10.2 | The mean investigator rated hyperactive score in the intervention groups was<br>0.7 lower<br>(4.56 lower to 3.16 higher) |

*(a) 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 Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | 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<br>(1 study)<br>6 weeks | LOW[a,b]<br>due to risk of bias, imprecision | | The mean investigator rated ADHD symptom score in the control groups was<br>27.47 | The mean investigator rated ADHD symptom score in the intervention groups was<br>5.58 lower<br>(11.18 lower to 0.02 higher) |
| ADHD inattention symptoms investigator rated (CAARS Inattentive subscale); 0-27; lower values are beneficial | 39<br>(1 study)<br>6 weeks | VERY LOW[a,b]<br>due to risk of bias, imprecision | | The mean investigator rated inattentive score in the control groups was<br>16.05 | The mean investigator rated inattentive score in the intervention groups was<br>4.74 lower<br>(7.83 to 1.65 lower) |
| ADHD hyperactivity symptoms investigator rated (CAARS | 39<br>(1 study)<br>6 weeks | VERY LOW[a,b]<br>due to risk of | | The mean investigator rated hyperactivity score in the control groups was | The mean investigator rated hyperactivity 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 Reboxetine versus placebo (95% CI) |
| Hyperactivity subscale); 0-27; lower values are beneficial | | bias, imprecision | | 11.47 | 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[a] 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[b] due to imprecision | RR 1.48 (0.15 to 15) | 59 per 1000 | 28 more per 1000 (from 50 fewer to 824 more) |

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

**Table 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[a] 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[a,b] 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) |

| 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 hyperactivity symptoms self-rated (CAARS Hyperactive/Impulsive subscale); 0-27, lower values are beneficial | 41<br>(1 study)<br>6 weeks | MODERATE[a] due to risk of bias | | The mean self-rated hyperactive/impulsive score in the control groups was<br>-11.35 | The mean self-rated hyperactive/impulsive score in the intervention groups was<br>15.25 lower<br>(22.19 to 8.31 lower) |
| Discontinuation due to adverse events | 44<br>(1 study)<br>6 weeks | VERY LOW[a,b] due to risk of bias, imprecision | OR 7.39<br>(0.15 to 372.38) | 0 events in control arm | 44 more per 1000<br>(from 71 fewer to 163 more) |
| Serious adverse events | 44<br>(1 study)<br>6 weeks | LOW[a,b] due to risk of bias, imprecision | RD 0.00<br>(-0.08 to 0.08) | 0 events in control arm | 0 events in both arms |

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

**Table 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<br>(1 study)<br>7 weeks | VERY LOW[a,b] due to risk of bias, imprecision | | The mean ADHD-RS in the control groups was<br>-12.4 | The mean ADHD-RS in the intervention groups was 1.3 lower<br>(8.77 lower to 6.17 higher) |
| ADHD total symptoms investigator rated (CAARS total scores0; 0-54, lower scores are | 42<br>(1 study)<br>6 weeks | MODERATE[b] 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) |

| 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) |
| beneficial, final values reported | | | | | |
| CGI score of 1 or 2 | 22<br>(1 study)<br>7 weeks | LOW[a,b]<br>due to risk of bias, imprecision | RR 2.33<br>(0.81 to 6.76) | 273 per 1000 | 363 more per 1000<br>(from 52 fewer to 1000 more) |
| Discontinuation due to adverse events | 22<br>(1 study)<br>7 weeks | VERY LOW[a,b]<br>due to risk of bias, imprecision | OR 0.14<br>(0 to 6.82) | 91 per 1000 | 77 fewer per 1000<br>(from 91 fewer to 315 more) |

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

**Table 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<br>(1 study)<br>7 weeks | LOW[a,b]<br>due to risk of bias, imprecision | | The mean ADHD-RS in the control groups was<br>-10.1 | The mean ADHD-RS in the intervention groups was<br>3.6 lower<br>(10.65 lower to 3.45 higher) |
| CGI-I score of 1 or 2 (much improved or very much improved) | 19<br>(1 study)<br>7 weeks | VERY LOW[a,b]<br>due to risk of bias, imprecision | RR 1.27<br>(0.56 to 2.9) | 500 per 1000 | 135 more per 1000<br>(from 220 fewer to 950 more) |
| Discontinued due to adverse events | 19<br>(1 study)<br>7 weeks | LOW[a,b]<br>due to risk of bias, imprecision | OR 0.08<br>(0 to 1.45) | 250 per 1000 | 224 fewer per 1000<br>(from 250 fewer to 76 more) |

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

**Table 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[a] 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[a] 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[b] 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) |
| 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[b] 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; | 192 (1 study) | LOW[a] due to risk of | | The mean brief-a score in the control groups was | The mean brief-a 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 placebo (95% CI) |
| lower values are beneficial | 9 weeks | bias | | -8.1 | 3.11 lower (7.25 to 1.03 higher) |
| Discontinuation due to adverse events | 338 (1 study) 9 weeks | LOW[a] 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) |

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

**Table 49: Clinical evidence summary: Modafinil versus dexamfetamine**

| 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 dexamfetamine (95% CI) |
| ADHD total symptoms investigator rated (DSM-IV total scores); 0-54, lower values are beneficial | 42 (1 study) 2 weeks | MODERATE[a] due to imprecision | | The mean investigator rated ADHD symptoms score in the control groups was 20 | The mean investigator rated ADHD symptoms score in the intervention 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[a] 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 | 42 (1 study) 2 weeks | MODERATE[a] due to imprecision | | The mean investigator rated hyperactive score in the control groups was | The mean investigator rated hyperactive score in the intervention groups was 1.7 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 Modafinil versus dexamfetamine (95% CI) |
| (DSM-IV Hyperactive subscale); 0-27, lower values are beneficial, final values reported | | | | 9 | (5.28 lower to 1.88 higher) |

*(a) 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 buspirone 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 buspirone versus placebo (95% CI) |
| ADHD total symptoms investigator rated (AISRS total scores); 0-54; lower values are beneficial | 244 (1 study) 8 weeks | LOW[a,b] due to risk of bias, imprecision | | See comment[c] | The mean ADHD symptoms (aisrs) in the intervention groups was 4.8 lower (7.74 to 1.86 lower) |
| ADHD inattention symptoms investigator rated inattention subscale (AISRS); 0-27; lower values beneficial | 244 (1 study) 8 weeks | LOW[a,b] due to risk of bias, imprecision | | See comment[c] | 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[a,b] due to risk of bias, imprecision | | See comment[c] | 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[b] due to imprecision | RR 1.04 (0.45 to 2.37) | 149 per 1000 | 6 more per 1000 (from 82 fewer to 204 more) |

*(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.*
*(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.*
*(c) A control group risk not reported.*

See appendix F for full GRADE tables.

### 1.1.4 Economic evidence

#### 1.1.4.1 Included studies

##### *1.1.4.1.1 2008 guideline literature*

One study from CG72 was included in this review[372]

The included study can be found in Table 51.

##### *1.1.4.1.2 Published literature*

Two health economic studies were identified in children with the relevant comparison and have been included in this review.[188,332] One economic evaluation was also identified in adults.[717]

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

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

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

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

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

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

#### 1.1.4.2 Excluded studies

Five studies [211, 250, 278, 357, 473, 718] from CG72, all in children, have been selectively excluded due to limited applicability and/or methodological limitations.

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

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

### 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[372](UK) | Directly applicable (a) | Potentially serious limitations(b) | 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<br>strategies could include; Methylphenidate- IR, Methylphenidate- MR-8 hours, Methylphenidate- MR-12 hours, Atomoxetine, Dexamfetamine, plus all the above medications combined with behavioural therapy.<br>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.<br>Uses EQ-5D. | 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 | PSA undertaken (number of simulations not reported).<br><br>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.<br><br>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 |
| 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.<br><br>MOST COST EFFECTIVE = A STRATEGY OF; IR-MPH – DEX – ATX – NT | | | | | | | |

| Study | Applicability | Limitations | Other comments | Incremental cost | Incremental effects (QALYs) | Cost-effectiveness | Uncertainty |
|---|---|---|---|---|---|---|---|
| (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)] | 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.<br><br>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':<br>• Subgroup 1: Stimulant naïve patients<br>  ○ a treatment algorithm of atomoxetine →IR-MPH→IR- | **Subgroup 1 (includes IR-MPH):** £408.34<br><br>**Subgroup 1 (includes XR-MPH):** £265.71<br><br>**Subgroup 2:** £480.94 | **Subgroup 1 (includes IR-MPH):** 0.0268<br><br>**Subgroup 1 (includes XR-MPH):** 0.0201<br><br>**Subgroup 2:** 0.0417 | **Subgroup 1 (includes IR-MPH):** £15,244<br><br>**Subgroup 1 (includes XR-MPH):** £13,241<br><br>**Subgroup 2:** £11,523 | Uncertainty around the ICER not reported.<br>Paper states a probabilistic analysis was done but data on this is not reported.<br><br>Multiple sensitivity analyses are stated as being undertaken however results are not reported.<br>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. |

| Study | Applicability | Limitations | Other comments | Incremental cost | Incremental effects (QALYs) | Cost-effectiveness | Uncertainty |
|---|---|---|---|---|---|---|---|
| | | | DEX→no treatment, with the comparator being the same sequence but without atomoxetine<br>○ same as above except IR-MPH is replaced with XR-MPH.<br>• Subgroup 2: Stimulant contraindicated (naive)<br>○ atomoxetine followed by no treatment if that fails, compared to no treatment alone. | | | | |
| Hong 2009 [332] (Spain) | Partially applicable [(c)] | Potentially serious limitations[(d)] | 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.<br><br>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':<br>• Subgroup 1: Stimulant naïve patients:<br>○ a treatment algorithm of atomoxetine →IR-MPH→no | **Subgroup 1 (includes IR-MPH)** [(e)]**:** £615<br><br>**Subgroup 1 (includes XR-MPH):** £277<br><br>**Subgroup 2:** £876 | **Subgroup 1 (includes IR-MPH):** 0.02<br><br>**Subgroup 1 (includes XR-MPH):** 0.013<br><br>**Subgroup 2:** 0.042 | **Subgroup 1 (includes IR-MPH):** £31,007<br><br>**Subgroup 1 (includes XR-MPH):** £21,971<br><br>**Subgroup 2:** £21,079 | Uncertainty around the ICER not reported.<br>Paper states a probabilistic analysis was done but data on this is not reported.<br><br>Multiple sensitivity analyses are stated as being undertaken however results are not reported.<br>Model most sensitive to the utility values used. ICER increased dramatically when the difference between the utilities for the different treatments was reduced. |

| Study | Applicability | Limitations | Other comments | Incremental cost | Incremental effects (QALYs) | Cost-effectiveness | Uncertainty |
|---|---|---|---|---|---|---|---|
| | | | treatment versus IR-MPH→atomoxetine→no treatment<br>○ same as above except IR-MPH is replaced with XR-MPH.<br>• Subgroup 2: Stimulant naïve patients with contraindications<br>○ 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 dexamfetamine*

*(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[716] (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<br><br>LDX vs ER-MPH = -£9 | LDX vs ATX = 0.01<br><br>LDX vs ER-MPH = 0.006 | LDX dominant<br><br>LDX dominant | PSA with 5000 simulations.<br>Probability LDX cost effective at £20,000; vs ATX = 80%, vs ER-MPH = 61%<br><br>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.*

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

*(b) 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. It is also acknowledged that the incremental results are very small and therefore small changes to the analysis could easily change the results to not being cost saving.*

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

King et al 2006[372] was replicated using the information in the study, to see what impact updating the cost of the interventions would have. The original base case result of King 2006 showed that the most cost effective strategy was;

Dexamfetamine – Methylphenidate IR – Atomoxetine – No treatment.

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

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

Methylphenidate IR – Atomoxetine – Dexamfetamine – No treatment.

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

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

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

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

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

#### 1.1.4.4 Unit costs

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

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

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

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

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

| Drug | Daily dose (or unit or total) | Cost (per unit) | Cost – monthly | Cost – annual | Source |
|---|---|---|---|---|---|
| **Methylphenidate hydrochloride** | | | | | |
| Methylphenidate immediate release | Low dose: 10mg per day | 5mg tablet (pack of 30) = £3.03 | £6.14 | £73.73 | Dose: BNF<br>Cost: BNF (DT price) |
| Methylphenidate immediate release | High dose: 60mg per day | 20mg tablet (pack of 30) = £10.92 | £33.22 | £398.58 | Dose: BNF<br>Cost: BNF (DT price) |
| Modified release tablet | Low dose: 18mg per day | 18mg tablet (pack of 30) = £31.19 | £31.62 | £379.48 | Dose: BNF<br>Cost: BNF (DT price) |
| Modified release tablet | High dose: 54mg per day | 54mg tablet (pack of 30) = £60.48 | £61.32 | £735.84 | Dose: BNF<br>Cost: BNF (DT price) |
| Modified release capsule | Low dose: 20mg per day | 20mg capsule (pack of 30) = £30.00 | £30.42 | £365.00 | Dose: BNF<br>Cost: BNF (DT price) |
| Modified release capsule | High dose: 60 mg per day | 60mg capsule (pack of 30) = £67.32 | £68.26 | £819.06 | Dose: BNF<br>Cost: BNF (NHS indicative price) (a) |
| **Atomoxetine** | | | | | |
| Capsule | Low dose: 40 mg per day | 40mg capsule (pack of 28) = £53.09 | £57.67 | £692.07 | Dose: BNF<br>Cost: BNF (DT price) |
| Capsule | High dose: 100 mg per day | 100mg capsule (pack of 28) = £70.79 | £76.90 | £922.80 | Dose: BNF<br>Cost: BNF (DT price) |
| Oral solution | High dose: 100 mg per day | 4mg/1ml oral solution (300 ml) = £85 | £215.45 | £2,585.42 | Dose: Using equivalent high tablet dose<br>Cost: BNF (DT price) |
| **Dexamfetamine** | | | | | |

| Drug | Daily dose (or unit or total) | Cost (per unit) | Cost – monthly | Cost – annual | Source |
|---|---|---|---|---|---|
| Tablet | Low dose: 5mg per day | 5mg tablet (pack of 28) = £21.53 | £23.39 | £280.66 | Dose: BNF Cost: BNF (DT price) |
| Tablet | High dose: 20mg per day | 10mg tablet (pack of 30) = £39.78 | £80.67 | £967.98 | Dose: BNF Cost: BNF (DT price) |
| Oral solution | High dose: 20mg per day | 5mg/5ml oral solution (500ml) = £114.49 | £139.30 | £1,671.55 | Dose: Using equivalent high tablet dose Cost: BNF (DT price) |
| **Lisdexamfetamine** | | | | | |
| | Low dose: 20mg per day (b) | 20mg capsule (pack of 28) = £54.62 | £59.33 | £712.01 | Dose: guideline committee Cost: BNF (DT price) |
| | Low dose: 30mg per day | 30mg capsule (pack of 28) = £58.24 | £63.27 | £759.20 | Dose: BNF Cost: BNF (DT price) |
| | High dose: 70mg per day | 70mg capsule (pack of 28) = £83.16 | £90.34 | £1,084.05 | Dose: BNF Cost: BNF (DT price) |
| **Other drugs (c)** | | | | | |
| Guanfacine hydrochloride (modified release) | 4mg per day | 4mg tablet (pack of 28) = £76.16 | £82.73 | £992.80 | Dose: Clinical review Cost: BNF (NHS indicative price) |
| Clonidine hydrochloride | 400 micrograms per day (d) | 100 microgram tablet (pack of 112) = £8.04 | £8.73 | £104.81 | Dose: Clinical review Cost: BNF (DT price) |
| Risperidone | 2mg per day | 1mg tablet (pack of 20) = £0.80 | £2.43 | £29.20 | Dose: Clinical review Cost: BNF (DT price) |
| Amantadine hydrochloride | 150mg per day | 100mg tablet (pack of 56) = £41.00 | £33.40 | £400.85 | Dose: Clinical review Cost: BNF (DT price) |
| Melatonin (modified release) | 6mg per day | 2mg tablet (pack of 30) = £15.39 | £46.81 | £561.74 | Dose: Clinical review Cost: BNF (DT price) |
| Bupropion hydrochloride (modified release) | 150mg per day | 150mg tablet (pack of 60) = £41.76 | £21.17 | £254.04 | Dose: Clinical review Cost: BNF (DT price) |
| Modafinil | 300mg per day | 100mg tablet (pack of 30) | £17.89 | £214.62 | Dose: Clinical review |

| Drug | Daily dose (or unit or total) | Cost (per unit) | Cost – monthly | Cost – annual | Source |
|---|---|---|---|---|---|
| | | = £5.88 | | | Cost: BNF (DT price) |
| Buspirone hydrochloride | 30mg per day | 10mg tablet (pack of 30) = £4.63 | £14.08 | £169.00 | Dose: Clinical review<br>Cost: BNF (DT price) |
| Aripiprazole | 20mg per day | 10mg tablet (pack of 28) = £2.77 | £6.02 | £72.22 | Dose: Clinical review<br>Cost: BNF (DT price) |
| Venlafaxine hydrochloride | 75mg per day | 37.5mg tablet (pack of 56) = £2.04 | £2.22 | £26.59 | Dose: Clinical review<br>Cost: BNF (DT price) |

*Source: BNF, October 2017.*
*(a) No drug tariff price available for the 60mg.*
*(b) A dose of 20mg is demonstrated here as committee opinion was that this is a dose that would be used in children, even though it is below the BNF starting dose.*
*(c) Guanfacine is the only drug from this list licensed for ADHD. It is less commonly used and is a newer drug so one example dose within the licensed range is demonstrated here. The doses of the other drugs below guanfacine were taken from the clinical review as there was no information in the BNF about doses for this condition.*
*(d) Based on a dose from a trial of 8micrograms per kg and assuming a 50kg child (a conservative estimate of weight)*

**Table 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 immediate release | Low dose: 20mg per day | 10mg tablet (pack of 30) = £5.49 | £11.13 | £133.59 | Dose: BNF<br>Cost: BNF (DT price) |
| Methylphenidate immediate release | High dose: 100mg per day | As above | £55.36 | £664.30 | Dose: BNF<br>Cost: BNF (DT price) |
| Modified release tablet | Low dose: 36mg per day | 36mg tablet (pack of 30) = £42.45 | £43.04 | £516.48 | Dose: BNF<br>Cost: BNF (DT price) |
| Modified release tablet | High dose: 108mg per day | 54mg tablet (a) (pack of 30) = £60.48 | £122.64 | £1,471.68 | Dose: BNF<br>Cost: BNF (DT price) |
| Modified release capsule | Low dose: 20mg per day | 20mg capsule (pack of 30) = £30.00 | £30.42 | £365.00 | Dose: BNF<br>Cost: BNF (DT price) |
| Modified release capsule | High dose: 100mg per day | 50mg capsule (pack of 30) = £62.52 | £126.78 | £1,521.32 | Dose: BNF<br>Cost: BNF (NHS indicative price) (a) |
| **Atomoxetine** | | | | | |

| Drug | Daily dose (or unit or total) | Cost (per unit) | Cost – monthly | Cost – annual | Source of dose |
|---|---|---|---|---|---|
| | Low dose: 40 mg per day | 40mg tablet (pack of 28) = £53.09 | £57.67 | £692.07 | Dose: BNF<br>Cost: BNF (DT price) |
| | High dose: 100 mg per day | 100mg tablet (pack of 28) = £70.79 | £92.28 | £1,107.36 | Dose: BNF<br>Cost: BNF (DT price) |
| **Lisdexamfetamine dimesylate** | | | | | |
| | Low dose: 30 mg per day | 30mg tablet (pack of 28) = £58.24 | £63.27 | £759.20 | Dose: BNF<br>Cost: BNF (DT price) |
| | High dose: 70 mg per day | 70mg tablet (pack of 28) = £83.16 | £90.34 | £1,084.05 | Dose: BNF<br>Cost: BNF (DT price) |
| **Dexamfetamine sulfate** | | | | | |
| | Low dose: 20mg per day | 10mg tablet (pack of 30) = £39.78 | £80.67 | £967.98 | Dose: BNF<br>Cost: BNF (DT price) |
| | High dose: 60mg per day | 20mg tablet (pack of 30) = £79.56 | £161.33 | £1,935.96 | Dose: BNF<br>Cost: BNF (NHS indicative price) (a) |
| **Other drugs** | | | | | |
| Guanfacine hydrochloride (modified release) | 4mg per day | 4mg tablet (pack of 28) = £76.16 | £82.73 | £992.80 | Dose: Estimate based on children's dose<br>Cost: BNF (NHS indicative price) |
| Bupropion hydrochloride (modified release) | 300 mg per day | 150mg tablet (pack of 60) = £41.76 | £42.34 | £508.08 | Dose: Clinical review<br>Cost: BNF (DT price) |
| Reboxetine (Edronax) | 8mg per day | 4mg tablet (pack of 60) = £18.91 | £19.17 | £230.07 | Dose: Clinical review<br>Cost: BNF (DT price) |
| Venlafaxine hydrochloride | 225 mg per day | 37.5mg tablet (pack of 56) = £2.04 | £6.65 | £79.78 | Dose: Clinical review<br>Cost: BNF (DT price) |

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

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

##### *1.1.6.1.1 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**

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

**Risperidone and methylphenidate versus methylphenidate**

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

#### *1.1.6.1.2 Children and young people aged 5 to 18*

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

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

**OROS Methylphenidate versus placebo**

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

**IR methylphenidate versus OROS methylphenidate**

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

**Lisdexamfetamine versus placebo**

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

**Methylphenidate versus lisdexamfetamine**

- No evidence was identified for quality of life, inattentive or hyperactivity ADHD symptoms and serious adverse events. No evidence for any of the important outcomes except

behaviour outcomes as measured by the WFIRS-P scale and academic achievement as measured by the CHIP-CE academic achievement subscale.

- There was a clinically important benefit of lisdexamfetamine for ADHD total symptoms (investigator rated; 1 study moderate quality) and CGI-I (1 study, low quality).
- There was no clinical difference for discontinuation due to adverse events, academic achievement and behaviour outcomes (1 study low quality).

**Atomoxetine versus placebo**

- No evidence for any of the important outcomes except behavioural outcomes measured by various scales and academic achievement measured by the CHIP-PRF achievement subscale.
- There was a clinically important benefit of atomoxetine for quality of life (2 studies moderate quality) (1 study low quality), treatment response (2 studies low quality), ADHD total symptoms (investigator rated; 3 studies low quality) (investigator rated; 6 studies moderate quality) (teacher rated; 5 studies moderate quality) (teacher rated; 1 study low quality) (parent rated; 9 studies high quality) (parent rated; 2 studies low quality) (parent rated; 3 studies moderate quality), ADHD inattention symptoms (investigator rated; 5 studies low quality) (teacher rated; 5 studies low quality) (parent rated; 9 studies low quality) (parent rated; 2 studies low quality) (parent rated; 3 studies moderate quality), ADHD hyperactivity symptoms (investigator rated; 5 studies moderate quality) (teacher rated; 4 studies moderate quality) (teacher rated; 1 study low quality) (parent rated; 12 studies moderate quality) (parent rated; 2 studies very low quality), CGI-I (5 studies moderate quality) and behavioural outcomes (2 studies low quality).
- There was no clinical difference for behavioural outcomes (3 studies moderate quality), academic achievement (1 study low quality), discontinuation due to adverse events (16 studies moderate quality) (2 studies low quality) and serious adverse events (3 studies low quality).

**Atomoxetine versus methylphenidate**

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

**Atomoxetine versus guanfacine extended release**

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

**Guanfacine versus placebo**

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

- There was no clinically important difference for ADHD inattention symptoms (investigator rated; 1 study moderate quality).

**Extended release Guanfacine versus placebo**

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

**Clonidine versus placebo**

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

**Clonidine versus methylphenidate**

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

**Clonidine versus desipramine**

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

**Clonidine versus carbamazepine**

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

**Desipramine versus placebo**

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

**Venlafaxine versus methylphenidate**

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

**Risperidone versus placebo**

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

**Ariprazole versus placebo**

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

**Buspirone versus methylphenidate**

- The only evidence identified was for ADHD total symptoms, discontinuation due to adverse events and serious adverse events.
- There was a clinically important benefit of methylphenidate for ADHD total symptoms (parent rated; 2 studies low to very low quality) (teacher rated; 1 study moderate quality).
- There was clinically important harm of buspirone for discontinuation due to adverse events (1 study very low quality).
- There was no clinical difference for serious adverse events (1 study low quality).

**Buproprion versus placebo**

- The only evidence identified was for ADHD total symptoms and discontinuation due to adverse events.
- There was a clinically important benefit of buproprion for ADHD total symptoms (parent and teacher rated, 2 studies moderate quality).
- There was clinically important harm of buproprion for discontinuation due to adverse events (2 studies low quality).

**Buproprion versus methylphenidate**

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

**Modafinil versus placebo**

- No evidence was identified for quality of life or ADHD hyperactivity or inattention symptoms. No evidence for any important outcomes.

- There was a clinically important benefit of modafinil for ADHD total symptoms (parent rated; 1 study low quality) (teacher rated; 2 studies very low quality) and CGI-I (1 study low quality).
- There was no clinical difference for serious adverse events (1 study low quality).
- There was clinically important harm of modafinil for discontinuation due to adverse events (1 study very low quality).

**Modafinil versus methylphenidate**

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

**Melatonin versus placebo**

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

**Amantadine versus methylphenidate**

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

**Methylphenidate and clonidine versus methylphenidate**

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

**Methylphenidate and clonidine versus clonidine**

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

**Methylphenidate and clonidine versus placebo**

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

**Atomoxetine and fluoxetine versus atomoxetine**

- The only evidence identified was for ADHD symptoms and discontinuation due to adverse events.

- There was a clinically important benefit of atomoxetine and fluoxetine combined for ADHD inattention symptoms (investigator rated; 1 study very low quality).
- There was no clinical difference for ADHD total and hyperactivity symptoms (investigator rated; 1 study very low quality) or discontinuation due to adverse events (1 study very low quality).

#### *1.1.6.1.3 Adults*

**Immediate release methylphenidate versus placebo**

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

**OROS methylphenidate versus placebo**

- There was no evidence for serious adverse events.
- There was a clinically important benefit of methylphenidate for treatment response (3 studies moderate quality), ADHD total symptoms (investigator rated; 4 studies low quality) (investigator rated; 2 studies moderate quality) (self-rated, 2 studies moderate quality) (self-rated; 2 studies low quality) (self-rated; 1 study low quality), ADHD inattention symptoms (investigator rated; 1 study low quality) (investigator rated; 1 study low quality) (self rated; 1 study moderate quality), ADHD hyperactivity symptoms (investigator rated; 2 studies low quality), CGI-I (3 studies moderate quality) and behaviour outcomes (1 study high quality), emotional dysregulation (1 study moderate quality).
- There was no clinical difference for ADHD inattention symptoms (investigator rated; 2 studies moderate quality), ADHD hyperactivity symptoms (investigator rated; 2 studies low quality)(self-rated; 1 study moderate quality) and emotional dysregulation (1 study very low quality).
- There was clinically important harm of methylphenidate for discontinuation due to adverse events (9 studies high quality) or quality of life (1 study high quality)

**Dexamfetamine versus placebo**

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

**Lisdexamfetamine versus placebo**

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

**Atomoxetine versus placebo**

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

**Guanfacine versus placebo**

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

**Guanfacine versus dexamfetamine**

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

**Reboxetine versus placebo**

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

**Venlafaxine versus placebo**

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

**Bupropion versus placebo**

- The only evidence identified was for ADHD total symptoms, CGI-I and discontinuation due to adverse events.
- There was a clinically important benefit of buproprion for ADHD total symptoms (investigator rated, 1 study moderate quality), CGI-I (1 study low quality) and discontinuation due to adverse events (1 study very low quality)
- There was no clinical difference for ADHD total symptoms (investigator rated, 1 study very low quality)

**Bupropion versus methylphenidate**

- The only evidence identified was for ADHD total symptoms, CGI-I and discontinuation due to adverse events.

- There was a clinically important benefit of buproprion for ADHD total symptoms (investigator rated, 1 study low quality), CGI-I (1 study very low quality) and discontinuation due to adverse events (1 study low quality).

**Modafinil versus placebo**

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

**Modafinil versus dexamfetamine**

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

**Atomoxetine and buspirone versus placebo**

- The only evidence identified was for ADHD symptoms and discontinuation due to adverse events.
- There was a clinically important benefit of atomoxetine and buspirone for ADHD total symptoms (investigator rated; 1 study low quality).
- There was no clinical difference for ADHD inattention or hyperactivity symptoms (investigator rated; 1 study low quality) or discontinuation due to adverse events (1 study 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 naive 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 (naive) 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 veryserious 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<br><br>Stratify by:<br>• Age: pre-school children (under 5 years old), children and young people (5-18 years), adults (over 18 years)<br>• Reason previous medication is unsuitable (non-response; intolerance; mixed population or unclear)<br>• The drug(s) previously received |
| **Intervention(s)** | The following treatments (all doses), received for a minimum of 2-weeks:<br>• CNS stimulants<br>  ○ methylphenidate<br>  ○ methylphenidate modified release<br>  ○ dexamfetamine<br>  ○ lisdexamfetamine dimesylate<br>• atomoxetine<br>• guanfacine<br>• clonidine<br>• Antidepressants (all drugs should be included separately and not pooled) except for class comparisons in the following groups:<br>  ○ Tricyclics<br>  ○ SSRIs<br>  ○ SNRIs<br>  ○ MAOIs<br>• Antipsychotics<br>  ○ Risperidone<br>  ○ Olanzapine<br>  ○ Clozapine<br>  ○ Haloperidol |

| | |
|---|---|
| | ○ Quetiapine<br>○ Aripriprazole<br>• Mood stabilisers<br>○ Carbamazepine<br>○ Valproate<br>○ Lamotrigine<br>○ Lithium<br>○ asenapine<br>• buspirone<br>• bupropion<br>• nicotine<br>• modafinil<br>• melatonin<br>• sativex<br>• anti-cholinesterase inhibitors (ACEi)<br>• Drugs used to treat Parkinson's disease<br><br>Combinations of the above (including where a medication is added to the previous medication(s)) |
| **Comparison(s)** | • Placebo<br>• Compared against each other<br>• Class vs. class comparisons for stimulants (methylphenidate short- and long-acting together; dexamfetamine and lisdexamfetamine) and SSRIs will also be included |
| **Outcomes** | 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.<br><br>**Critical**<br><br>• Quality of life [continuous]<br>• ADHD symptoms (total; parent) [continuous] [children and young people]<br>• ADHD symptoms (total; teacher) [continuous] [children and young people]<br>• ADHD symptoms (total; self-rated in children 13-18 years and adults) [continuous]<br>• ADHD symptoms (total; carer/partner) [continuous] [adults]<br>• ADHD symptoms (total; investigator) [continuous]<br>• ADHD symptoms (inattention; parent) [continuous] [children and young people]<br>• ADHD symptoms (inattention; teacher) [continuous] [children and young people]<br>• ADHD symptoms (inattention; self-rated in children 13-18 years and adults) [continuous]<br>• ADHD symptoms (inattention; carer/partner) [continuous] [adults]<br>• ADHD symptoms (inattention; investigator) [continuous]<br>• ADHD symptoms (hyperactivity; parent) [continuous] [children and young people]<br>• ADHD symptoms (hyperactivity; teacher) [continuous] [children and young people]<br>• ADHD symptoms (hyperactivity; self-rated in children 13-18 years and adults) [continuous]<br>• ADHD symptoms (hyperactivity; carer/partner) [continuous] [adults]<br>• ADHD symptoms (hyperactivity; investigator) [continuous] |

| | |
|---|---|
| | • Clinical Global Impressions scale (improved or much improved) [dichotomous]<br><br>**Important**<br><br>• Serious adverse events (all) [dichotomous]<br>• Behavioural (children)/Functional (adults) measures [continuous]<br>• Emotional dysregulation [continuous]<br>• Academic outcomes (children) [continuous]<br>• Substance use (alcohol and drug use) [dichotomous]<br>• Self-harm [dichotomous] |
| **Study design** | RCTs, systematic reviews of RCTs |

### 1.2.2 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[474] Methods specific to this review question are described in the review protocol in appendix A.

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

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

### 1.2.3 Clinical evidence

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

No relevant clinical studies were identified.

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.

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

Six randomised trials across 9 papers were included in the review; [139, 197, 206, 207, 257, 349, 378, 470, 691] these are summarised in Table 60 below. Evidence from these studies is summarised in the clinical evidence summary tables below

**Table 58: Lisdexamfetamine dimesylate versus placebo for ADHD in Children and Young People (substitute 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) 4 weeks | VERY LOW[a,b] due to risk of bias, imprecision | RR 1.84 (0.76 to 4.47) | 429 per 1000 | 360 more per 1000 (from 103 fewer to 1000 more) |
| Adverse events leading to hospitalisation/death/disability | 26 (1 study) 4 weeks | VERY LOW[a,b] 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) |

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

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

**Table 59: 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)<br>A decreased score is an improvement in ADHD symptoms. Range 0-54. | 201<br>(1 study)<br>9 weeks | MODERATE[a] 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<br>41.9 | The mean ADHD total symptoms (investigator rated ADHD-rs-iv, change score, 0-54, high is poor) in the intervention groups was<br>6.90 lower<br>(10.32 to 3.48 lower) |
| Hyperactivity/impulsivity (Investigator rated, ADHD-RS-IV, high is poor)<br>A decreased score is an improvement in ADHD symptoms. Range 0-27. | 201<br>(1 study)<br>9 weeks | MODERATE[a] due to imprecision | | The mean hyperactivity/impulsivity (investigator rated, ADHD-rs-iv, high is poor) in the control groups was<br>19.4 | The mean hyperactivity/impulsivity (investigator rated, ADHD-rs-iv, high is poor) in the intervention groups was 0.63 standard deviations lower<br>(0.91 to 0.35 lower) |
| Inattention (Investigator rated, ADHD-RS-IV, high is poor)<br>A decreased score is an improvement in ADHD symptoms. Range 0-27. | 201<br>(1 study)<br>9 weeks | MODERATE[a] due to imprecision | | The mean inattention (investigator rated, ADHD-rs-iv, high is poor) in the control groups was<br>22.5 | The mean inattention (investigator rated, ADHD-rs-iv, high is poor) in the intervention groups was<br>0.62 standard deviations lower<br>(0.91 to 0.34 lower) |
| CGI-S improvement of at least one category.<br>A decreased score is an improvement in ADHD symptoms. | 192<br>(1 study)<br>9 weeks | MODERATE[a] due to imprecision | RR 1.09<br>(1 to 1.2) | 866 per 1000 | 78 more per 1000<br>(from 0 more to 173 more) |
| Discontinued treatment due to adverse event | 262<br>(1 study)<br>9 weeks | LOW due to imprecision | RR 0.84<br>(0.34 to 2.05) | 75 per 1000 | 12 fewer per 1000<br>(from 49 fewer to 78 more) |
| Adverse events leading to | 262 | LOW due to | RD 0 (-0.01 to | 0 events in control arm | 0 fewer 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 Lisdexamfetamine dimesylate versus atomoxetine (95% CI) |
| hospitalisation/death/ disability (serious TEAEs) | (1 study) 9 weeks | imprecision | 0.01) | | (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 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) |

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

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.

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

#### 1.2.3.3 Excluded studies

See the excluded studies list in appendix I.

#### 1.2.3.4 Summary of clinical studies included in the evidence review

**Table 60: 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).<br>Treatment augmentation: atomoxetine continued. | Children (6-12 years old) with ADHD not responding to atomoxetine (n=17). Mean age: 9.6 years old. | • Adverse events leading to hospitalisation/ death/disability<br>• 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) on the CGI-I scale.<br>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, 691] | Guanfacine AM (n=154) or guanfacine PM (n=153) versus placebo (n=154)<br>Treatment augmentation: CNS stimulant continued. | Children (6 to 17 years old) with ADHD who are taking CNS stimulants (mixed amphetamine salts, lisdexamfetamine dimesylate, methylphenidate, dexmethylphenidate) but have a partial or suboptimal response (n=461). Mean age: 10.8 years old. | • Clinical Global Impressions Improvement<br>• ADHD severity<br>• 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.<br>Mean optimal dose of guanfacine was 0.088 mg/kg/day. |
| Dittmann 2014, Dittmann 2013, Nagy | Lisdexamfetamine dimesylate (n=133) versus atomoxetine | Children (6-17 years old) with ADHD who had an inadequate | • Clinical Global Impressions Improvement<br>• ADHD symptoms | Patients were excluded if they experienced intolerable side |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| 2015[206, 207, 470] | (n=134)<br>Treatment substitution: methylphenidate stopped. | response to previous methylphenidate treatment (n=267).<br>Mean age: 10.6 years old. | • ADHD symptom subscores<br>• Adverse events leading to hospitalisation/death/disability<br>• Discontinuation of treatment due to adverse events<br>• Weiss Functional Impairment Rating Scale | effects with MPH or failed to respond to more than one course of MPH.<br>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 alterative to methylphenidate.<br>Mean optimal dose at week 4:<br>Lisdexamfetamine: 52.5 mg/day<br>Atomoxetine: 40.2 mg/day. |
| Gadow 2014[257] | Risperidone (and parent training) (n=84) versus placebo (and parent training) (n=84)<br>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. | • ADHD severity<br>• ADHD severity subscores<br>• Behavioural measures (ODD severity, peer conflict scale, CD severity) | An alternative to OROS methylphenidate was offered to those unable to tolerate medication or swallow pills.<br>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.<br>Week 9 dose:<br>Methylphenidate: 46 mg/day for the risperidone group and 45 mg/day for the placebo group.<br>Risperidone: 1.7 mg/day<br>Placebo: 1.9 mg/day |
| Jain 2011[349] | Lisdexamfetamine dimesylate (n=19) versus placebo (n=7)<br>Treatment substitution: methylphenidate stopped. | Children (6-12 years old) with ADHD who had not responded to previous methylphenidate treatment (n=26). Mean age: 9. | • Clinical response via ADHD-RS-IV and CGI-I<br>• Adverse events leading to hospitalisation/ death/disability | Non-response to methylphenidate was an ADHD-RS-IV score of >/=18 while receiving treatment.<br>Varied fixed dose of lisdexamfetamine from 30 mg/day to 70 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | | mg/day depending on randomisation. |
| Kollins 2011[378] | Clonidine (n=102) versus placebo (n=96)<br>Treatment augmentation: stimulants continued. | Children aged 6-17 years old with hyperactive or combined ADHD subtype and insufficient response to stimulant treatment (n=198).<br>Mean age: 10.5. | • ADHD severity<br>• ADHD severity subscores<br>• Discontinuation of treatment due to adverse events | Insufficient response defined to be a total ADHD-RS-IV score of >/= 26.<br>Mean dose of clonidine was 0.3 mg/day in weeks 4 and 5. |

See appendix D for full evidence tables.

#### 1.2.3.5 Included studies (adults)

One study was included in the review; [134] this is are summarised in **Table 61** below. Evidence from these studies is summarised in the clinical evidence summary below (**Table 69**).

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.

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

**Table 61: Summary of studies included in the review**

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Butterfield 2016[134] | Guanfacine (n=13) versus placebo (n=13)<br>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. | • ADHD symptoms<br>• 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.<br>Mean final dispensed dose was 4.8 mg/day. Range of 2 to 6 mg/day. |

### 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 62: 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[a,b,c] 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[,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) |

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

**Table 63: 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[a,b] due to risk of | 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 | bias, imprecision | 4.47) | | |
| Adverse events leading to hospitalisation/death/disability | 26 (1 study) 4 weeks | VERY LOW[a,b] 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) |

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

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

**Table 64: 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[a] 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 improvement in ADHD | 201 (1 study) 9 weeks | MODERATE[a] due to imprecision | | The mean hyperactivity/impulsivity (investigator rated, ADHD-rs-iv, high is poor) in the control groups was 19.4 | The mean hyperactivity/impulsivity (investigator rated, ADHD-rs-iv, high is poor) in the intervention groups was 0.63 standard deviations lower (0.91 to 0.35 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) |
| symptoms. Range 0-27. | | | | | |
| Inattention (Investigator rated, ADHD-RS-IV, high is poor)<br>A decreased score is an improvement in ADHD symptoms. Range 0-27. | 201<br>(1 study)<br>9 weeks | MODERATE[a] due to imprecision | | The mean inattention (investigator rated, ADHD-rs-iv, high is poor) in the control groups was<br>22.5 | The mean inattention (investigator rated, ADHD-rs-iv, high is poor) in the intervention groups was<br>0.62 standard deviations lower<br>(0.91 to 0.34 lower) |
| CGI-S improvement of at least one category.<br>A decreased score is an improvement in ADHD symptoms. | 192<br>(1 study)<br>9 weeks | MODERATE[a] due to imprecision | RR 1.09<br>(1 to 1.2) | 866 per 1000 | 78 more per 1000<br>(from 0 more to 173 more) |
| Discontinued treatment due to adverse event | 262<br>(1 study)<br>9 weeks | LOW[a] due to imprecision | RR 0.84<br>(0.34 to 2.05) | 75 per 1000 | 12 fewer per 1000<br>(from 49 fewer to 78 more) |
| Adverse events leading to hospitalisation/death/ disability (serious TEAEs) | 262<br>(1 study)<br>9 weeks | LOW[a] due to imprecision | RD 0 (-0.01 to 0.01) | 0 events in control arm | 0 fewer per 1000<br>(from 15 fewer to 15 more) |
| Function/behaviour (Parent rated, WFIRS-P, 0-3, high is poor)<br>A decreased score is an improvement in ADHD symptoms. 50 items scored 0-3 each. | 220<br>(1 study)<br>9 weeks | MODERATE[a] due to imprecision | | The mean function/behaviour (parent rated, wfirs-p, 0-3, high is poor) in the control groups was<br>0.59 | The mean function/behaviour (parent rated, wfirs-p, 0-3, high is poor) in the intervention groups was<br>0.08 lower<br>(0.17 lower to 0.01 higher) |

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

**Table 65: 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[a,b,c] 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[a,b,c] 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[a,b,c] 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[a,b,c] 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[a,b,c] 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)<br>A decreased score is an improvement in ADHD symptoms. Range 0-27 | 303<br>(1 study)<br>8 weeks | VERY LOW[a,b,c]<br>due to risk of bias, indirectness, imprecision | | | The mean ADHD-RS-IV hyperactivity/impulsivity subscale reduction was<br>0.36 lower standard deviations lower<br>(0.59 to 0.14 lower) |

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

**Table 66: 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<br>(1 study)<br>8 weeks | VERY LOW [a,b,c]<br>due to risk of bias, indirectness, imprecision | RR 1.22 (1.03 to 1.44) | 579 per 1000 | 127 more per 1000<br>(from 17 more to 255 more) |
| Early discontinuation of treatment due to adverse events | 305<br>(1 study)<br>9 weeks | VERY LOW [a,b,c]<br>due to risk of bias, indirectness, | RR 6.04 (0.74 to 49.57) | 7 per 1000 | 33 more per 1000<br>(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) |
| | | imprecision | | | |
| Adverse events leading to hospitalisation/death/disability (severe TEAEs) | 305 (1 study) 9 weeks | VERY LOW [a,b,c] 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 [a,b,c] 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[a,b,c] 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 [a,b,c] due to risk of bias, indirectness, imprecision | | | The mean ADHD-RS-IV hyperactivity/impulsivity subscale: placebo adjusted lS mean reduction was 0.40 lower standard deviations lower (0.62 to 0.17 lower) |

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

*(b) Downgraded by 1 increment if the majority of the evidence included an indirect population or 2 increments if the majority of the evidence included a very indirect population.*

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

**Table 67: Clonidine 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 Clonidine versus placebo (95% CI) |
| ADHD total symptoms (ADHD-RS-IV improvement, high is poor)<br>A decreased score is an improvement in ADHD symptoms. Range 0-54. | 197<br>(1 study) | VERY LOW[a,b] due to risk of bias, imprecision | | The mean ADHD total symptoms (ADHD-rs-iv improvement, high is poor) in the control groups was<br>39 | The mean ADHD total symptoms (ADHD-rs-iv improvement, high is poor) in the intervention groups was<br>4.20 lower<br>(7.62 to 0.78 lower) |
| Inattention (ADHD-RS-IV, high is poor)<br>A decreased score is an improvement in ADHD symptoms. Range 0-27 | 197<br>(1 study)<br>5 weeks | VERY LOW[a,b] due to risk of bias, imprecision | | The mean inattention (ADHD-rs-iv, high is poor) in the control groups was<br>-5.8 | The mean inattention (ADHD-rs-iv, high is poor) in the intervention groups was<br>2.00 lower<br>(3.90 to 0.10 lower) |
| Hyperactivity/impulsivity (ADHD-RS-IV, high is poor)<br>A decreased score is an improvement in ADHD symptoms. Range 0-27. | 197<br>(1 study)<br>5 weeks | VERY LOW[a,b] due to risk of bias, imprecision | | The mean hyperactivity/impulsivity (ADHD-rs-iv, high is poor) in the control groups was<br>-5.8 | The mean hyperactivity/impulsivity (ADHD-rs-iv, high is poor) in the intervention groups was<br>2.10 lower<br>(3.92 to 0.28 lower) |
| Discontinued treatment due to TEAE | 198<br>(1 study)<br>5 weeks | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.31 (0.03 to 2.96) | 31 per 1000 | 22 fewer per 1000<br>(from 30 fewer to 61 more) |

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

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

**Table 68: Risperidone and parent training versus placebo and parent training for ADHD in children and young people (augmentation of 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 placebo (95% CI) |
| ADHD total symptoms (parent rated ADHD-SC4, Severity Score, 0-3, high is poor)<br>40 item treatment response measure that includes DSM-IV scales of ADHD and ODD and the peer conflict scale. | 137<br>(1 study)<br>6 weeks | MODERATE [a]<br>due to imprecision | | The mean ADHD total symptoms (parent rated ADHD-sc4, severity score, 0-3, high is poor) in the control groups was<br>1 | The mean ADHD total symptoms (parent rated ADHD-sc4, severity score, 0-3, high is poor) in the intervention groups was<br>0.20 lower<br>(0.4 lower to 0 higher) |
| ADHD total symptoms (teacher rated ADHD-SC4, Severity Score, 0-3, high is poor)<br>ADHD-SC4 is a 40 item treatment response measure that includes DSM-IV scales of ADHD and ODD and the peer conflict scale. | 86<br>(1 study)<br>6 weeks | LOW [a,b]<br>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<br>0.8 | The mean ADHD total symptoms (teacher rated ADHD-sc4, severity score, 0-3, high is poor) in the intervention groups was<br>0.20 lower<br>(0.43 lower to 0.03 higher) |
| Inattention (parent rated ADHD-SC4 Severity, 0-3, high is poor)<br>ADHD-SC4 is a 40 item treatment response measure that includes DSM-IV scales of ADHD and ODD and the peer conflict scale. | 137<br>(1 study)<br>6 weeks | MODERATE [a]<br>due to imprecision | | The mean inattention (parent rated ADHD-sc4 severity, 0-3, high is poor) in the control groups was<br>1.1 | The mean inattention (parent rated ADHD-sc4 severity, 0-3, high is poor) in the intervention groups was<br>0.20 lower<br>(0.42 lower to 0.02 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) |
| Inattention (teacher rated ADHD-SC4 Severity, 0-3, high is poor)<br>ADHD-SC4 is a 40 item treatment response measure that includes DSM-IV scales of ADHD and ODD and the peer conflict scale. | 86<br>(1 study)<br>6 weeks | LOW[a,b]<br>due to risk of bias, imprecision | | The mean inattention (teacher rated ADHD-sc4 severity, 0-3, high is poor) in the control groups was<br>1 | The mean inattention (teacher rated ADHD-sc4 severity, 0-3, high is poor) in the intervention groups was<br>0.20 lower<br>(0.47 lower to 0.07 higher) |
| Hyperactivity (parent rated ADHD-SC4 Severity Subscore, 0-3, high is poor)<br>ADHD-SC4 is a 40 item treatment response measure that includes DSM-IV scales of ADHD and ODD and the peer conflict scale. | 137<br>(1 study)<br>6 weeks | MODERATE[a]<br>due to imprecision | | The mean hyperactivity (parent rated ADHD-sc4 severity subscore, 0-3, high is poor) in the control groups was<br>0.8 | The mean hyperactivity (parent rated ADHD-sc4 severity subscore, 0-3, high is poor) in the intervention groups was<br>0.20 lower<br>(0.44 lower to 0.04 higher) |
| Hyperactivity (teacher rated ADHD-SC4 Severity Subscore, 0-3, high is poor)<br>ADHD-SC4 is a 40 item treatment response measure that includes DSM-IV scales of ADHD and ODD and the peer conflict scale. | 86<br>(1 study)<br>6 weeks | LOW[a,b]<br>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<br>0.4 | The mean item rating ADHD-SC4 severity subscore: hyperactivity (teacher rating) in the intervention groups was<br>0.10 standard deviations higher<br>(0.14 lower to 0.34 higher) |
| Impulsivity (parent rated ADHD-SC4 Severity Subscore, 0-3, high is poor)<br>ADHD-SC4 is a 40 item treatment response | 137<br>(1 study)<br>6 weeks | MODERATE[a]<br>due to imprecision | | The mean impulsivity (parent rated ADHD-sc4 severity subscore, 0-3, high is poor) in the control groups was<br>0.8 | The mean impulsivity (parent rated ADHD-sc4 severity subscore, 0-3, high is poor) in the intervention groups was<br>0.30 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) |
| measure that includes DSM-IV scales of ADHD and ODD and the peer conflict scale. | | | | | (0.57 to 0.03 lower) |
| Impulsivity (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[a,b] due to risk of bias, imprecision | | The mean impulsivity (teacher rated ADHD-sc4 severity subscore, 0-3, high is poor) in the control groups was 0.7 | The mean impulsivity (teacher rated 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[a] 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[a,b] 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[a] 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 | 86 | MODERATE | | The mean function/behaviour | The mean function/behaviour (teacher |

| 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) |
| (teacher rated Peer Conflict Scale, 0-3, high is poor) | (1 study)<br>6 weeks | [b]<br>due to risk of bias | | (teacher rated peer conflict scale, 0-3, high is poor) in the control groups was<br>0.2 | rated peer conflict scale, 0-3, high is poor) in the intervention groups was<br>0 higher<br>(0.15 lower to 0.15 higher) |
| Function/behaviour (parent rated CD DSM-IV, 0-3, high is poor) | 150<br>(1 study)<br>6 weeks | MODERATE [a]<br>due to imprecision | | The mean function/behaviour (parent rated cd dsm-iv, 0-3, high is poor) in the control groups was<br>0.2 | The mean function/behaviour (parent rated cd dsm-iv, 0-3, high is poor) in the intervention groups was<br>0.10 lower<br>(0.16 to 0.04 lower) |
| Function/behaviour (teacher rated CD DSM-IV, 0-3, high is poor) | 69<br>(1 study)<br>6 weeks | VERY LOW[a,b]<br>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<br>0.1 | The mean function/behaviour (teacher rated cd dsm-iv, 0-3, high is poor) in the intervention groups was<br>0 higher<br>(0.12 lower to 0.12 higher) |

*(a) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.*
*(b) 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.

#### *1.2.3.6.3 Clinical evidence (adults)*

**Table 69: 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)<br>Participants returned to study site for | 26<br>(1 study)<br>10 weeks | VERY LOW[a,b]<br>due to risk of bias, imprecision | | The mean ADHD total symptoms (ADHD-rs, 0-54, high is poor) in the control | The mean ADHD total symptoms (ADHD-rs, 0-54, high is poor) in the intervention |

| 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) |
| evaluation of ADHD symptoms | | | | groups was<br>10.92 | groups was<br>0.93 higher<br>(5.44 lower to 7.3 higher) |
| CGI-S (change score, 0-7)<br>Participants returned to study site for evaluation of ADHD symptoms | 26<br>(1 study) | VERY LOW[a,b]<br>due to risk of bias, imprecision | | The mean cgi-s (change score, 0-7) in the control groups was<br>1 | The mean cgi-s (change score, 0-7) in the intervention groups was<br>0.15 lower<br>(0.75 lower to 0.45 higher) |
| Adverse events leading to hospitalisation/death/disabilities | 26<br>(1 study)<br>10 weeks | LOW[a,b]<br>due to risk of bias | RD 0 (-0.14 to 0.14) | 0 events in control arm | 0 fewer per 1000<br>(from 138 fewer to 138 more) |

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

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

## 1.2.4 Economic evidence

### 1.2.4.1 Included studies

#### *1.2.4.1.1 2008 guideline literature*

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

#### *1.2.4.1.2 Published literature*

Seven health economic studies were identified with the relevant comparison and have been included in this review. [188],[332],[221],[644],[557],[395],[716] These are summarised in the health economic evidence profiles below (**Table 70**, **Table 71**, **Table 72**, **Table 73**) and the health economic evidence tables in appendix H.

Two of these studies compare an atomoxetine treatment algorithm with standard care or no treatment in subgroups of children with ADHD who have either failed stimulants, or are averse or contraindicated to them, in keeping with the populations of this sequencing review. Hong 2009[332] is a different version of Cottrell 2008[188] model but is thought to be sufficiently different and is presented as a separate study. Subgroups from these studies that were stimulant naïve are reported in the pharmacological effectiveness review.

Three studies compare types of extended release methylphenidate with immediate release methylphenidate in children who are responding sub-optimally to immediate release methylphenidate because of inadequate medication intake. Van der Schans 2015[644] and Schawo 2015[557] are different versions of the Faber 2008[221] model but are thought to be sufficiently different and are presented as separate studies.

Lachaine 2016[395] compares guanfacine extended release added as an adjunct to long-acting stimulants with long-acting stimulants alone in children who are only partially responding to the stimulants.

Finally Zimovetz 2016[716] compares Lisdexamfetamine with Atomoxetine in children who had an inadequate response to Methylphenidate.

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

### 1.2.4.2 Excluded studies

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

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

### 1.2.5 Summary of studies included in the economic evidence review

**Table 70: 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)] | 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.<br><br>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:<br><br>Subgroup 1: Stimulant failed patients;<br>Treatment algorithm of atomoxetine →IR-DEX→no treatment. Comparator is the same sequence without | Subgroup 1: £448.78<br><br>Subgroup 2 (a) (includes IR-MPH): £373.79<br><br>Subgroup 2 (b) (includes XR-MPH): £256.3<br><br>Subgroup 3: £395.98 | Subgroup 1: 0.03<br><br>Subgroup 2 (a) (includes IR-MPH): 0.0235<br><br>Subgroup 2 (b) (includes XR-MPH): 0.0181<br><br>Subgroup 3: 0.0320 | Subgroup 1: £14,945<br><br>Subgroup 2 (a) (includes IR-MPH): £15,878<br><br>Subgroup 2 (b) (includes XR-MPH): £14,169<br><br>Subgroup 3: £12,370 | Uncertainty around the ICER not reported.<br>Paper states a probabilistic analysis was done but data on this is not reported.<br><br>Multiple sensitivity analyses are stated as being undertaken however results are not reported.<br>Model most sensitive to the utility values used. |

| Study | Applicability | Limitations | Other comments | Incremental cost | Incremental effects (QALYs) | Cost-effectiveness | Uncertainty |
|---|---|---|---|---|---|---|---|
| | | | atomoxetine<br>Subgroup 2a: Stimulant averse (exposed) patients;<br>Treatment algorithm of atomoxetine →IR-MPH→IR-DEX→no treatment. Comparator is the same sequence without atomoxetine<br>Subgroup 2b: same as above except IR-MPH is replaced with XR-MPH.<br>Subgroup 3: Stimulant contraindicated (exposed) patients;<br>Atomoxetine followed by no treatment if that fails, compared to no treatment alone. | | | | |
| Hong 2009[332] (Spain) | Partially applicable [(c)] | Potentially serious limitations[(d)] | 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. | £831 (e) | 0.039 | £21,528 | Uncertainty around the ICER not reported.<br>Paper states a probabilistic analysis was done but data on this is not reported.<br><br>Multiple sensitivity analyses are stated as being undertaken however results are not reported.<br>Model most sensitive to the utility values used. |

| Study | Applicability | Limitations | Other comments | Incremental cost | Incremental effects (QALYs) | Cost-effectiveness | Uncertainty |
|---|---|---|---|---|---|---|---|
| | | | 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:<br><br>Stimulant failed patients:<br>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 dexamfetamine*

*(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) Non UK. 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.*

**Table 71: 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) | 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.<br>Patients going into the primary phase are youths with sub optimal symptom control from | £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.<br>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[644] (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:<br>£597 [(f)]<br><br>Medikinet/ Equasym vs MPH IR:<br>-£449 | MPH OROS vs MPH IR:<br>0.318<br><br>Medikinet/ Equasym vs MPH IR:<br>0.318 | MPH OROS vs MPH IR:<br>£1,879<br><br>Medikinet/ Equasym vs MPH IR:<br>Dominant | A series of univariate sensitivity analyses were performed on most of the model parameters. This involved varying base case values +/-25%.<br>In addition a multivariate sensitivity analysis was |

| Study | Applicability | Limitations | Other comments | Incremental cost | Incremental effects (QALYs) | Cost-effectiveness | Uncertainty |
|---|---|---|---|---|---|---|---|
| | | | 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.<br>Staying on IR MPH is then compared to switching to modified release versions; OROS MPH, or Medikinet CR/Equasym XL.<br>Treatment effect is based on a combination of assumptions from a panel of experts and some literature.<br><br>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. | | | The Medikinet/ Equasym comparator is dominant overall because it is cheaper than MPH OROS and has the same QALYs. | performed where the worst case parameter values were analysed.<br>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. |
| Schawo 2015[557] (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<br><br>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 |
|---|---|---|---|---|---|---|---|
| | | | The model has 4 states, and a 12 year time horizon with cycles of 1 day.<br>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.<br><br>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. | | incremental cost reported in the sensitivity analysis that excluded caregiver utility. | | rates of OROS were assumed equal to IR MPH. This analysis also resulted in zero incremental QALYs. |

*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 dexamfetamine*

*(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 72: 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 [395](Canada) | Partially applicable [(a)] | Potentially serious limitations [(b)] | 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.<br><br>Treatment effect based on a single 8 week trial.<br><br>Effect outcome is QALYs and also patient weeks with a response.<br><br>Costs include interventions costs and costs in each health state related to managing ADHD. | £373 [(c)] | QALYs = 0.028<br><br>Patient weeks with a response = 6.57 | £13,321 | Probabilistic sensitivity analysis done. 95% probability of intervention being cost effective.<br><br>Several one-way sensitivity analyses were performed by varying a single variable individually within lower and upper bounds of all key parameters.<br>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.<br><br>In a sensitivity analysis where patients were maintained on treatment and could transition between heath states during the |

| 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 Golobal 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 he ministry of health perspective has been reported here.*

**Table 73: Health economic evidence profile: [Lisdexamfetamine versus Atomoxetine]**

| Study | Applicability | Limitations | Other comments | Incremental cost | Incremental effects (QALYs) | Cost-effectiveness | Uncertainty |
|---|---|---|---|---|---|---|---|
| Zimovetz 2016 [716](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.<br>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%.<br><br>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.<br><br>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 |
|---|---|---|---|---|---|---|---|
| | | | | | | | an ICER of £4,968 when using the head to head trial utilities.<br>LDX remained cost effective in all sensitivity analyses and was dominant in two of them; assumptions about drug costs, and using MTC effectiveness. |

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

*(a) UK perspective. EQ-5D.*

*(b) 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. It is also acknowledged that the incremental results are very small and therefore small changes to the analysis could easily change the results to not being cost saving.*

Subgroup 3 of the Cottrell[188] study, and the subgroup presented from the Hong[332] study, have similar interventions (atomoxetine followed by no treatment compared to no treatment, and atomoxetine compared to no treatment, respectively), yet they have quite different ICERS. One reason for this is that the cost of atomoxetine in the Hong study, which is European, is around twice the cost atomoxetine in the Cottrell study, which might explain why the incremental cost in Hong is about twice that of Cottrell. One concern the committee had abaout the Cottrell and Hong studies was that the studies assumed atomoxetine did not have an insomnia side effect, which the commitee believed was an underestimate. Had this been included in the Cottrell study, it may have had some effect on the result, but it is uncertain if it would have such a large effect as to increase the ICER above the NICE threshold.

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

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

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

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

#### 1.2.5.1 Unit costs

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

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

### 1.2.6 Resource impact

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

## 1.2.7 Evidence statements

### 1.2.7.1 Clinical evidence statements

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

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

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

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

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

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

- Clinical benefit of lisdexamfetamine compared to atomoxetine for investigator rated ADHD total, hyperactivity and inattention symptoms (1 study low quality)
- 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).

**Guanfacine versus placebo**

- Clinical benefit of guanfacine for CGI-I (1 study low quality, children and young people)
- Clinical harm of methylphenidate in adverse events leading to hospitalisation/death/disability (1 study very low quality, children and young people)
- No cilinical 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)

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

- No clinicall 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)

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

- 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)
- 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)
- 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 The committee's discussion of the evidence for pharmacological efficacy

This review should be read alongside Evidence reports; D: Safety of pharmacological treatment and F: Combination treatment. See evidence report F for the committee's discussion on when to decide on which treatment approach to take (pharmacological or non-pharmacological).

## 1.3.1 Interpreting the evidence

### 1.3.1.1 The outcomes that matter most

The committee considered quality of life, ADHD symptoms, CGI assessment of response and serious adverse events to be critical outcomes. ADHD symptoms were separately considered as total, hyperactivity and inattention subscales. The committee did not prioritise any one subscale. ADHD symptoms were separately considered when reported by self, parent, teacher and investigator. The committee considered that all had their merit but that symptoms reported by teacher or investigator were likely to be the most objective assessment of effect because even if the trials were blinded, parents might have been aware of the drug or placebo status, given the effect profile of some of the stimulant medication used for ADHD.

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

The committee recognised the importance of evaluating in detail the adverse events reported for pharmacological treatments and evidence report D explores further the potential impacts of the short and long term adverse effects of pharmacological interventions. All the outcomes in the adverse effects review were considered to be critical for supporting decision making about drug choice and initiating treatment. The outcomes were; total number of participants with an adverse event, all-cause mortality, suicide or suicidal ideation, cardiac mortality, cardiac events including tachycardia/palpitations (defined by >/120bpm) or systolic or diastolic blood pressure changes, substance misuse, abnormal growth ( height and weight), increase in seizures in people with epilepsy, psychotic symptoms, disturbed sleep, liver damage, increased tics, tremors congenital defects amongst people who are pregnant, sexual dysfunction.

### 1.3.1.2 The quality of the evidence

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

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

Studies rarely reported quality of life or functional measures but frequently just ADHD symptoms. The committee noted that these were often reported by the people taking the

drugs themselves (if adults) or parents who, even if the trials were blinded, might have been aware of the drug or placebo status, given the effect profile of some of the stimulant medication used for ADHD. Some studies did use teacher reports who were less likely to be aware.

#### 1.3.1.3 Benefits and harms

Treatment approach

Evidence report F: Combination treatment evaluates the evidence comparing pharmacological and non-pharmacological treatments and the combination of treatment approaches. The 'committee's discussion on the evidence' section in evidence report F sets out the committee's reasons for treatment approach for the different age groups. The review in this report focuses on medication choices.

Medication choice

As undertaking a network meta analysis was not possible to combine all the clinical data in any of the age groups (see the methodology chapter for further details), the committee had the difficult task of evaluating the different pairwise comparisons presented to them and trying to draw conclusions on both the direct but also indirect relationships between drug treatments. In terms of the pathway of drugs that were recommended for all the age groups the committee agreed that stimulants are effective against placebo, and in clinical practice are the most commonly used ADHD treatment and are favoured because of their fast acting nature.

The short term adverse effects of ADHD drugs are well known and this was reflected in the evidence identified in this review and in Evidence report D. A lot of people taking ADHD medication do report short term adverse effects (for example, sleep difficulties and weight loss) that can be troublesome and impact on adherence to treatment. Careful initiation and titration of medication is important to address these issues. Although adverse effects are commonly reported the drugs reported here appear to be safe at least in the short term with very few serious adverse events reported. There is a lack of information on the long term use of medication for ADHD and particular there are concerns about the long term impact of stimulants on children and young people's growth.

In summary, the evidence on adverse events is lacking; the quality of the evidence is mostly short term and of low quality, there is lack of good quality long term data and there is a scarcity of trials comparing drugs. The committee noted that when comparing the adverse events of the different drugs there is an absence of evidence and this is not evidence of the equivalence of the adverse events (or an absence of events) across the treatments. The committee based the treatment recommendations on the limited evidence base, their experience of the benefits and harms of treatment and through consensus.

Formulation choice

There are short and long acting formulations of stimulants. There are many circumstances to consider when deciding whether a short or long acting formulation of methylphenidate is used. From the experience of the committee; most clinicians would tend to use the long acting formulation in school children but may titrate with short acting to assess adverse effects and often a mix of short and long acting is used according to the person's needs. A direct comparison of the two preparations did not show any differences in effectiveness or adverse effects. A modified release formulation can provide more stability in symptom control throughout the day, and also can help prevent the stigma associated with ADHD compared to if children have to take multiple tablets per day necessitating going to the 'office' in front of peers for example. Therefore there may be a wider impact on quality of life than only through control of symptoms. For these reasons the committee stated in the recommendation that stimulants in either formulation can be offered.

#### *1.3.1.3.1 Children under the age of 5*

The committee agreed that there was insufficient evidence to justify routine use of medication in this age group. The committee discussed at length the appropriateness of recommending stimulants for very young children. The committee noted that there is a very high non acceptance of pharmacological treatments in the under 5 years age group and this is reflected in the high dropout rates in some of the studies. The committee were aware of concerns about the impact of stimulants on the growth and development of young children, particularly the theoretical concern related to the impact of methylphenidate on the growing brain; however, they did not find any evidence that reflected this concern. The committee also acknowledged other reports of the positive effect long term impact of stimulants on the brain. Drawing on their experience the committee discussed how untreated ADHD could have long lasting negative impacts on a child's life.

Taking into account the uncertainty around the evidence in this population the committee agreed that if ADHD symptoms are having a persistent significant impairment across domains after non-pharmacological approaches have been implemented and reviewed it is then only in this context that medication should be considered, The committee were clear that this would be very unusual in this age group and should only be considered having carefully reviewed the diagnosis and other options. The committee reinforced this with a recommendation that emphasised medication should only be considered in the context of an ADHD service with specialist experience of young children.

#### *1.3.1.3.2 Children aged 5 years and over and young people*

There is a larger evidence base in this age group compared to children aged under 5 and this shows a benefit of medication compared to placebo. As outlined above the short term adverse effects of medication are well known and can be managed with the careful initiation and titration of a drug. The committee acknowledged and discussed in detail the concerns about recommending medication for ADHD symptoms in children and young people.The committee were aware of concerns about the impact of stimulants on the growth and development of children, particularly the theoretical concern related to the impact of methylphenidate on the growing brain; however, they did not find any evidence that reflected this concern, the committee also acknowledged other reports of the positive effect long term impact of stimulants on the brain.

Drawing on their experience the committee discussed how the impact of unrecognised and untreated ADHD can be serious and far reaching. People report negative impacts on academic achievement, commonly underachieving at school, poorer social relationships and participation in life activities both leisure and work. People with ADHD are over represented in criminal justice systems, have more physical accidents including with cars and have a higher risk of addictive behaviour with resultant impact.

Taking into account the evidence about the effectiveness of medication, the known impacts of adverse events and the concerns about growth in children the committee recommended that ADHD group support for parents and carers and environmental modifications should be the first line of treatment. If a child or young person is still experiencing persistent impairment in at least one domain then they should be offered medication having carefully reviewed the diagnosis and undertaken baseline assessments and with regular reviews.

#### *1.3.1.3.3 Medication choices for children aged 5 to 18 and adults*

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

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

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

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

#### *1.3.1.3.4 People with ADHD and co-existing conditions*

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

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

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

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

### 1.3.2 Cost effectiveness and resource use

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

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

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

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

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

(ER-MPH). This study found that LDX dominated both ATX and ER-MPH. This study was rated as directly applicable because it was from a UK NHS perspective and used EQ-5D data for QALYs. It has very serious limitations such as a potential conflict of interest as it is funded by the makers of a LDX product, also no additional treatment was assumed following non response/discontinuation. It conducted a network meta-analysis for treatment effect and discontinuations and some studies in their NMA were not included in the guideline clinical review. As the results particularly of the LDX vs MPH comparison were very close together in terms of outcomes (cost difference of £9) then changes to the model may well change the conclusions. Therefore cost effectiveness of LDX vs MPH or ATX is potentially uncertain.

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

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

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

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

If UK evidence is prioritised higher weight would be given to King 2006, Cottrell 2008, and Zimovetz 2017. The first two studies tell us that different sequences are cost effective that still involve the 3 main drugs - atomoxetine, dexamfetamine (or lisdexamfetamine, that has the same active component), and methylphenidate, and the study in adults informs that lisdexamfetamine could be more cost effective than atomoxetine and extended release methylphenidate. Overall a mixed picture, but these are the 3 that have been recommended

previously and remain at the top of the treatment algorithms in this update. Sequences of treatment are discussed in more detail below.

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

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

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

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

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

Taking all of this information alongside the economic evidence;

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

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

For most subgroups of people with ADHD and a co-existing condition, the sequence is the same, although there are exceptions where the committee wanted to alter the sequence depending on the co-morbidity or risk factors such as risk of misuse. These were consensus based recommendations.

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

It is accepted that there is a lack of longer term safety data on pharmacological treatments. Economic evaluations included adverse events or discontinuations, but these tend to be short term events. These may have a longer term cost or quality of life impact dependent on what these longer term adverse events might be, which could impact cost effectiveness. Recommendations made in the adverse events review ensure that people with ADHD are regularly followed up and monitored in order to ensure that the treatment the patient is taking is the right choice for them.

Although offering medication to children aged over 5's years and young people is generally already current practice, the previous guideline separated those with moderate impairment from those with severe impairment, and drug treatment was only offered first line to those with severe impairment. It was not possible in this update to divide the populations by severity. The committee recommended offering medication to children and young people over 5 years old if their ADHD symptoms are having a persistent significant impairment on at least one domain of their everyday life even after environmental modifications. This may include some people who were previously categorised as being of moderate severity from the classification of the previous guideline. There is difficulty in practice in defining the severity of ADHD and an element of clinician judgement is needed. The opinion of the committee was although this may mean more people could receive drugs than the previous guideline, in practice the help-seeking population are likely to be mostly made up of children who meet the criteria for more severe ADHD rather than moderate. In addition, by definition ADHD (whether mild, moderate, or severe) involves impairment, and thus by using the definition 'persistent significant impairment' in the recommendation, and stating that medication should also only be offered after ADHD support and environmental modifications have been implemented and reviewed, suggests that medication would only be offered to those with more severe enduring impairment. Hence overall the committee did not feel that there would be a significant impact on practice in terms of the overall population being prescribed medication.

#### *1.3.2.1.3 Cost effectiveness and resource use for adults aged over 18*

The pathway begins the same as for children by recommending stimulants as first line, for adults this is either methylphenidate or lisdexamfetamine as the committee consensus was that the clinical evidence supports either and offering a choice is more helpful in practice. As mentioned previously, one economic evaluation for adults was identified comparing lisdexamfetamine to extended release methylphenidate and atomoxetine, and found that lisdexamfetamine was likely to be dominant. The clinical review found that both formulations of methylphenidate were effective compared to placebo. Lisdexamfetamine was also found to have benefit compared to placebo. There weren't as many direct comparisons of different drugs for adults however as there were for children.

Dexamfetamine was again placed after lisdexamfetamine. This was mainly due to the increase in price of the drug since the previous guideline. As lisdexamfetamine is a prodrug of dexamfetamine, it has a longer effect profile so can avoid someone taking multiple doses per day. This can help reduce stigma associated with ADHD when multiple doses have to be

taken throughout the day. Lisdexamfetamine is also a fairly new drug not available at the time of the last guideline. For adults in particular there is a much larger price difference between dexamafetamine and lisdexamfetamine because much higher doses of dexamfetamine are taken for adults which is driving its higher price, and as more than one tablet a day is taken the number of tablets needed per day means more tablets are required overall.

The licensing around some of the drugs was also a factor in determining their placement in the pathway. Atomoxetine for example is only licensed in adults if they had childhood symptoms. Therefore atomoxetine was a second line treatment for adults, followed by a referral to tertiary services before guanfacine could be prescribed in adults because it is not licensed for adults.

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

#### *1.3.2.1.4 Cost effectiveness and resource use summary*

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

### 1.3.3 Other factors the committee took into account

Alongside the recommendations on medication and throughout the guideline the committee have emphasised the importance of having a good relationship with the person with ADHD ( or their parents and carers) and making treatment decisions together with as much information as possible. It is important that anyone that receives medication is closely and carefully monitored The committee agreed that effective strategies for reviewing treatment, monitoring behavioural response and managing adverse events were critical when deciding on and continuing with treatment options and improving adherence to treatment in people with ADHD. The committee acknowledged the variation in the implementation in follow up and monitoring across the UK. They referred to the recommendations from the original guideline that recommended shared care arrangements with primary care. Some of the committee noted that in their experience specialist nurses undertook this role.

# 1.4 The committee's discussion of the evidence for sequencing pharmacological treatment

## 1.4.1 Interpreting the evidence

### 1.4.1.1 The outcomes that matter most

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

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

### 1.4.1.2 The quality of the evidence

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

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

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

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

#### 1.4.1.3 Benefits and harms

##### *1.4.1.3.1 Children under the age of 5*

In addition to the scarcity of evidence on anything other than methylphenidate no sequencing evidence was found in this age stratum. The committee did not make specific recommendations on the sequence of medication to use in this group as they considered it to be uncommon that medication was used in this age group and recommended it should only be done after seeking expert advice.

##### *1.4.1.3.2 Children and young people aged 5 to 18*

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

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

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

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

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

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

##### *1.4.1.3.3 Adults over 18*

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

#### *1.4.1.3.4 Summary*

The committee considered that the body of evidence in general did not support the use of combined therapies other than in the very specific situations outlined in the recommendations for risperidone. The majority of the sequencing trials included in this review were smaller and varied greatly; this meant they couldn't be combined to increase power. As a whole the evidence was of lower quality than the trials assessing the effectiveness of medication, they also predominantly compared adding/substituting with a new medication and not adding/substituting with placebo. Therefore the committee broadly based their recommendations around the sequence of medication on the body of efficacy evidence in the general pharmacological efficacy review.

The committee discussed how long to wait to determine whether or not treatment was successful. Different medications have different expected times to onset of effect and may also require titration to an optimal tolerated dose. The committee suggested 6 weeks as a starting point at which point they would hope to see some benefits, in ADHD symptoms even if not yet in terms of overall impact, from effective medication. A shorter time point may not insure that people have a truly adequate trial of medication but a longer time point would risk leaving people on ineffective medication for a prolonged period. The choice of 6 weeks was a consensus recommendation based on the committee's experience and not on evidence identified in these reviews. The committee also noted that the expected time to efficacy may vary depending on the circumstances of an individual being treated (for example if trial period is occurring during a particularly challenging period of their personal or work life).

### 1.4.2 Cost effectiveness and resource use

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

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

Three studies compare types of extended release methylphenidate with immediate release methylphenidate in children who are responding sub-optimally to immediate release methylphenidate because of inadequate medication intake. Faber 2008 was a Markov model with a 10 year time horizon. 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 are required go into the markov phase. Staying on IR MPH is then compared to optimal response with OROS MPH (a type of extended release MPH). There are 4 states in each arm (not the same for both arms). The study found OROS MPH to be cost effective. This was rated as partially applicable because it is a non UK study, it uses different but similar discount rates to NICE, and does not use EQ-5D and utilities are not from the public. It has potentially serious limitations such as a potential conflict of interest, a lot of assumptions/inputs from a panel of experts and limited data. Van der Schans 2015 is an updated version of the Faber model using slightly different health states and inputs. It also compares different versions of modified release methylphenidate (OROS MPH, or Medikinet CR/Equasym XL (these two interventions were grouped together)). This study found that MPH OROS was cost effective versus immediate release MPH, but that Medikinet/Equasym was dominant versus immediate release MPH. The Medikinet/ Equasym comparator is dominant overall because it is cheaper than MPH OROS and has the same QALYs. The applicability and quality rating given to the study was the same as for Faber 2008. The final of these three studies was Schawo 2015. This was again based on Faber but some structural aspects of the model were slightly different such as a 12 year time horizon and different assumptions about health states. Schawo found that OROS MPH was dominant. This study was also partially applicable with very serious limitations because it makes the most assumptions of the three. The three studies comparing extended release methylphenidate to immediate release have a range of results, although they are all pointing in the same direction, and this is most likely because of a number of structural and data differences in the three models.

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

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

No evidence was found in adults.

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

In summary it is difficult to draw conclusions; although there is some UK evidence showing that atomoxetine first line is cost effective (in people who have tried stimulants), there is also have evidence saying that lisdexamfetamine is cost effective compared to atomoxetine in children who are partially responding to methylphenidate (and clinical evidence supports this

also). Hence in people who may have tried stimulants before and either cannot tolerate or have failed them, the committee agreed that lisdexamfetamine and atomoxetine are likely to be choices that might be tried next in the pathway. There is no economic evidence directly comparing guanfacine with other treatments, only the Lachaine study which looked at guanfacine as an adjunct to stimulant treatment (versus stimulant treatment alone). More discussion around how the order of the drug treatments in the pathway was decided can be found in the pharmacological effectiveness rationale section above.

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# Appendices

# Appendix A: Review protocols

## A.1 Pharmacological efficacy

**Table 74: 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<br><br>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<br><br>Stratified by:<br>Age – under 5, 5 to 18, over 18 |
| Eligibility criteria – interventions | The following treatments (all doses), received for a minimum of 2 weeks:<br>Methylphenidate<br>Methylphenidate modified release<br>Dexamfetamine<br>Lisdexamfetamine dimesylate<br>Atomoxetine<br>Guanfacine<br>Clonidine<br>Tricyclic antidepressants<br>SSRIs<br>SNRIs<br>MAOIs<br>Risperidone<br>Olanzapine<br>Clozapine<br>Haloperidol<br>Quetiapine<br>Aripiprazole<br>Carbamazepine<br>Valproate<br>Lamotrigine<br>Lithium<br>Asenapine<br>Buspirone<br>Bupropion<br>Nicotine<br>Modafinil<br>Melatonin |

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

| Field | Content |
|---|---|
| | from individual study, dichotomous outcomes will be extracted. |
| Eligibility criteria – study design | Blinded RCTs only |
| Other inclusion exclusion criteria | 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.<br>Crossover trials will be excluded if there is an inappropriate washout period (specific to pharmacokinetics of drug involved)<br>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) |
| Proposed sensitivity / subgroup analysis, or meta-regression | Presence or absence of co-existing conditions (inc. intellectual disability, ASD, epilepsy, affective disorders, tic disorder, personality disorder, addiction, CD/ODD)<br>Additional age groups (13-18, 18-25, 25-65, >65)<br>Severity (mild, moderate severe)<br>Dose (low, medium, high)<br>Diagnostic method (DSM vs ICD)<br>Region (UK vs Europe vs US vs Japan)<br>Setting (looked after/secure estate vs general)<br>Titration (fixed dose vs titrated) |
| 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) | Pairwise meta-analyses were performed using Cochrane Review Manager (RevMan5).<br>GRADEpro was used to assess the quality of evidence for each outcome.<br>Endnote for bibliography, citations, sifting and reference management. |
| Information sources – databases and dates | Clinical search databases to be used: Medline, Embase, Cochrane Library,PsycINFO<br>Date: From October 2007<br>Health economics search databases to be used: Medline, Embase, NHSEED, HTA<br>Date: Medline, Embase from 2014<br>NHSEED, HTA – from 2008<br>Language: Restrict to English only<br>Supplementary search techniques: backward citation searching<br>Key papers: Not known |
| 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<br>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.<br>Staff from NGC undertook systematic literature searches, critically appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual. |
| Sources of funding / support | NGC is funded by NICE and hosted by the Royal College of Physicians. |
| Name of sponsor | NGC is funded by NICE and hosted by the Royal College of Physicians. |
| Roles of sponsor | NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England. |
| PROSPERO registration number | Not registered |

**Table 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 | Populations, interventions and comparators must be as specified in the clinical review protocols in appendix A above.<br>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).<br>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 |
|---|---|
| | will be checked for relevant studies, which will then be ordered.)<br>Unpublished reports will not be considered unless submitted as part of a call for evidence.<br>Studies must be in English. |
| Search strategy | A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B [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 |
| Review strategy | Studies not meeting any of the search criteria above will be excluded. Studies published before 2001, abstract-only studies and studies from non-OECD countries or the USA will also be excluded.<br>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.<br>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).[474]<br><br>Inclusion and exclusion criteria<br>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.<br>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.<br>If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.<br><br>Where there is discretion<br>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.<br><br>The health economist will be guided by the following hierarchies.<br>Setting:<br>UK NHS (most applicable).<br>OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).<br>OECD countries with predominantly private health insurance systems (for example, Switzerland).<br>Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.<br>Health economic study type:<br>Cost–utility analysis (most applicable).<br>Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). |

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

# A.2 Pharmacological sequencing

**Table 76: 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<br><br>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<br><br>Stratified by:<br>• Age (children under 5, children and young people aged 5 to 18, adults aged 18 years and over)<br>• Drug previously received<br>• Drug response |
| Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s) | Antidepressants; Tricyclics<br>Tricyclic antidepressants ; SSRIs<br>Tricyclic antidepressants ; MNRIs<br>Tricyclic antidepressants ; MAOIs<br>Antipsychotics; Risperidone<br>Antipsychotics; Quetiapine<br>Antipsychotics; Olanzapine<br>Antipsychotics; Clozapine<br>Antipsychotics; Aripiprazole |

| | |
|---|---|
| | Antipsychotics; Haloperidol<br>CNS stimulants; Methylphenidate (including modified-release preparations)<br>CNS stimulants; Atomoxetine<br>CNS stimulants; Dexamfetamine<br>CNS stimulants; Modafanil<br>CNS stimulants; Lisdexamfetamine dimesylate<br>Bupropion<br>Nicotine; Nicotine skin patches<br>Nicotine; Nicotine (other formulation)<br>Clonidine<br>No treatment<br>No treatment; Standard treatment<br>No treatment; Placebo<br>Guanfacine<br>Melatonin<br>Mood stabilisers; Carbamazepine<br>Mood stabilisers; Valproate<br>Mood stabilisers; Lamotrigine<br>Mood stabilisers; Buspirone<br>Mood stabilisers; Lithium<br>Mood stabilisers; Asenapine<br>Sativex<br>Anti-cholinesterase inhibitors<br>Drugs used to treat Parkinson's disease (adults only)<br>Combination of the above (including where a medication is added to the previous medication) |
| Eligibility criteria – comparator(s) / control or reference (gold) standard | All interventions will be compared with each other, unless otherwise stated |
| Outcomes and prioritisation | 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.<br><br>**Critical**<br><br>• Quality of life [continuous]<br>• ADHD symptoms (total; parent) [continuous] [children and young people]<br>• ADHD symptoms (total; teacher) [continuous] [children and young people]<br>• ADHD symptoms (total; self-rated in children 13-18 years and adults) [continuous]<br>• ADHD symptoms (total; carer/partner) [continuous] [adults]<br>• ADHD symptoms (total; investigator) [continuous]<br>• ADHD symptoms (inattention; parent) [continuous] [children and young people]<br>• ADHD symptoms (inattention; teacher) [continuous] [children and young people]<br>• ADHD symptoms (inattention; self-rated in children 13-18 years and adults) [continuous]<br>• ADHD symptoms (inattention; carer/partner) [continuous] [adults] |

| | |
|---|---|
| | • ADHD symptoms (inattention; investigator) [continuous]<br>• ADHD symptoms (hyperactivity; parent) [continuous] [children and young people]<br>• ADHD symptoms (hyperactivity; teacher) [continuous] [children and young people]<br>• ADHD symptoms (hyperactivity; self-rated in children 13-18 years and adults) [continuous]<br>• ADHD symptoms (hyperactivity; carer/partner) [continuous] [adults]<br>• ADHD symptoms (hyperactivity; investigator) [continuous]<br>• Clinical Global Impressions scale (improved or much improved ) [dichotomous]<br><br>**Important**<br><br>• Serious adverse events (all) [dichotomous]<br>• Behavioural (children)/Functional (adults) measures [continuous]<br>• Emotional dysregulation [continuous]<br>• Academic outcomes (children) [continuous]<br>• Substance use (alcohol and drug use) [dichotomous]<br>• Self-harm [dichotomous] |
| Eligibility criteria – study design | Systematic review<br>RCT<br>Unit of randomisation: patient, site |
| Other inclusion exclusion criteria | Crossover studies permitted<br>Minimum length of treatment 2-weeks<br><br>Exclusions:<br>• Open label trials<br>• Crossover trials with inappropriate washout period<br>• Treatment duration <2 weeks<br>• 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 | • Presence or absence of co-existing conditions (inc. intellectual disability, ASD, epilepsy, affective disorders, tic disorder, personality disorder, addiction, CD/ODD)<br>• Additional age groups (13-18, 18-25, 25-65, >65)<br>• Severity (mild, moderate severe)<br>• Dose (low, medium, high)<br>• Diagnostic method (DSM vs ICD)<br>• Region (UK vs Europe vs US vs Japan)<br>• Setting (looked after/secure estate vs general)<br>Titration (fixed dose vs titrated) |
| Selection process – duplicate screening / selection / analysis | No duplicate screening was deemed necessary for this question, for more information please see the separate Methods report for this guideline. |
| Data management (software) | • Pairwise meta-analyses were performed using Cochrane Review |

| | |
|---|---|
| | Manager (RevMan5).<br>• GRADEpro was used to assess the quality of evidence for each outcome.<br>• Endnote for bibliography, citations, sifting and reference management. |
| Information sources – databases and dates | Clinical search databases to be used: Medline, Embase, Cochrane Library,PsycINFO<br><br>Date: From October 2007<br><br>Health economics search databases to be used: Medline, Embase, NHSEED, HTA<br><br>Date: Medline, Embase from 2014<br><br>NHSEED, HTA – from 2008<br><br>Language: Restrict to English only<br><br>Supplementary search techniques: backward citation searching<br><br>Key papers: Not known |
| Identify if an update | Not an update |
| Author contacts | https://www.nice.org.uk/guidance/cg72 |
| Highlight if amendment to previous protocol | 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 | Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual<br>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. |
| 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.<br>Staff from NGC undertook systematic literature searches, appraised the |

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

**Table 77: 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.<br>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).<br>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.)<br>Unpublished reports will not be considered unless submitted as part of a call for evidence.<br>Studies must be in English. |
| Search strategy | A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B. For questions being updated, the search will be run from Decmber 2007, which was the cut-off date for the searches conducted for NICE guideline CG72 |
| Review strategy | Studies not meeting any of the search criteria above will be excluded. Studies published before 2001, abstract-only studies and studies from non-OECD countries or the USA will also be excluded.<br>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.<br>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).[474]<br><br>Inclusion and exclusion criteria<br>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.<br>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.<br>If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. |

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

# Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual, Oct 2014, updated 2017 https://www.nice.org.uk/guidance/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869. 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 78: Database date parameters and filters used**

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

**Medline (Ovid) search terms**

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

| | |
|---|---|
| 11. | pervasive developmental disorder*.ti,ab. |
| 12. | (asd or pdd or pdd-nos).ti,ab. |
| 13. | or/9-12 |
| 14. | hyperkinesis/ |
| 15. | (hyperactiv* or inattent* or hyperkin* or hyper-kin*).ti,ab. |
| 16. | 14 or 15 |
| 17. | 13 and 16 |
| 18. | 8 or 17 |
| 19. | limit 18 to English language |
| 20. | letter/ |
| 21. | editorial/ |
| 22. | news/ |
| 23. | exp historical article/ |
| 24. | Anecdotes as Topic/ |
| 25. | comment/ |
| 26. | case report/ |
| 27. | (letter or comment*).ti. |
| 28. | or/20-27 |
| 29. | randomized controlled trial/ or random*.ti,ab. |
| 30. | 28 not 29 |
| 31. | animals/ not humans/ |
| 32. | Animals, Laboratory/ |
| 33. | exp animal experiment/ |
| 34. | exp animal model/ |
| 35. | exp Rodentia/ |
| 36. | (rat or rats or mouse or mice).ti. |
| 37. | or/30-36 |
| 38. | 19 not 37 |
| 39. | randomized controlled trial.pt. |
| 40. | controlled clinical trial.pt. |
| 41. | randomi#ed.ab. |
| 42. | placebo.ab. |
| 43. | drug therapy.fs. |
| 44. | randomly.ab. |
| 45. | trial.ab. |
| 46. | groups.ab. |
| 47. | or/39-46 |
| 48. | Clinical Trials as topic.sh. |
| 49. | trial.ti. |
| 50. | or/39-42,44,48-49 |
| 51. | Meta-Analysis/ |
| 52. | Meta-Analysis as Topic/ |
| 53. | (meta analy* or metanaly* or metaanaly* or meta regression).ti,ab. |
| 54. | ((systematic* or evidence*) adj3 (review* or overview*)).ti,ab. |
| 55. | (reference list* or bibliograph* or hand search* or manual search* or relevant |

| | |
|---|---|
| | journals).ab. |
| 56. | (search strategy or search criteria or systematic search or study selection or data extraction).ab. |
| 57. | (search* adj4 literature).ab. |
| 58. | (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab. |
| 59. | cochrane.jw. |
| 60. | ((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab. |
| 61. | or/51-60 |
| 62. | 38 and (50 or 61) |

**Embase (Ovid) search terms**

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

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

**Cochrane Library (Wiley) search terms**

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

| | |
|---|---|
| #13. | (asd or pdd or pdd-nos):ti,ab |
| #14. | (or #10-#13) |
| #15. | [mh ^hyperkinesis] |
| #16. | (hyperactiv* or inattent* or hyperkin* or hyper-kin*):ti,ab |
| #17. | #15 or #16 |
| #18. | #14 and #17 |
| #19. | #9 and #17 |

**PsycINFO (ProQuest) search terms**

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

## B.2 Health Economics literature search strategy

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

**Table 79: Database date parameters and filters used**

| Database | Dates searched | Search filter used |
|---|---|---|
| Medline | 2014 – 28 April 2017 | Exclusions<br>Health economics |
| Embase | 2014 – 28 April 2017 | Exclusions<br>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 | |

**Medline (Ovid) search terms**

| | |
|---|---|
| 1. | "attention deficit and disruptive behavior disorders"/ or attention deficit disorder with hyperactivity/ |
| 2. | ((attenti* or disrupt*) adj3 (adolescent* or adult* or behav* or child* or class or classes or classroom* or condition* or difficult* or disorder* or learn* or people or person* or poor or problem* or process* or youngster*)).ti. |
| 3. | ((attenti* or disrupt*) adj3 disorder*).ab. |
| 4. | (ADHD or addh or ad hd or ad??hd).ti,ab. |
| 5. | (attenti* adj3 deficit*).ti,ab. |
| 6. | (((hyperkin* or hyper kin*) adj1 (syndrome* or disorder*)) or hkd).ti,ab. |
| 7. | (minimal brain adj2 (dysfunct* or disorder*)).ti,ab. |
| 8. | or/1-7 |
| 9. | limit 8 to English language |
| 10. | letter/ |
| 11. | editorial/ |
| 12. | news/ |
| 13. | exp historical article/ |
| 14. | Anecdotes as Topic/ |
| 15. | comment/ |
| 16. | case report/ |
| 17. | (letter or comment*).ti. |
| 18. | or/10-17 |
| 19. | randomized controlled trial/ or random*.ti,ab. |
| 20. | 18 not 19 |
| 21. | animals/ not humans/ |
| 22. | Animals, Laboratory/ |
| 23. | exp animal experiment/ |
| 24. | exp animal model/ |
| 25. | exp Rodentia/ |
| 26. | (rat or rats or mouse or mice).ti. |
| 27. | or/20-26 |
| 28. | 9 not 27 |
| 29. | Economics/ |
| 30. | Value of life/ |
| 31. | exp "Costs and Cost Analysis"/ |
| 32. | exp Economics, Hospital/ |
| 33. | exp Economics, Medical/ |
| 34. | Economics, Nursing/ |
| 35. | Economics, Pharmaceutical/ |
| 36. | exp "Fees and Charges"/ |
| 37. | exp Budgets/ |
| 38. | budget*.ti,ab. |
| 39. | cost*.ti. |

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

**Embase (Ovid) search terms**

| | |
|---|---|
| 1. | attention deficit disorder/ |
| 2. | ((attenti* or disrupt*) adj3 (adolescent* or adult* or behav* or child* or class or classes or classroom* or condition* or difficult* or disorder* or learn* or people or person* or poor or problem* or process* or youngster*)).ti. |
| 3. | ((attenti* or disrupt*) adj3 disorder*).ab. |
| 4. | (ADHD or addh or ad hd or ad??hd).ti,ab. |
| 5. | (attenti* adj3 deficit*).ti,ab. |
| 6. | (((hyperkin* or hyper kin*) adj1 (syndrome* or disorder*)) or hkd).ti,ab. |
| 7. | (minimal brain adj2 (dysfunct* or disorder*)).ti,ab. |
| 8. | or/1-7 |
| 9. | limit 8 to English language |
| 10. | letter.pt. or letter/ |
| 11. | note.pt. |
| 12. | editorial.pt. |
| 13. | case report/ or case study/ |
| 14. | (letter or comment*).ti. |
| 15. | or/10-14 |
| 16. | randomized controlled trial/ or random*.ti,ab. |
| 17. | 15 not 16 |
| 18. | animal/ not human/ |
| 19. | nonhuman/ |
| 20. | exp Animal Experiment/ |
| 21. | exp Experimental Animal/ |
| 22. | animal model/ |

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

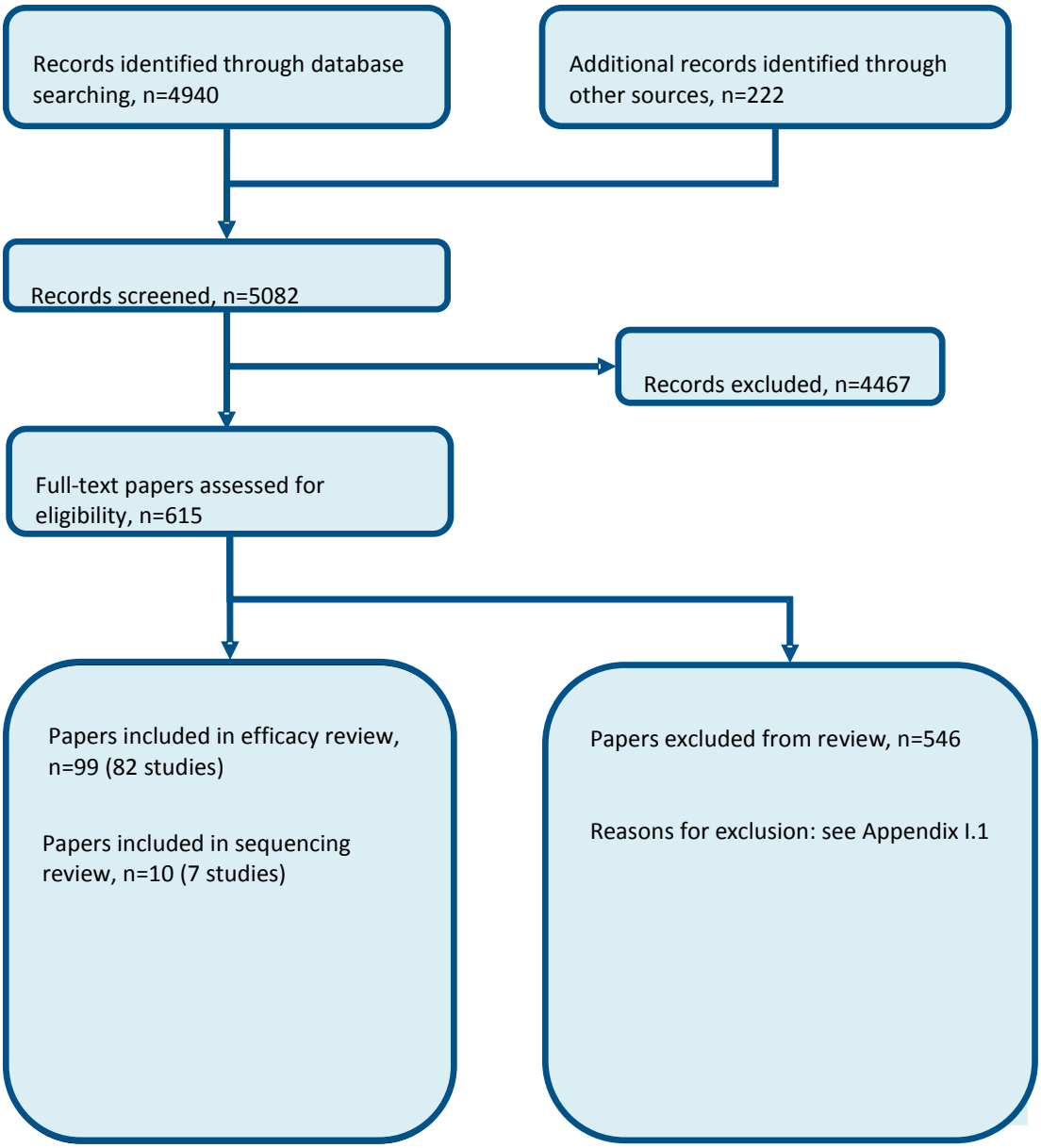
**NHS EED and HTA (CRD) search terms**

| | |
|---|---|
| #1. | MeSH DESCRIPTOR Attention Deficit and Disruptive Behavior Disorders |
| #2. | MeSH DESCRIPTOR Attention Deficit Disorder with Hyperactivity |
| #3. | (((attenti* or disrupt*) adj3 (adolescent* or adult* or behav* or child* or class or classes or classroom* or condition* or difficult* or disorder* or learn* or people or person* or poor or problem* or process* or youngster*))):TI |
| #4. | (((attenti* or disrupt*) adj3 disorder*)) |
| #5. | ((ADHD or addh or ad hd or ad??hd)) |
| #6. | ((attenti* adj3 deficit*)) |
| #7. | ((((hyperkin* or hyper kin*) adj1 (syndrome* or disorder*)) or hkd)) |
| #8. | ((minimal brain adj2 (dysfunct* or disorder*))) |

| | |
|---|---|
| #9. | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 |
| #10. | (#9) IN NHSEED, HTA |

# Appendix C: Clinical evidence selection

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



# 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] |
|---|---|
| | 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<br>Further details: 1. Dose: Moderate 2. Method of titration: Titrated to optimum dose<br><br>(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<br>Further details: 1. Dose: Moderate 2. Method of titration: Titrated to optimum dose |
| 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] |
|---|---|
| - 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<br>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:<br>- 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<br>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; 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 | (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<br>Further details: 1. Dose: 2. Method of titration:<br><br>(n=81) Intervention 2: No treatment - Placebo. Identical capsules and dosage. Duration 10 weeks. Concurrent medication/care: Not specified<br>Further details: 1. Dose: 2. Method of titration: |
| 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]) |
|---|---|
| - 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,<br>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<br>- Actual outcome: ADHD-RS-IV with adult prompts hyperactivity/impulsivity subscale LS mean change scores (adjusted for baseline) at 10 weeks;<br>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<br><br>- 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<br>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<br><br>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months<br>- Actual outcome: Drop out due to adverse events at 10 weeks;<br>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 | |
| 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[436], Adler 2009[10], Kollins 2011[381]) |
|---|---|
| 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[436], Adler 2009[10], Kollins 2011[381]) |
|---|---|
| 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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose (Titrated to fixed dose).<br><br>(n=117) Intervention 2: CNS stimulants - Lisdexamfetamine dimesylate. Following a 7 to 28 day washout |

| Study (subsidiary papers) | Adler 2008[11] (Mattingly 2013[436], Adler 2009[10], Kollins 2011[381]) |
|---|---|
| | 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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose (Titrated to fixed dose).<br><br>(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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose (Titrated to fixed dose).<br><br>(n=62) Intervention 4: No treatment - Placebo. Identical capsules. Duration 4 weeks. Concurrent medication/care: Not specified<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose (Titrated to fixed dose).<br><br>(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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose (Titrated to fixed dose).<br><br>(n=39) Intervention 6: CNS stimulants - Lisdexamfetamine dimesylate. LDX with prior AMPH treatment before screening. Duration 4 weeks. Concurrent medication/care: None reported<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose<br><br>(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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear |
| Funding | Academic or government funding (Shire Development Inc.) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LISDEXAMFETAMINE DIMESYLATE 30MG versus PLACEBO<br><br>Protocol outcome 1: CGI at <3- or >6-months | |

| Study (subsidiary papers) | Adler 2008[11] (Mattingly 2013[436], Adler 2009[10], Kollins 2011[381]) |
|---|---|

- 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 2008[11] (Mattingly 2013[436], Adler 2009[10], Kollins 2011[381]) |
|---|---|
| - 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<br><br>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OVERALL LDX TREATMENT GROUP versus PLACEBO<br><br>Protocol outcome 1: Dropped out due to adverse events at <3- or >6-months<br>- 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<br><br>Protocol outcome 2 (Dropped out due to adverse events):<br>Low risk of attrition bias |

| Study | Adler 2009[12] |
|---|---|
| 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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose<br><br>(n=218) Intervention 2: No treatment - Placebo. Placebo. Duration 16 weeks. Concurrent medication/care: not specified<br>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] |
|---|---|
| AAQoL 0-100 Top=High is good outcome; Risk of bias: High; Indirectness of outcome: No indirectness<br>- 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<br>- 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<br>- 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<br>- 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<br><br>Protocol outcome 2: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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<br>- 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<br>- 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<br>- 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 | Protocol outcome 1 (quality of life): high risk of bias due to attrition bias<br>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 |

| Study | Adler 2009[12] |
|---|---|
| | 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 2009[16] (Brown 2011[121]) |
|---|---|
| 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 2009[16] (Brown 2011[121]) |
|---|---|
| | Duration 6 months. Concurrent medication/care: Not stated<br>Further details: 1. Dose: 2. Method of titration:<br><br>(n=251) Intervention 2: No treatment - Placebo. No details provided. Duration 6 months. Concurrent medication/care: Not stated<br>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]) |
|---|---|
| (SD 8.2); n=243, Group 2: mean -5 (SD 7.3); n=248; ASRS 0-54?? Top=High is poor outcome<br>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<br>- 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<br>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<br>- Actual outcome: AISRS hyperactive/impulsive subscale change scores at 6 months;<br>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<br>- Actual outcome: AISRS inattention subscale change scores at 6 months;<br>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<br>- Actual outcome: Adult ADHD Self-Report (ASRS): Screening Version (change score) -Evening inattentive subscore at 6 months;<br>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<br><br>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months<br>- Actual outcome: Drop-outs due to adverse events at 6 months; Group 1: 43/250, Group 2: 14/251<br>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 |
| 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 | 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 2009[21] |
|---|---|
| | 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<br>Further details: 1. Dose: 2. Method of titration:<br><br>(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.<br>Further details: 1. Dose: 2. Method of titration: |
| 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 2009[21] |
|---|---|
| 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<br><br>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months<br>- Actual outcome for Adult: Dropped out due to adverse events at 7 weeks; Group 1: 16/110, Group 2: 6/116<br>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 | |
| 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 2005[25] |
|---|---|
| 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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose<br><br>(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<br>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 2005[25] |
|---|---|
| - 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<br>Protocol outcome 2: Low risk of bias |

| Study | Amiri 2008[35] |
|---|---|
| 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 | (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<br>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)).<br><br>(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<br>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)). |
| Funding | Academic or government funding (Tehran University of Medical Sciences) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MODAFANIL GROUP versus METHYLPHENIDATE GROUP<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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 | |
| 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 2008[35] |
|---|---|
| | <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 2012[34] |
|---|---|
| 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 | (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<br>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).<br><br>(n=22) Intervention 2: No treatment - Placebo. Matching Placebo (Starch) to active treatment. Duration 6 weeks. Concurrent medication/care: Not reported<br>Further details: 1. Dose: 2. Method of titration: |
| Funding | Academic or government funding |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VENLAFAXINE GROUP versus PLACEBO GROUP<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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<br>- 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<br>- 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<br>- 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<br><br>Protocol outcome 2: Serious adverse events at All<br>- 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<br><br>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months<br>- 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 | |
| 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 2012[34] |
|---|---|
| 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 2002[633] |
|---|---|
| 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[633] |
|---|---|
| Indirectness of population | No indirectness |
| Interventions | (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<br>Further details: 1. Dose: Mixed (Mean 25.7mg/day). 2. Method of titration: Titrated to optimum dose<br><br>(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<br>Further details: 1. Dose: Mixed (0.25mg per day mean). 2. Method of titration: Titrated to optimum dose<br><br>(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<br>Further details: 1. Dose: Mixed (Clonidine mean 0.25mg/day and 26.1mg per day MPH). 2. Method of titration: Titrated to optimum dose<br><br>(n=32) Intervention 4: No treatment - Placebo. Placebo. Duration 16 weeks. Concurrent medication/care: Not stated<br>Further details: 1. Dose:  2. Method of titration: |
| Funding | Academic or government funding (NIC, GCRC and Tourette Syndrome Association) |

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

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,

| Study | Anon 2002[633] |
|---|---|
| Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 4<br>- Actual outcome for Children (up to 18 years): ASQ parent total scores at 12 weeks; Mean; ;<br>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<br><br>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS) versus PLACEBO<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- Actual outcome for Children (up to 18 years): ASQ teacher total scores at 12 weeks; Mean; ;<br>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<br>- Actual outcome for Children (up to 18 years): ASQ parent total scores at 12 weeks; Mean; ;<br>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<br><br>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CLONIDINE versus PLACEBO<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- Actual outcome for Children (up to 18 years): ASQ teacher total scores at 12 weeks; Mean; ;<br>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<br>- Actual outcome for Children (up to 18 years): ASQ parent total scores at 12 weeks; Mean; ;<br>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<br><br>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CLONIDINE AND METHYLPHENIDATE versus PLACEBO<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- Actual outcome for Children (up to 18 years): ASQ teacher total scores at 12 weeks; Mean; ;<br>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<br>- Actual outcome for Children (up to 18 years): ASQ parent total scores at 12 weeks; Mean; ;<br>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 | |
| 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[633] |
|---|---|
| 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 | (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<br>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).<br><br>(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<br>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). |
| 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<br>- 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<br>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 | (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<br>Further details: 1. Dose:  2. Method of titration: Titrated to optimum dose<br><br>(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<br>Further details: 1. Dose:  2. Method of titration: |
| Funding | Study funded by industry (Lilly, Shire, Janssen and PediaMed) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE versus PLACEBO<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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<br>- 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:<br><br>Protocol outcome 2: Behavioural outcomes at <3- or >6-months<br>- 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 | |
| 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):<br>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<br>CGI-I: high risk of attrition bias<br>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 | (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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose<br><br>(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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose<br><br>(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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose<br><br>(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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose<br><br>(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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not |

| Study | Arnold 2014[50] |
|---|---|
| | stated / Unclear |
| Funding | Study funded by industry (Cephalon Inc (now owned by Teva Pharmaceuticals Industries Ltd)) |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MODAFANIL 255MG/DAY versus PLACEBO

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

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

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

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

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MODAFANIL 340MG/DAY versus PLACEBO

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

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

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

| 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: 19/73, Group 2: 6/74; Risk of bias: High; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MODAFANIL 425MG/DAY versus PLACEBO

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

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

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

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

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MODAFANIL 510MG/DAY versus PLACEBO

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

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

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

| Study | Arnold 2014[50] |
|---|---|
| Protocol outcome 4: Dropped out due to adverse events at <3- or >6-months<br>- 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<br>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 | (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<br>Further details: 1. Dose:  2. Method of titration:<br><br>(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<br>Further details: 1. Dose:  2. Method of titration: |
| Funding | Principal author funded by industry (Eli Lilly and Company) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE versus PLACEBO<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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<br>- 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<br><br>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months<br>- 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 | |
| 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<br>Further details: 1. Dose: 2. Method of titration: |

| Study | Barrickman 1995[67] |
|---|---|
| | (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<br>Further details: 1. Dose: 2. Method of titration: |
| Funding | Funding not stated |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BUPROPION versus METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS)<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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<br>- 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<br>- 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<br><br>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months<br>- 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<br>Protocol outcome 2: low risk of bias |

| Study | Biederman 2006[95] |
|---|---|
| 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 that 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<br>Further details: 1. Dose: Mixed 2. Method of titration: Fixed dose (Titrated to fixed dose). |

| Study | Biederman 2006[95] |
|---|---|
| | (n=51) Intervention 2: No treatment - Placebo. Placebo. Duration 4 weeks. Concurrent medication/care: Not specified<br>Further details: 1. Dose:  2. Method of titration: |
| Funding | Study funded by industry (Cephalon Inc, Frazer) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MODAFANIL versus PLACEBO<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>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<br><br>Protocol outcome 2: Serious adverse events at All<br>- Actual outcome for Children (up to 18 years): Serious adverse events at 4 weeks; Group 1: 0/197, Group 2: 0/51<br>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<br><br>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months<br>- 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<br>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 | |
| 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 2006[90] |
|---|---|
| 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 2006[90] |
|---|---|
| | Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose<br><br>(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<br>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<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br><br>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months<br>- 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<br>Protocol outcome 2: Low risk of bias |

| Study (subsidiary papers) | Biederman 2007[87] (Childress 2014[155], Lopez 2008[418]) |
|---|---|
| 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[418]) |
|---|---|
| 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<br>Further details: 1. Dose: 2. Method of titration:<br><br>(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[418]) |
|---|---|
| | 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<br>Further details: 1. Dose: 2. Method of titration:<br><br>(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<br>Further details: 1. Dose: 2. Method of titration:<br><br>(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<br>Further details: 1. Dose: 2. Method of titration:<br><br>(n=218) Intervention 5: CNS stimulants - Lisdexamfetamine dimesylate. All LDX groups combined. Duration 4 weeks. Concurrent medication/care: None reported<br>Further details: 1. Dose: 2. Method of titration: |
| Funding | Funding not stated |

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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[418]) |
|---|---|
| adverse events, loss to follow-up and lack of efficacy, protocol violations<br>- 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<br>Risk of bias: All domain - ; Indirectness of outcome: No indirectness<br>- 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;<br>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; 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 sever 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] |
|---|---|
| | >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. |
| 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 | 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 |
| Indirectness of population | No indirectness |
| Interventions | (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).<br><br>(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.<br>Further details: 1. Dose: 2. Method of titration:<br><br>(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).<br><br>(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 |

| 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) |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GUANFACINE 2MG versus PLACEBO

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

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

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

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

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GUANFACINE 3MG versus PLACEBO

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

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

| Study | Biederman 2008[89] |
|---|---|
| is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness<br>- 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<br>- 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<br><br>Protocol outcome 3: Behavioural outcomes at <3- or >6-months<br>- 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<br><br>Protocol outcome 4: Dropped out due to adverse events at <3- or >6-months<br>- 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<br><br>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GUANFACINE 4MG versus PLACEBO<br><br>Protocol outcome 1: CGI at <3- or >6-months<br>- 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<br><br>Protocol outcome 2: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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<br>- 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<br><br>Protocol outcome 3: Behavioural outcomes at <3- or >6-months<br>- 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<br><br>Protocol outcome 4: Dropped out due to adverse events at <3- or >6-months<br>- 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 2008[89] |
|---|---|
| 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 2010[91] |
|---|---|
| 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, amnestic 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<br>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.<br>Concurrent medication/care: Not stated<br>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)) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS) versus PLACEBO<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br><br>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months<br>- 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 | |
| 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<br>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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose<br><br>(n=34) Intervention 2: No treatment - Placebo. No details given. Duration 6 weeks. Concurrent medication/care: Not reported<br>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]) |
|---|---|
| Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br><br>Protocol outcome 2: Behavioural outcomes at <3- or >6-months<br>- 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<br><br>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months<br>- 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 | |
| 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<br>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 | (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%<br>Further details: 1. Dose:  2. Method of titration:<br>Comments: Atomoxetine taken in AM - placebo taken in PM<br><br>(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%<br>Further details: 1. Dose:  2. Method of titration:<br>Comments: Placebo taken in AM - Atomoxetine taken in PM<br><br>(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% |

| Study | Block 2009[100] |
|---|---|
| | Further details: 1. Dose:  2. Method of titration: |
| Funding | Study funded by industry (Lilly USA, LLC) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE GROUPS COMBINED versus PLACEBO AM AND PM GROUP<br><br>Protocol outcome 2: ADHD symptoms at <3- or >6-months<br>- Actual outcome: ADHD RS  Total Score at 6 weeks;<br>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. | |
| 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 2003[110] |
|---|---|
| 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 | (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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose<br><br>(n=38) Intervention 2: No treatment - Placebo. Placebo was given in a similar fashion to methylphenidate. Duration 4 weeks. Concurrent medication/care: Not reported<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear |
| 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<br>Further details: 1. Dose:  2. Method of titration: Fixed dose<br><br>(n=25) Intervention 2: No treatment - Placebo. Matching placebo to active treatment. Duration 6 weeks. Concurrent medication/care: not reported<br>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<br><br>Protocol outcome 1: Dropped out due to adverse events at <3- or >6-months<br>- 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[663] |
|---|---|
| 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<br>Further details: 1. Dose: Mixed 2. Method of titration: Titrated to optimum dose<br><br>(n=52) Intervention 2: No treatment - Placebo. Placebo. Duration 7 weeks. Concurrent medication/care: Not stated<br>Further details: 1. Dose: 2. Method of titration: |
| Funding | Study funded by industry (Eli Lilly ) |

| Study | Brown 2006[118]; Weiss 2005[663] |
|---|---|
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE versus PLACEBO<br><br>Protocol outcome 1: Quality of life at <3- or >6-months<br>- 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<br><br>Protocol outcome 2: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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 | |
| 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<br>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).<br><br>(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<br>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] |
|---|---|
| Protocol outcome 1: Behavioural outcomes at <3- or >6-months<br>- 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<br><br>Protocol outcome 2: Serious adverse events at All<br>- 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 | |
| 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[387]) |
|---|---|
| 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 2013[140] (Kooij 2013[387]) |
|---|---|
| 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 | (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<br>Further details: 1. Dose:  2. Method of titration:<br><br>(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<br>Further details: 1. Dose:  2. Method of titration:<br><br>(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 |

| Study (subsidiary papers) | LAMDA-II (EudraCT number: 2007-002111-82) trial: Casas 2013[140] (Kooij 2013[387]) |
|---|---|
| | Further details: 1. Dose: 2. Method of titration: |
| Funding | Study funded by industry (Authors received grants from Janssen0Cilag, 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 Dunnets 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 Dunnets 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 Dunnets 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 2013[140] (Kooij 2013[387]) |
|---|---|
| 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<br>- 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<br>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<br><br>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months<br>- Actual outcome: Discontinuation due to adverse events at 13 weeks; Group 1: 15/89, Group 2: 19/92<br>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<br><br>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OROS MPH 54 MG GROUP versus PLACEBO GROUP<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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 Dunnets 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<br>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<br>- 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 Dunnets 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<br>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 2013[140] (Kooij 2013[387]) |
|---|---|

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 Dunnets 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 2013[140] (Kooij 2013[387]) |
|---|---|
| | adjusted for multiplicity using the Dunnets 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<br>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<br>- 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 Dunnets 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<br>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<br>- 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 Dunnets 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<br>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<br>- - Actual outcome: Serious adverse events (suicide attempt) at 13 weeks;<br>Risk of bias: All domain - ; Indirectness of outcome: No indirectness<br>- Actual outcome: Investigator rated Conners Adult ADHD Rating Scale (CAARS-O: SV); LS mean adjusted; hyperactivity/impulsivity subscale at 13 weeks;<br>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<br>- Actual outcome: Investigator rated Conners Adult ADHD Rating Scale (CAARS-O: SV); LS mean adjusted; inattention subscale at 13 weeks;<br>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[387]) |
|---|---|
| Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months<br>- Actual outcome: Discontinuation due to adverse events at 13 weeks; Group 1: 19/92, Group 2: 1/97<br>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 | (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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose<br><br>(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<br>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 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 c-morbid 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.<br>Concurrent medication/care: No concomitant psychotropic treatment was allowed during the study<br>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).<br><br>(n=11) Intervention 2: No treatment - Placebo. Matching placebo to active treatment. Duration 2 weeks.<br>Concurrent medication/care: No concomitant psychotropic treatment was allowed during the study<br>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 | (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<br>Further details: 1. Dose:  2. Method of titration:<br><br>(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<br>Further details: 1. Dose:  2. Method of titration:<br><br>(n=25) Intervention 3: No treatment - Placebo. Placebo. Duration 4 weeks. Concurrent medication/care: not stated<br>Further details: 1. Dose:  2. Method of titration: |
| Funding | Other (Local trust - TENOVUS-Scotland initiative) |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE LOW DOSE (0.3 MG/KG/DOSE) versus PLACEBO

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:

| Study | Coghill 2007[172] |
|---|---|
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE HIGH DOSE 0.6MG/KG/DOSE versus PLACEBO<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>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:<br>- Actual outcome: Teachers Conners' Global Index at 4 weeks; Group 1: mean 58.5 (SD 12.8); n=25,<br>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:<br>- Actual outcome: Clinical Global Impressions-Improvement-CGI-I at 4 weeks;<br>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: | |
| 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 2013[167] (Coghill 2014[171], Banaschewski 2013[61], Coghill 2014[170]) |
|---|---|
| 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<br>Further details: 1. Dose: 2. Method of titration:<br><br>(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 2013[167] (Coghill 2014[171], Banaschewski 2013[61], Coghill 2014[170]) |
|---|---|
| | 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<br>Further details: 1. Dose: 2. Method of titration:<br><br>(n=110) Intervention 3: No treatment - Placebo. Placebo. Duration 7 weeks. Concurrent medication/care: Not stated<br>Further details: 1. Dose: 2. Method of titration: |
| 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]) |
|---|---|

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

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

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: 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:

| Study (subsidiary papers) | NCT00763971 trial: Coghill 2013[167] (Coghill 2014[171], Banaschewski 2013[61], Coghill 2014[170]) |
|---|---|

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 may 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 2013[167] (Coghill 2014[171], Banaschewski 2013[61], Coghill 2014[170]) |
|---|---|
| non compliance 2, 4 refused further participation, 54 lack of efficacy, 4 other<br>- 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<br>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<br><br>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months<br>- Actual outcome: adverse event leading to discontinuation of drug at 7 weeks; Group 1: 2/72, Group 2: 4/63<br>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<br><br>Protocol outcome 3: Academic outcomes (literacy and numeracy) at <3- or >6-months<br>- Actual outcome: CHIP-CE PRF academic achievement subscale at 7 weeks;<br>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 | |
| 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 1980[178] |
|---|---|
| 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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose<br><br>(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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not |

| Study | Conners 1980[178] |
|---|---|
| | stated / Unclear |
| Funding | Academic or government funding (The study was supported by a grant from the National Institute of Mental Health Psychopharmacology branch) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS) versus PLACEBO<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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 | |
| 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 1996[177] |
|---|---|
| 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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose<br><br>(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<br>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] |
|---|---|
| Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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<br><br>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months<br>- 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<br>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 | (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.<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose<br><br>(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.<br>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 Devellopment 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<br>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-Hossein 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 buspirone. |
| 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) (Al 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 buspirone). |

| Study | Davari-Ashtiani 2010[198] |
|---|---|
| Indirectness of population | No indirectness |
| Interventions | (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<br>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).<br><br>(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<br>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). |
| Funding | Academic or government funding (Behavioural Sciences Research Center of Shahid Beheshti University of Medical Sciences (Tehran, Iran)) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BUSPIRONE versus METHYLPHENIDATE<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- Actual outcome for Children (up to 18 years): >/=30% 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<br><br>Protocol outcome 2: Serious adverse events at All<br>- 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<br><br>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months<br>- 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 | |
| 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 2010[198] |
|---|---|
| | 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)<br>Protocol outcome 3 (drop out due to adverse events): low risk of bias |

| Study | De Jong 2009[200] |
|---|---|
| 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) sever 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 | (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<br>Further details: 1. Dose:  2. Method of titration:<br><br>(n=20) Intervention 2: No treatment - Placebo. Duration 4 weeks. Concurrent medication/care: Not specified<br>Further details: 1. Dose:  2. Method of titration:<br><br>(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<br>Further details: 1. Dose:  2. Method of titration:<br><br>(n=16) Intervention 4: No treatment - Placebo. Placebo. Duration 4 weeks. Concurrent medication/care: not specified<br>Further details: 1. Dose:  2. Method of titration: |
| 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] |
|---|---|
| 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: --<br>- 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: --<br>- 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<br><br>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE (ADHD ONLY) versus PLACEBO (ADHD ONLY)<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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<br>- 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<br>- 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<br>- 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 | |
| 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 2009[202] |
|---|---|
| | Further details: 1. Dose: 2. Method of titration:<br><br>(n=32) Intervention 2: No treatment - Placebo. Duration 8 weeks. Concurrent medication/care: antipsychotics,<br>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<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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<br>- 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<br>- 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<br>- 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<br><br>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months<br>- 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 2011[208] (Wehmeier 2011[656]) |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=181) |

| Study (subsidiary papers) | Dittmann 2011[208] (Wehmeier 2011[656]) |
|---|---|
| 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 | (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.<br>Further details: 1. Dose: 2. Method of titration:<br><br>(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.<br>Further details: 1. Dose: 2. Method of titration: |

| Study (subsidiary papers) | Dittmann 2011[208] (Wehmeier 2011[656]) |
|---|---|
| | (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.<br>Further details: 1. Dose: 2. Method of titration:<br><br>(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.<br>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 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 2011[208] (Wehmeier 2011[656]) |
|---|---|
| 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<br>Protocol outcome 2: Low |

| Study (subsidiary papers) | Durell 2010-1[215] (Durell 2010-2[215]) |
|---|---|
| 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]) |
|---|---|
| | 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%<br>Further details: 1. Dose: 2. Method of titration:<br><br>(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%<br>Further details: 1. Dose: 2. Method of titration:<br><br>(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%<br>Further details: 1. Dose: 2. Method of titration:<br><br>(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%<br>Further details: 1. Dose: 2. Method of titration: |
| Funding | Funding not stated |

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

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

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

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

| Study (subsidiary papers) | Durell 2010-1[215] (Durell 2010-2[215]) |
|---|---|
| - 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 2013[216] (Durell 2014[217], Durrell 2014[218]) |
|---|---|
| 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 2013[216] (Durell 2014[217], Durrell 2014[218]) |
|---|---|
| | 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<br>Further details: 1. Dose:  2. Method of titration:<br><br>(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<br>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 2013[216] (Durell 2014[217], Durrell 2014[218]) |
|---|---|
| Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months<br>- 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 2009[220] |
|---|---|
| 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 2009[220] |
|---|---|
| | 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.<br>Further details: 1. Dose:  2. Method of titration:<br><br>(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.<br>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<br><br>Protocol outcome 1: Quality of life at <3- or >6-months<br>- 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<br><br>Protocol outcome 2: ADHD symptoms at <3- or >6-months<br>- 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 | |
| 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 | Protocol outcome 1 (Quality of life)<br>High risk of bias due to high risk of outcome reporting bias (outcome was in the study protocol but not fully reported)<br>Protocol outcome 2 (ADHD symptoms) |

| Study | Escobar 2009[220] |
|---|---|
| | Low risk of bias |

| Study | Findling 2008[235] |
|---|---|
| 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[235] |
|---|---|
| Indirectness of population | No indirectness: Approximately 20% of the population had used previous treatment |
| Interventions | (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)<br>Further details: 1. Dose:  2. Method of titration:<br><br>(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)<br>Further details: 1. Dose:  2. Method of titration: Titrated to optimum dose<br><br>(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)<br>Further details: 1. Dose:  2. Method of titration: Titrated to optimum dose |
| 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[235] |
|---|---|
| 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[260] (Gadow 1995[262];Gadow 2007 [261]) |
|---|---|
| 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[260] (Gadow 1995[262];Gadow 2007 [261]) |
|---|---|
| Interventions | (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<br><br>(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<br><br>(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<br><br>(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 |
| 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[260] (Gadow 1995[262];Gadow 2007 [261]) |
|---|---|

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:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE 0.3MG 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 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:

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:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE 0.5MG 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 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:

| Study | Gadow 2008[260] (Gadow 1995[262];Gadow 2007 [261]) |
|---|---|
| Protocol outcome 2: Behavioural outcomes at <3- or >6-months<br>- 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,<br>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; 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[267] |
|---|---|
| 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 ≥ 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[267] |
|---|---|
| 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 | (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)<br>Further details: 1. Dose: 2. Method of titration:<br><br>(n=34) Intervention 2: No treatment - Placebo. Placebo. Duration 6 weeks. Concurrent medication/care: 58.8% previously on psychostimulants<br>Further details: 1. Dose: 2. Method of titration: |
| 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[267] |
|---|---|
| - 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<br>- 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<br>- 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<br>- 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<br>- 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<br>- 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<br><br>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months<br>- 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<br>Protocol outcome 2: low risk of bias |

| Study | Geller 2007[272] |
|---|---|
| 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[272] |
|---|---|
| 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 | (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.<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose<br><br>(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.<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear |
| Funding | Study funded by industry |

| Study | Geller 2007[272] |
|---|---|
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE versus PLACEBO<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- Actual outcome for Children (up to 18 years): Treatment response (defined as ≥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<br><br>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months<br>- 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 | |
| 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<br>Protocol outcome 2: Low risk of bias |

| Study | Ghuman 2009[275] |
|---|---|
| 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 □ 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[275] |
|---|---|
| | 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.<br>Further details: 1. Dose: 2. Method of titration: |

| Study | Ghuman 2009[275] |
|---|---|
| | (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.<br>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[275] |
|---|---|
| - 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:<br>- 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<br>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:<br>- 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<br>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:<br>- 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<br>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:<br>- 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<br>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:<br>- 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<br>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: | |
| 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[282] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |

| Study | Ginsberg 2012[282] |
|---|---|
| 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[282] |
|---|---|
| | 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 | (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.<br>Further details: 1. Dose: Not applicable / Not stated / Unclear (72mg/day). 2. Method of titration: Fixed dose (Titrated to fixed dose of 72mg/day).<br><br>(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.<br>Further details: 1. Dose:  2. Method of titration: |
| 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[282] |
|---|---|
| Protocol outcome 2: Behavioural outcomes at <3- or >6-months<br>- 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[287] |
|---|---|
| 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 2016[287] |
|---|---|
| | 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<br>Further details: 1. Dose: Mixed 2. Method of titration: Titrated to optimum dose<br><br>(n=179) Intervention 2: No treatment - Placebo. Placebo. Duration 6 weeks. Concurrent medication/care: Not specified<br>Further details: 1. Dose: 2. Method of titration: |
| Funding | Study funded by industry (Ortho-McNeil Janssen Scientific Affairs) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS) versus PLACEBO<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>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<br><br>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months<br>- Actual outcome for Adult: Drop out due to adverse events at 6 weeks; Group 1: 8/178, Group 2: 5/179<br>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 | |
| 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 2013[288] |
|---|---|
| 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[288] |
|---|---|
| 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 | (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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose<br><br>(n=196) Intervention 2: No treatment - Placebo. No details given . Duration 10 weeks. Concurrent medication/care: Not reported<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear |
| Funding | Study funded by industry (Eli Lilly) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE versus PLACEBO | |

| Study | Goto 2013[288] |
|---|---|
| Protocol outcome 1: Quality of life at <3- or >6-months<br>- 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<br><br>Protocol outcome 2: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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<br>- 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<br><br>Protocol outcome 3: Behavioural outcomes at <3- or >6-months<br>- 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<br><br>Protocol outcome 4: Dropped out due to adverse events at <3- or >6-months<br>- 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[293] |
|---|---|
| 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[293] |
|---|---|
| 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<br>Further details: 1. Dose:  2. Method of titration:<br><br>(n=159) Intervention 2: No treatment - Placebo. Placebo. Duration 3 weeks. Concurrent medication/care: Not specified<br>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[293] |
|---|---|
| PREPARATIONS) versus PLACEBO<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>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<br><br>Protocol outcome 2: Serious adverse events at All<br>- Actual outcome for Children (up to 18 years): Serious Adverse events at 3 weeks; Group 1: 0/155, Group 2: 0/159<br>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<br><br>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months<br>- Actual outcome for Children (up to 18 years): Discontinuation due to adverse events at 3 weeks; Group 1: 2/155, Group 2: 0/159<br>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 | |
| 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[306] |
|---|---|
| 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 |

| | |
|---|---|
| | Further details: 1. Dose: Mixed 2. Method of titration: Titrated to optimum dose<br><br>(n=21) Intervention 2: No treatment - Placebo. Placebo. Duration 6 weeks. Concurrent medication/care: No details<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: |
| Funding | Academic or government funding (Tehran University of Medical Sciences) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BUPROPION versus PLACEBO<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- Actual outcome for Adult: CAARS final values at 6 weeks; Group 1: mean 23.71 (SD 15.34); n=21,<br>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: | |
| 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 2015[309]** |
|---|---|
| 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[309] |
|---|---|
| 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[309] |
|---|---|
| | Further details: 1. Dose:  2. Method of titration:<br><br>(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.<br>Further details: 1. Dose:  2. Method of titration:<br><br>(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.<br>Further details: 1. Dose:  2. Method of titration:<br><br>(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.<br>Further details: 1. Dose:  2. Method of titration:<br><br>(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.<br>Further details: 1. Dose:  2. Method of titration:<br><br>(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 |

| Study | NCT00844753 trial: Handen 2015[309] |
|---|---|
| | 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.<br>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, Nolam 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, Nolam 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, Nolam 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[309] |
|---|---|
| | - 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<br>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<br>- 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<br>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<br>- 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<br>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<br><br>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATX TREATMENT GROUPS versus PLACEBO GROUPS<br><br>Protocol outcome 1: Dropped out due to adverse events at <3- or >6-months<br>- 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<br>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 |

| Study | NCT00844753 trial: Handen 2015[309] |
|---|---|
| | |
| 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 2012[316] (Harfterkamp 2014[315]) |
|---|---|
| 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[316] (Harfterkamp 2014[315]) |
|---|---|
| Indirectness of population | No indirectness |
| Interventions | (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<br>Further details: 1. Dose: 2. Method of titration:<br><br>(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<br>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 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[316] (Harfterkamp 2014[315]) |
|---|---|
| - 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<br><br>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months<br>- 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[341] |
|---|---|
| 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[341] |
|---|---|
| | 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 | (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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear (Mean 3.6(1.3)mg). 2. Method of titration: Titrated to optimum dose<br><br>(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<br>Further details: 1. Dose: Mixed (42.1(20.1)mg per day mean). 2. Method of titration: Titrated to optimum dose<br><br>(n=111) Intervention 3: No treatment - Placebo. Placebo. Duration 10 to 13 weeks. Concurrent medication/care: Not specified<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose |
| 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[341] |
|---|---|
| Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 24; Group 2 Number missing: 23<br><br>Protocol outcome 2: ADHD symptoms at <3- or >6-months<br>- 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<br>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<br><br>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months<br>- 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<br>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<br><br>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GUANFACINE versus PLACEBO<br><br>Protocol outcome 1: CGI at <3- or >6-months<br>- 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<br>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<br><br>Protocol outcome 2: ADHD symptoms at <3- or >6-months<br>- 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<br>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<br><br>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months<br>- 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<br>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<br><br>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE versus PLACEBO<br><br>Protocol outcome 1: CGI at <3- or >6-months<br>- 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<br>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 | |

| Study | Huss 2015[341] |
|---|---|
| Protocol outcome 2: ADHD symptoms at <3- or >6-months<br>- 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<br>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<br><br>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months<br>- 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<br>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 | |
| 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[349] |
|---|---|
| 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[349] |
|---|---|
| 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 >/= 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.<br>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).<br><br>(n=7) Intervention 2: No treatment - Placebo. Placebo for 4 weeks. Duration 4 weeks. Concurrent medication/care: 1 week washout period before LDX treatment.<br>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: >/= 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 >/= 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 >/= 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[349] |
|---|---|
| | |
| 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[347] |
|---|---|
| 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 2017[347] |
|---|---|
| | 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.<br>Further details: 1. Dose: 2. Method of titration: Fixed dose (0.5mg/d).<br><br>(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.<br>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[347] |
|---|---|
| mean 1.77 (SD 0.41); n=42, Group 2: mean 2.04 (SD 0.41); n=42<br>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[351] |
|---|---|
| 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[351] |
|---|---|
| | (Minimum score of 26 on ADHD-RS-IV). |
| Indirectness of population | No indirectness |
| Interventions | (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<br>Further details: 1. Dose: Mixed 2. Method of titration: Fixed dose<br><br>(n=78) Intervention 2: No treatment - Placebo. Placebo. Duration 8 weeks. Concurrent medication/care: Not specified<br>Further details: 1. Dose: 2. Method of titration: |
| 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[351] |
|---|---|
| Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months<br>- 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<br>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[346] |
|---|---|
| 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[346] |
|---|---|
| | 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 | (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.<br>Further details: 1. Dose:  2. Method of titration:<br><br>(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<br>Further details: 1. Dose:  2. Method of titration: |
| 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[346] |
|---|---|
| (SD 5.6); n=20; ADHD-RS 0-27 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness<br>- 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<br>- 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<br>- 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<br><br>Protocol outcome 2: Serious adverse events at All<br>- 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<br><br>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months<br>- 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 | |
| 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[362] |
|---|---|
| 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[362] |
|---|---|
| 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<br>Further details: 1. Dose:  2. Method of titration:<br><br>(n=23) Intervention 2: No treatment – Placebo. Placebo. Duration 6 weeks. Concurrent medication/care: not stated<br>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[362] |
|---|---|
| | |
| 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[367] |
|---|---|
| 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 2004[367] |
|---|---|
| | 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<br>Further details: 1. Dose: Mixed 2. Method of titration: Titrated to optimum dose<br><br>(n=64) Intervention 2: No treatment - Placebo. Placebo. Duration 8 weeks. Concurrent medication/care: Not stated<br>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<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>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<br>- 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<br>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<br>- 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<br>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<br><br>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months<br>- Actual outcome for Children (up to 18 years): Discontinuation due to adverse events at 8 weeks; Group 1: 6/133, Group 2: 1/64<br>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; 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[379] |
|---|---|
| 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:<br><br>(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[379] |
|---|---|
| | |
| Funding | Study funded by industry (Shire Development Inc) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GXR GROUP versus PLACEBO GROUP<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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<br>- 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<br>- 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<br><br>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months<br>- 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[386] |
|---|---|
| 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[386] |
|---|---|
| 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 | (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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose<br><br>(n=45) Intervention 2: No treatment - Placebo. Identical placebo tablets were dispensed by the study pharmacy. Duration 3 weeks. Concurrent medication/care: Not reported<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear |
| 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<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months | |

| Study | Kooij 2004[386] |
|---|---|
| - 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<br><br>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months<br>- 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[390] |
|---|---|
| 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 2005[390] |
|---|---|
| | 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 1.2mgkg per day. Duration 5 weeks. Concurrent medication/care: Not stated (but psychotropic/other drugs effecting CNS excluded)<br>Further details: 1. Dose: 2. Method of titration:<br>(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 1.2mgkg per day. Duration 5 weeks. Concurrent medication/care: Not stated (but psychotropic/other drugs effecting CNS excluded)<br>Further details: 1. Dose: 2. Method of titration: |
| Funding | Principal author funded by industry (Grants from Eli Lilly, GlaxoSmithKline, Cephalon and McNeil) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE and FLUOXETINE versus ATOMOXETINE<br>- 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<br>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<br>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<br>Actual outcome: drop out due to adverse events at 5 weeks; Group 1 3/127; Group 2 1/37 | |
| 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[391] |
|---|---|
| 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-IIIA 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)<br>Further details: 1. Dose:  2. Method of titration:<br><br>(n=50) Intervention 2: No treatment - Placebo. Single daily oral dose, but divided doses were permitted if |

| Study | Kratochvil 2011[391] |
|---|---|
| | 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)<br>Further details: 1. Dose: 2. Method of titration: |
| Funding | Academic or government funding (NIMH (and also Eli Lilly and some universities)) |

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

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

Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months
- 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 2001[393] |
|---|---|

| Study | Kuperman 2001[393] |
|---|---|
| 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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose<br><br>(n=8) Intervention 2: CNS stimulants - Methylphenidate (including modified-release preparations). |

| Study | Kuperman 2001[393] |
|---|---|
| | 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.<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose<br><br>(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.<br>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 Glaxo Wellcome) |

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

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

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

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

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

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

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

| Study | Kuperman 2001[393] |
|---|---|
| Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months<br>- 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<br><br>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS) versus PLACEBO<br><br>Protocol outcome 1: CGI at <3- or >6-months<br>- 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<br><br>Protocol outcome 2: ADHD symptoms at <3- or >6-months<br>- 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<br><br>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months<br>- 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 | |
| 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[401] |
|---|---|
| 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[401] |
|---|---|
| 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 Hamilon 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 | (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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose<br><br>(n=37) Intervention 2: No treatment - Placebo. Placebo tablets were given once daily. Duration 10 weeks. Concurrent medication/care: Not reported<br>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 Eli Lilly and Company) |

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 at 10 weeks; Group 1: mean 19.6 (SD 17.8); n=36, Risk of bias: High; Indirectness of outcome: No indirectness

| Study | Lee 2014[401] |
|---|---|
| Protocol outcome 2: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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<br>- 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<br>- 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<br><br>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months<br>- 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[430] |
|---|---|
| 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[430] |
|---|---|
| | 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.<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose<br><br>(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.<br>Further details: 1. Dose: 2. Method of titration: |
| Funding | Study funded by industry (Eli Lilly and Company) |

| Study | Martenyi 2010[430] |
|---|---|
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE versus PLACEBO<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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<br>- 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<br>- 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<br><br>Protocol outcome 2: Serious adverse events at All<br>- 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<br><br>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months<br>- 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[446] |
|---|---|
| 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 2008[446] |
|---|---|
| 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[446] |
|---|---|
| | Further details: 1. Dose:  2. Method of titration:<br><br>(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<br>Further details: 1. Dose:  2. Method of titration:<br><br>(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<br>Further details: 1. Dose:  2. Method of titration:<br><br>(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<br>Further details: 1. Dose:  2. Method of titration:<br><br>(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<br>Further details: 1. Dose:  2. Method of titration: |

| Study | NCT00246220;CR002479 trial: Medori 2008[446] |
|---|---|
| | |
| Funding | Study funded by industry (Janssen Pharmaceutica) |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE 36MG (INCLUDING MODIFIED-RELEASE PREPARATIONS) versus PLACEBO GROUP

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:

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:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE 36MG (INCLUDING MODIFIED-RELEASE PREPARATIONS) versus METHYLPHENIDATE 72MG (INCLUDING MODIFIED-RELEASE PREPARATIONS)

Protocol outcome 1: ADHD symptoms at <3- or >6-months
- Actual outcome: CAARS Self Form Total Scores (mean change scores) at 5 weeks;

| Study | NCT00246220;CR002479 trial: Medori 2008[446] |
|---|---|
| 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:<br>- Actual outcome: CAARS Observer Form - Total (mean change scores) at 5 weeks;<br>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:<br><br>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months<br>- Actual outcome: Drop out due to adverse events at 5 weeks;<br>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:<br><br>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OROS MPH COMBINED versus PLACEBO GROUP<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>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:<br>- 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<br>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: | |
| 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 | Merged with Newcorn 2005 trial: Michelson 2001[452] |
|---|---|
| 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<br>Further details: 1. Dose: Moderate 2. Method of titration: Titrated to optimum dose<br><br>(n=84) Intervention 2: No treatment - Placebo. Placebo. Duration 8 weeks. Concurrent medication/care: Not specified<br>Further details: 1. Dose:  2. Method of titration: |

| Study | Merged with Newcorn 2005 trial: Michelson 2001[452] |
|---|---|
| | |
| Funding | Study funded by industry (research funded by Eli Lilly and Company) |

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 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

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

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

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

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

| Study | Merged with Newcorn 2005 trial: Michelson 2001[452] |
|---|---|
| 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 2002[450] |
|---|---|
| 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 2002[450] |
|---|---|
| | Further details: 1. Dose: Mixed 2. Method of titration: Titrated to optimum dose<br><br>(n=85) Intervention 2: No treatment - Placebo. Placebo. Duration 6 weeks. Concurrent medication/care: Not stated<br>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<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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<br>- 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<br><br>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months<br>- 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<br>Protocol outcome 2 (discontinuation): low risk of bias |

| Study | Michelson 2003[449] |
|---|---|
| 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[449] |
|---|---|
| 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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose<br><br>(n=266) Intervention 2: No treatment - Placebo. Identical regimen to active treatment. Duration 8 weeks. Concurrent medication/care: nil<br>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[449] |
|---|---|
| - Actual outcome for Adult: CAARS-INV inattentive subscale, study 1 at 8 weeks;<br>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%<br>- Actual outcome for Adult: CAARS-INV hyperactive/impulsive subscale, study 1 at 8 weeks;<br>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%<br>- Actual outcome for Adult: CAARS-INV hyperactive/impulsive subscale, study 2 at 8 weeks;<br>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%<br>- Actual outcome for Adult: CAARS-INV inattentive subscale, study 2 at 8 weeks;<br>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%<br><br>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months<br>- Actual outcome for Adult: Drop out due to adverse events at 8 weeks; Group 1: 11/141, Group 2: 6/139<br>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%<br>- Actual outcome for Adult: Drop out due to adverse events (study 2) at 8 weeks; Group 1: 12/129, Group 2: 3/127<br>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% | |
| 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[457] |
|---|---|
| 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[457] |
|---|---|
| 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<br>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)<br><br>(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.<br>Further details: 1. Dose: Not applicable / Not stated / Unclear (100-150mg/day depending on weight). 2. |

| Study | Mohammadi 2010[457] |
|---|---|
| | 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) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AMANTADINE versus METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS)<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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<br>- 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<br>- 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 2012[456] |
|---|---|
| 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[456] |
|---|---|
| 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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear (20-30 mg/day). 2. Method of titration: Fixed dose (Fixed dose dependent on weight).<br><br>(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<br>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 2012[456] |
|---|---|
| - 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 2009[460] |
|---|---|
| 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 2009[460] |
|---|---|
| | 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 naive). 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-naive<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose (Titrated to target dose).<br><br>(n=51) Intervention 2: No treatment - Placebo. Placebo. Duration 12 weeks. Concurrent medication/care: Treatment naive<br>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[460] |
|---|---|
| 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<br>- 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<br>- 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[469] |
|---|---|
| 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 2006[469] |
|---|---|
| | aggression, stereotypies 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.<br>Further details: 1. Dose: 2. Method of titration: Fixed dose<br><br>(n=20) Intervention 2: No treatment – Placebo. Placebo. Duration 6 months. Concurrent medication/care: No medication was given concurrently<br>Further details: 1. Dose: 2. Method of titration: |
| Funding | Funding not stated |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RISPERIDONE versus PLACEBO<br><br>Protocol outcome 1: Behavioural outcomes at <3- or >6-months<br>- 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 2009[471] |
|---|---|
| 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[471] |
|---|---|
| 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 420 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<br>Further details: 1. Dose:  2. Method of titration:<br><br>(n=25) Intervention 2: Mood stabilisers – Carbamazepine. No dosage details provided. Duration 4 weeks. Concurrent medication/care: Not reported<br>Further details: 1. Dose:  2. Method of titration: |
| Funding | Academic or government funding |

| Study | Nair 2009[471] |
|---|---|
| Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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<br>- 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<br>- 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<br>- 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[476] |
|---|---|
| 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[476] |
|---|---|
| | 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 | (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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose<br><br>(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 mediation was permitted<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose<br><br>(n=27) Intervention 3: No treatment - Placebo. Placebo. Duration 6 weeks. Concurrent medication/care: No concomitant medication was permitted<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear |
| 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[476] |
|---|---|
| 7.2); n=82; ADHD-RS 0-27 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness<br>- 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<br>- 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<br>- 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<br><br>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE versus PLACEBO<br><br>Protocol outcome 1: Quality of life at <3- or >6-months<br>- 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<br><br>Protocol outcome 2: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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<br>- 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<br><br>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OROS METHYLPHENIDATE versus PLACEBO<br><br>Protocol outcome 1: Quality of life at <3- or >6-months<br>- 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<br><br>Protocol outcome 2: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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<br>- 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 2008[476] |
|---|---|
| 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<br>Protocol outcome 2: Very high risk of bias |

| Study (subsidiary papers) | Newcorn 2013[479] (Stein 2015[599]) |
|---|---|
| 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[479] (Stein 2015[599]) |
|---|---|
| | randomised to treatment groups. These remained in the full set analysis when considering the intent to treat analyses. |
| Indirectness of population | No indirectness |
| Interventions | (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<br>Further details: 1. Dose:  2. Method of titration:<br><br>(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<br>Further details: 1. Dose:  2. Method of titration:<br><br>(n=113) Intervention 3: No treatment - Placebo. Placebo (AM) and Placebo (PM). Duration 8 weeks. Concurrent medication/care: None reported<br>Further details: 1. Dose:  2. Method of titration:<br><br>(n=227) Intervention 4: Guanfacine. AM and PM combined data. Duration 8 weeks. Concurrent medication/care: None reported<br>Further details: 1. Dose:  2. Method of titration: |

| Study (subsidiary papers) | Newcorn 2013[479] (Stein 2015[599]) |
|---|---|
| Funding | Study funded by industry (Clinical research and writing/editorial support was funded by the sponsor, Shire Development LLC) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GUANFACINE ALL ACTIVE versus PLACEBO<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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<br>- 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<br><br>Protocol outcome 2: Academic outcomes (literacy and numeracy) at <3- or >6-months<br>- 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 | |
| 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 2008[491] (Daviss 2008[199], Cannon 2009[136]) |
|---|---|
| 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 2008[491] (Daviss 2008[199], Cannon 2009[136]) |
|---|---|
| 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 Ioqa 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 Iowa 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 n 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[491] (Daviss 2008[199], Cannon 2009[136]) |
|---|---|
| | 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<br>Further details: 1. Dose:  2. Method of titration:<br><br>(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.<br>Further details: 1. Dose:  2. Method of titration:<br><br>(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.<br>Further details: 1. Dose:  2. Method of titration:<br><br>(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 |

| Study (subsidiary papers) | Palumbo 2008[491] (Daviss 2008[199], Cannon 2009[136]) |
|---|---|
| | 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.<br>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) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE versus PLACEBO<br><br>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<br>Protocol outcome 2: Behavioural outcomes at 16 weeks: CGAS mean difference adjusted for baseline; very high risk of bias. Indirectness of outcome: No indirectness<br>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<br>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CLONIDINE versus PLACEBO<br>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<br>Protocol outcome 2: Behavioural outcomes at 16 weeks: CGAS mean difference adjusted for baseline; very high risk of bias. Indirectness of outcome: No indirectness<br>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<br>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COMBINATION versus PLACEBO<br>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<br>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 | |
| 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[494] |
|---|---|
| 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 dexamfetamine. 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 - Dexamfetamine. 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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose |

| Study | Paterson 1999[494] |
|---|---|
| | (n=21) Intervention 2: No treatment - Placebo. Placebo tablets were given with identical instructions to dexamfetamine tablets. Duration 6 weeks. Concurrent medication/care: Not reported<br>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: DEXAMFETAMINE versus PLACEBO<br><br>Protocol outcome 1: CGI at <3- or >6-months<br>- 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 2006[291] (Kollins 2006[375]) |
|---|---|
| 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[291] (Kollins 2006[375]) |
|---|---|
| | 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. |
| Exclusion criteria | 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 |
| Recruitment/selection of patients | 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 |
| Age, gender and ethnicity | 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% |
| Further population details | 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 |

| Study (subsidiary papers) | PATS trial: Greenhill 2006[291] (Kollins 2006[375]) |
|---|---|
| | (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 | (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<br>Further details: 1. Dose:  2. Method of titration:<br><br>(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<br>Further details: 1. Dose:  2. Method of titration:<br><br>(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<br>Further details: 1. Dose:  2. Method of titration:<br><br>(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<br>Further details: 1. Dose:  2. Method of titration:<br><br>(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 |

| Study (subsidiary papers) | PATS trial: Greenhill 2006[291] (Kollins 2006[375]) |
|---|---|
| | Further details: 1. Dose: 2. Method of titration: |
| Funding | Academic or government funding (National institute of Mental Health and various US universities) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS) versus PLACEBO<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>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:<br>- 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<br>Risk of bias: All domain - ; Indirectness of outcome: No indirectness<br><br>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months<br>- 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<br>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 | Pliszka 2000[503] |
|---|---|
| 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[503] |
|---|---|
| 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 | (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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose<br><br>(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<br>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 Richwood Inc) |

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

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

| Study | Pliszka 2000[503] |
|---|---|
| indirectness<br><br>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months<br>- 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<br>Protocol outcome 2: Low risk of bias |

| Study (subsidiary papers) | Reimherr 2007[522] (Robison 2010[530]) |
|---|---|
| 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[522] (Robison 2010[530]) |
|---|---|
| | 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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose<br><br>(n=47) Intervention 2: No treatment - Placebo. Placebo. Duration 4 weeks. Concurrent medication/care: not stated<br>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[522] (Robison 2010[530]) |
|---|---|
| eliminated after randomization but before treatment, not stated why); Group 2 Number missing: 1, Reason: reasons not stated<br>- Actual outcome: CGI-I Score of 1 or 2 at 4 weeks;<br>Risk of bias: All domain - ; Indirectness of outcome: No indirectness<br>- 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<br>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[524] |
|---|---|
| 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 2012[524] |
|---|---|
| | 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 | (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<br>Further details: 1. Dose:  2. Method of titration:<br><br>(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<br>Further details: 1. Dose:  2. Method of titration: |
| Funding | Study funded by industry (Medice, Germany) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE (EXTENDED RELEASE) versus PLACEBO<br><br>Protocol outcome 1: CGI at <3- or >6-months<br>- 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<br><br>Protocol outcome 2: ADHD symptoms at <3- or >6-months<br>- 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<br><br>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months<br>- 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 | |
| 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 2012[524] |
|---|---|
| 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 2010[527] |
|---|---|
| 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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose<br><br>(n=17) Intervention 2: No treatment - Placebo. Placebo. Duration 6 weeks. Concurrent medication/care: No |

| Study | Riahi 2010[527] |
|---|---|
| | details<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear |
| Funding | Academic or government funding (Tehran University of Medical Sciences) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: REBOXETINE versus PLACEBO<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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<br>- 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<br>- 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<br><br>Protocol outcome 2: Behavioural outcomes at <3- or >6-months<br>- 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<br>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months<br>- 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 2009[533] (Rosler 2010[535]) |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=359) |

| Study (subsidiary papers) | Rosler 2009[533] (Rosler 2010[535]) |
|---|---|
| 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 | (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<br>Further details: 1. Dose: 2. Method of titration:<br><br>(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<br>Further details: 1. Dose: 2. Method of titration: |

| Study (subsidiary papers) | Rosler 2009[533] (Rosler 2010[535]) |
|---|---|
| | |
| 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<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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 2003[539] |
|---|---|
| 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[539] |
|---|---|
| | 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 | (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<br>Further details: 1. Dose: Mixed 2. Method of titration: Titrated to optimum dose<br><br>(n=11) Intervention 2: No treatment - Placebo. Placebo. Duration 5.3 weeks (+/- 3.3 weeks). Concurrent medication/care: Not specified<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear |
| Funding | Funding not stated |

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 total scores at 6 weeks (mean); Group 1: mean 14 (SD 6.7); n=11, Group 2: mean 14.7 (SD

| Study | Rugino 2003[539] |
|---|---|
| 3.2); n=11; ADHD-RS-IV 0-54 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness<br><br>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months<br>- 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[540] |
|---|---|
| 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 2016[540] |
|---|---|
| | 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 | (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.<br>Further details: 1. Dose: Mixed 2. Method of titration: Titrated to optimum dose<br><br>(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.<br>Further details: 1. Dose: Mixed 2. Method of titration: Titrated to optimum dose |
| 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[540] |
|---|---|
| | - 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<br>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<br>- 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<br>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<br><br>Protocol outcome 3: Behavioural outcomes at <3- or >6-months<br>- 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<br>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<br><br>Protocol outcome 4: Serious adverse events at All<br>- 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<br>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<br><br>Protocol outcome 5: Dropped out due to adverse events at <3- or >6-months<br>- 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<br>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 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 2016[540] |
|---|---|
| | months |

| Study | Sallee 2009[546] |
|---|---|
| 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<br>Further details: 1. Dose: Mixed 2. Method of titration: Fixed dose |

| Study | Sallee 2009[546] |
|---|---|
| | (n=66) Intervention 2: No treatment - Placebo. Placebo. Duration 6 weeks (plus 3 weeks discontinuation).<br>Concurrent medication/care: Not specified<br>Further details: 1. Dose: 2. Method of titration: |
| Funding | Principal author funded by industry (Shire Development) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GUANFACINE versus PLACEBO<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>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<br>- Actual outcome for Children (up to 18 years): Treatment response (CGI I score of 1 or 2) at 6 weeks;<br>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<br><br>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months<br>- Actual outcome for Children (up to 18 years): Drop out due to adverse events at 6 weeks;<br>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 | |
| 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 2001[553] |
|---|---|
| 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[553] |
|---|---|
| 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); WISCR 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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose<br><br>(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[553] |
|---|---|
| | ineffective medication<br>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) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GUANFACINE versus PLACEBO<br><br>Protocol outcome 1: CGI at <3- or >6-months<br>- 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<br>- 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<br><br>Protocol outcome 2: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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 | |
| 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<br>Protocol outcome 2: Low risk of bias |

| Study | Scahill 2015[554] |
|---|---|
| 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[554] |
|---|---|
| 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 | (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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose<br><br>(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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear |

| Study | Scahill 2015[554] |
|---|---|
| Funding | Academic or government funding (Funded by NIMH grants) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GUANFACINE EXTENDED RELEASE versus PLACEBO<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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<br><br>Protocol outcome 2: Behavioural outcomes at <3- or >6-months<br>- 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<br><br>Protocol outcome 3: Serious adverse events at All<br>- 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<br><br>Protocol outcome 4: Dropped out due to adverse events at <3- or >6-months<br>- 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 | |
| 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[576] |
|---|---|
| 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[576] |
|---|---|
| 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 Conners 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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose |

| Study | Simonoff 2013[576] |
|---|---|
| | (n=61) Intervention 2: No treatment - Placebo. a matching placebo in identical "doses" was manufactured. Duration 16 weeks. Concurrent medication/care: Not reported<br>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) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MPH GROUP versus PLACEBO GROUP<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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<br>- 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<br>- 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<br><br>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months<br>- 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 | |
| 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<br>Protocol outcome 2: Low risk of bias |

| Study | Singer 1995[577] |
|---|---|
| Study type | RCT (Patient randomised; Crossover: 1 week) |

| Study | Singer 1995[577] |
|---|---|
| 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 IIIR 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 | (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<br>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).<br><br>(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 |

| Study | Singer 1995[577] |
|---|---|
| | 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.<br>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.).<br><br>(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<br>Further details: 1. Dose: 2. Method of titration: |
| Funding | Academic or government funding (Tourette Syndrome Association and the United States Public Health Service) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DESIPRAMINE versus PLACEBO<br><br>Protocol outcome 1: Behavioural outcomes at <3- or >6-months<br>- 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<br><br>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CLONIDINE versus DESIPRAMINE<br><br>Protocol outcome 1: Behavioural outcomes at <3- or >6-months<br>- 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<br><br>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CLONIDINE versus PLACEBO<br><br>Protocol outcome 1: Behavioural outcomes at <3- or >6-months<br>- 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 | |
| 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 1995[577] |
|---|---|
| Risk of bias details | Low risk of bias |

| Study | Spencer 1995[593] |
|---|---|
| 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<br>Further details: 1. Dose: 2. Method of titration: |

| Study | Spencer 1995[593] |
|---|---|
| | (n=25) Intervention 2: No treatment - Placebo. Placebo. Duration 3 weeks. Concurrent medication/care: Not specified<br>Further details: 1. Dose:  2. Method of titration: |
| Funding | Funding not stated |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS)  versus PLACEBO<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>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 | |
| 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 2002[592] |
|---|---|
| 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[592] |
|---|---|
| | 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 | (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.<br>Concurrent medication/care: Not reported<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose<br><br>(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.<br>Concurrent medication/care: Not reported<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear<br><br>(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.<br>Concurrent medication/care: Not reported<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear |

| Study | Spencer 2002[592] |
|---|---|
| | (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.<br>Concurrent medication/care: Not reported<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose |
| Funding | Study funded by industry (Funded by Eli Lilly and Company) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE (STUDY 1) versus PLACEBO (STUDY 1)<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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<br>- 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<br>- 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<br><br>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE (STUDY 2) versus PLACEBO (STUDY 2)<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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<br>- 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<br>- 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 2002[592] |
|---|---|
| | <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 2002[590] |
|---|---|
| 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 2002[590] |
|---|---|
| | medication was allowed in the trial.<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose<br><br>(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.<br>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<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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 2008[598] |
|---|---|
| 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[598] |
|---|---|
| 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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose<br><br>(n=56) Intervention 2: No treatment - Placebo. Placebo tablet titrated in the same way as Atomoxetine. Duration 8 weeks. Concurrent medication/care: Nil<br>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[598] |
|---|---|
| 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<br>- 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<br>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<br><br>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months<br>- Actual outcome for Children (up to 18 years): Discontinuation because of adverse event at 8 weeks; Group 1: 2/61, Group 2: 1/56<br>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 | Spencer 2005[591](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[591](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 | (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<br>Further details: 1. Dose: 2. Method of titration:<br><br>(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 |

| Study | Spencer 2005[591](Biederman 2006)[90] |
|---|---|
| | not permitted during the protocol<br>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<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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 2008[598] |
|---|---|
| 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[598] |
|---|---|
| | 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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose<br><br>(n=56) Intervention 2: No treatment - Placebo. Placebo tablet titrated in the same way as Atomoxetine. Duration 8 weeks. Concurrent medication/care: Nil<br>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[598] |
|---|---|
| - 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<br><br>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months<br>- Actual outcome for Children (up to 18 years): Discontinuation because of adverse event at 8 weeks; Group 1: 2/61, Group 2: 1/56<br>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[608] |
|---|---|
| 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 Montogmery 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 of 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[608] |
|---|---|
| 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 | (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.<br>Further details: 1. Dose:  2. Method of titration:<br><br>(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.<br>Further details: 1. Dose:  2. Method of titration:<br><br>(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.<br>Further details: 1. Dose:  2. Method of titration: |
| Funding | Study funded by industry (Pfizer Global Research) |

| Study | Sutherland 2012[608] |
|---|---|
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE versus PLACEBO<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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<br>- 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<br>- 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<br>- 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<br><br>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE AND BUSPIRONE versus PLACEBO<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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<br>- 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<br>- 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<br>- 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 | |
| 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 | Takahashi 2009[615] |
|---|---|
| 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<br>Further details: 1. Dose:  2. Method of titration:<br><br>(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<br>Further details: 1. Dose:  2. Method of titration: |

| Study | Takahashi 2009[615] |
|---|---|
| | (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.<br>Further details: 1. Dose: 2. Method of titration:<br><br>(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<br>Further details: 1. Dose: 2. Method of titration: |
| 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[615] |
|---|---|
| Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months<br>- Actual outcome: Discontinuation due to adverse events at 8 weeks; Risk of bias: Low; Indirectness of outcome: No indirectness<br><br>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE 1.8MG versus PLACEBO<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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<br>- 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<br><br>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months<br>- Actual outcome: Discontinuation 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 low risk of bias |

| Study | Takahashi 2014 [616] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=284) |
| Countries and setting | Conducted in Japan; Setting: 39 sites across 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 | Adults (18 years and over) |

| Study | Takahashi 2014 [616] |
|---|---|
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Subjects aged 18-64 years, met the diagnosis of ADHD according to DSM-IV before the age of 7 years based on Conners' Adult ADHD diagnostic interview for DSM-IV Japanese version (CAADID). Participants were also required to have a DSM-IV score of 24 or more on the CAARS-O:IR screening version. |
| Exclusion criteria | Subjects excluded if they were a non-responder to methylphenidate and/or had a history of hypersensitivity or intolerance to MPH or had been treated with MPH or any other medications for ADHD within 4 weeks before the screening visit. Diagnosis of bipolar I disorder, schizophrenia, schizoaffective disorder, severe OCD, PDD, or suicidality. Patients with confirmed cancer or other serious illnesses were also excluded. |
| Recruitment/selection of patients | Subjects were recruited 22 February 2011 to 19 April 2012 |
| Age, gender and ethnicity | Age - Range: 18-64. Gender (M:F): 139:145. Ethnicity: Not specified |
| Further population details | 1. ADHD subtype: 55% inattentive, 64% combined, 1% hyperactive 2. Age: Not specified 3. At risk population: General population 4. Comorbidities: Not specified 5. Diagnostic method: DSM. 6. Line of treatment: Unclear line 7. Severity: Baseline CAARS-O:SV score of 31.75 |
| Indirectness of population | No indirectness |
| Interventions | (n=143) Intervention 1: OROS Methylphenidate.4 week titration period, 4 week efficacy period. Started on 18mg/day on the first week and increased by increments of 18mg a week up to maximum dose of 72mg per day until an individually optimised dose was achieved. Duration 8 weeks. Concurrent medication/care: Not specified<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose<br><br>(n=141) Intervention 2: No treatment - Placebo. Duration 8 weeks. Concurrent medication/care: Not specified<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear |
| Funding | Janssen Pharmaceutical KK, Japan |

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

Protocol outcome 1: ADHD symptoms (observer rated) at <3- or >6-months
- Actual outcome for Adults (over 18 years): CAARS-O:SV total scores at 8 weeks; Group 1: mean -19.5 (SD 15.42); n=143, Group 2: mean -12.5 (SD 15.97); n=140; CAARS-O:SV 0-84 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Children (up to 18 years): CAARS-O:SV inattention scores at 8 weeks; Group 1: mean -8 (SD 6.26); n=143, Group 2: mean -5 (SD 5.93); n=140; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Children (up to 18 years): CAARS-O:SV hyperactivity scores at 8 weeks; Group 1: mean -4.5 (SD 4.51); n=143, Group 2: mean -2.9

| Study | Takahashi 2014 [616] |
|---|---|
| (SD 4.84); n=140; Risk of bias: Low; Indirectness of outcome: No indirectness<br><br>Protocol outcome 2: ADHD symptoms (self rated) at <3- or >6-months<br>- Actual outcome for Adults (over 18 years): CAARS-S:SV total scores at 8 weeks; Group 1: mean -18 (SD 16.45); n=141, Group 2: mean -10.9 (SD 16.55); n=140; CAARS-O:SV 0-84 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness<br>- Actual outcome for Children (up to 18 years): CAARS-S:SV inattention scores at 8 weeks; Group 1: mean -6.5 (SD 6.35); n=141, Group 2: mean -3.4 (SD 5.99); n=140; Risk of bias: Low; Indirectness of outcome: No indirectness<br>- Actual outcome for Children (up to 18 years): CAARS-S:SV hyperactivity scores at 8 weeks Group 1: mean -4.2 (SD 4.73); n=141, Group 2: mean -3.2 (SD 5.02); n=140; Risk of bias: Low; Indirectness of outcome: No indirectness<br><br>Protocol outcome 2: Quality of life at <3- or >6-months<br>- Actual outcome for Adults (over 18 years): Q-LES-Q total scores at 8 weeks Group 1: mean 2.4 (SD 14); n=142, Group 2: mean 0.8 (SD 12.69); n=140; Q-LES-Q 16-80 Top=High is good outcome; Risk of bias: Low; Indirectness of outcome: No indirectness<br><br>Protocol outcome 3: Discontinued due to adverse events at <3- or >6-months<br>- Actual outcome for Adults (over 18 years): Drop out due to adverse events at 8 weeks; Group 1: 6/143, Group 2: 1/141; Risk of bias: Low; Indirectness of outcome: No indirectness | |
| Protocol outcomes not reported by the study | 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: Low risk of bias<br>Protocol outcome 2: Low risk of bias<br>Protocol outcome 3: Low risk of bias |

| Study | Taylor 2000[620] |
|---|---|
| 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 |

| Study | Taylor 2000[620] |
|---|---|
| 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 |
| 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 | (n=22) Intervention 1: CNS stimulants - Dexamfetamine. Patients were given 5mg of dexamfetamine; 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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose<br><br>(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 |

| Study | Taylor 2000[620] |
|---|---|
| | as tolerated up to four capsules per dose (a maximum of 8 capsules daily). Duration 2 weeks. Concurrent medication/care: No details given<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose<br><br>(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 details given<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear |
| Funding | Funding not stated |

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

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

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MODAFANIL versus DEXAMFETAMINE

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

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

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

| Study | Taylor 2000[620] |
|---|---|
| - 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<br>- 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<br>- 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 | |
| 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[621] |
|---|---|
| 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 |

| Study | Taylor 2001[621] |
|---|---|
| | 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 |
| Indirectness of population | No indirectness |
| Interventions | (n=17) Intervention 1: CNS stimulants - Dexamfetamine. 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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose<br><br>(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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose<br><br>(n=17) Intervention 3: No treatment - Placebo. Placebo capsules contained lactose. Duration 2 weeks. Concurrent medication/care: No concomitant medication was permitted<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear |
| Funding | Funding not stated |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DEXAMFETAMINE 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

| Study | Taylor 2001[621] |
|---|---|
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DEXAMFETAMINE versus PLACEBO<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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<br>- 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<br><br>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GUANFACINE versus PLACEBO<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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<br>- 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 | |
| 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[625] |
|---|---|
| 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 | Adequate method of assessment/diagnosis: DSM-IV as operationalised by clinical interview and standard |

| Study | Tenenbaum 2002[625] |
|---|---|
| condition | 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 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 | (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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Mixed (Titrated to fixed dose).<br><br>(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 |

| Study | Tenenbaum 2002[625] |
|---|---|
| | 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 Henkel Corporation) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS) versus PLACEBO<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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[631] |
|---|---|
| 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 |

| Study | Tramontina 2009[631] |
|---|---|
| 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 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<br>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).<br><br>(n=25) Intervention 2: No treatment - Placebo. Matching placebo to active treatment. Duration 6 weeks. Concurrent medication/care: No concomitant treatment allowed<br>Further details: 1. Dose:  2. Method of titration: |
| Funding | Equipment / drugs provided by industry (part funded by Bristol-Myers Squib) |

| Study | Tramontina 2009[631] |
|---|---|
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ARIPIPRAZOLE versus PLACEBO<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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); 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 2007[639] |
|---|---|
| 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 |

| Study | Van der Heijden 2007[639] |
|---|---|
| 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. |
| 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<br>Further details: 1. Dose: 2. Method of titration:<br><br>(n=53) Intervention 2: No treatment - Placebo. Identical appearing tablets as active treatment at 7 pm. Duration 4 weeks. Concurrent medication/care: None reported<br>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

| Study | Van der Heijden 2007[639] |
|---|---|
| - 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<br>- 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<br><br>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months<br>- 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; 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[647] |
|---|---|
| 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 |

| Study | Wang 2007[647] |
|---|---|
| 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 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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose<br><br>(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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose |
| Funding | Funding not stated |

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

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

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

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

| Study | Wang 2007[647] |
|---|---|
| - 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 | |
| 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<br>Protocol outcome 3: Low risk of bias |

| Study | Weiss 2005[663] |
|---|---|
| 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: |

| Study | Weiss 2005[663] |
|---|---|
| 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 |
| Interventions | (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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose<br><br>(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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear |
| 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);

| Study | Weiss 2005[663] |
|---|---|
| n=51; ADHD-RS 0-54 Top=High is poor outcome; Risk of bias: ; Indirectness of outcome: No indirectness<br><br>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months<br>- 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<br><br>Protocol outcome 4: Academic outcomes (literacy and numeracy) at <3- or >6-months<br>- 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<br>Protocol 3: Low risk of bias |

| Study | Wender 1985[666] |
|---|---|
| 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 |

| Study | Wender 1985[666] |
|---|---|
| | 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%) |
| 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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose<br><br>(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<br>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<br><br>Protocol outcome 1: Behavioural outcomes at <3- or >6-months<br>- 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 | Quality of life at <3- or >6-months; CGI at <3- or >6-months; ADHD symptoms at <3- or >6-months; Serious |

| Study | Wender 1985[666] |
|---|---|
| study | 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[667] |
|---|---|
| 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 | (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 of2mg/kg/d and administered as evenly divided dose twice daily) or placebo. Duration 9 weeks. Concurrent medication/care: Not reported |

| Study | Wernicke 2004[667] |
|---|---|
| | Further details: 1. Dose:  2. Method of titration: Titrated to optimum dose<br><br>(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<br>Further details: 1. Dose:  2. Method of titration:<br><br>(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<br>Further details: 1. Dose:  2. Method of titration: Titrated to optimum dose<br><br>(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<br>Further details: 1. Dose:  2. Method of titration: Titrated to optimum dose |
| Funding | Study funded by industry (Eli Lilly and Company) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE - CHILDREN versus PLACEBO - CHILDREN<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br><br>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE - ADULTS versus PLACEBO - ADULTS<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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 | |
| 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 | Wernicke 2004[667] |
|---|---|
| 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 2009[672](Wietecha 2013[670]; Saylor 2009[552]) |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=209) |
| 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 | -- |

| Study | Wietecha 2009[672](Wietecha 2013[670]; Saylor 2009[552]) |
|---|---|
| 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<br>Further details: 1. Dose: 2. Method of titration:<br><br>(n=89) Intervention 2: No treatment - Placebo. Placebo. Duration 16 weeks. Concurrent medication/care: No details<br>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: ADHD+DYSLEXIA (ATOMOXETINE)-ACUTE PHASE versus PLACEBO ( ACUTE PHASE)<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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<br>- 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<br>- 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<br>- 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<br>- 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- |

| Study | Wietecha 2009[672](Wietecha 2013[670]; Saylor 2009[552]) |
|---|---|
| | 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 2011[658] |
|---|---|
| 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<br>Further details: 1. Dose: 2. Method of titration: |

| Study | Wehmeier 2011[658] |
|---|---|
| | (n=62) Intervention 2: No treatment. Matching placebo. Duration 8 weeks. Concurrent medication/care: Not specified<br>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<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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;<br>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<br>- 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;<br>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<br>- 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;<br>Risk of bias: All domain - ; Indirectness of outcome: No indirectness<br><br>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months<br>- 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<br>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 | |
| 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[657] (Wehmeier 2015[655], Wehmeier 2014[653]) |
|---|---|
| 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 |

| Study (subsidiary papers) | Wehmeier 2012[657] (Wehmeier 2015[655], Wehmeier 2014[653]) |
|---|---|
| | 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) |
| 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 | (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 |

| Study (subsidiary papers) | Wehmeier 2012[657] (Wehmeier 2015[655], Wehmeier 2014[653]) |
|---|---|
| | 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<br>Further details: 1. Dose: 2. Method of titration:<br><br>(n=62) Intervention 2: No treatment - Placebo. Matching Placebo to active treatment. Duration 8 weeks. Concurrent medication/care: Not reported<br>Further details: 1. Dose: 2. Method of titration: |
| Funding | Study funded by industry (Lilly Deutschland , German affiliate of Eli Lilly and Company) |

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

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

| Study (subsidiary papers) | Wehmeier 2012[657] (Wehmeier 2015[655], Wehmeier 2014[653]) |
|---|---|
| - 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<br><br>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months<br>- 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 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 attrition bias |

| Study | Wilens 2008[689] |
|---|---|
| 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. |

| Study | Wilens 2008[689] |
|---|---|
| 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 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 | (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 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<br>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.).<br><br>(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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: |
| 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

| Study | Wilens 2008[689] |
|---|---|
| - 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<br>- 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<br>- 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<br><br>Protocol outcome 3: Behavioural outcomes at <3- or >6-months<br>- 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); n=48; OCDS ? Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness<br><br>Protocol outcome 4: Dropped out due to adverse events at <3- or >6-months<br>- 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[695] |
|---|---|
| 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 |

| Study | Wilens 2015[695] |
|---|---|
| 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% population had previously used stimulant medication). 7. Severity: Mixed |
| Indirectness of population | No indirectness |
| Interventions | (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<br>Further details: 1. Dose:  2. Method of titration:<br><br>(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<br>Further details: 1. Dose:  2. Method of titration: |
| 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

| Study | Wilens 2015[695] |
|---|---|
| (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)<br>- Actual outcome for Children (up to 18 years): ADHD-RS-IV inattentive subscale at 13 weeks;<br>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)<br><br>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months<br>- Actual outcome for Children (up to 18 years): Early termination (any reason) at 15 weeks; Group 1: 51/157, Group 2: 52/155<br>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)<br>- Actual outcome for Children (up to 18 years): Early termination (for adverse event) at 15 weeks; Group 1: 9/157, Group 2: 3/155<br>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)<br><br>Protocol outcome 3: Academic outcomes (literacy and numeracy) at <3- or >6-months<br>- Actual outcome for Children (up to 18 years): WFIRS-P Learning and School (LS) subscale at 13 weeks;<br>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) | |
| 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[702] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | (n=278) |

| Study | Wolraich 2001[702] |
|---|---|
| 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 |
| 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 | (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<br>Further details: 1. Dose: Mixed 2. Method of titration: Mixed<br><br>(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 |

| Study | Wolraich 2001[702] |
|---|---|
| | 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:<br><br>(n=89) Intervention 3: No treatment - Placebo. Placebo. Duration 4 weeks. Concurrent medication/care: Behavioural interventions allowed if started before the trial<br>Further details: 1. Dose: 2. Method of titration: |
| Funding | Study funded by industry (AZLA Corporation) |

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

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

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OROS 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 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,

| Study | Wolraich 2001[702] |
|---|---|
| Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 13<br>- Actual outcome for Children (up to 18 years): SNAP-IV parent rated hyperactivity/impulsivity subscale at 4 weeks;<br>Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low,<br>Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 13<br>- Actual outcome for Children (up to 18 years): Treatment response (CGI score of 1 or 2) at 4 weeks;<br>Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low,<br>Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 38<br><br>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months<br>- Actual outcome for Children (up to 18 years): Drop out due to adverse events at 4 weeks;<br>Risk of bias: All domain - ; Indirectness of outcome: No indirectness<br><br>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IR METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS) versus PLACEBO<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- Actual outcome for Children (up to 18 years): SNAP-IV teacher rated inattention subscale at 4 weeks;<br>Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low,<br>Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 38<br>- Actual outcome for Children (up to 18 years): SNAP-IV parent rated hyperactivity/impulsivity subscale at 4 weeks;<br>Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low,<br>Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 13; Group 2 Number missing: 38<br>- Actual outcome for Children (up to 18 years): Treatment response (CGI score of 1 or 2) at 4 weeks;<br>Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low,<br>Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 13; Group 2 Number missing: 38<br><br>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months<br>- Actual outcome for Children (up to 18 years): Drop out due to adverse events at 4 weeks;<br>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; 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[711] (Wietecha 2012[671]) |
|---|---|

| Study (subsidiary papers) | Young 2011[711] (Wietecha 2012[671]) |
|---|---|
| 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 condition | Adequate method of assessment/diagnosis: DSM-IV |
| 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 |

| Study (subsidiary papers) | Young 2011[711] (Wietecha 2012[671]) |
|---|---|
| | Further details: 1. Dose: 2. Method of titration:<br><br>(n=234) Intervention 2: No treatment - Placebo. Placebo. Duration 24 weeks. Concurrent medication/care: not stated<br>Further details: 1. Dose: 2. Method of titration: |
| Funding | Study funded by industry (Lilly USA) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE versus PLACEBO<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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<br>- 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<br>- 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<br>- 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<br>- Actual outcome for Adult: AISRS scale hyperactivity subscale score (adjusted) at 24 weeks; Risk of bias: Very high; Indirectness of outcome: No indirectness<br>- Actual outcome for Adult: CGI-ADHD-S at 24 weeks; Risk of bias: Very high; Indirectness of outcome: No indirectness<br>- 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<br><br>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months<br>- 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<br><br>Protocol outcome 3: Emotional dysregulation at <3- or >6-months<br>- 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 | Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; |

| Study (subsidiary papers) | Young 2011[711] (Wietecha 2012[671]) |
|---|---|
| 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 |
| 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[712] |
|---|---|
| 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 |

| Study | Zarinara 2010[712] |
|---|---|
| | (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 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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear (50-75 mg/day). 2. Method of titration: Fixed dose (Dose titrated according to weight).<br><br>(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<br>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<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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

## D.2.1 Pre-School children (under 6 years of age)

No evidence found.

## 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 if 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 |

| Study | Carlson 2007[139] |
|---|---|
| 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 (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 | (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.<br>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).<br><br>(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.<br>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). |

| Study | Carlson 2007[139] |
|---|---|
| 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<br><br>Protocol outcome 1: Serious adverse events at All<br>- 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 bias: Very high; Indirectness of outcome: No indirectness<br><br>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months<br>- 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 2014[197] (Wilens 2012[691]) |
|---|---|
| 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- |

| Study (subsidiary papers) | NCT00734578 trial: Cutler 2014[197] (Wilens 2012[691]) |
|---|---|
| | 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 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 | (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<br>Further details: 1. Dose: High (Mean (SD) 3.3 (1) mg/day). 2. Method of titration: Titrated to optimum dose<br><br>(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<br>Further details: 1. Dose: High (Mean (SD) 3.2 (1) mg/day). 2. Method of titration: Titrated to optimum dose<br><br>(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<br>Further details: 1. Dose: Not applicable / Not stated / Unclear (Placebo). 2. Method of titration: Not applicable / Not stated / Unclear (Unclear). |

| Study (subsidiary papers) | NCT00734578 trial: Cutler 2014[197] (Wilens 2012[691]) |
|---|---|
| | |
| 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
- 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

| Study (subsidiary papers) | NCT00734578 trial: Cutler 2014[197] (Wilens 2012[691]) |
|---|---|
| (95%CI -3.6 to -0.9); Risk of bias: High; Indirectness of outcome: No indirectness<br><br>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months<br>- 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<br>- 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 | |
| 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 2014[206] (Nagy 2015[470], Dittmann 2013[207]) |
|---|---|
| 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 amfetamine 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 |

| Study (subsidiary papers) | NCT01106430 trial: Dittmann 2014[206] (Nagy 2015[470], Dittmann 2013[207]) |
|---|---|
| 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-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 | (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.<br>. Duration 9 weeks. Concurrent medication/care: Patients were required to discontinue any psychoactive medication for a 7 day washout period prior to baseline<br>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. ).<br>Comments: Patients to who were unable to tolerate the study drug were withdrawn from the study.<br><br>(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. .<br>Duration 9 weeks. Concurrent medication/care: Patients were required to discontinue any psychoactive medication for a 7 day washout period prior to baseline<br>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. |

| Study (subsidiary papers) | NCT01106430 trial: Dittmann 2014[206] (Nagy 2015[470], Dittmann 2013[207]) |
|---|---|
| | 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.).<br>Comments: Patients to who were unable to tolerate the study drug were withdrawn from the study. |
| Funding | Study funded by industry (Shire) |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LDX GROUP versus ATX GROUP

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

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

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

Protocol outcome 4: Adverse events leading to hospitalisation/death/disabilityevents 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

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

| | |
|---|---|
| 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 (subsidiary papers) | NCT01106430 trial: Dittmann 2014[206] (Nagy 2015[470], Dittmann 2013[207]) |
|---|---|
| | months |

| Study | Gadow 2014[257] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| 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 |

| Study | Gadow 2014[257] |
|---|---|
| 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 throughout 9 week intervention period.<br>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).<br><br>(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.<br>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). |
| 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

| Study | Gadow 2014[257] |
|---|---|
| - 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<br>- 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<br>- Actual outcome for Children (up to 18 years): ADHD-SC4 Severity Subscore: Hyperactivity (parent rating) at 6 weeks (9th week of complete study); 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<br><br>Protocol outcome 2: Behavioural outcomes at <3- or >6-months<br>- 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<br>- 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<br>- 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<br>- 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<br>- 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<br>- 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[349] |
|---|---|
| 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 | Adequate method of assessment/diagnosis: DSM-IV-TR criteria |

| Study | Jain 2011[349] |
|---|---|
| condition | |
| 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 |
| 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 >/= 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.<br>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).<br><br>(n=7) Intervention 2: No treatment - Placebo. Placebo for 4 weeks. Duration 4 weeks. Concurrent medication/care: 1 week washout period before LDX treatment.<br>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: >/= 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

| Study | Jain 2011[349] |
|---|---|
| Protocol outcome 2: Serious adverse events at All<br>- 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 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 | Kollins 2011[378] |
|---|---|
| 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 >/= 26 on ADHD-RS-IV after 4 weeks of stimulant treatment. Other inclusion criteria were intelligence quotient >/= 80 and BMI >/= 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 |

| Study | Kollins 2011[378] |
|---|---|
| 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). |
| Indirectness of population | No indirectness |
| Interventions | (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 ).<br><br>(n=96) Intervention 2: No treatment - Placebo. Placebo. Duration 8 weeks. Concurrent medication/care: 62% patients were on methylphenidate and 38% on amphetamines.<br>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 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. ) |

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

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

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

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

| Study | Kollins 2011[378] |
|---|---|
| - 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 | |
| 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 |

### D.2.3 Adults

| Study | Butterfield 2016[134] |
|---|---|
| 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. |

| Study | Butterfield 2016[134] |
|---|---|
| | 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 applicable / Not stated / Unclear (Baseline score of >/=28 by ADHD-RS or CGI-RS of >/=4. ). |
| Indirectness of population | No indirectness |
| Interventions | (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.<br>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<br><br>(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.<br>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). |
| Funding | Academic or government funding (Study sponsorship by Shire. ) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GUANFACINE versus PLACEBO<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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 | |
| 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 2: ADHD total symptoms parent/ teacher rated at 4 weeks (SNAP-IV parent-teacher composite scores of </=1)**

| Study or Subgroup | Methylphenidate Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Greenhill 2006 | 13 | 53 | 7 | 61 | 100.0% | 2.14 [0.92, 4.96] |
| **Total (95% CI)** | | **53** | | **61** | **100.0%** | **2.14 [0.92, 4.96]** |
| Total events | 13 | | 7 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.77 (P = 0.08)

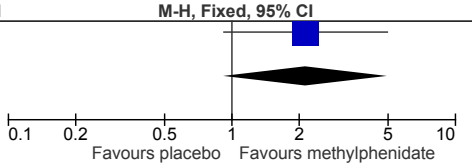



**Figure 3: ADHD total symptoms parent rated at 4 weeks; Conners' Parent Rating Scale DSM-IV ADHD subscale; 0-54; lower values are beneficial**

| Study or Subgroup | Methylphenidate Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Ghuman 2008 | 21.83 | 8.06 | 7 | 30.75 | 9.18 | 7 | 100.0% | -8.92 [-17.97, 0.13] |
| **Total (95% CI)** | | | **7** | | | **7** | **100.0%** | **-8.92 [-17.97, 0.13]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.93 (P = 0.05)

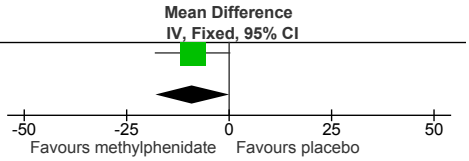
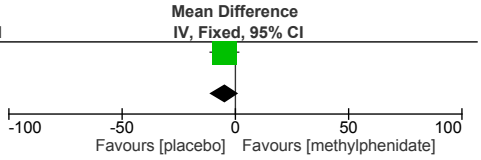



**Figure 4: Behaviour symptoms at 4 weeks (CGAS; 0-100; higher values are beneficial)**

| Study or Subgroup | Methylphenidate Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Ghuman 2008 | 49.5 | 5.05 | 7 | 54.33 | 6.85 | 7 | 100.0% | -4.83 [-11.13, 1.47] |
| **Total (95% CI)** | | | **7** | | | **7** | **100.0%** | **-4.83 [-11.13, 1.47]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.50 (P = 0.13)




#### Risperidone versus methylphenidate

**Figure 5: ADHD total symptoms at 6 weeks (ADHD-RS total scores) parent rated; 0-54, Lower values are beneficial, final values reported**

| Study or Subgroup | Risperidone Mean | SD | Total | Methylphenidate Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Arabgol 2015 | 16.64 | 9.83 | 18 | 15.3 | 6.3 | 15 | 100.0% | 1.34 [-4.21, 6.89] |
| **Total (95% CI)** | | | **18** | | | **15** | **100.0%** | **1.34 [-4.21, 6.89]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.47 (P = 0.64)

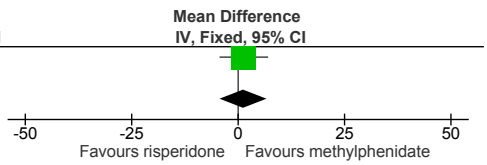


**Figure 6: ADHD inattention symptoms at 6 weeks (ADHD-RS inattentive subscale) parent rated; 0-27, Lower values are beneficial**

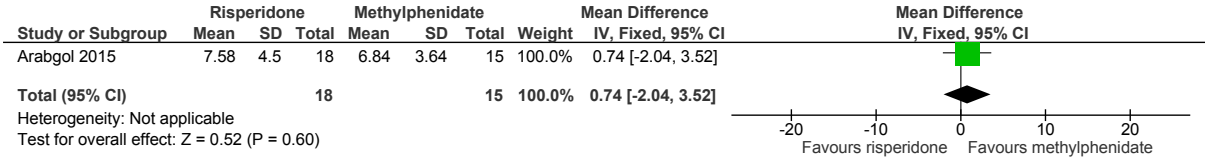



**Figure 7: ADHD hyperactivity symptoms at 6 weeks (ADHD-RS hyperactive subscale) parent rated; 0-27, lower values are beneficial**

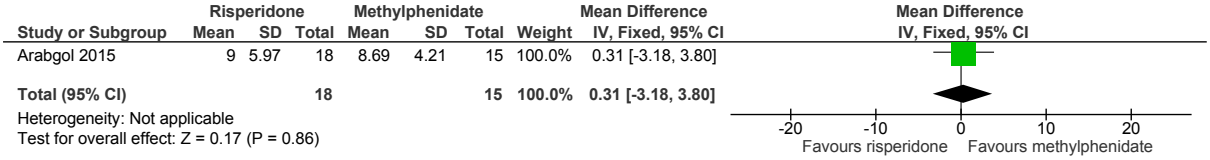



**Figure 8: Discontinuation due to adverse events at 6 weeks**


## Risperidone and methylphenidate versus methylphenidate

**Figure 9: ADHD total symptoms (6 weeks PT; parent rated; CPRS total scores, low scores are beneficial, 0-81)**

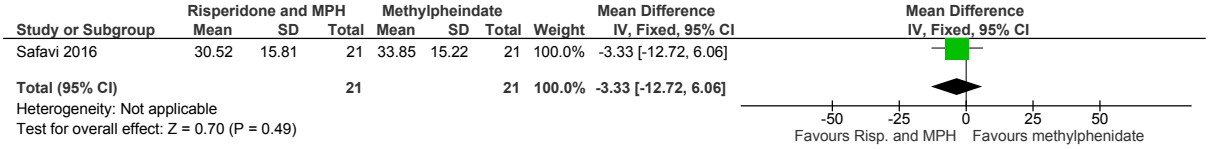



**Figure 10: ADHD inattention symptoms (6 weeks PT; parent rated; CPRS inattention subscale; high is poor, 0-18)**

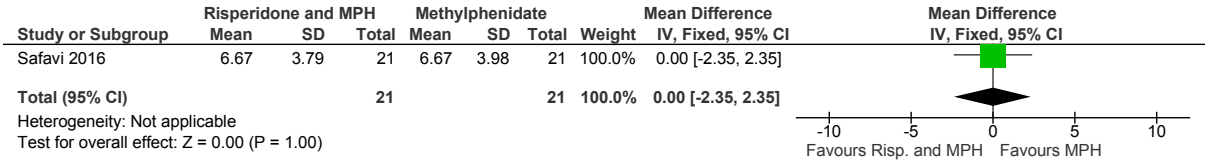


**Figure 11: ADHD hyperactivity symptoms (6 weeks PT; parent rated; CPRS hyperactivity subscale; high is poor, 0-18)**

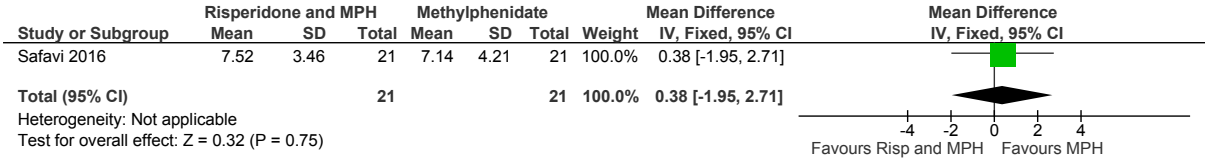



**Figure 12: CGI-I score of 1 or 2 (6 weeks PT)**

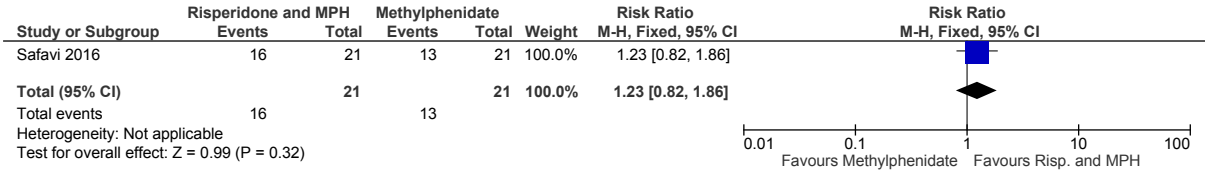



**Figure 13: Behaviour outcomes (6 weeks PT; parent rated; CPRS oppositional defiant disorder subscale; 0-18, high is poor)**

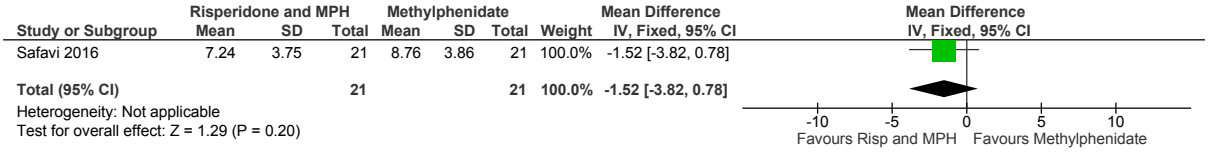
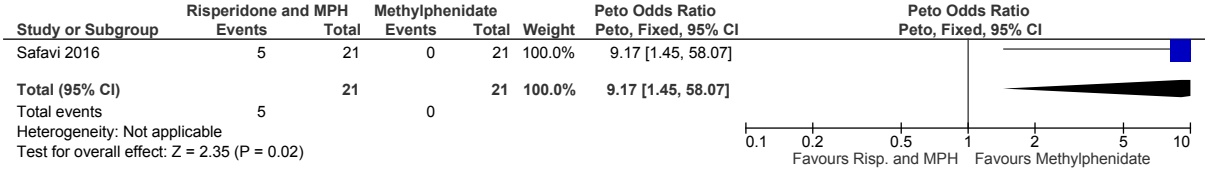



**Figure 14: Discontinued due to adverse events (6 weeks PT)**



## E.1.2 Children and adolescents (aged 5 to 18)

### Immediate release methylphenidate versus placebo

**Figure 15: 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)**

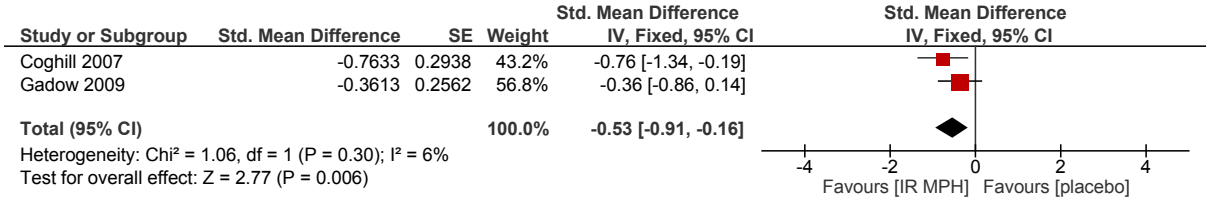



**Figure 16: ADHD total symptoms parent rated (16 weeks PT; ASQ-Parent total score; 0-20; low values are beneficial; change scores reported)**

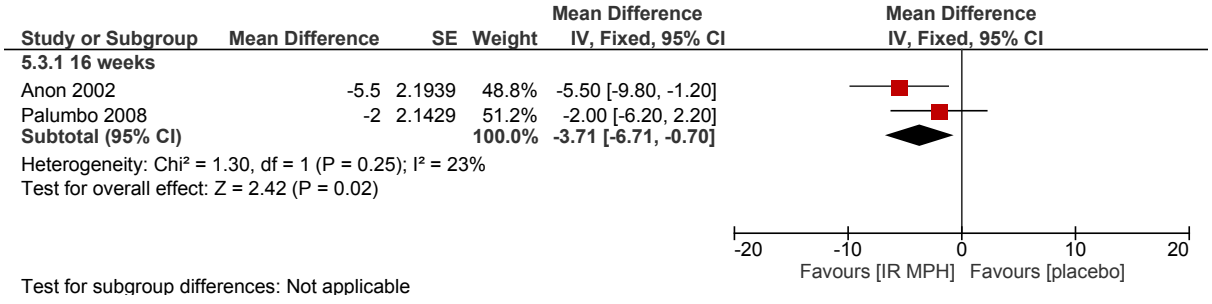



**Figure 17: ADHD total symptoms parent rated (16 weeks PT; parent rated ADHD index; 0-30, lower values are beneficial; final values reported)**

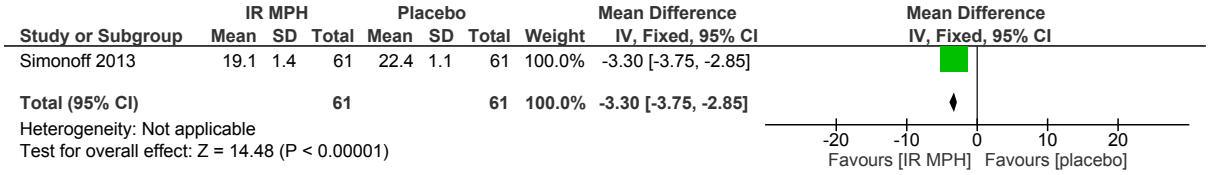



**Figure 18: ADHD total symptoms teacher rated ( 4-7 week crossover trials; Abbreviated Parent Rating scale and parent rated ADHD index; lower values are beneficial; final values reported)**

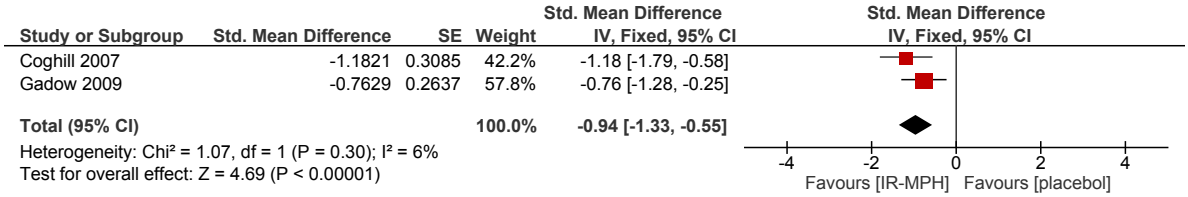


**Figure 19: ADHD total symptoms teacher rated (16 weeks PT, ASQ-teacher total score; 0-20; lower values are beneficial; change scores reported)**

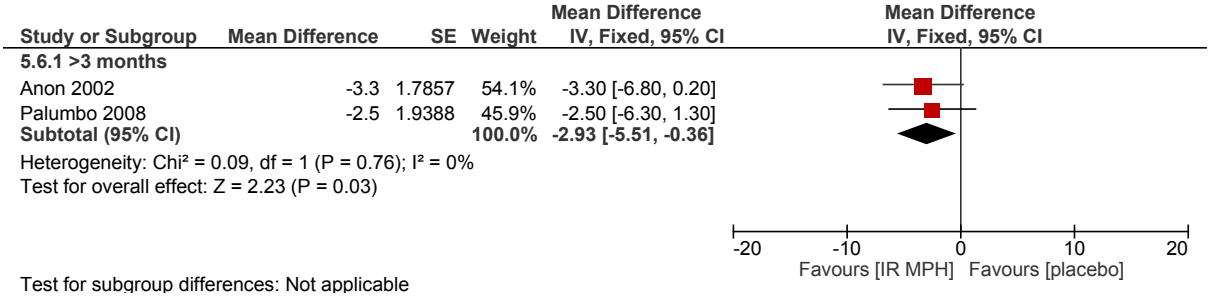



**Figure 20: ADHD total symptoms teacher rated (16 weeks PT; parent rated ADHD index; 0-30 lower values are beneficial; final values reported)**

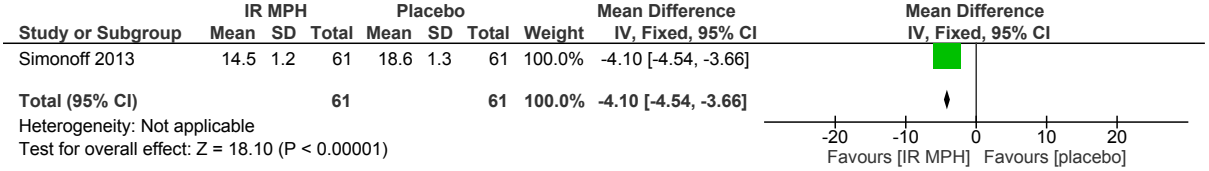



**Figure 21: ADHD hyperactivity symptoms parent rated (4-8 weeks; PT; SNAP-IV and Parent Symptom Questionnaire hyperactivity subscales; lower values are beneficial; final values reported)**

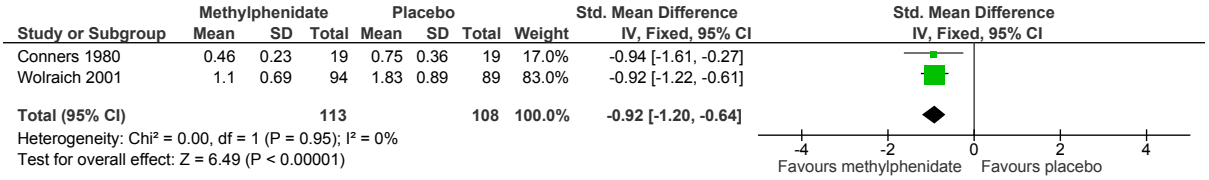



**Figure 22: ADHD hyperactivity symptoms parent rated at 16 weeks (Conners Parent ADHD index hyperactive subscale; low scores are beneficial, 0-15)**

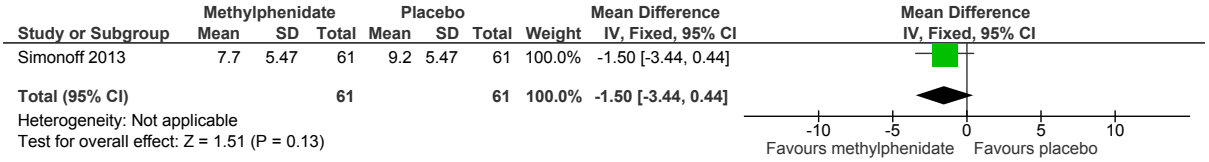



**Figure 23: ADHD hyperactivity symptoms teacher rated (4 weeks; PT; SNAP-IV hyperactivity subscales; 0-3; lower values are beneficial)**

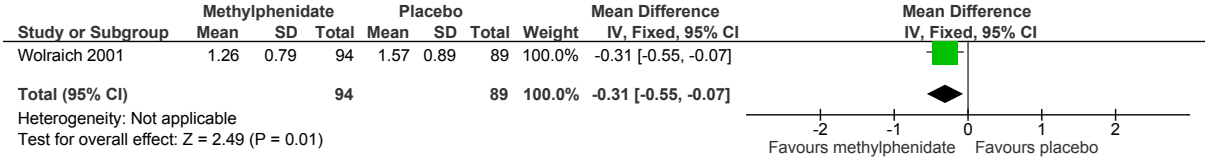


**Figure 24: ADHD hyperactivity symptoms teacher rated at 16 weeks (Conners Teacher ADHD index hyperactive subscale; low scores are beneficial, 0-15)**

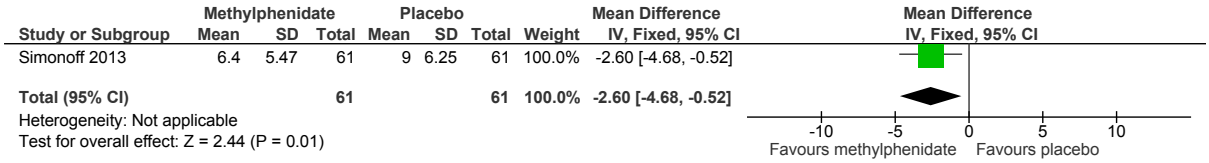



**Figure 25: ADHD inattention symptoms parent rated (SNAP-IV inattention subscale) at 4 weeks; 0-3; lower values are beneficial**

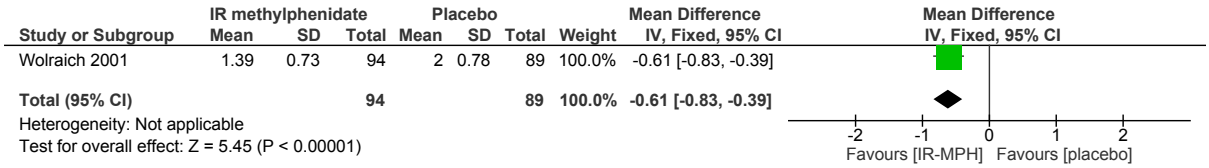



**Figure 26: ADHD inattention symptoms teacher rated (SNAP-IV inattention subscale) at 4 weeks; 0-3; lower values are beneficial**

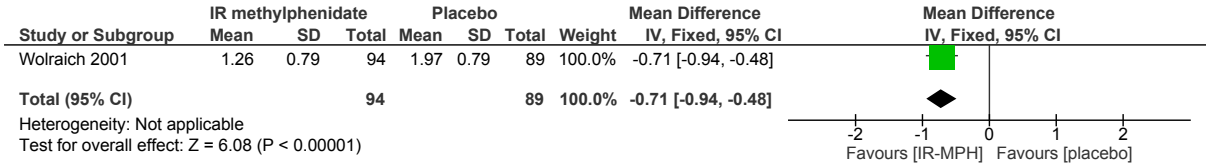



**Figure 27: Clinical Global Impressions score of 1 or 2 at 3 to 9 weeks**

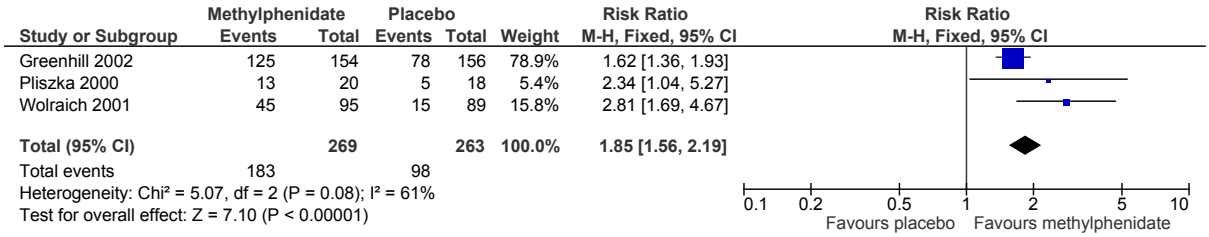



**Figure 28: Behavioural outcomes at 16 weeks (Children's Global Assessment Scale; 0-100; higher values are beneficial)**

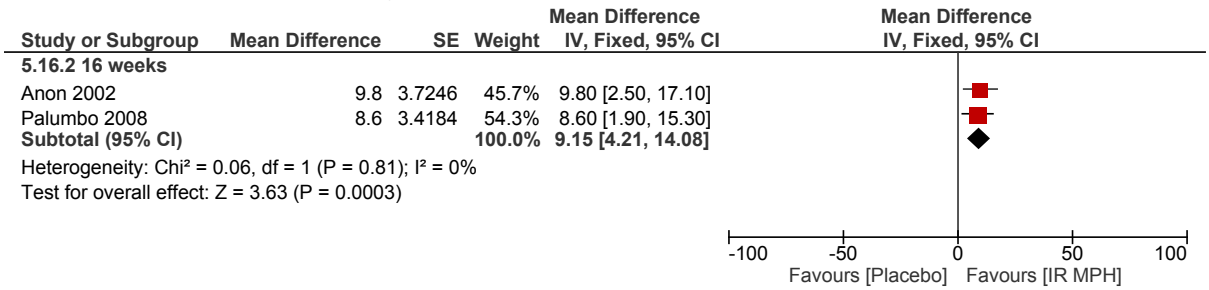


**Figure 29: Discontinuation due to adverse events at 3 to 16 weeks**

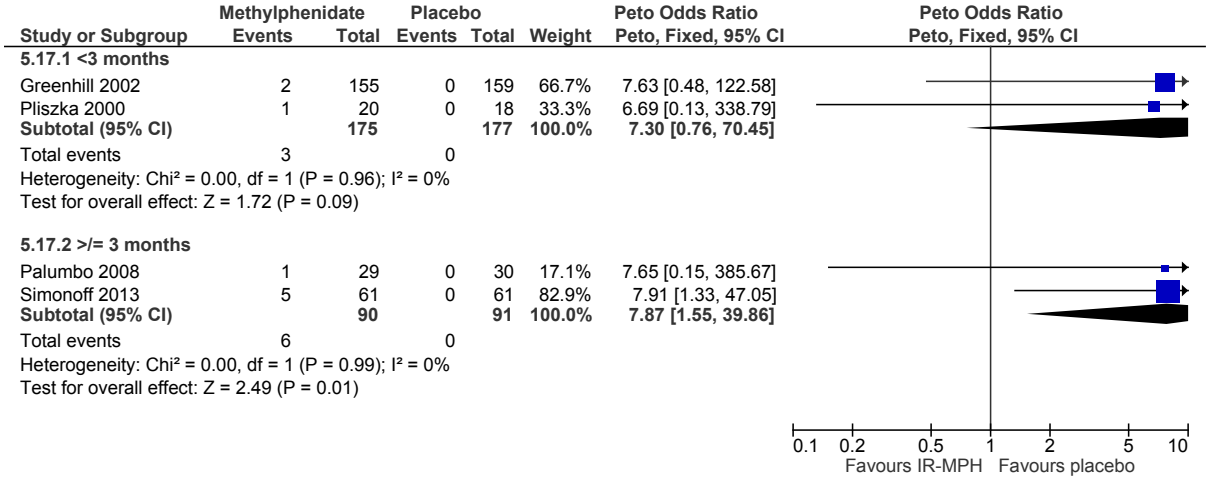
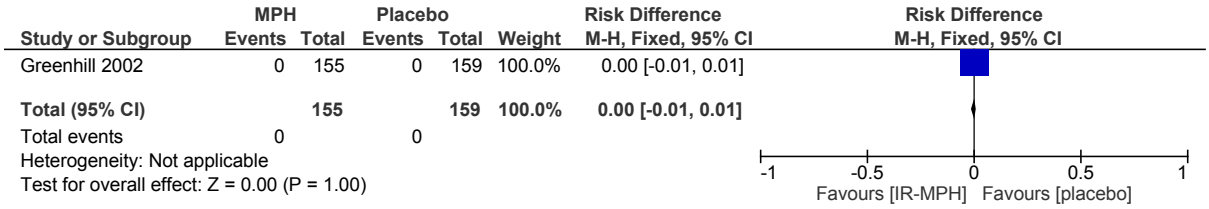



**Figure 30: Serious adverse events at 3 weeks**




## OROS methylphenidate versus placebo

**Figure 31: Quality of Life (Child Health Questionnaire at 6 weeks; 0-100, higher values are beneficial)**

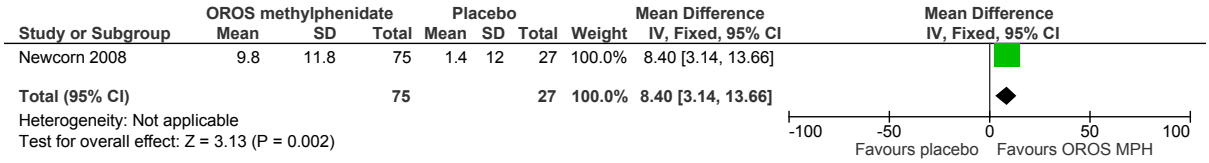



**Figure 32: ADHD total symptoms parent rated at 6 weeks (CPRS total scores: 0-54, lower values are beneficial, change scores reported)**

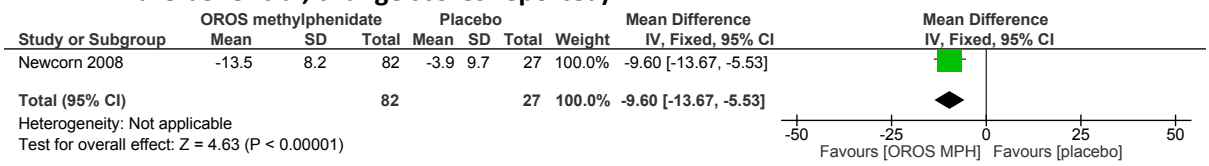


**Figure 33: ADHD total symptoms parent rated at 4 weeks (SNAP-IV total scores: 0-3, lower values are beneficial, final values)**

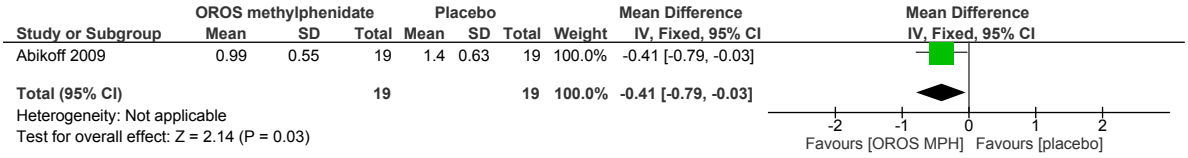



**Figure 34: ADHD total symptoms teacher rated (SNAP-IV total scores at 4 weeks; 0-3; lower values are beneficial)**

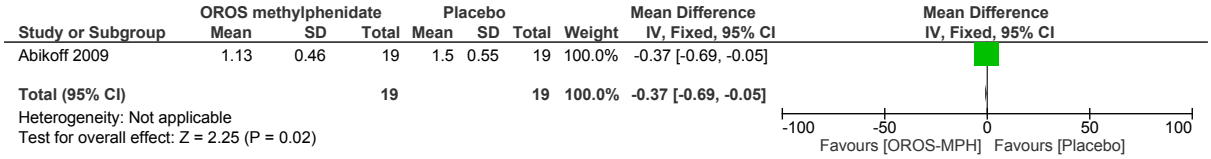



**Figure 35: ADHD total symptoms investigator rated (7 weeks; ADHD-RS total scores; 0-54; lower values are beneficial)**

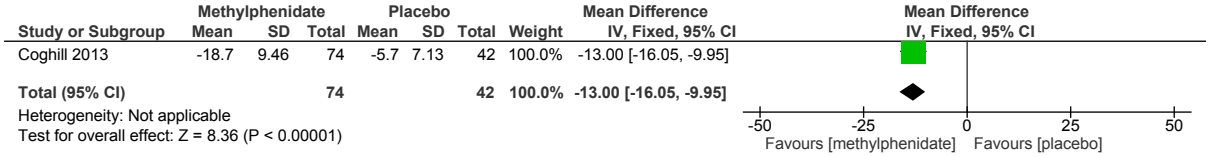



**Figure 36: ADHD inattention symptoms investigator rated (ADHD-RS Inattentive subscale at 6 weeks; 0-27; lower values are beneficial**

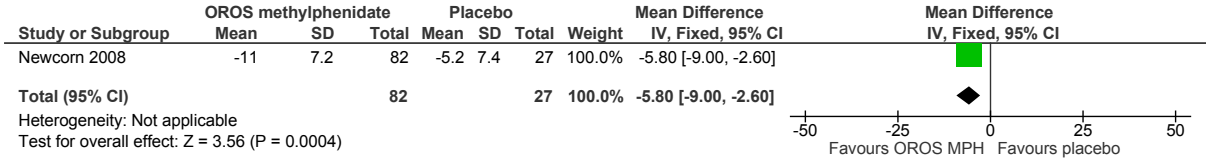



**Figure 37: ADHD inattention symptoms teacher rated (SNAP-IV inattention subscale) at 4 weeks; 0-3; lower values are benficial**

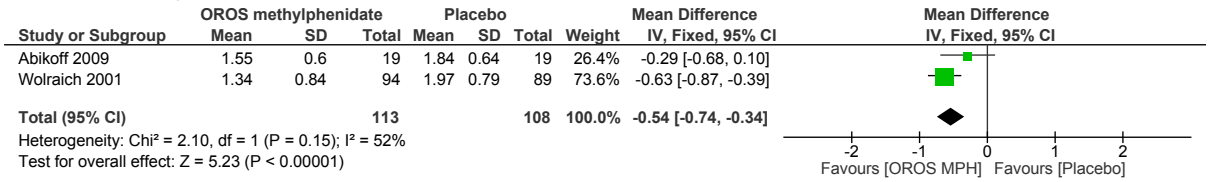


**Figure 38: ADHD inattention symptoms parent rated (SNAP-IV inattention subscale) at 4 weeks; 0-3; lower values are benficial**

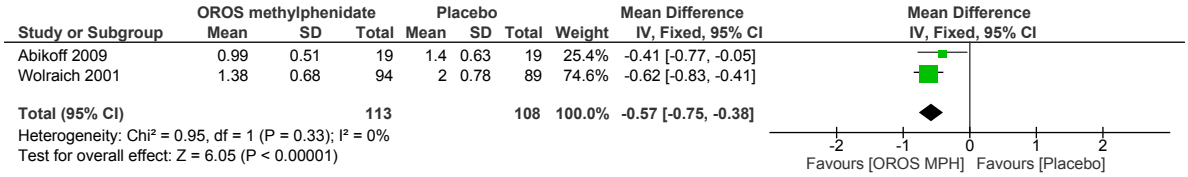



**Figure 39: ADHD hyperactivity symptoms investigator rated (ADHD-RS hyperactive subscale) at 6 weeks; 0-27, lower values are reported**

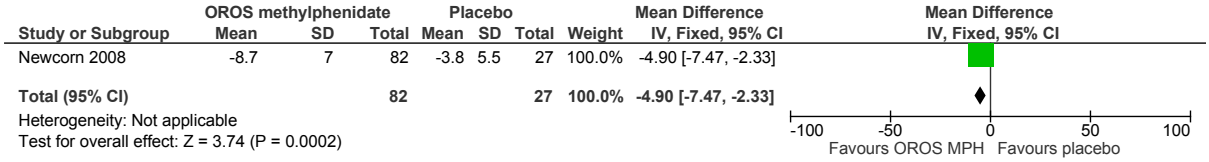



**Figure 40: ADHD hyperactivity symptoms teacher rated (SNAP-IV hyperactivity subscale) at 4 weeks; 0-3; lower values are benficial**

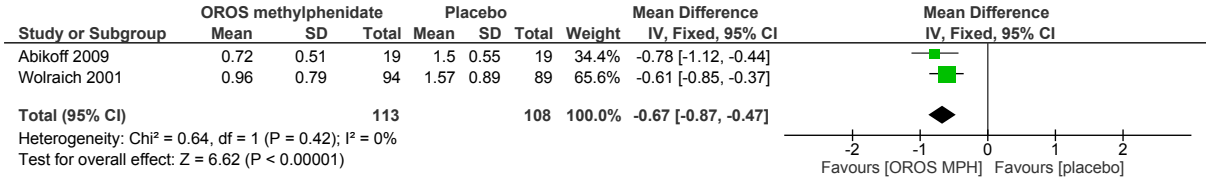



**Figure 41: ADHD hyperactivity symptoms parent rated (SNAP-IV hyperactivity subscale) at 4 weeks; 0-3; lower values are beneficial**

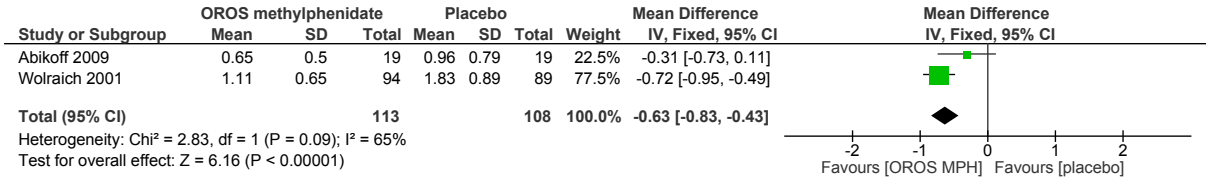



**Figure 42: Clinical Global Impressions – Improvement (score of 1 or 2) at 4 to 7 weeks**

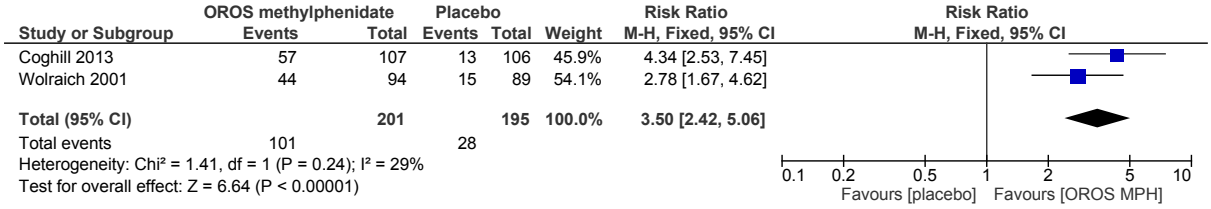



**Figure 43: Behavioural outcome at 7 weeks (WFIRS-P; high values are beneficial)**

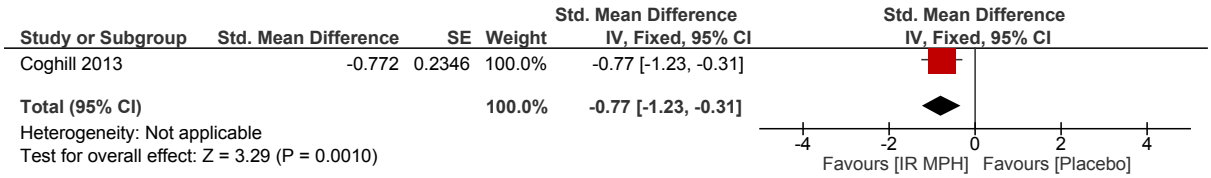



**Figure 44: Academic achievement at 7 weeks (CHIP-CE academic achievement subscale); 0-100; high scores are beneficial**

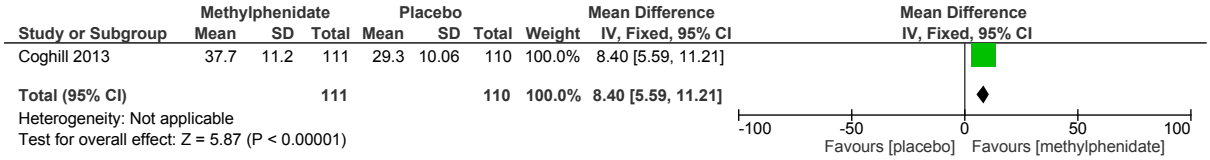
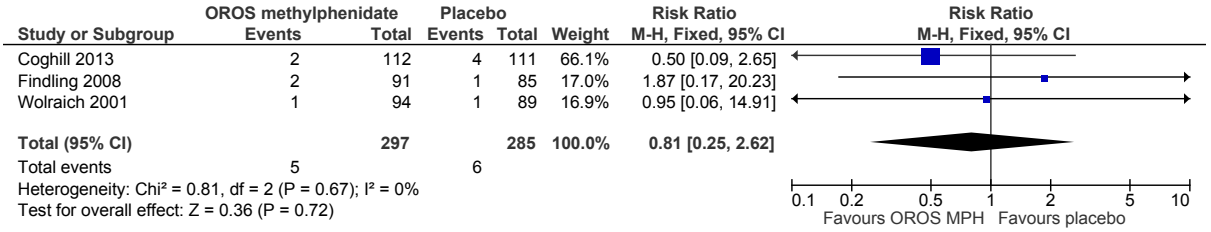



**Figure 45: Discontinuation due to adverse events at 4 to 7 weeks**




## IR methylphenidate versus OROS methylphenidate

**Figure 46: ADHD inattention symptoms teacher rated (SNAP-IV inattention subscale at 4 weeks; 0-3; lower values are beneficial)**

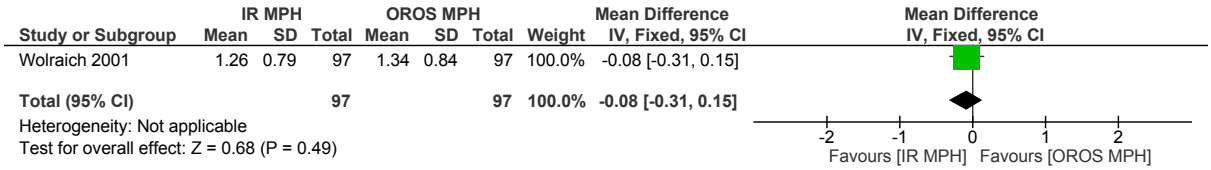



**Figure 47: ADHD inattention symptoms parent rated (SNAP-IV inattention subscale at 4 weeks; 0-3; lower values are beneficial)**

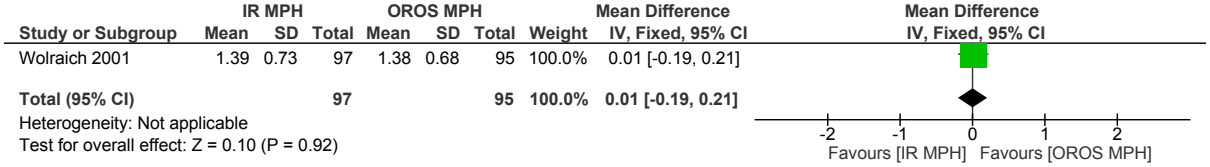


**Figure 48: ADHD hyperactivity symptoms teacher rated (SNAP-IV hyperactivity subscale at 4 weeks; 0-3; lower values are beneficial)**

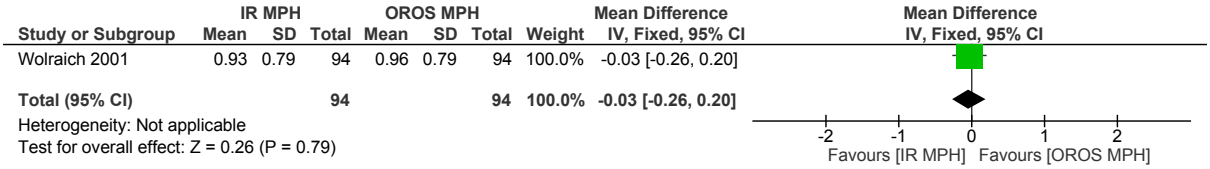



**Figure 49: ADHD hyperactivity symptoms parent rated (SNAP-IV hyperactivity subscale at 4 weeks; 0-3; lower values are beneficial)**

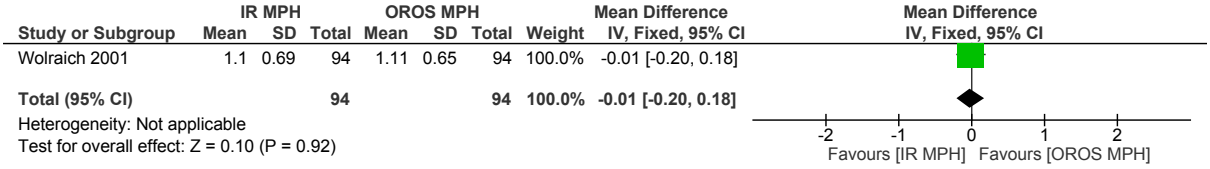



**Figure 50: Clinical global impressions – improvement (score of 1 or 2) at 4 weeks**

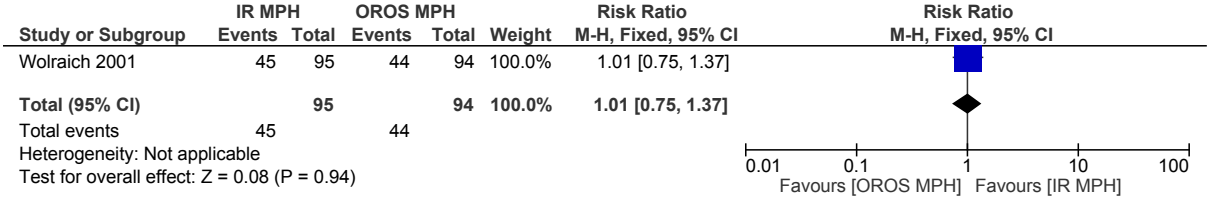
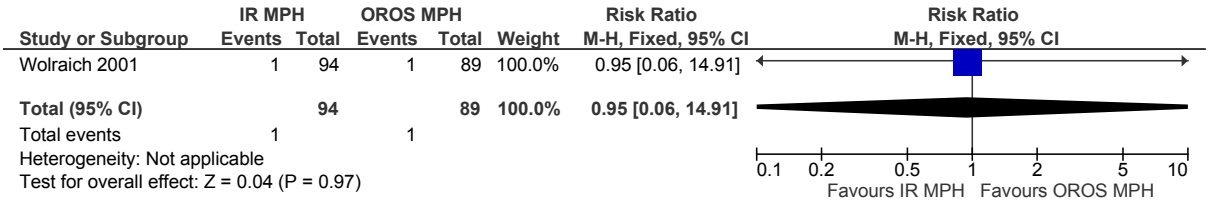



**Figure 51: Discontinuation due to adverse events at 4 weeks**




## Lisdexamfetamine versus placebo

**Figure 52: ADHD total symptoms investigator rated (ADHD-RS total scores; 0-54, low values are beneficial)**

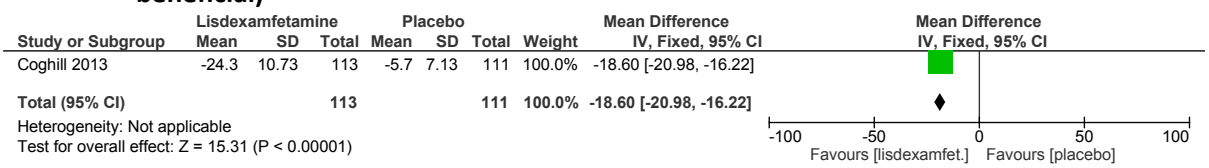


**Figure 53: CGI-I scores of 1 or 2 at 7 weeks**

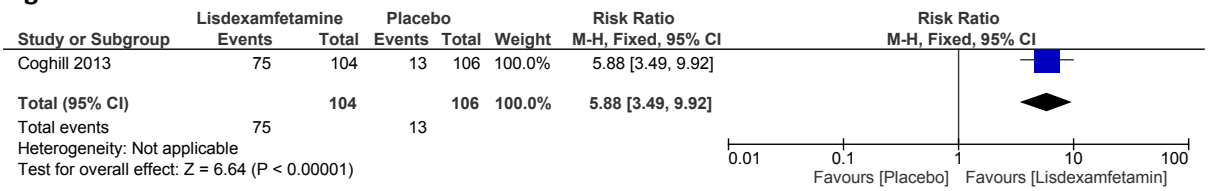



**Figure 54: Academic achievement at 7 weeks (CHIP-CE academic achievement subscale); 0-100, high scores are beneficial**

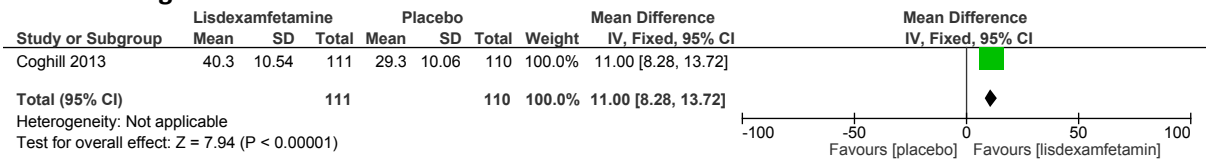



**Figure 55: Behavioural outcomes at 7 weeks (WFIRS-P); 0-3; low values are benficial**

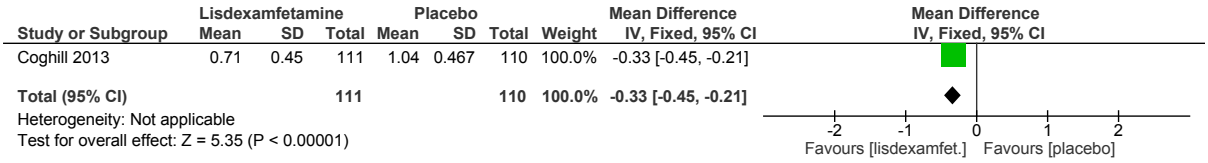
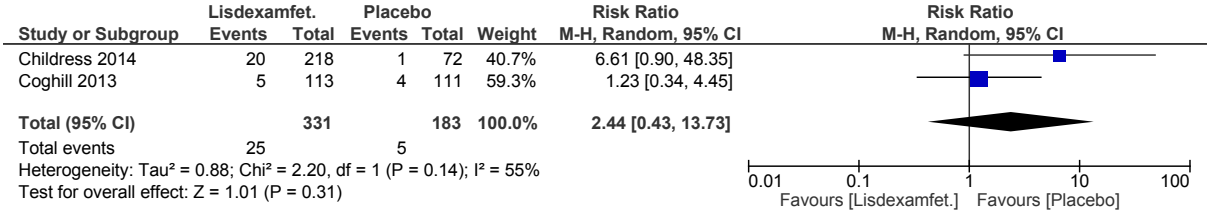
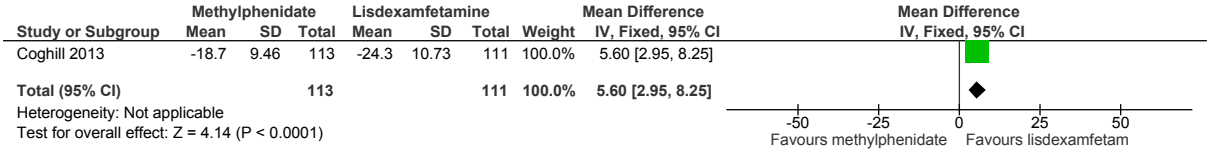



**Figure 56: Discontinuation due to adverse events at 4-7 weeks**

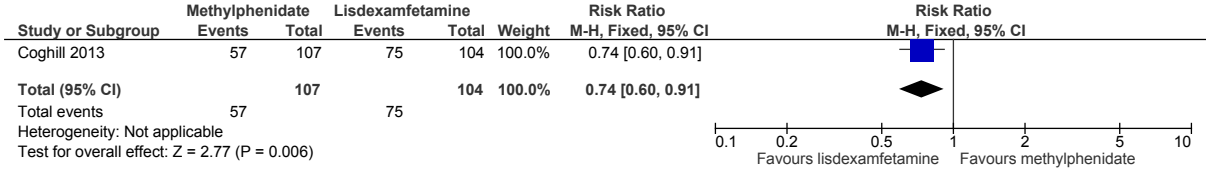



## Methylphenidate versus lisdexamfetamine

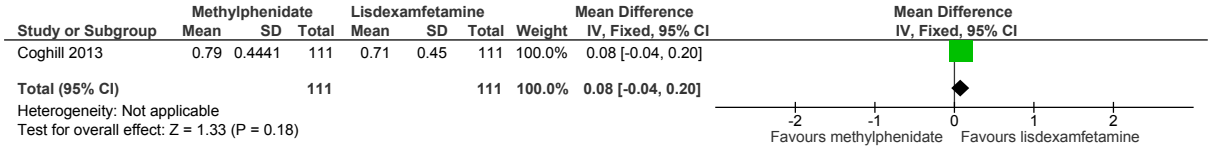
**Figure 57: ADHD total symptoms investigator rated at 7 weeks (ADHD-RS total scores); 0-72; low values are beneficial**



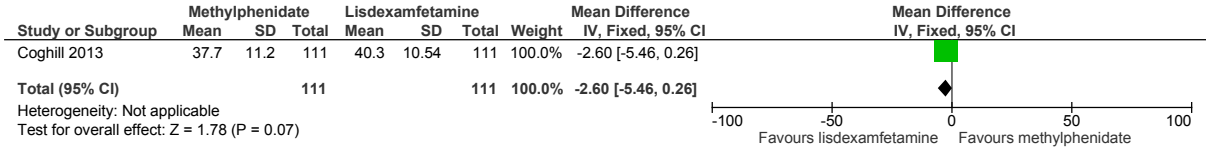
### Figure 58: CGI-I scores of 1 or 2 at 7 weeks



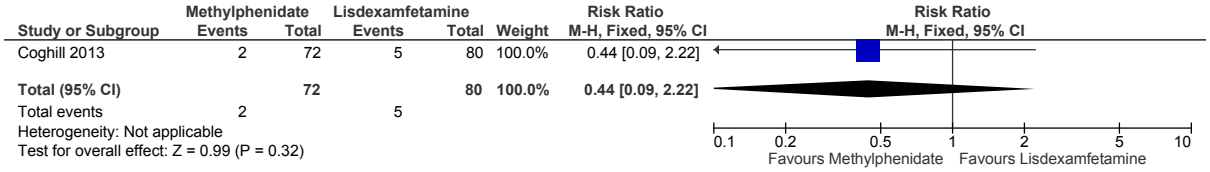

### Figure 59: Behavioural outcomes at 7 weeks (WFIRS-P; 0-3; low values are beneficial)




### Figure 60: Academic achievement at 7 weeks (CHIP-CE academic achievement subscale); 0-100, final values reported; high scores are beneficial




### Figure 61: Discontinuation due to adverse events at 7 weeks




## Atomoxetine versus placebo

### Figure 62: Quality of Life at 8 to 10 weeks (CHQ and CHIP-CE; change scores reported; high values are beneficial)

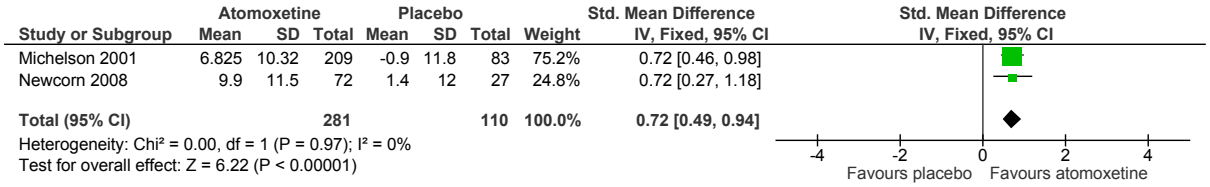


**Figure 63: Quality of Life at 8 to 10 weeks (KINDL-R; 0-100; final values reported; high values are beneficial)**

| Study or Subgroup | Atomoxetine Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Wehmeier 2011b | 68.8 | 11.87 | 121 | 60.9 | 13.72 | 59 | 100.0% | 7.90 [3.81, 11.99] |
| **Total (95% CI)** | | | **121** | | | **59** | **100.0%** | **7.90 [3.81, 11.99]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 3.79 (P = 0.0002)

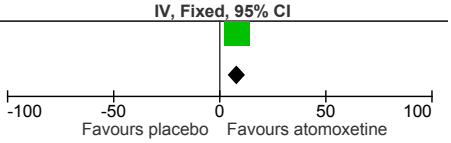



**Figure 64: Treatment response at 6 to 12 weeks (defined as 25% reduction in ABC-H and CGI-I of 1 or 2 or a 25% reduction on ADHD-RS investigator rated total scores)**

| Study or Subgroup | Atomoxetine Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Arnold 2006 | 9 | 16 | 4 | 16 | 42.0% | 2.25 [0.87, 5.83] |
| Geller 2007 | 54 | 64 | 10 | 69 | 58.0% | 5.82 [3.25, 10.43] |
| **Total (95% CI)** | | **80** | | **85** | **100.0%** | **3.91 [1.54, 9.89]** |
| Total events | 63 | | 14 | | | |

Heterogeneity: Tau² = 0.30; Chi² = 2.84, df = 1 (P = 0.09); I² = 65%
Test for overall effect: Z = 2.87 (P = 0.004)

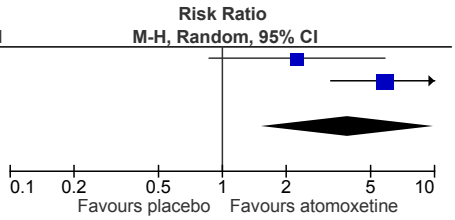



**Figure 65: ADHD total symptoms at 6 to 13 weeks (ADHD-RS and SNAP-IV total scores; investigator rated); low scores are beneficial, final values and change scores reported**

| Study or Subgroup | Std. Mean Difference | SE | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|
| **8.4.1 Final values** | | | | |
| Dittmann 2011 | -0.1502 | 0.159 | 34.5% | -0.15 [-0.46, 0.16] |
| Hafterkamp 2016 (Hafterkamp 2014) | -0.8057 | 0.2115 | 32.4% | -0.81 [-1.22, -0.39] |
| Wehmeier 2012 | -1.1922 | 0.1946 | 33.1% | -1.19 [-1.57, -0.81] |
| **Subtotal (95% CI)** | | | **100.0%** | **-0.71 [-1.35, -0.07]** |
| Heterogeneity: Tau² = 0.28; Chi² = 18.14, df = 2 (P = 0.0001); I² = 89% | | | | |
| Test for overall effect: Z = 2.17 (P = 0.03) | | | | |
| **8.4.2 Change scores** | | | | |
| Block 2009 | -0.1234 | 0.1339 | 17.6% | -0.12 [-0.39, 0.14] |
| Gau 2007 | -0.0608 | 0.1685 | 16.1% | -0.06 [-0.39, 0.27] |
| Hervas 2014 | -0.287 | 0.1346 | 17.5% | -0.29 [-0.55, -0.02] |
| Kelsey 2004 | -0.7196 | 0.1613 | 16.4% | -0.72 [-1.04, -0.40] |
| Spencer 2002a | -0.7892 | 0.186 | 15.4% | -0.79 [-1.15, -0.42] |
| Wernicke 2004 | -0.8602 | 0.1504 | 16.9% | -0.86 [-1.15, -0.57] |
| **Subtotal (95% CI)** | | | **100.0%** | **-0.47 [-0.75, -0.18]** |
| Heterogeneity: Tau² = 0.10; Chi² = 26.28, df = 5 (P < 0.0001); I² = 81% | | | | |
| Test for overall effect: Z = 3.24 (P = 0.001) | | | | |

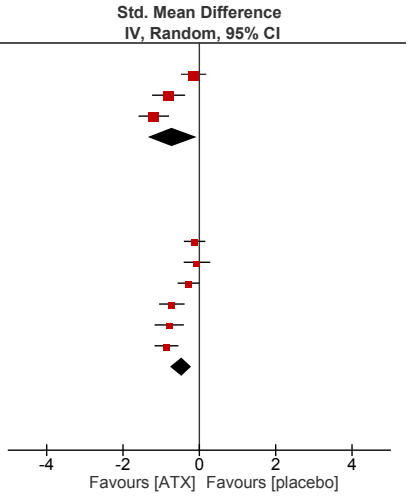



**Figure 66: ADHD total symptoms teacher rated at 6 to 9 weeks (multiple scales including ADHD-RS and SNAP-IV total scores; low scores are beneficial)**

| Study or Subgroup | Atomoxetine Mean | SD | Total | Placebo Mean | SD | Total | Weight | Std. Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Dell'Agnello 2009 | 21.8 | 8.9 | 100 | 28.4 | 6.1 | 32 | 15.7% | -0.79 [-1.20, -0.38] |
| Gau 2007 | -6.8 | 16.9 | 72 | 0.8 | 10.3 | 34 | 15.4% | -0.50 [-0.91, -0.09] |
| Kratochvil 2011 | -13.2 | 11.2 | 44 | -5.8 | 8.4 | 49 | 14.8% | -0.75 [-1.17, -0.33] |
| Takahashi 2009 | -10.65 | 8.362 | 180 | -8.1 | 7.1 | 61 | 30.9% | -0.32 [-0.61, -0.02] |
| Weiss 2005 | -14.5 | 10 | 123 | -7.2 | 9.7 | 51 | 23.3% | -0.73 [-1.07, -0.40] |
| **Total (95% CI)** | | | **519** | | | **227** | **100.0%** | **-0.58 [-0.74, -0.42]** |

Heterogeneity: Chi² = 5.71, df = 4 (P = 0.22); I² = 30%
Test for overall effect: Z = 7.00 (P < 0.00001)

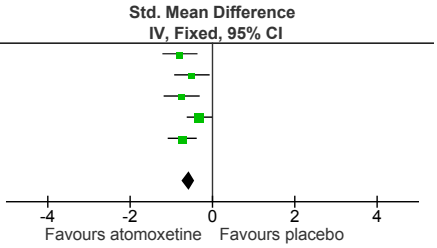


**Figure 67: ADHD total symptoms teacher rated at 16 weeks (ADHD-RS total scores; 0-54, low scores are beneficial)**

| Study or Subgroup | Atomoxetine Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Wietecha 2013 | -8.26 | 10.3859 | 21 | -3.6 | 10.3859 | 22 | 100.0% | -4.66 [-10.87, 1.55] |
| **Total (95% CI)** | | | **21** | | | **22** | **100.0%** | **-4.66 [-10.87, 1.55]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.47 (P = 0.14)

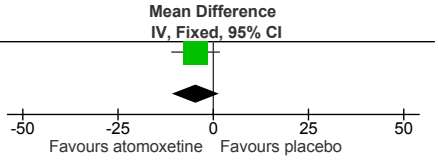



**Figure 68: ADHD total symptoms parent rated at 4 to 12 weeks (multiple scales including ADHD-RS and CPRS total scores; low scores are beneficial; change scores reported)**

| Study or Subgroup | Std. Mean Difference | SE | Weight | Std. Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|
| **8.5.1 <3 months change scores** | | | | |
| Bangs 2007 | -0.8096 | 0.1754 | 11.7% | -0.81 [-1.15, -0.47] |
| Dell'Agnello 2009 | -0.0755 | 0.2032 | 8.7% | -0.08 [-0.47, 0.32] |
| Gau 2007 | -0.7068 | 0.2139 | 7.9% | -0.71 [-1.13, -0.29] |
| Handen 2015 | -0.7023 | 0.2957 | 4.1% | -0.70 [-1.28, -0.12] |
| Kratochvil 2011 | -0.2593 | 0.1916 | 9.8% | -0.26 [-0.63, 0.12] |
| Michelson 2001 | -0.6184 | 0.1585 | 14.3% | -0.62 [-0.93, -0.31] |
| Michelson 2002 | -0.6781 | 0.1593 | 14.2% | -0.68 [-0.99, -0.37] |
| Newcorn 2008 | -0.5705 | 0.1363 | 19.4% | -0.57 [-0.84, -0.30] |
| Spencer 2008 | -0.5685 | 0.1896 | 10.0% | -0.57 [-0.94, -0.20] |
| **Subtotal (95% CI)** | | | **100.0%** | **-0.56 [-0.68, -0.45]** |

Heterogeneity: Chi² = 11.57, df = 8 (P = 0.17); I² = 31%
Test for overall effect: Z = 9.39 (P < 0.00001)

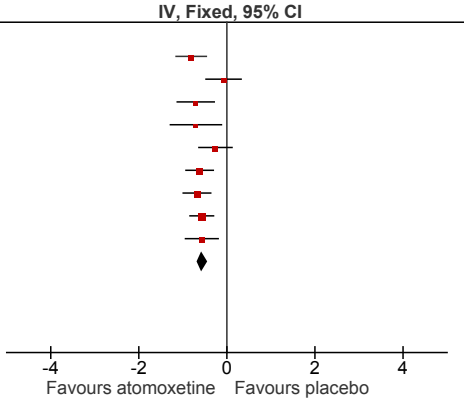



**Figure 69: ADHD total symptoms parent rated at 4 weeks (ADHD-RS total scores; 0-54; low scores are beneficial; final values reported)**

| Study or Subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| De Jong 2009 (ADHD + RD) | 22.44 | 10.64 | 20 | 35.17 | 9.26 | 20 | 43.8% | -12.73 [-18.91, -6.55] |
| De Jong 2009 (ADHD) | 30.86 | 8.56 | 16 | 35.2 | 7.12 | 16 | 56.2% | -4.34 [-9.80, 1.12] |
| **Total (95% CI)** | | | **36** | | | **36** | **100.0%** | **-8.01 [-12.10, -3.92]** |

Heterogeneity: Chi² = 3.98, df = 1 (P = 0.05); I² = 75%
Test for overall effect: Z = 3.84 (P = 0.0001)

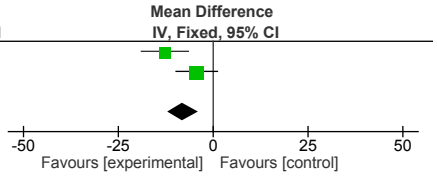



**Figure 70: ADHD total symptoms parent rated at 12-18 weeks (ADHD-RS total scores; 0-54; low scores are beneficial)**

| Study or Subgroup | Atomoxetine Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Allen 2005 | -10.9 | 10.9 | 74 | -4.9 | 10.3 | 71 | 56.9% | -6.00 [-9.45, -2.55] |
| Montoya 2009 | 26.3 | 12.7 | 100 | 34.8 | 12.3 | 51 | 38.5% | -8.50 [-12.69, -4.31] |
| Wietecha 2013 | -18.07 | 41.15 | 62 | -11.77 | 25.835 | 58 | 4.5% | -6.30 [-18.51, 5.91] |
| **Total (95% CI)** | | | **236** | | | **180** | **100.0%** | **-6.98 [-9.58, -4.37]** |

Heterogeneity: Chi² = 0.83, df = 2 (P = 0.66); I² = 0%
Test for overall effect: Z = 5.25 (P < 0.00001)

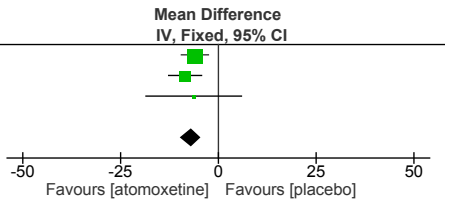


**Figure 71: ADHD inattention symptoms at 6 to 9 weeks (ADHD-RS inattentive subscale Investigator rated; 0-27; low scores are beneficial; final values and change scores reported)**

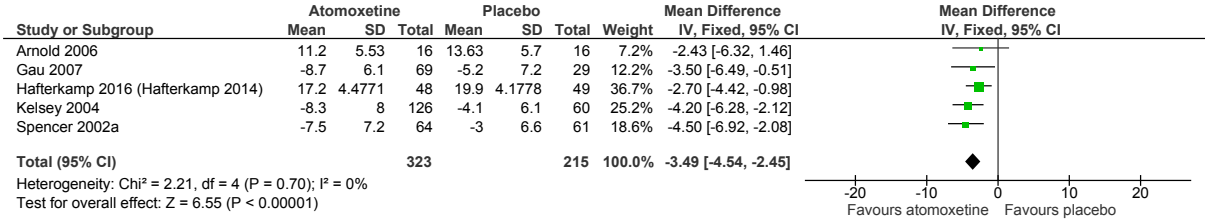



**Figure 72: ADHD inattention symptoms at 6 to 16 weeks (ADHD-RS inattentive subscale teacher rated; 0-27; low scores are beneficial)**

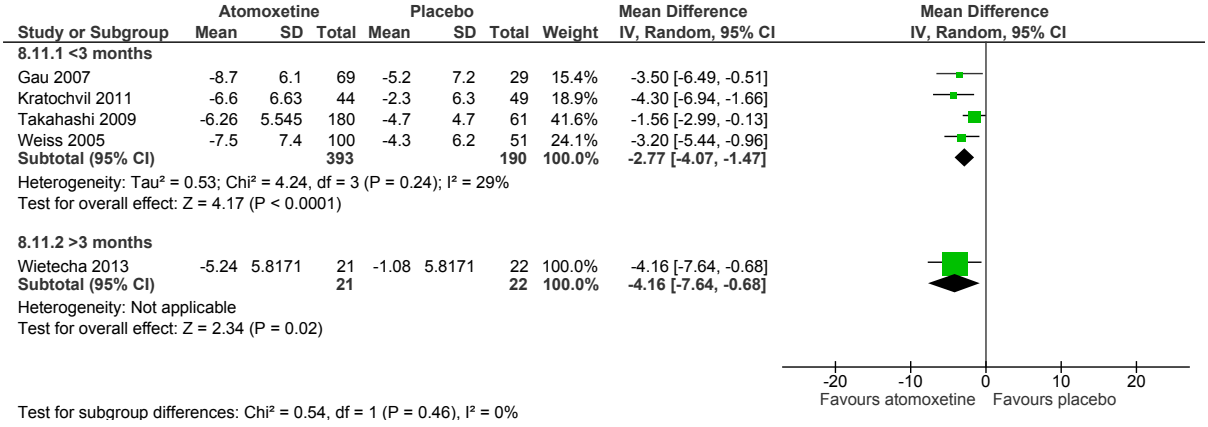



**Figure 73: ADHD inattention symptoms at 4 to 12 weeks (ADHD-RS and SNAP-IV inattentive subscale; parent rated); low scores are beneficial; change scores reported**

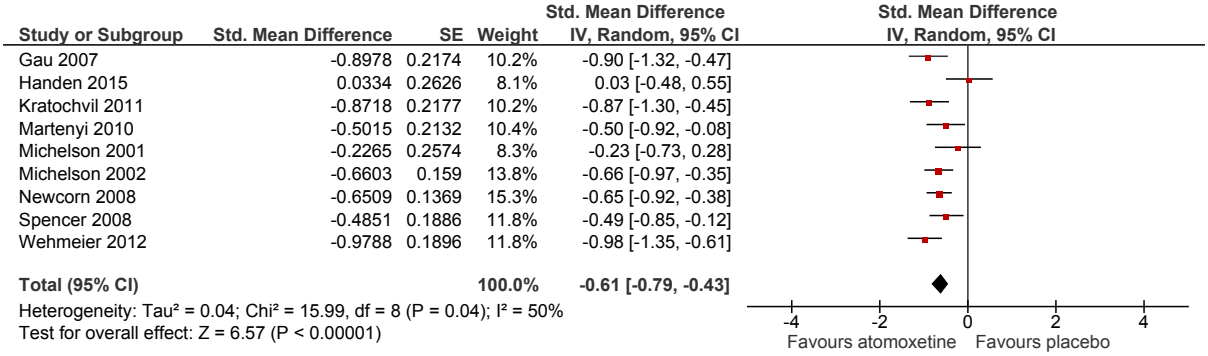



**Figure 74: ADHD inattention symptoms at 4 weeks (ADHD-RS inattentive subscale; parent rated; 0-27 low scores are beneficial; final values reported)**

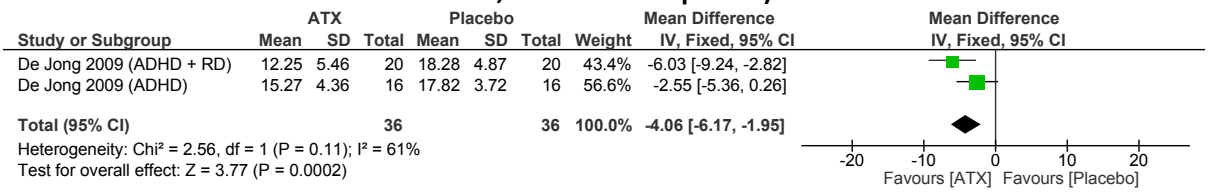


**Figure 75: ADHD inattention symptoms at 12 to 18 weeks (ADHD-RS inattentive subscale; parent rated; 0-27; low scores are beneficial)**

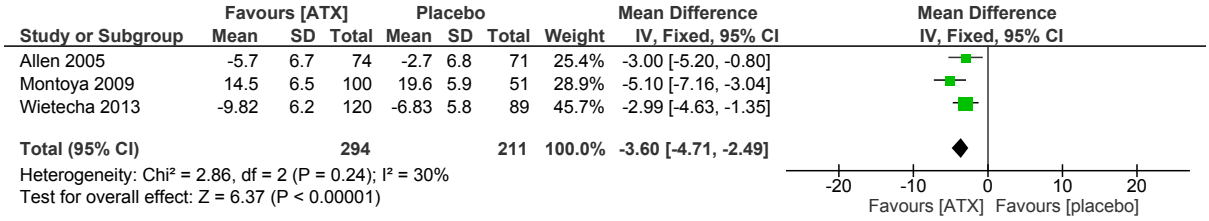



**Figure 76: ADHD hyperactivity symptoms at 6 to 9 weeks (ADHD-RS hyperactivity subscale, investigator rated); 0-27; low values are beneficial, change scores and final values reported**

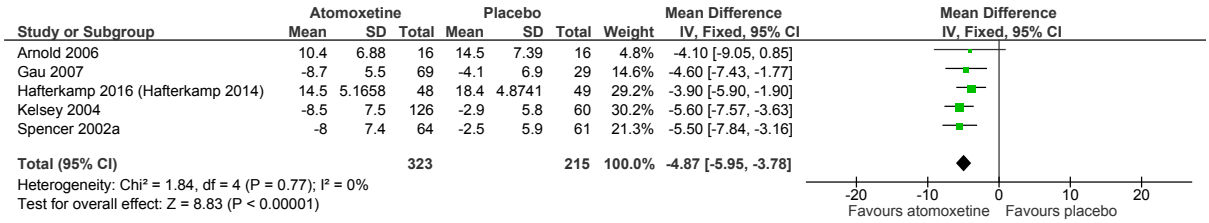



**Figure 77: ADHD hyperactivity symptoms teacher rated at 4 to 12 weeks (ADHD-RS hyperactivity subscale; 0-27; low values are beneficial)**

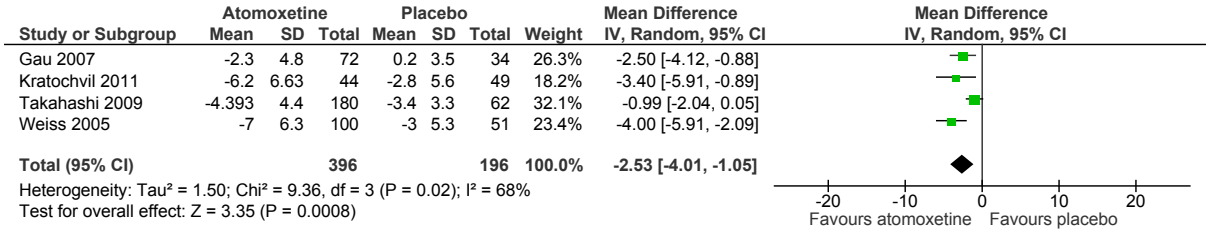



**Figure 78: ADHD hyperactivity symptoms teacher rated at 18 weeks (ADHD-RS hyperactivity subscale; 0-27; low values are beneficial)**

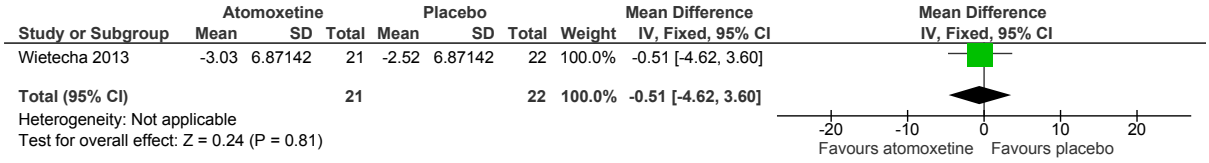


**Figure 79: ADHD hyperactivity symptoms parent rated at 4 to 12 weeks (multiple scales including ADHD-RS and CPRS hyperactivity subscales; low values are beneficial; change scores reported)**

| Study or Subgroup | Std. Mean Difference | SE | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|
| Gau 2007 | -0.486 | 0.2108 | 10.6% | -0.49 [-0.90, -0.07] |
| Handen 2015 | -0.433 | 0.2997 | 6.8% | -0.43 [-1.02, 0.15] |
| Kratochvil 2011 | -0.3378 | 0.2092 | 10.7% | -0.34 [-0.75, 0.07] |
| Martenyi 2010 | -0.666 | 0.2144 | 10.4% | -0.67 [-1.09, -0.25] |
| Michelson 2001 | -0.4191 | 0.1546 | 14.3% | -0.42 [-0.72, -0.12] |
| Michelson 2002 | -0.5709 | 0.158 | 14.0% | -0.57 [-0.88, -0.26] |
| Newcorn 2008 | -0.6401 | 0.2262 | 9.8% | -0.64 [-1.08, -0.20] |
| Spencer 2008 | -0.5639 | 0.1896 | 11.9% | -0.56 [-0.94, -0.19] |
| Wehmeier 2012 | -1.2658 | 0.1965 | 11.5% | -1.27 [-1.65, -0.88] |
| **Total (95% CI)** | | | **100.0%** | **-0.60 [-0.78, -0.42]** |

Heterogeneity: Tau² = 0.04; Chi² = 15.22, df = 8 (P = 0.06); I² = 47%
Test for overall effect: Z = 6.53 (P < 0.00001)

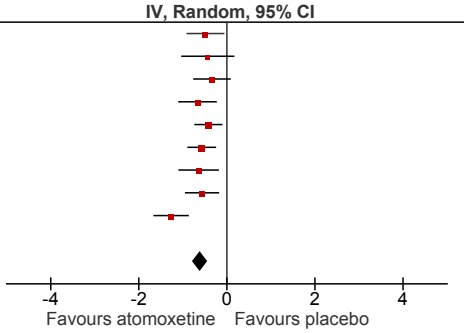



**Figure 80: ADHD hyperactivity symptoms at 4 weeks (ADHD-RS hyperactivity subscale, parent rated; 0-27; low values are beneficial; final values reported)**

| Study or Subgroup | ATX Mean | ATX SD | ATX Total | Placebo Mean | Placebo SD | Placebo Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| De Jong 2009 (ADHD + RD) | 10.32 | 5.68 | 20 | 17.03 | 5.01 | 20 | 48.7% | -6.71 [-10.03, -3.39] |
| De Jong 2009 (ADHD) | 15.51 | 4.56 | 16 | 17.24 | 3.84 | 16 | 51.3% | -1.73 [-4.65, 1.19] |
| **Total (95% CI)** | | | **36** | | | **36** | **100.0%** | **-4.16 [-9.03, 0.72]** |

Heterogeneity: Tau² = 9.86; Chi² = 4.87, df = 1 (P = 0.03); I² = 79%
Test for overall effect: Z = 1.67 (P = 0.10)

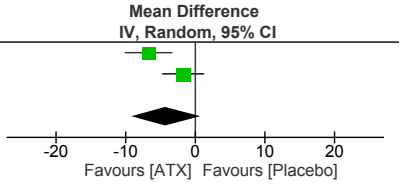



**Figure 81: ADHD hyperactivity symptoms at 12 to 18 weeks (ADHD-RS hyperactivity subscales, parent rated; 0-27; low values are beneficial)**

| Study or Subgroup | Atomoxetine Mean | Atomoxetine SD | Atomoxetine Total | Placebo Mean | Placebo SD | Placebo Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Allen 2005 | -5.2 | 5.3 | 74 | -2.1 | 4.8 | 71 | 63.5% | -3.10 [-4.74, -1.46] |
| Montoya 2009 | 11.9 | 7.3 | 100 | 15.2 | 7.7 | 51 | 26.4% | -3.30 [-5.85, -0.75] |
| Wietecha 2013 | -3.03 | 6.8714 | 21 | -2.52 | 6.8714 | 22 | 10.2% | -0.51 [-4.62, 3.60] |
| **Total (95% CI)** | | | **195** | | | **144** | **100.0%** | **-2.89 [-4.20, -1.58]** |

Heterogeneity: Chi² = 1.45, df = 2 (P = 0.48); I² = 0%
Test for overall effect: Z = 4.32 (P < 0.0001)

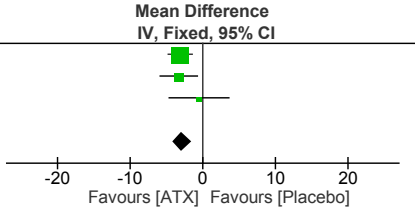



**Figure 82: CGI-I score of 1 or 2 at 4 to 13 weeks**

| Study or Subgroup | Atomoxetine Events | Atomoxetine Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Arnold 2006 | 9 | 16 | 4 | 16 | 5.0% | 2.25 [0.87, 5.83] |
| Bangs 2007 | 33 | 69 | 12 | 67 | 15.2% | 2.67 [1.51, 4.72] |
| Hafterkamp 2016 (Hafterkamp 2014) | 9 | 48 | 4 | 49 | 5.0% | 2.30 [0.76, 6.96] |
| Huss 2014 | 63 | 112 | 49 | 111 | 61.6% | 1.27 [0.98, 1.66] |
| Kratochvil 2011 | 18 | 49 | 10 | 44 | 13.2% | 1.62 [0.84, 3.12] |
| **Total (95% CI)** | | **294** | | **287** | **100.0%** | **1.63 [1.31, 2.03]** |
| Total events | 132 | | 79 | | | |

Heterogeneity: Chi² = 7.02, df = 4 (P = 0.13); I² = 43%
Test for overall effect: Z = 4.38 (P < 0.0001)

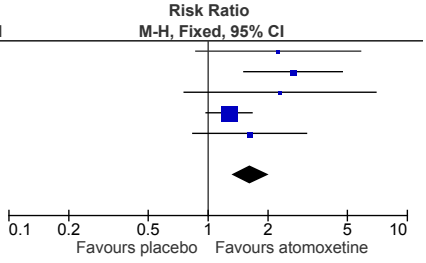


**Figure 83: Behavioural measures at 6 to 12 weeks (multiple scales including ABC and childrens' social behaviour questionnaire; final values and change scores, low scores are beneficial)**

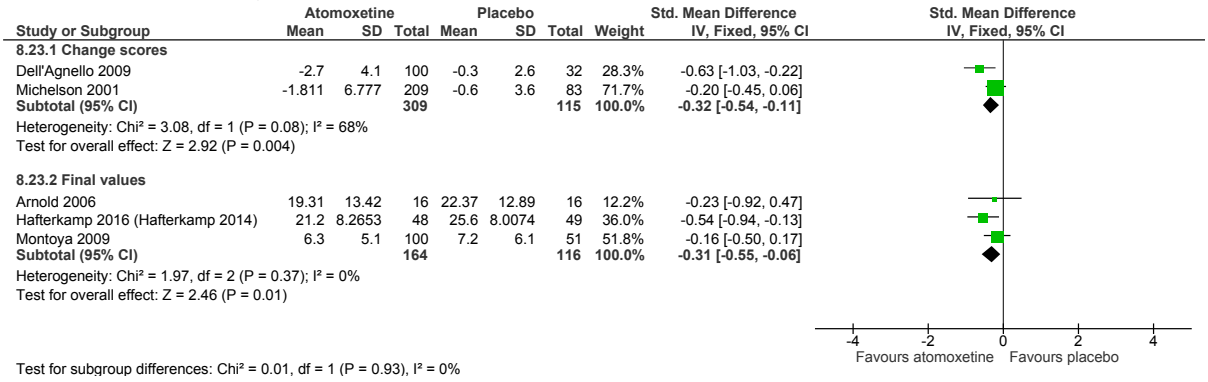



**Figure 84: Academic achievement at 12 weeks (CHIP-PRF Achievement subscale; high scores are beneficial, range 0-30)**

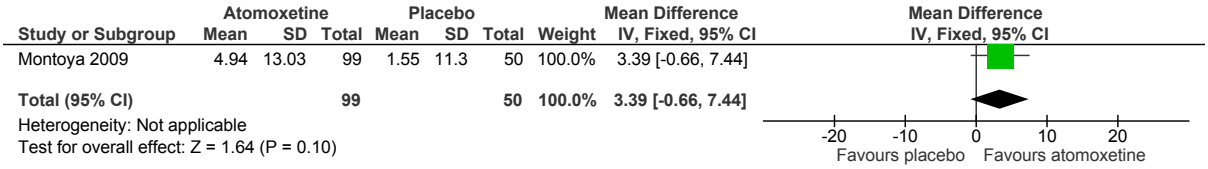
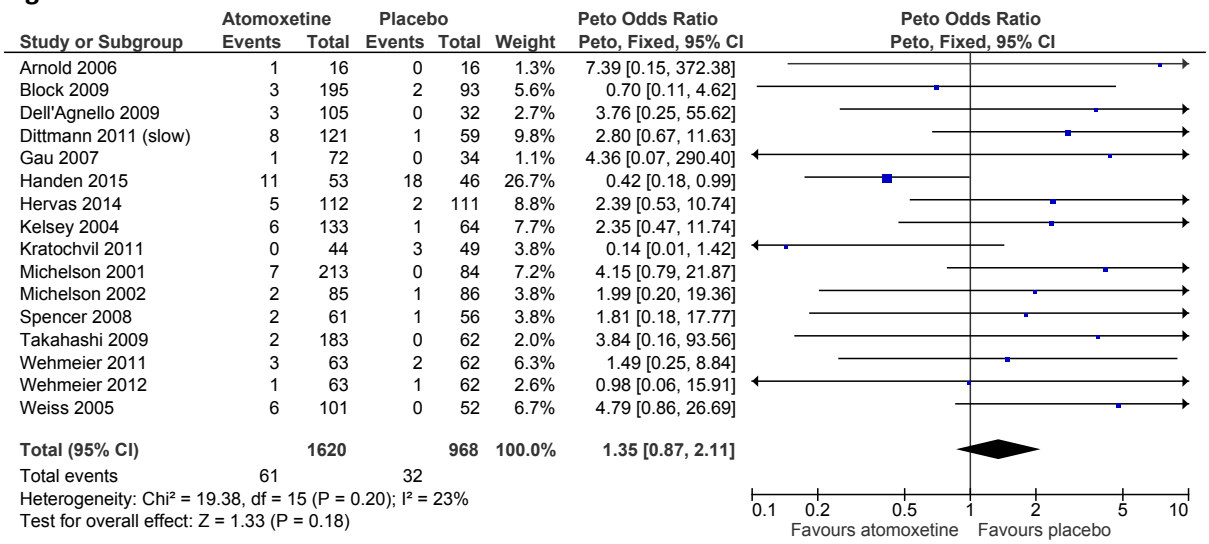


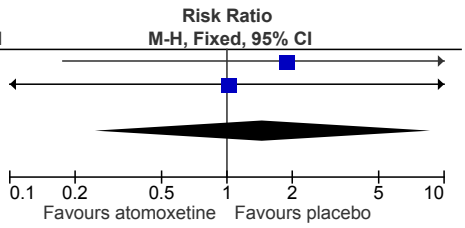

**Figure 85: Discontinuation due to adverse events at 3 to 10 weeks**



### Figure 86: Discontinuation due to adverse events at 12-18 weeks

| Study or Subgroup | Atomoxetine Events | Atomoxetine Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Allen 2005 | 2 | 76 | 1 | 72 | 51.0% | 1.89 [0.18, 20.45] |
| Geller 2007 | 1 | 87 | 1 | 89 | 49.0% | 1.02 [0.07, 16.10] |
| **Total (95% CI)** | | **163** | | **161** | **100.0%** | **1.47 [0.25, 8.71]** |
| Total events | 3 | | 2 | | | |

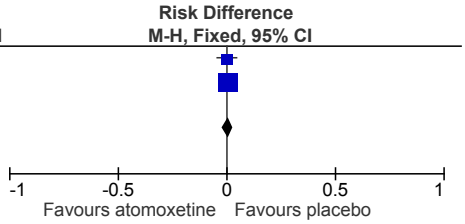
Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² = 0%
Test for overall effect: Z = 0.42 (P = 0.67)




### Figure 87: Serious adverse events at 6 to 10 weeks

| Study or Subgroup | Atomoxetine Events | Atomoxetine Total | Placebo Events | Placebo Total | Weight | Risk Difference M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Martenyi 2010 | 0 | 72 | 0 | 33 | 32.8% | 0.00 [-0.04, 0.04] |
| Takahashi 2009 | 1 | 183 | 0 | 62 | 67.2% | 0.01 [-0.02, 0.03] |
| **Total (95% CI)** | | **255** | | **95** | **100.0%** | **0.00 [-0.02, 0.03]** |
| Total events | 1 | | 0 | | | |

Heterogeneity: Chi² = 0.04, df = 1 (P = 0.83); I² = 0%
Test for overall effect: Z = 0.31 (P = 0.75)

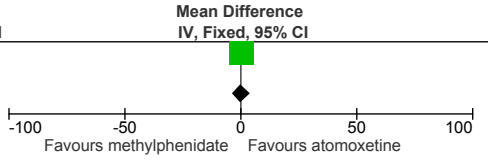



## Atomoxetine versus methylphenidate

### Figure 88: Quality of life (Child Health Questionnaire) at 6 weeks; 0-100, higher values are beneficial

| Study or Subgroup | Atomoxetine Mean | Atomoxetine SD | Atomoxetine Total | Methyphenidate Mean | Methyphenidate SD | Methyphenidate Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Newcorn 2008 | 9.9 | 11.5 | 72 | 9.8 | 11.8 | 75 | 100.0% | 0.10 [-3.67, 3.87] |
| **Total (95% CI)** | | | **72** | | | **75** | **100.0%** | **0.10 [-3.67, 3.87]** |

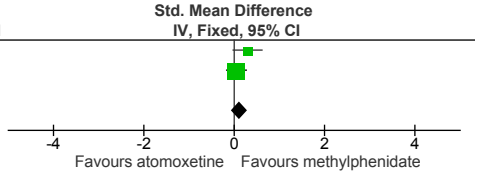
Heterogeneity: Not applicable
Test for overall effect: Z = 0.05 (P = 0.96)




### Figure 89: ADHD total symptoms parent rated (CPRS and ADHD-RS total scores) at 6-8 weeks; lower values are beneficial

| Study or Subgroup | Atomoxetine Mean | Atomoxetine SD | Atomoxetine Total | Methyphenidate Mean | Methyphenidate SD | Methyphenidate Total | Weight | Std. Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Newcorn 2008 | -10.9 | 9.2 | 78 | -13.5 | 8.2 | 76 | 31.8% | 0.30 [-0.02, 0.61] |
| Wang 2007 | -21.1 | 10.3 | 162 | -21.6 | 9.6 | 164 | 68.2% | 0.05 [-0.17, 0.27] |
| **Total (95% CI)** | | | **240** | | | **240** | **100.0%** | **0.13 [-0.05, 0.31]** |

Heterogeneity: Chi² = 1.58, df = 1 (P = 0.21); I² = 37%
Test for overall effect: Z = 1.41 (P = 0.16)




### Figure 90: ADHD inattention symptoms parent rated (CPRS and ADHD-RS inattentive subscale; at 6-8 weeks; lower values are beneficial)

| Study or Subgroup | Atomoxetine Mean | Atomoxetine SD | Atomoxetine Total | Methyphenidate Mean | Methyphenidate SD | Methyphenidate Total | Weight | Std. Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Newcorn 2008 | -9.7 | 7.1 | 82 | -11 | 7.2 | 82 | 33.4% | 0.18 [-0.13, 0.49] |
| Wang 2007 | -11.3 | 5.7 | 162 | -12 | 5.4 | 164 | 66.6% | 0.13 [-0.09, 0.34] |
| **Total (95% CI)** | | | **244** | | | **246** | **100.0%** | **0.14 [-0.03, 0.32]** |

Heterogeneity: Chi² = 0.08, df = 1 (P = 0.77); I² = 0%
Test for overall effect: Z = 1.59 (P = 0.11)

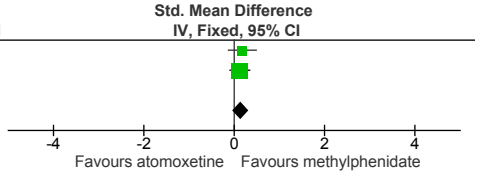


**Figure 91: ADHD hyperactivity symptoms parent rated (CPRS and ADHD-RS hyperactive subscale) at 6-8 weeks; lower values are beneficial**

| Study or Subgroup | Atomoxetine Mean | SD | Total | Methyphenidate Mean | SD | Total | Weight | Std. Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Newcorn 2008 | -8.2 | 7.2 | 82 | -8.7 | 7 | 82 | 33.5% | 0.07 [-0.24, 0.38] |
| Wang 2007 | -9.7 | 5.8 | 162 | -9.5 | 5.5 | 164 | 66.5% | -0.04 [-0.25, 0.18] |
| **Total (95% CI)** | | | **244** | | | **246** | **100.0%** | **-0.00 [-0.18, 0.18]** |

Heterogeneity: Chi² = 0.30, df = 1 (P = 0.58); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)

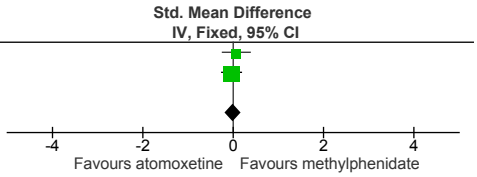



**Figure 92: Behavioural outcomes (CPRS Oppositional subscale) at 8 weeks; 0-18; lower values are beneficial**

| Study or Subgroup | Atomoxetine Mean | SD | Total | Methyphenidate Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Wang 2007 | -3 | 3.9 | 162 | -3.4 | 4.1 | 164 | 100.0% | 0.40 [-0.47, 1.27] |
| **Total (95% CI)** | | | **162** | | | **164** | **100.0%** | **0.40 [-0.47, 1.27]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.90 (P = 0.37)

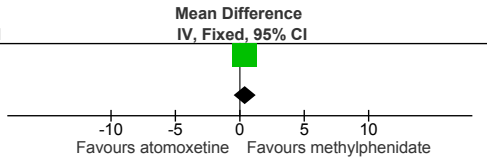
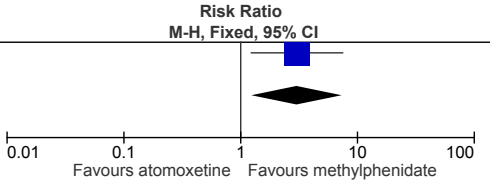



**Figure 93: Discontinuation due to adverse events at 8 weeks**

| Study or Subgroup | Atomoxetine Events | Total | Methyphenidate Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Wang 2007 | 18 | 164 | 6 | 166 | 100.0% | 3.04 [1.24, 7.46] |
| **Total (95% CI)** | | **164** | | **166** | **100.0%** | **3.04 [1.24, 7.46]** |
| Total events | 18 | | 6 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 2.42 (P = 0.02)




## Atomoxetine versus guanfacine ER

**Figure 94: ADHD total symptoms investigator rated (ADHD-RS total scores) at 10 to 13 weeks; 0-54; lower values are beneficial**

| Study or Subgroup | Atomoxetine Mean | SD | Total | Guanfacine Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Huss 2014 | -15 | 13.07 | 111 | -23.9 | 12.41 | 114 | 100.0% | 8.90 [5.57, 12.23] |
| **Total (95% CI)** | | | **111** | | | **114** | **100.0%** | **8.90 [5.57, 12.23]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 5.24 (P < 0.00001)

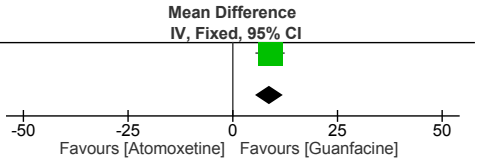



**Figure 95: Clinical global impressions – improvement at 10 to 13 weeks; scores of 1 or 2**

| Study or Subgroup | Atomoxetine Events | Total | Guanfacine Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Hervas 2014 | 63 | 112 | 76 | 114 | 100.0% | 0.84 [0.68, 1.04] |
| **Total (95% CI)** | | **112** | | **114** | **100.0%** | **0.84 [0.68, 1.04]** |
| Total events | 63 | | 76 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.60 (P = 0.11)

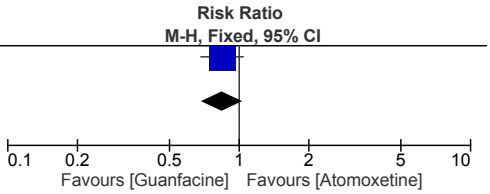
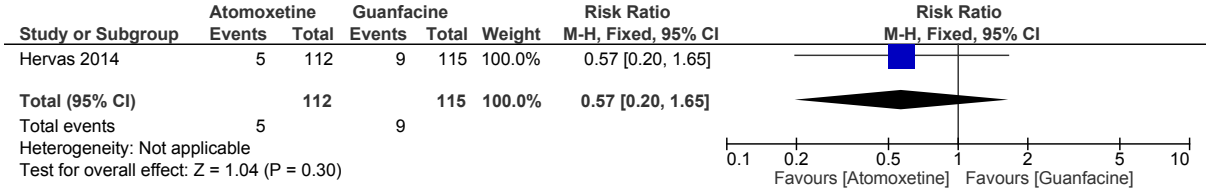


**Figure 96: Discontinuation due to adverse events at 10 to 13 weeks**




## Guanfacine versus placebo

**Figure 97: ADHD total symptoms investigator rated (ADHD-RS total scores) at 8 weeks; 0-54; low values are beneficial**

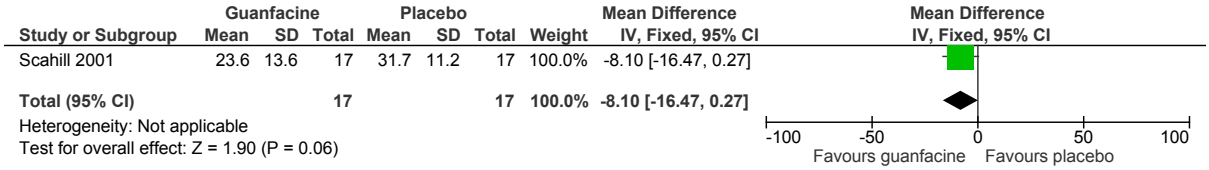



**Figure 98: ADHD inattention symptoms investigator rated (ADHD-RS inattentive subscale) at 8 weeks; 0-27, low values are beneficial**

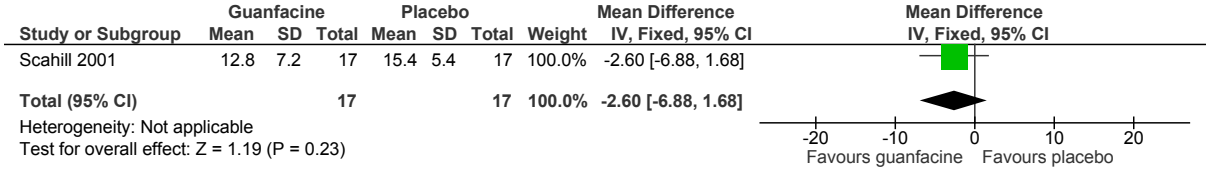



**Figure 99: ADHD hyperactivity symptoms investigator rated (ADHD-RS hyperactive subscale) at 8 weeks; 0-27, low values are beneficial**

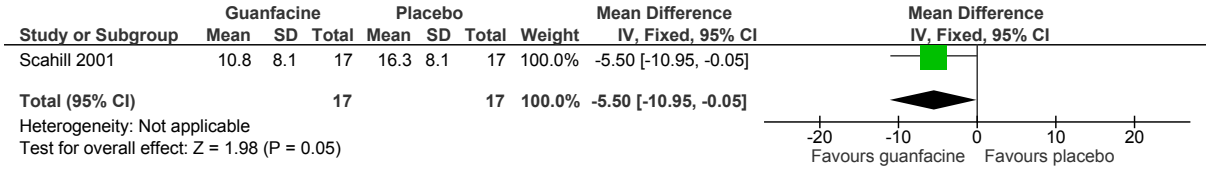
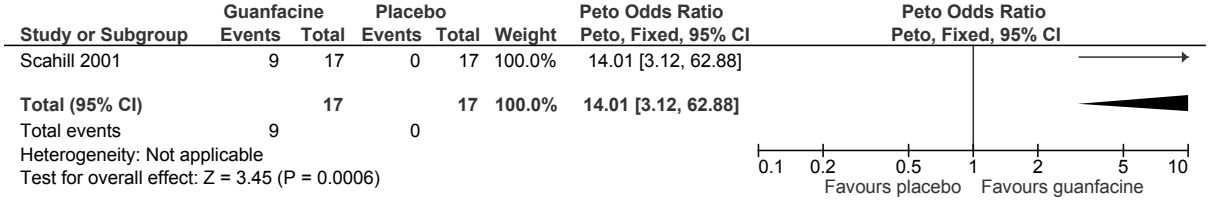



**Figure 100: CGI-I score of 1 or 2 at 8 weeks**



## Extended release guanfacine versus placebo

**Figure 101: ADHD total symptoms investigator rated at 5 to 13 weeks (ADHD-RS total scores); 0-54; low values are beneficial**

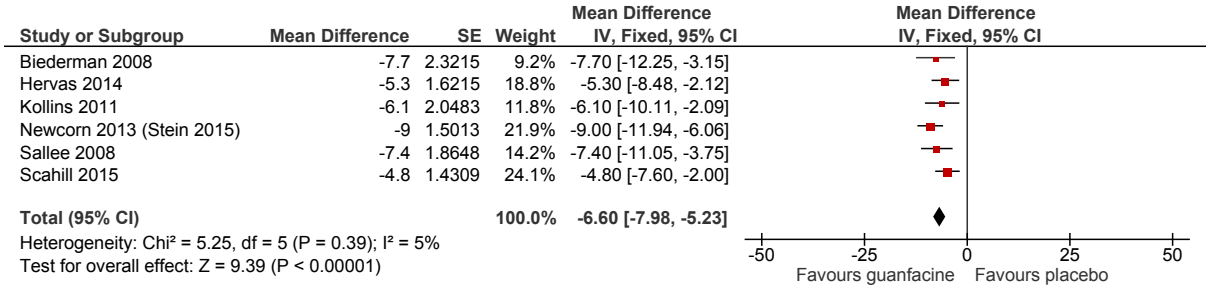



**Figure 102: ADHD inattention symptoms investigator rated at 6 to 8 weeks (ADHD-RS inattentive subscale); 0-27; low values are beneficial**

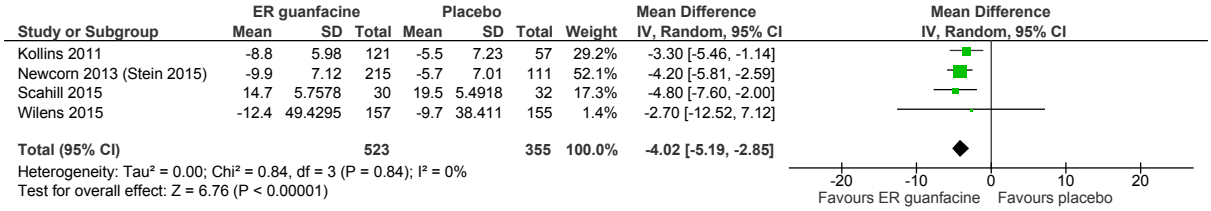



**Figure 103: ADHD hyperactivity symptoms investigator rated at 6 to 8 weeks (ADHD-RS hyperactive/impulsive subscale; 0-27 ; low values are beneficial; change scores reported)**

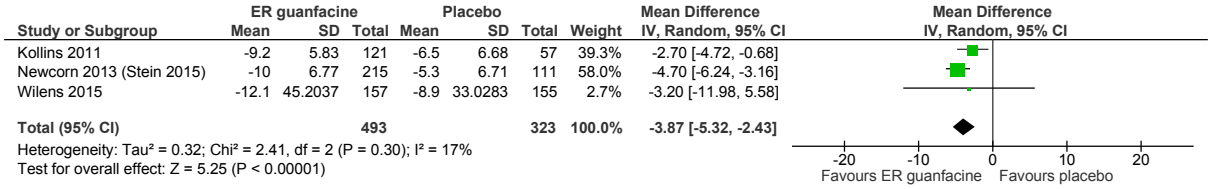



**Figure 104: ADHD hyperactivity symptoms investigator rated (ABC hyperactive subscale at 8 weeks; 0-20, low values are beneficial; final values reported)**

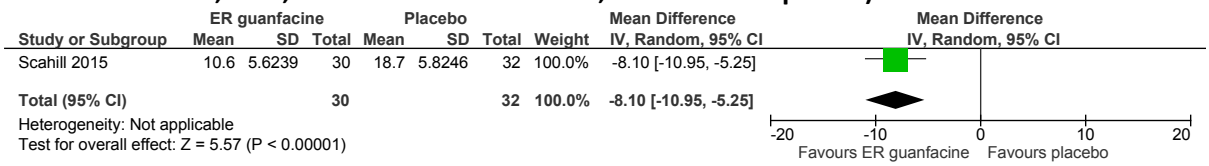


**Figure 105: Clinical Global Impressions (improvement) score of 1 or 2 at 5-13 weeks**

| Study or Subgroup | ER Guanfacine Events | ER Guanfacine Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Biederman 2008 | 140 | 259 | 22 | 86 | 23.1% | 2.11 [1.45, 3.08] |
| Huss 2014 | 76 | 114 | 49 | 111 | 34.7% | 1.51 [1.18, 1.93] |
| Kollins 2011 | 65 | 121 | 19 | 57 | 18.0% | 1.61 [1.08, 2.41] |
| Sallee 2008 | 139 | 258 | 20 | 66 | 22.2% | 1.78 [1.21, 2.61] |
| Scahill 2015 | 15 | 30 | 3 | 32 | 2.0% | 5.33 [1.71, 16.59] |
| **Total (95% CI)** | | **782** | | **352** | **100.0%** | **1.80 [1.52, 2.14]** |
| Total events | 435 | | 113 | | | |

Heterogeneity: Chi² = 6.49, df = 4 (P = 0.17); I² = 38%
Test for overall effect: Z = 6.87 (P < 0.00001)

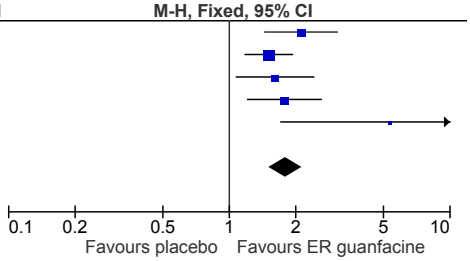



**Figure 106: Academic achievement at 8 weeks (Weiss functional impairment rating scale academic performance, low scores are beneficial)**

| Study or Subgroup | Std. Mean Difference | SE | Weight | Std. Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|
| Newcorn 2013 (Stein 2015) | -0.34 | 0.102 | 100.0% | -0.34 [-0.54, -0.14] |
| **Total (95% CI)** | | | **100.0%** | **-0.34 [-0.54, -0.14]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 3.33 (P = 0.0009)

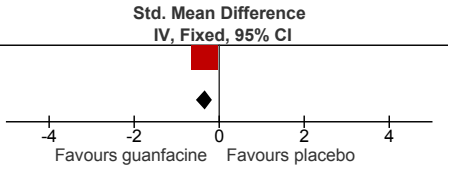



**Figure 107: Discontinuation due to adverse events at 5 to 13 weeks**

| Study or Subgroup | ER guanfacine Events | ER guanfacine Total | Placebo Events | Placebo Total | Weight | Peto Odds Ratio Peto, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Biederman 2008 | 42 | 259 | 1 | 86 | 29.8% | 3.96 [1.89, 8.27] |
| Connor 2010 | 14 | 138 | 1 | 79 | 13.7% | 3.95 [1.33, 11.72] |
| Huss 2014 | 9 | 115 | 1 | 111 | 10.1% | 5.11 [1.44, 18.10] |
| Kollins 2011 | 4 | 121 | 1 | 57 | 4.5% | 1.76 [0.26, 11.77] |
| Newcorn 2013 (Stein 2015) | 16 | 221 | 0 | 112 | 14.4% | 4.85 [1.68, 14.01] |
| Sallee 2008 | 19 | 258 | 5 | 66 | 15.2% | 0.97 [0.35, 2.72] |
| Scahill 2015 | 2 | 30 | 0 | 32 | 2.1% | 8.18 [0.50, 133.94] |
| Wilens 2015 | 8 | 157 | 2 | 157 | 10.2% | 3.44 [0.98, 12.10] |
| **Total (95% CI)** | | **1299** | | **700** | **100.0%** | **3.26 [2.18, 4.87]** |
| Total events | 114 | | 11 | | | |

Heterogeneity: Chi² = 7.55, df = 7 (P = 0.37); I² = 7%
Test for overall effect: Z = 5.75 (P < 0.00001)

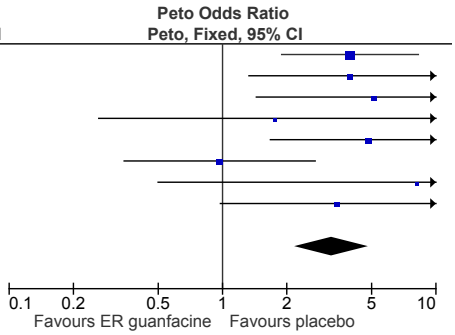
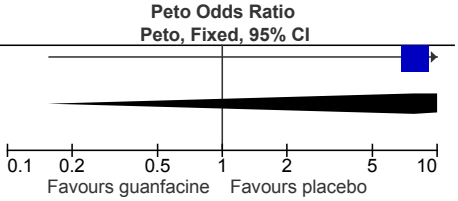



**Figure 108: Serious adverse events at 8 weeks**

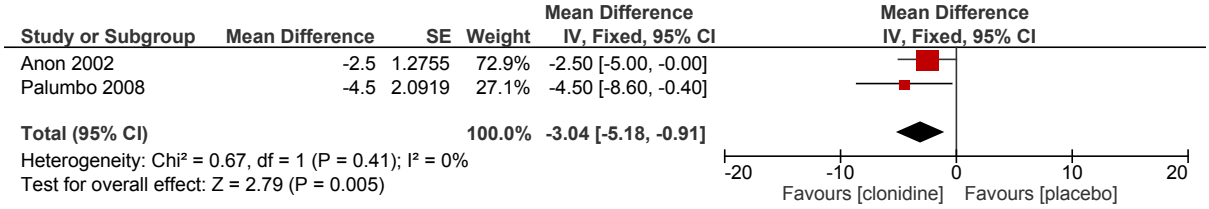
| Study or Subgroup | Guanfacine Events | Guanfacine Total | Placebo Events | Placebo Total | Weight | Peto Odds Ratio Peto, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Scahill 2015 | 1 | 30 | 0 | 32 | 100.0% | 7.90 [0.16, 398.87] |
| **Total (95% CI)** | | **30** | | **32** | **100.0%** | **7.90 [0.16, 398.87]** |
| Total events | 1 | | 0 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.03 (P = 0.30)

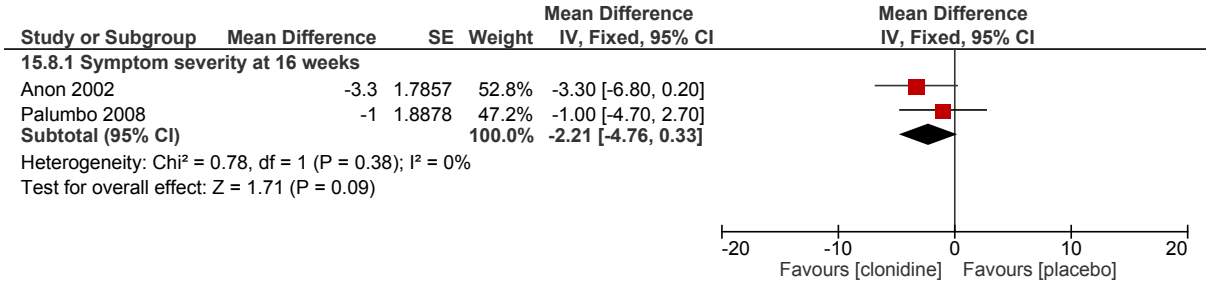


## Clonidine versus placebo

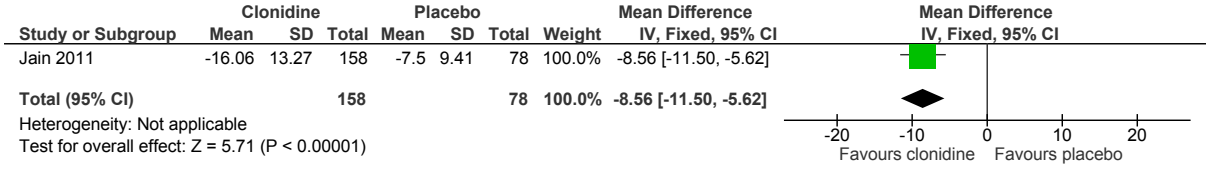
### Figure 109: ADHD total symptoms parent rated at 16 weeks (Conners ASQ-P total score; 0-20 low values are beneficial)



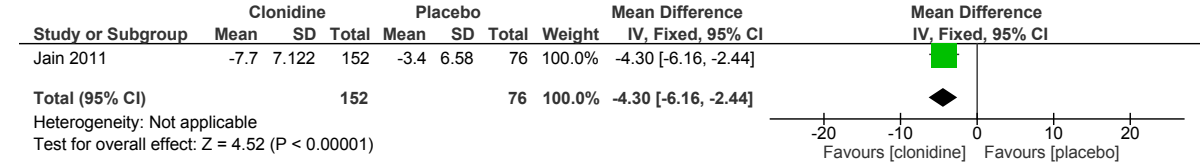

### Figure 110: ADHD total symptoms teacher rated at 16 weeks (Conners ASQ-T total score; 0-20, low values are beneficial)




### Figure 111: ADHD total symptoms investigator rated at 16 weeks (ADHD-RS total scores); 0-27 low values are beneficial




### Figure 112: ADHD inattention symptoms investigator rated at 16 weeks (ADHD-RS inattention subscale); 0-27, low values are beneficial




### Figure 113: ADHD hyperactivity symptoms investigator rated at 16 weeks (ADHD RS hyperactivity subscale); 0-27, lower values are beneficial

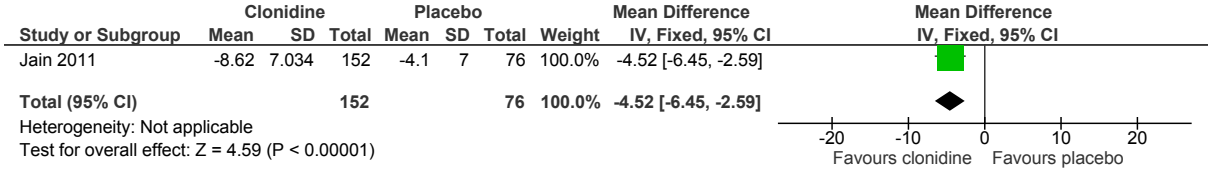


**Figure 114: ADHD hyperactivity symptoms parent rated at 6 weeks (Mother/Teacher CBCL Hyperactivity subscale); 0-100, lower values are beneficial**

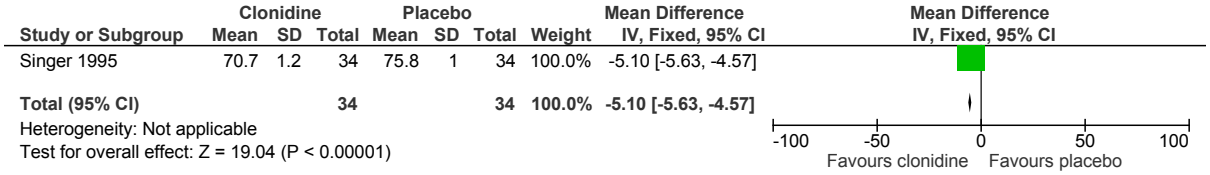



**Figure 115: Behaviour outcome at 16 weeks (Children's Global Assessment Scale; 0-100, higher values are beneficial)**

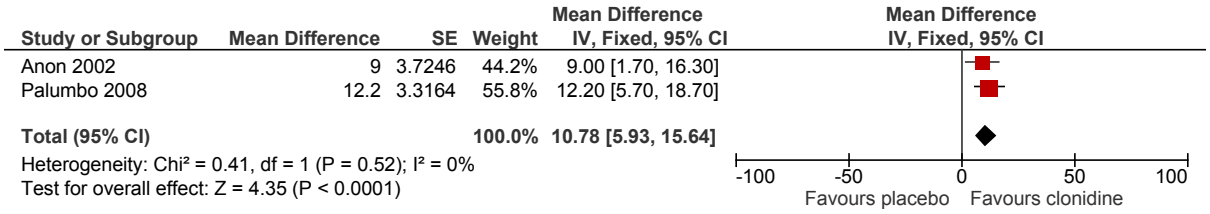



**Figure 116: Discontinuation due to adverse events at 16 weeks**

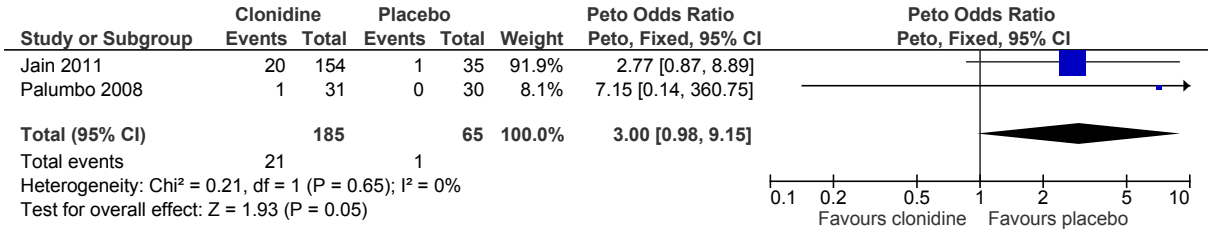
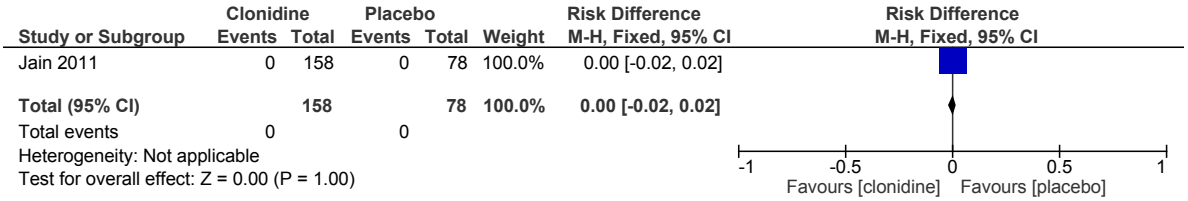



**Figure 117: Serious adverse events at 16 weeks**




## Clonidine versus methylphenidate

**Figure 118: ADHD total symptoms teacher rated (Conners ASQ-T total score) at 16 weeks; 0-20, low values are beneficial**

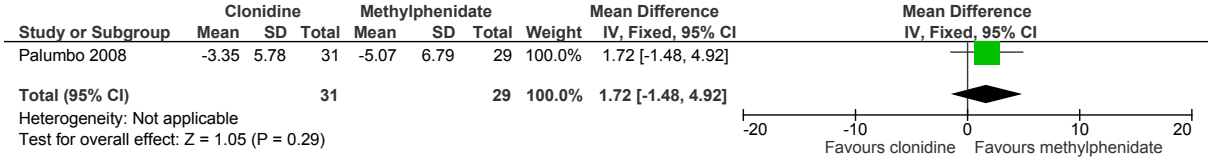


**Figure 119: ADHD total symptoms parent rated (Conners ASQ-P total score) at 16 weeks; 0-20, low values are beneficial, change score reported**

| Study or Subgroup | Mean Difference | SE | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|
| Palumbo 2008 | 2.5 | 1.7857 | 100.0% | 2.50 [-1.00, 6.00] |
| **Total (95% CI)** | | | **100.0%** | **2.50 [-1.00, 6.00]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.40 (P = 0.16)

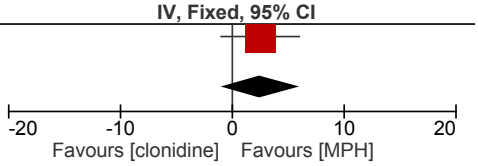



**Figure 120: Behaviour (Children's Global Assessment Scale at 16 weeks; 0-100, high values are beneficial)**

| Study or Subgroup | Mean Difference | SE | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|
| Palumbo 2008 | -3.6 | 2.7552 | 100.0% | -3.60 [-9.00, 1.80] |
| **Total (95% CI)** | | | **100.0%** | **-3.60 [-9.00, 1.80]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.31 (P = 0.19)

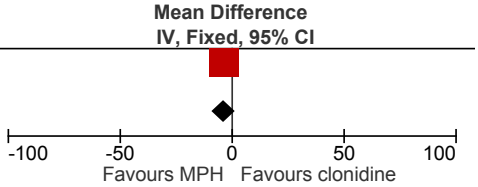
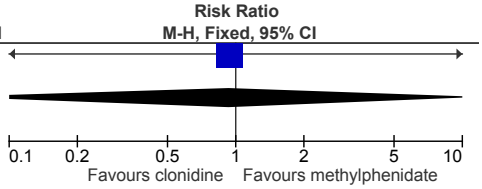



**Figure 121: Discontinuation due to adverse events at 16 weeks**

| Study or Subgroup | Clonidine Events | Clonidine Total | Methylphenidate Events | Methylphenidate Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Palumbo 2008 | 1 | 31 | 1 | 29 | 100.0% | 0.94 [0.06, 14.27] |
| **Total (95% CI)** | | **31** | | **29** | **100.0%** | **0.94 [0.06, 14.27]** |
| Total events | 1 | | 1 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.05 (P = 0.96)

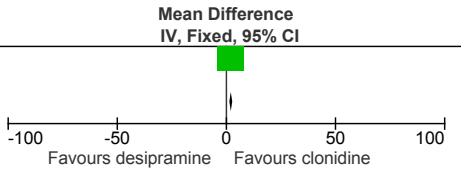



## Clonidine versus desipramine

**Figure 122: ADHD hyperactivity symptoms parent/teacher rated (Mother/Teacher CBCL Hyperactivity subscale) at 6 weeks; 0-100, high values are beneficial**

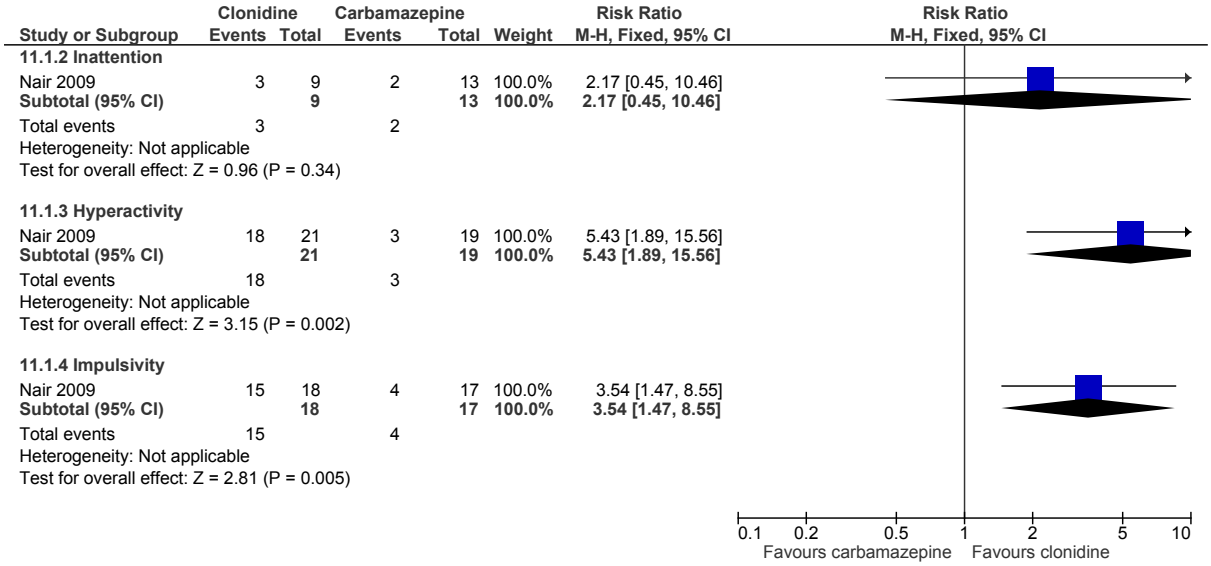
| Study or Subgroup | Clonidine Mean | Clonidine SD | Clonidine Total | Desipramine Mean | Desipramine SD | Desipramine Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Singer 1995 | 70.7 | 1.2 | 34 | 68.6 | 1.4 | 34 | 100.0% | 2.10 [1.48, 2.72] |
| **Total (95% CI)** | | | **34** | | | **34** | **100.0%** | **2.10 [1.48, 2.72]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 6.64 (P < 0.00001)



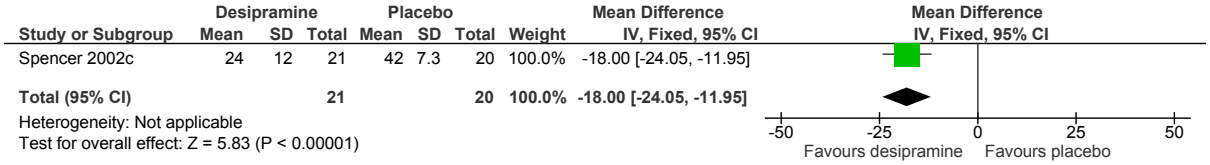
## Clonidine versus carbamazepine

### Figure 123: Treatment response at 4 weeks investigator rated (25% improvement on the Vanderbilt scale)

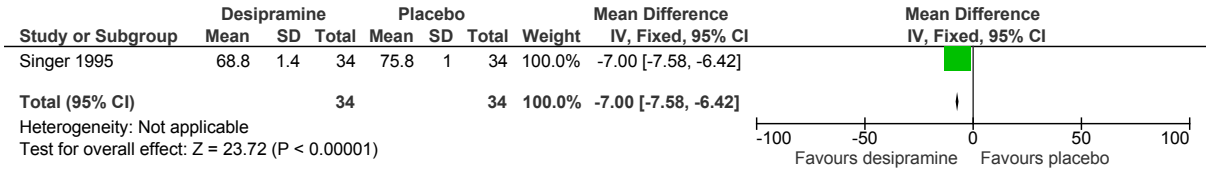



## Desipramine versus placebo

### Figure 124: ADHD total symptoms investigator rated at 9 weeks (ADHD-RS total scores); 0-54, low values are beneficial

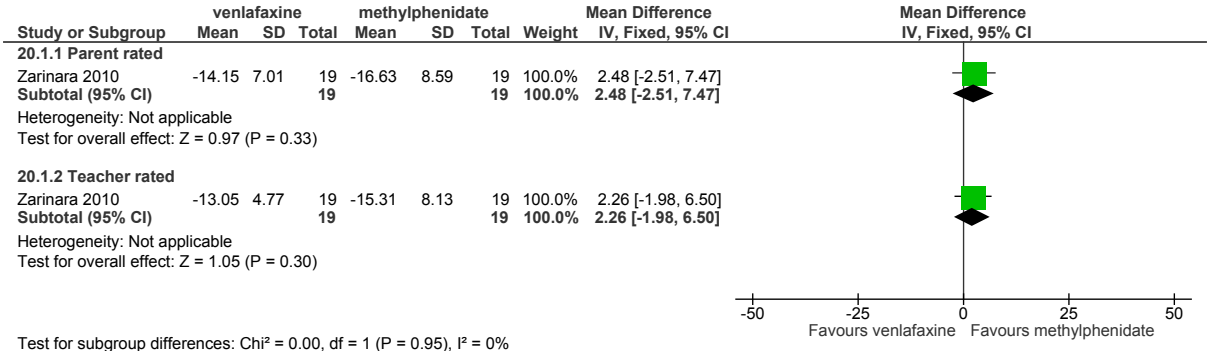



### Figure 125: ADHD hyperactivity symptoms at 6 weeks parent/teacher rated (Mother/Teacher CBCL Hyperactivity subscale), 0-100, low values are beneficial



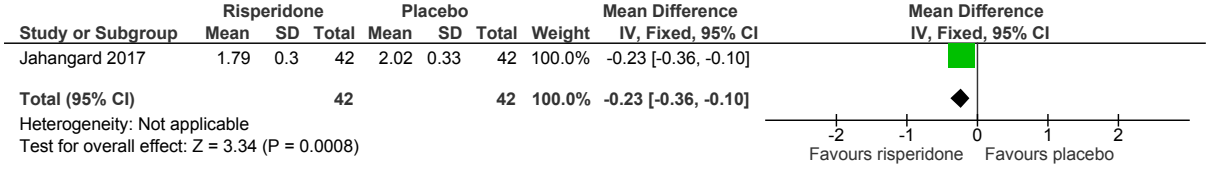
## Venlafaxine versus methylphenidate

### Figure 126: ADHD total symptoms parent and teacher rated at 6 weeks (ADHD-RS total score; 0-54; low values are beneficial, change scores)

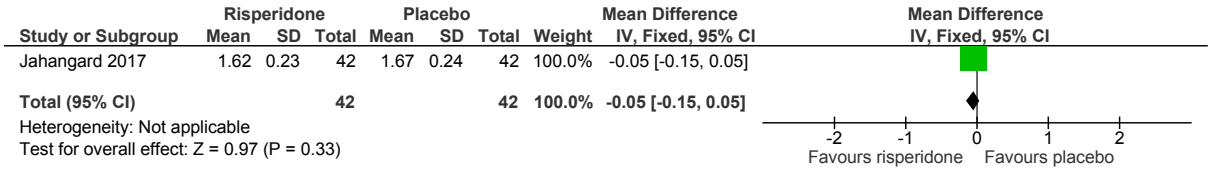



## Risperidone versus placebo

### Figure 127: ADHD inattention symptoms (8 weeks PT; parent rated; CPRS inattention subscale; 0-3; low is beneficial)




### Figure 128: ADHD hyperactivity symptoms (8 weeks PT; parent rated; CPRS hyperactivity subscale; 0-3; low is beneficial)




### Figure 129: Behaviour outcomes at 8 to 10 weeks (Aberrant Behaviour Checklist and CPRS oppositional subscale; low values are beneficial)

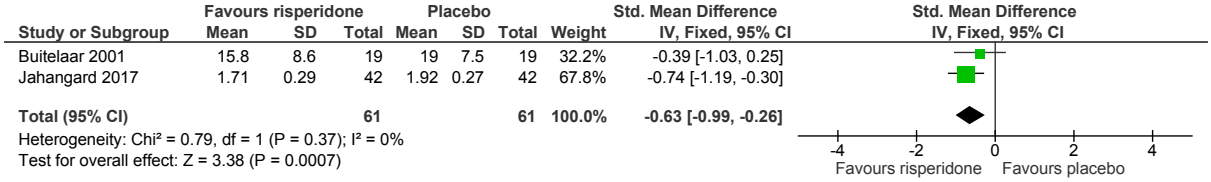


**Figure 130: Behaviour outcomes at 24 weeks (Children's Global Assessment Scale; 0-100; high values are beneficial)**

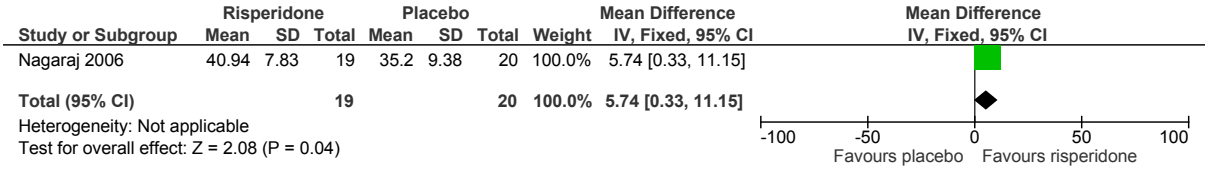
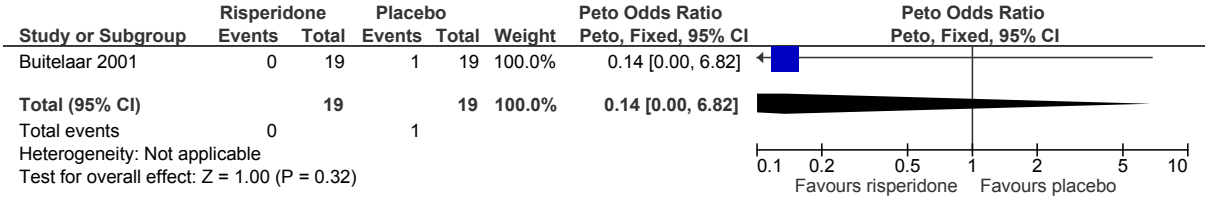
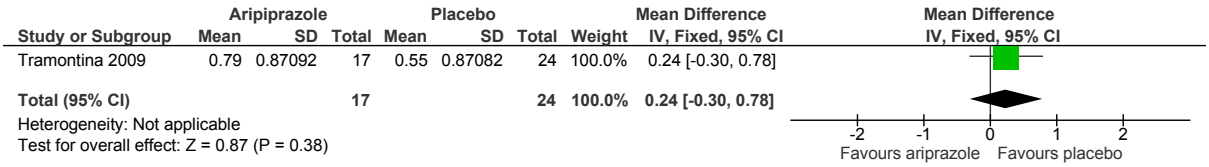



**Figure 131: Serious adverse events at 6 weeks**




## Ariprazole versus placebo

**Figure 132: ADHD total symptoms parent rated at 6 weeks (SNAP-IV total scores); 0-3; lower values are beneficial**




## Buspirone versus methylphenidate

**Figure 133: Treatment response at 6 weeks (more than 30% reduction in ADHD-RS total scores)**

**Figure 134: ADHD total symptoms parent and teacher rated at 6 weeks (ADHD-RS total scores); 0-54; low values are beneficial**

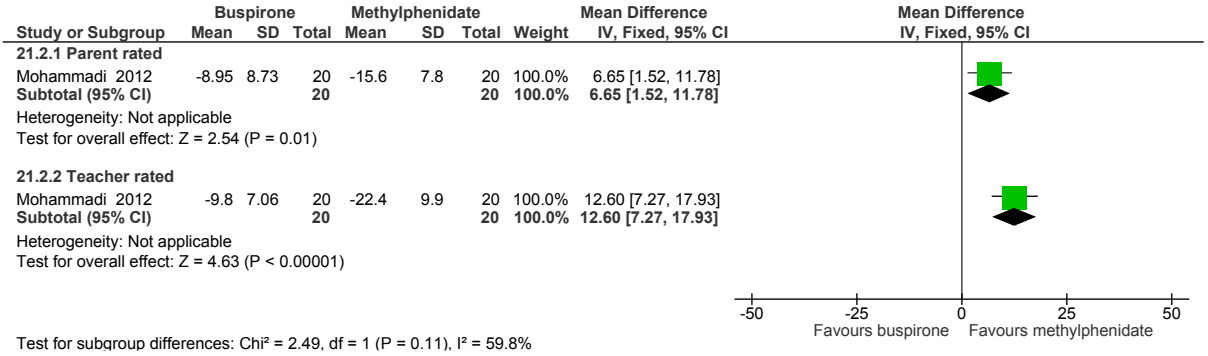



**Figure 135: Discontinuation due to adverse events at 6 weeks**

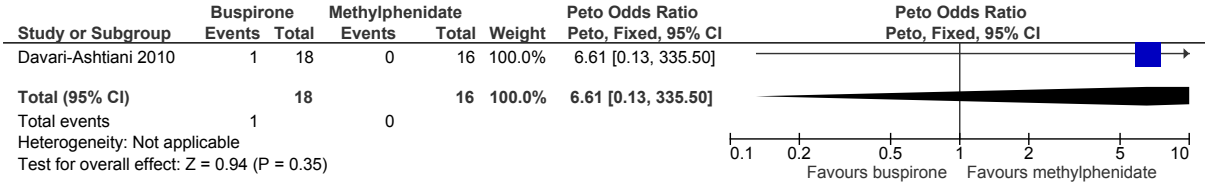
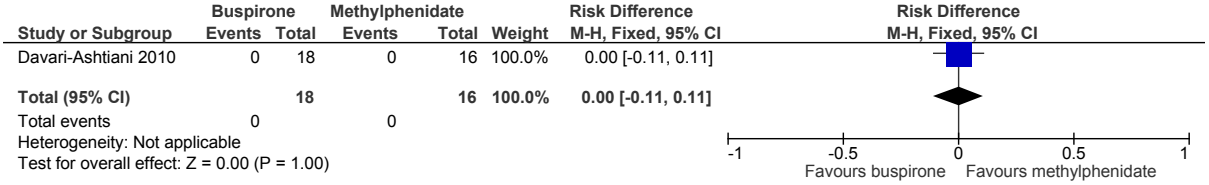



**Figure 136: Serious adverse events at 6 weeks**




## Bupropion versus placebo

**Figure 137: ADHD total symptoms parent rated (CPTQ-P and Conners Abbreviated Parent Questionnaire) at 4 to 6 weeks; low values are beneficial, final values reported**

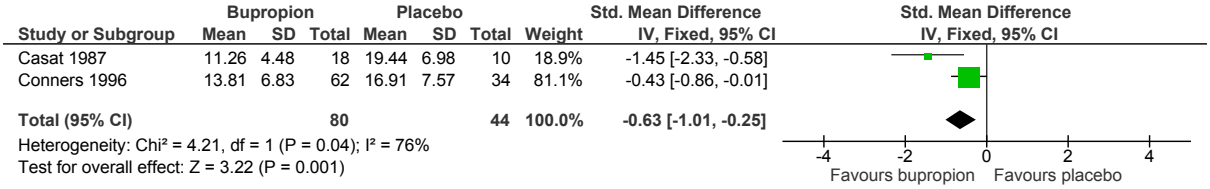


**Figure 138: ADHD total symptoms teacher rated (CPTQ-T and Conners Abbreviated Teacher Questionnaire) at 4 to 6 weeks; low values are beneficial**

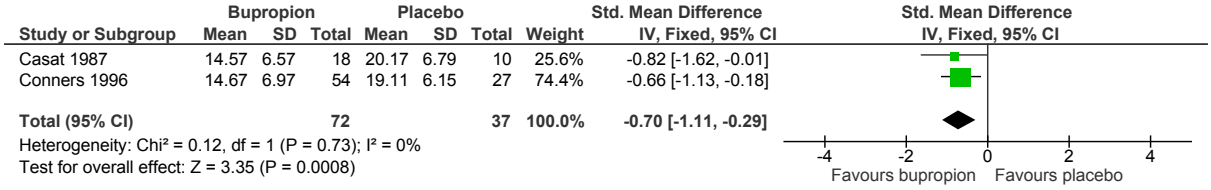
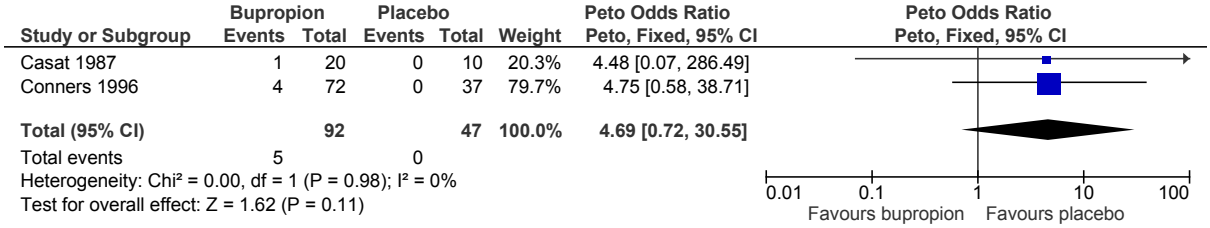



**Figure 139: Discontinuation due to adverse events at 4 to 6 weeks**




## Bupropion versus methylphenidate

**Figure 140: ADHD total symptoms parent rated at 6 weeks PT (ADHD-RS total scores); 0-54; low values are beneficial; change scores reported**

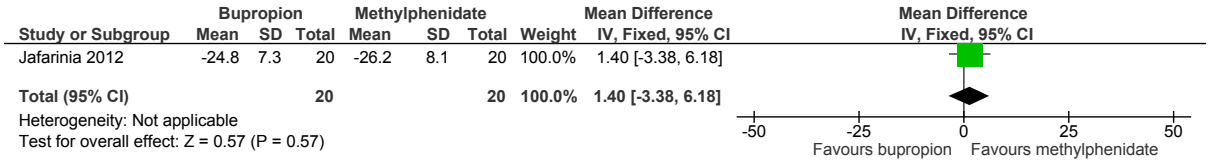



**Figure 141: ADHD total symptoms parent rated at 6 weeks crossover (IOWA conners rating scale; 0-30; low values are beneficial; final values reported)**

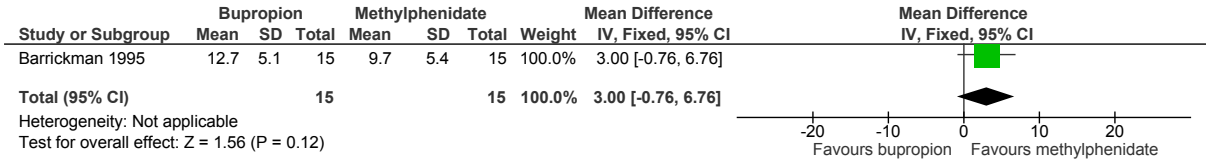



**Figure 142: ADHD total symptoms teacher rated at 6 weeks PT (ADHD-RS total scores); 0-54; low values are beneficial; change scores reported**

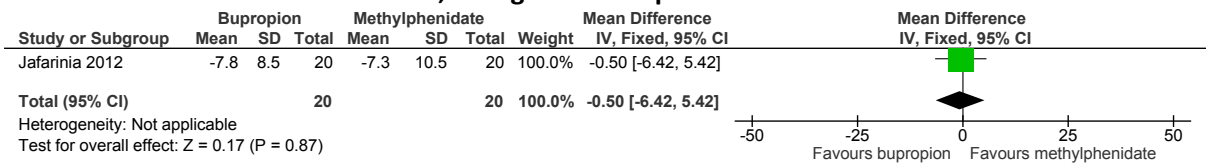


**Figure 143: ADHD total symptoms teacher rated at 6 weeks crossover (IOWA conners rating scale; 0-30; low values are beneficial; final values reported)**

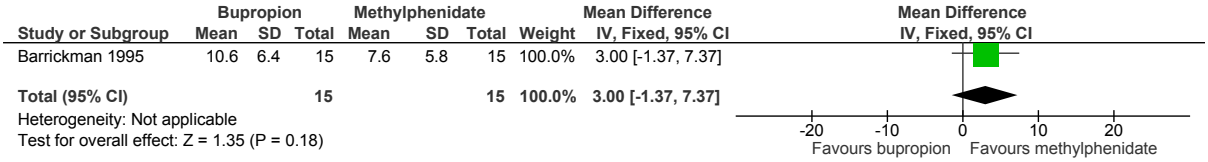



**Figure 144: ADHD inattention symptoms parent rated at 6 weeks PT (ADHD-RS inattention subscale scores); 0-27; low values are beneficial, change scores reported**

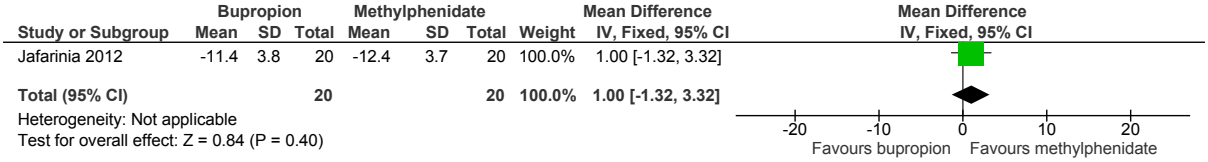



**Figure 145: ADHD inattention symptoms parent rated at 6 weeks crossover (IOWA conners rating scale inattention subscale; 0-15; low values are beneficial, final values reported)**

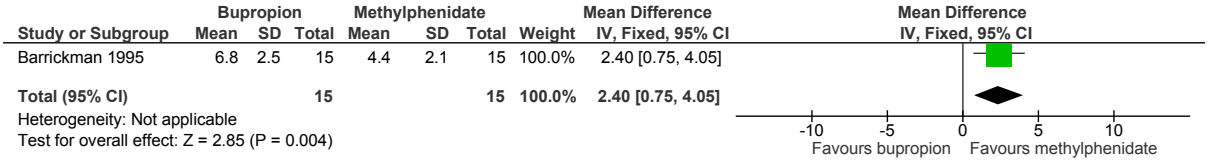



**Figure 146: ADHD inattention symptoms at 6 weeks PT (ADHD-RS inattention subscale scores teacher rated); 0-27; low values are beneficial; change scores reported**

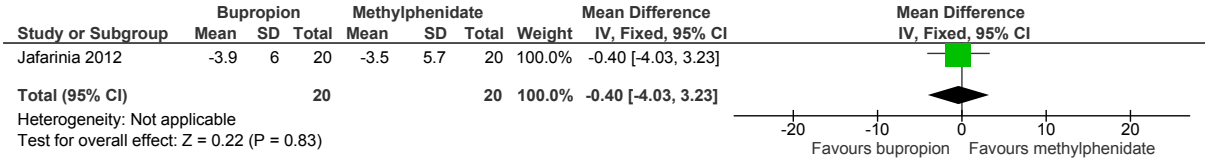



**Figure 147: ADHD inattention symptoms teacher rated at 6 weeks crossover (IOWA conners rating scale; 0-15; low values are beneficial; final values reported)**

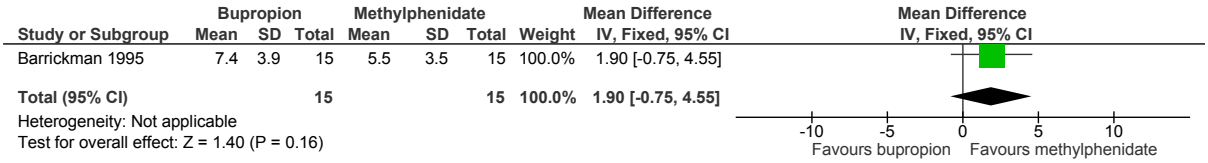


**Figure 148: ADHD hyperactivity symptoms parent rated at 6 weeks (ADHD-RS hyperactivity subscale scores); 0-27; low values are beneficial**

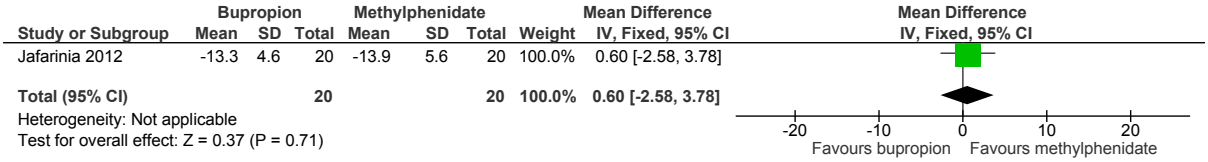



**Figure 149: ADHD hyperactivity symptoms teacher rated at 6 weeks (ADHD-RS hyperactivity subscale scores); 0-27; low values are beneficial**

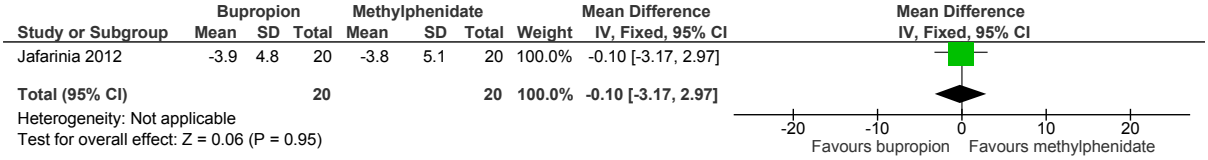



**Figure 150: Discontinuation due to adverse events at 6 weeks**

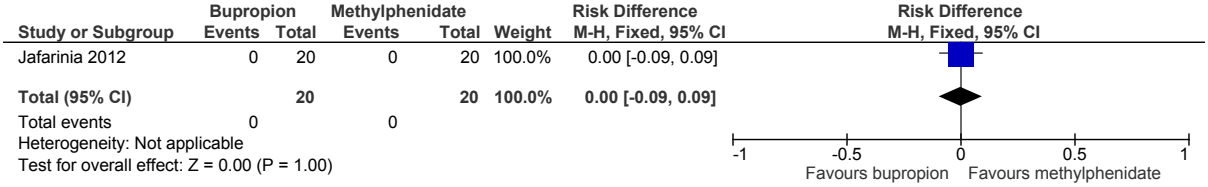
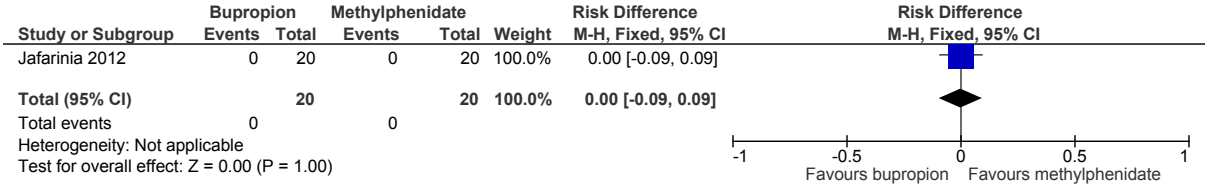



**Figure 151: Serious adverse events at 6 weeks**




## Modafinil versus placebo

**Figure 152: ADHD total symptoms parent rated at 5 weeks (ADHD-RS total scores); 0-54; low values are beneficial**

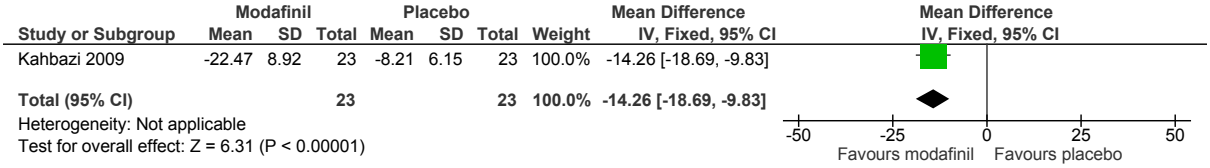


**Figure 153: ADHD total symptoms teacher rated at 5-6 weeks (ADHD-RS total scores); 0-54, lower values are beneficial**

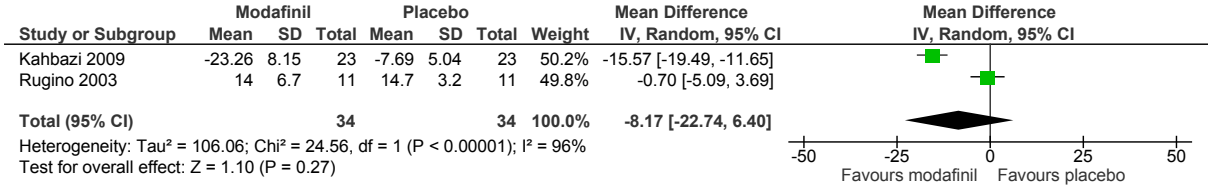



**Figure 154: CGI score of 1 or 2 at 9 weeks**

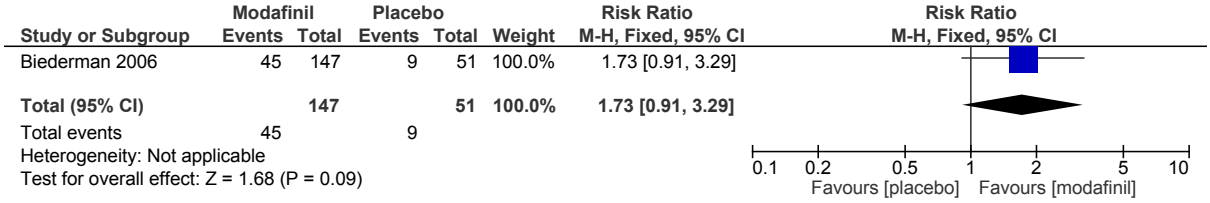



**Figure 155: Serious adverse events at 9 weeks**

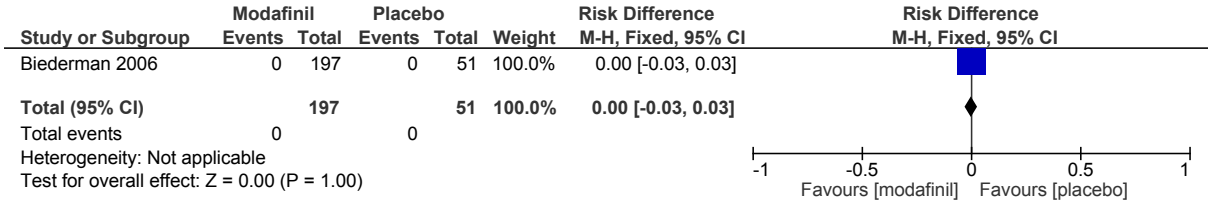
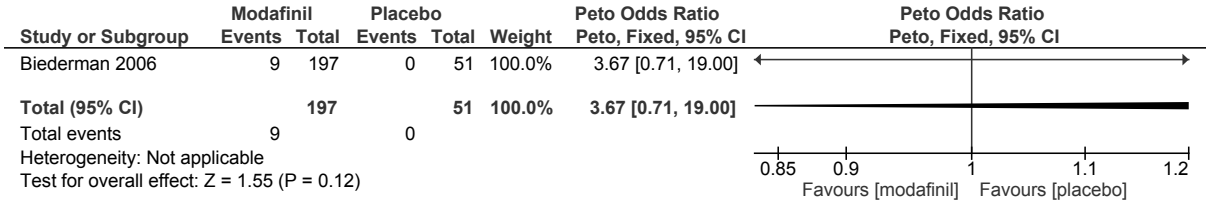
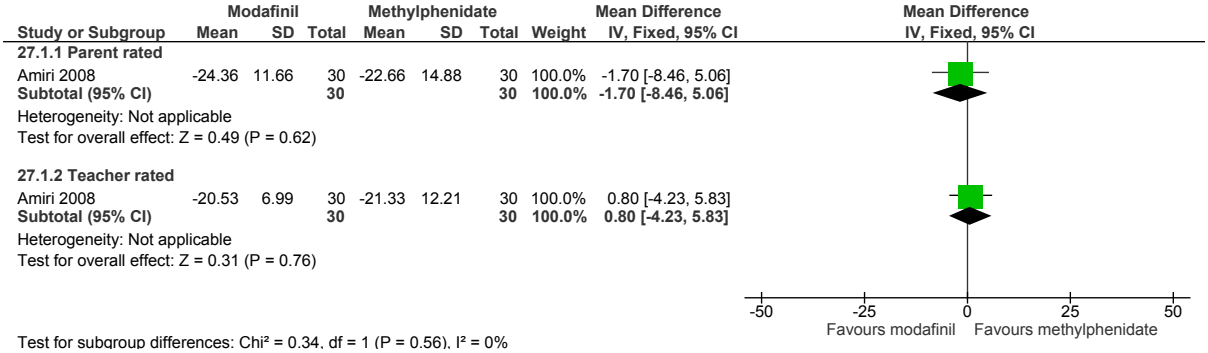



**Figure 156: Discontinuation due to adverse events at 9 weeks**



## Modafinil versus methylphenidate

**Figure 157: ADHD total symptoms parent and teacher rated at 6 weeks (ADHD-RS total scores); 0-54; low scores are beneficial**




## Melatonin versus placebo

**Figure 158: Quality of Life at 4 weeks (TNO-AZL Questionnaire for Children's Health-Related Quality of Life), 0-224; higher values are beneficial**

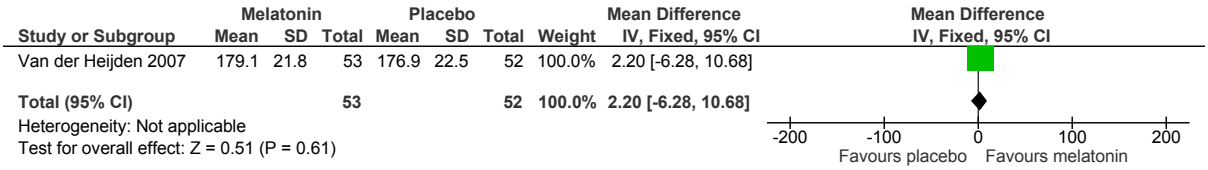



**Figure 159: Behavioural outcomes at 4 weeks (Teachers Report Form); 0-100; lower values are beneficial**

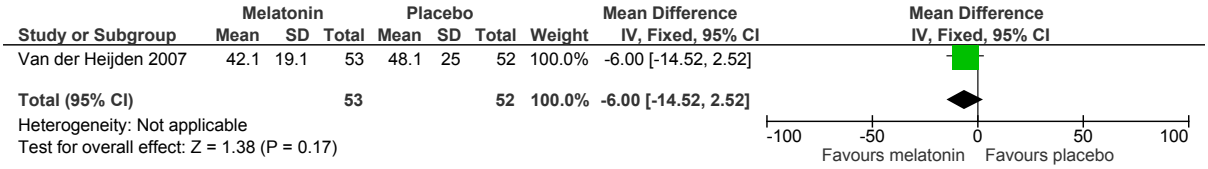
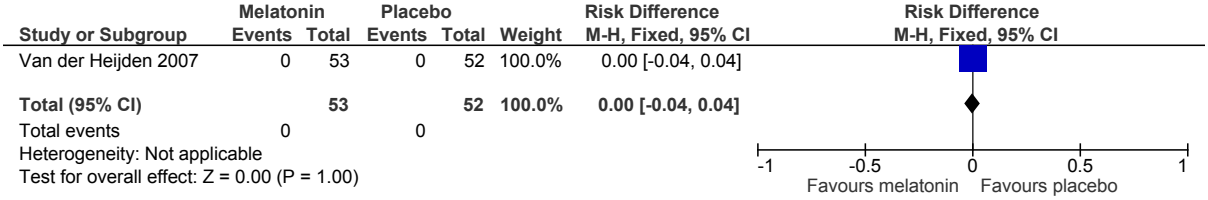


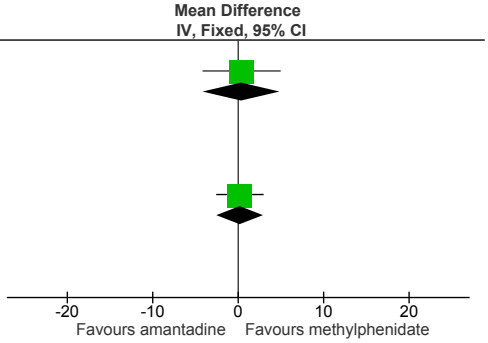

**Figure 160: Discontinuation due to adverse events at 4 weeks**



## Amantadine versus methylphenidate

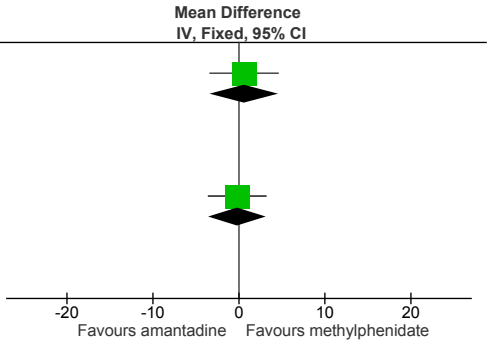
### Figure 161: ADHD inattention symptoms at 6 weeks (ADHD-RS inattention subscale - Parent and teacher rated); 0-27, lower values are beneficial

| Study or Subgroup | Amantadine Mean | SD | Total | Methylphenidate Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **29.1.1 Parent rated** | | | | | | | | |
| Mohammadi 2010 | 8.85 | 8.11 | 19 | 8.45 | 5.85 | 19 | 100.0% | 0.40 [-4.10, 4.90] |
| **Subtotal (95% CI)** | | | **19** | | | **19** | **100.0%** | **0.40 [-4.10, 4.90]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 0.17 (P = 0.86) | | | | | | | | |
| **29.1.2 Teacher rated** | | | | | | | | |
| Mohammadi 2010 | 8.8 | 5.19 | 19 | 8.6 | 3.01 | 19 | 100.0% | 0.20 [-2.50, 2.90] |
| **Subtotal (95% CI)** | | | **19** | | | **19** | **100.0%** | **0.20 [-2.50, 2.90]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 0.15 (P = 0.88) | | | | | | | | |




### Figure 162: ADHD hyperactivity symptoms at 6 weeks (ADHD-RS hyperactivity subscale – Parent and teacher rated; 0-27, lower values are beneficial)

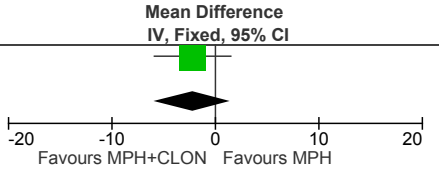
| Study or Subgroup | Amantadine Mean | SD | Total | Methylphenidate Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **29.2.1 Parent rated** | | | | | | | | |
| Mohammadi 2010 | 9.4 | 6.75 | 19 | 8.8 | 5.65 | 19 | 100.0% | 0.60 [-3.36, 4.56] |
| **Subtotal (95% CI)** | | | **19** | | | **19** | **100.0%** | **0.60 [-3.36, 4.56]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 0.30 (P = 0.77) | | | | | | | | |
| **29.2.2 Teacher rated** | | | | | | | | |
| Mohammadi 2010 | 10.15 | 6.29 | 19 | 10.35 | 3.95 | 19 | 100.0% | -0.20 [-3.54, 3.14] |
| **Subtotal (95% CI)** | | | **19** | | | **19** | **100.0%** | **-0.20 [-3.54, 3.14]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 0.12 (P = 0.91) | | | | | | | | |




## Methylphenidate and clonidine versus methylphenidate

### Figure 163: ADHD total symptoms teacher rated at 16 weeks (Conners ASQ-T total scores; 0-20; low scores are beneficial)

| Study or Subgroup | MPH+CLON Mean | SD | Total | MPH Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Palumbo 2008 | -7.28 | 7.91 | 32 | -5.07 | 6.79 | 29 | 100.0% | -2.21 [-5.90, 1.48] |
| **Total (95% CI)** | | | **32** | | | **29** | **100.0%** | **-2.21 [-5.90, 1.48]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 1.17 (P = 0.24) | | | | | | | | |




### Figure 164: ADHD total symptoms parent rated at 16 weeks (Conners ASQ-P total scores; 0-20; low scores are beneficial)

| Study or Subgroup | Mean Difference | SE | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|
| Palumbo 2008 | -3 | 1.7347 | 100.0% | -3.00 [-6.40, 0.40] |
| **Total (95% CI)** | | | **100.0%** | **-3.00 [-6.40, 0.40]** |
| Heterogeneity: Not applicable | | | | |
| Test for overall effect: Z = 1.73 (P = 0.08) | | | | |

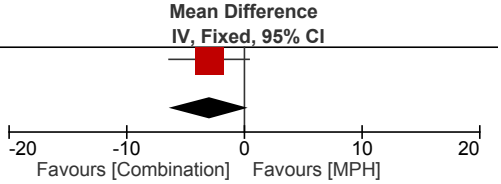


**Figure 165: Behaviour at 16 weeks (Childrens global assessment scale; 0-100; high scores are beneficial)**

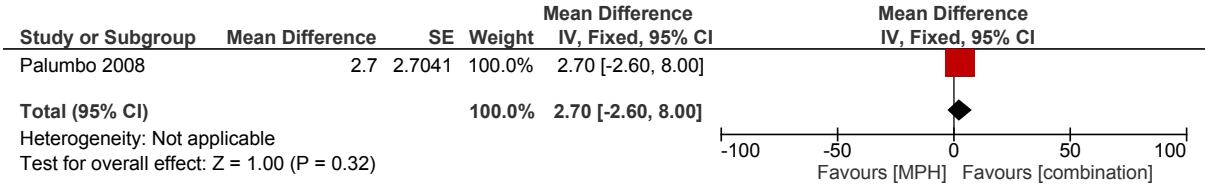
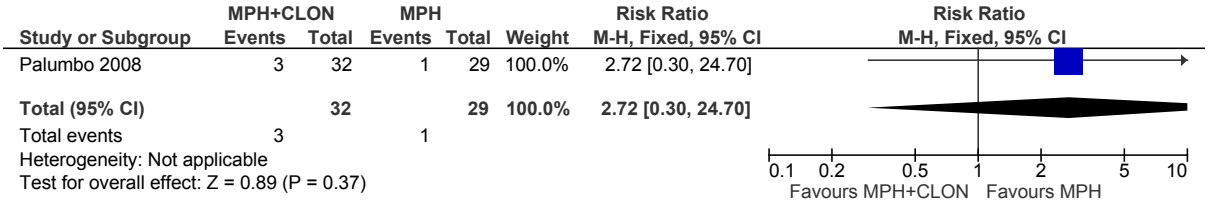



**Figure 166: Discontinuation due to adverse events at 16 weeks**




## Methylphenidate and clonidine versus clonidine

**Figure 167: ADHD total symptoms teacher rated at 16 weeks (Conners ASQ-T total scores; 0-20; low scores are beneficial)**

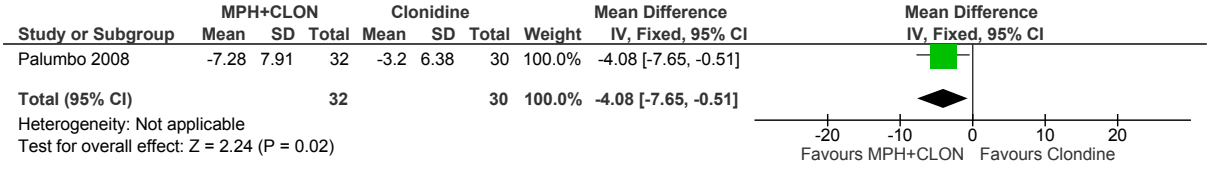



**Figure 168: Behaviour at 16 weeks (Childrens global assessment scale; 0-100; high scores are beneficial)**

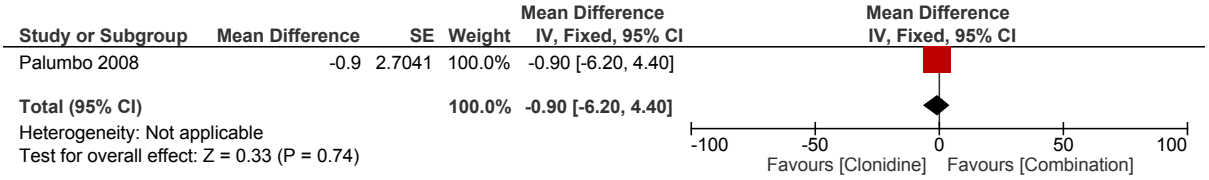
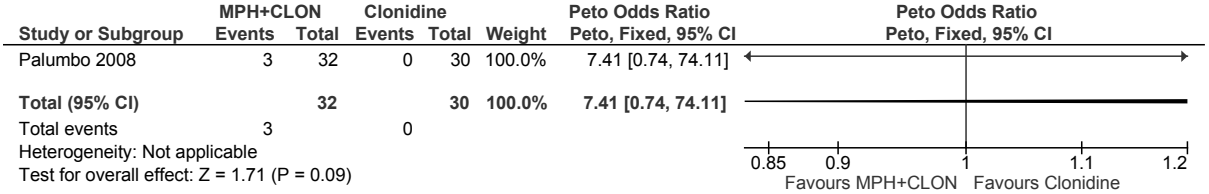
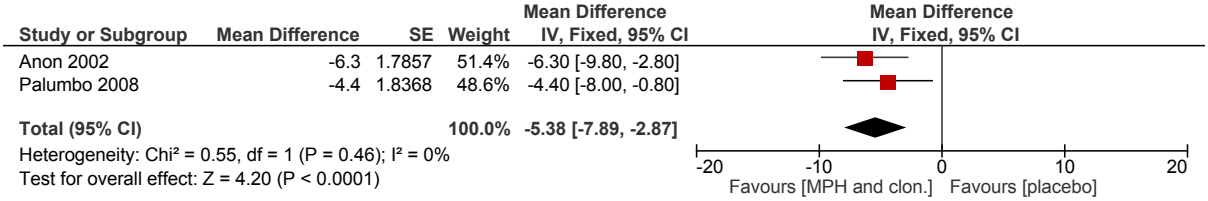



**Figure 169: Discontinuation due to adverse events at 16 weeks**

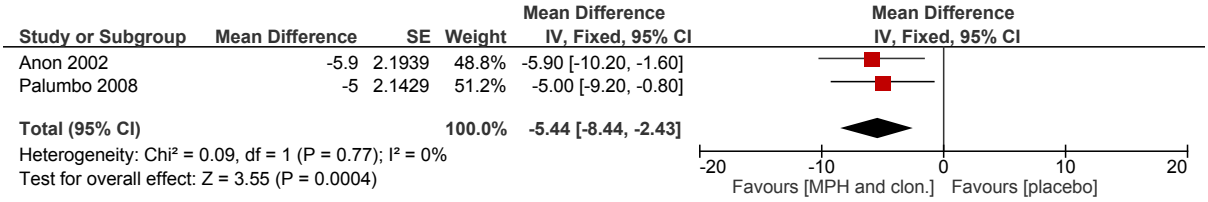


## Methylphenidate and clonidine versus placebo

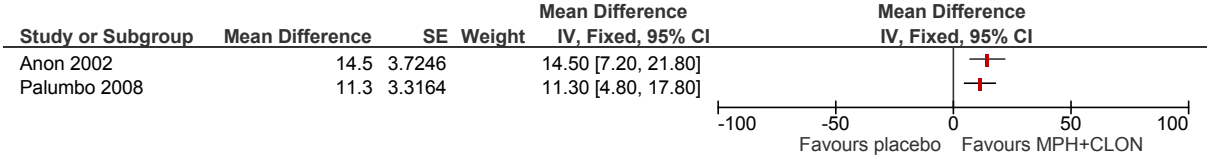
### Figure 170: ADHD total symptoms teacher rated at 16 weeks (Conners ASQ-T total scores; 0-20; low scores are beneficial)



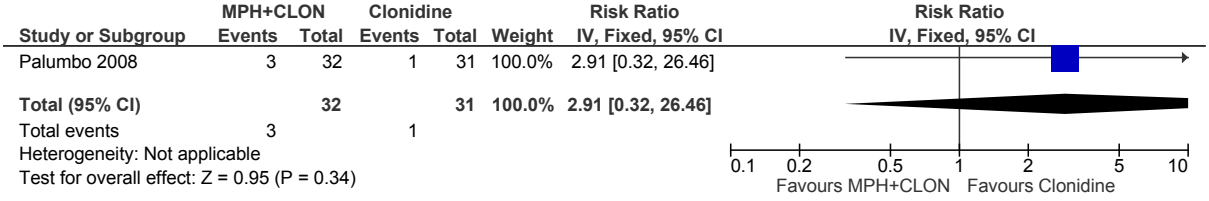

### Figure 171: ADHD total symptoms parent rated at 16 weeks (Conners ASQ-P total scores; 0-20; low scores are beneficial)




### Figure 172: Behaviour at 16 weeks (Childrens global assessment scale; 0-100; high scores are beneficial)




### Figure 173: Discontinuation due to adverse events at 16 weeks




## Amotoxetine and fluoxetine versus atomoxetine and placebo

### Figure 174: ADHD total symptoms investigator rated (8 weeks; ADHD-RS total scores; 0-54; low scores are beneficial)

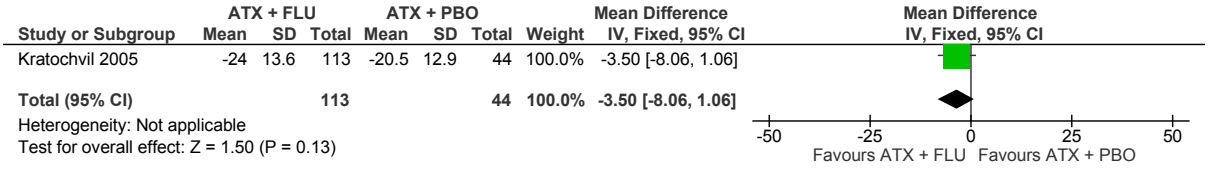


**Figure 175: ADHD inattention symptoms investigator rated (8 weeks; ADHD-RS inattention subscale scores; 0-27; low scores are beneficial)**

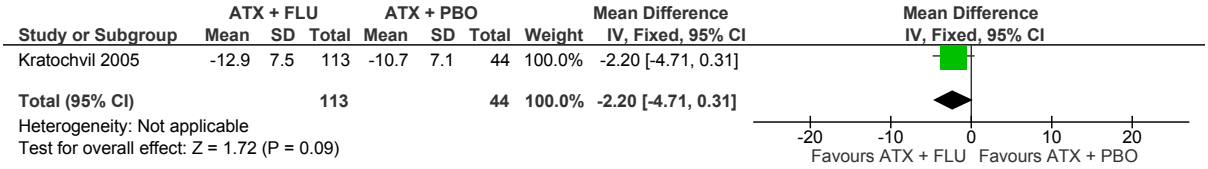



**Figure 176: ADHD hyperactivity symptoms investigator rated (8 weeks; ADHD-RS hyperactivity subscale scores; 0-27; low scores are beneficial)**

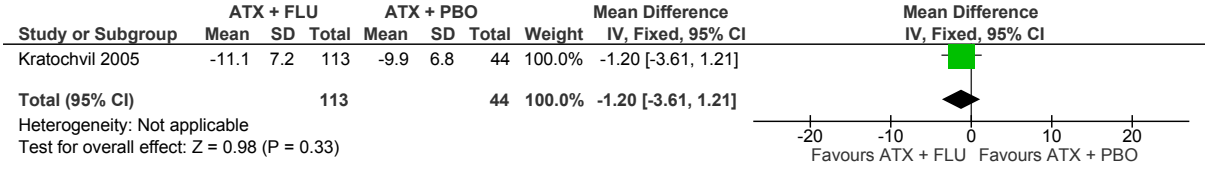
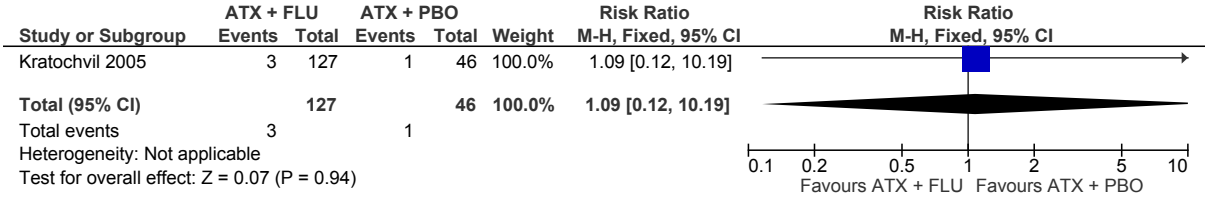



**Figure 177: Discontinuation due to adverse events at 8 weeks**




## E.1.3 Adults

### Immediate release methylphenidate versus placebo

**Figure 178: 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)**

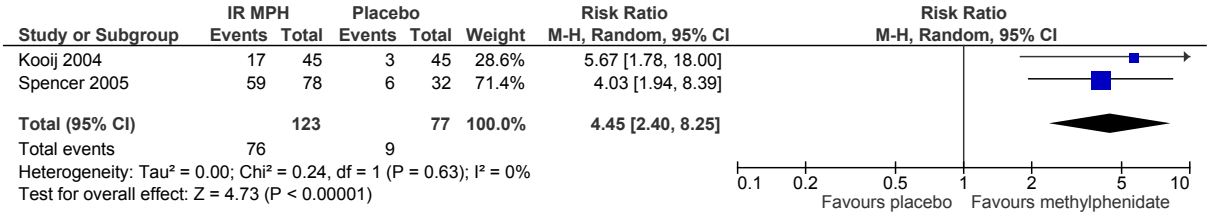



**Figure 179: ADHD total symptoms investigator rated (CAARS and Barkleys ADHD Rating Scale total scores at 3-4 weeks; final values reported; lower values are beneficial)**

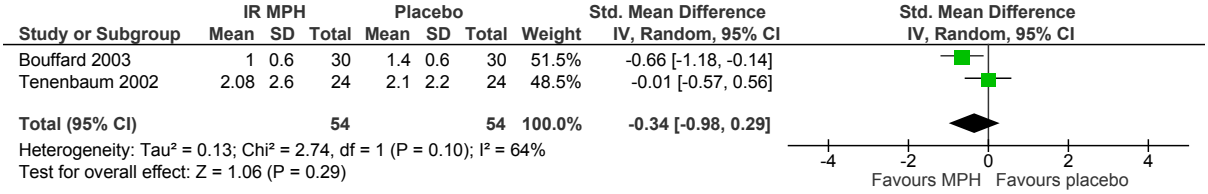


**Figure 180: ADHD total symptoms investigator rated (ADHD-RS total scores at 7 weeks; 0-54, change scores reported; lower values are beneficial)**

| Study or Subgroup | IR MPH Mean | IR MPH SD | IR MPH Total | Placebo Mean | Placebo SD | Placebo Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Kuperman 2001 | -10.1 | 8.3 | 8 | -12.4 | 10.6 | 11 | 100.0% | 2.30 [-6.20, 10.80] |
| **Total (95% CI)** | | | **8** | | | **11** | **100.0%** | **2.30 [-6.20, 10.80]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.53 (P = 0.60)

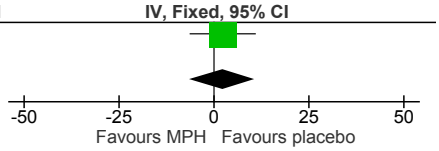



**Figure 181: CGI-I score of 1 or 2 at 7 weeks**

| Study or Subgroup | IR MPH Events | IR MPH Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Kuperman 2001 | 4 | 8 | 3 | 11 | 71.6% | 1.83 [0.56, 6.01] |
| Spencer 1995 | 18 | 23 | 1 | 23 | 28.4% | 18.00 [2.62, 123.88] |
| **Total (95% CI)** | | **31** | | **34** | **100.0%** | **6.42 [2.31, 17.85]** |
| Total events | 22 | | 4 | | | |

Heterogeneity: Chi² = 5.37, df = 1 (P = 0.02); I² = 81%
Test for overall effect: Z = 3.56 (P = 0.0004)

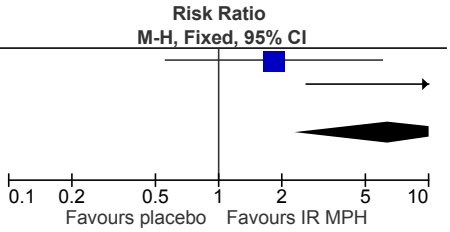



**Figure 182: Behaviour outcome at 2 to 4 weeks (Global assessment of functioning and Problem behaviour scale); final values reported; high values are beneficial )**

| Study or Subgroup | IR MPH Mean | IR MPH SD | IR MPH Total | Placebo Mean | Placebo SD | Placebo Total | Weight | Std. Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Bouffard 2003 | 1.5 | 0.5 | 30 | 0.9 | 0.5 | 30 | 42.9% | 1.18 [0.63, 1.74] |
| Wender 1985 | 69.17 | 9.66 | 37 | 61.26 | 8.02 | 37 | 57.1% | 0.88 [0.40, 1.36] |
| **Total (95% CI)** | | | **67** | | | **67** | **100.0%** | **1.01 [0.65, 1.37]** |

Heterogeneity: Chi² = 0.66, df = 1 (P = 0.42); I² = 0%
Test for overall effect: Z = 5.49 (P < 0.00001)

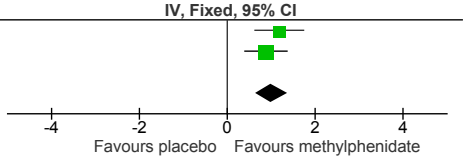
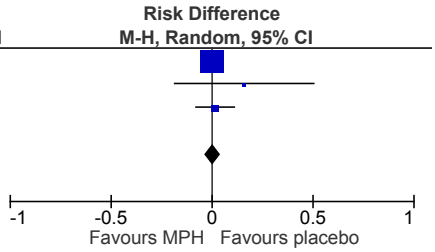



**Figure 183: Discontinuation due to adverse events at 3-7 weeks**

| Study or Subgroup | IR MPH Events | IR MPH Total | Placebo Events | Placebo Total | Weight | Risk Difference M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Kooij 2004 | 0 | 45 | 0 | 45 | 82.3% | 0.00 [-0.04, 0.04] |
| Kuperman 2001 | 2 | 8 | 1 | 11 | 1.2% | 0.16 [-0.19, 0.50] |
| Spencer 2005 | 9 | 104 | 3 | 42 | 16.4% | 0.02 [-0.08, 0.11] |
| **Total (95% CI)** | | **157** | | **98** | **100.0%** | **0.00 [-0.03, 0.04]** |
| Total events | 11 | | 4 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 1.56, df = 2 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.23 (P = 0.82)




## OROS release methylphenidate versus placebo

**Figure 184: Quality of life at 8 weeks (Q-LES-Q total sores; 0-80; high scores are beneficial)**

| Study or Subgroup | Methylphenidate Mean | Methylphenidate SD | Methylphenidate Total | Placebo Mean | Placebo SD | Placebo Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Takahashi 2014 | 2.4 | 14 | 142 | 0.8 | 12.69 | 140 | 100.0% | 1.60 [-1.52, 4.72] |
| **Total (95% CI)** | | | **142** | | | **140** | **100.0%** | **1.60 [-1.52, 4.72]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.01 (P = 0.31)

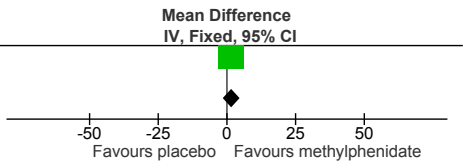


**Figure 185: Treatment response (defined as CGI-I score of 1 or 2 and 30% reduction on AISRS and 30% reduction on WRAADDS) at 6-8 weeks**

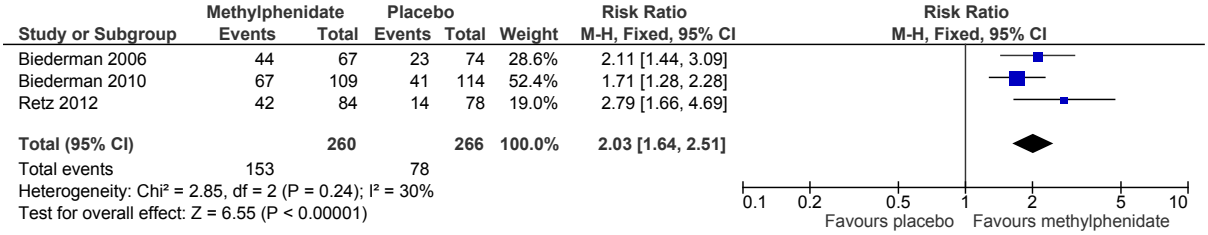



**Figure 186: ADHD total symptoms investigator rated (multiple scales including CAARS-O:SV and ADHD-RS total scores) at 5 to 13 weeks; low values are beneficial, final values and change scores reported)**

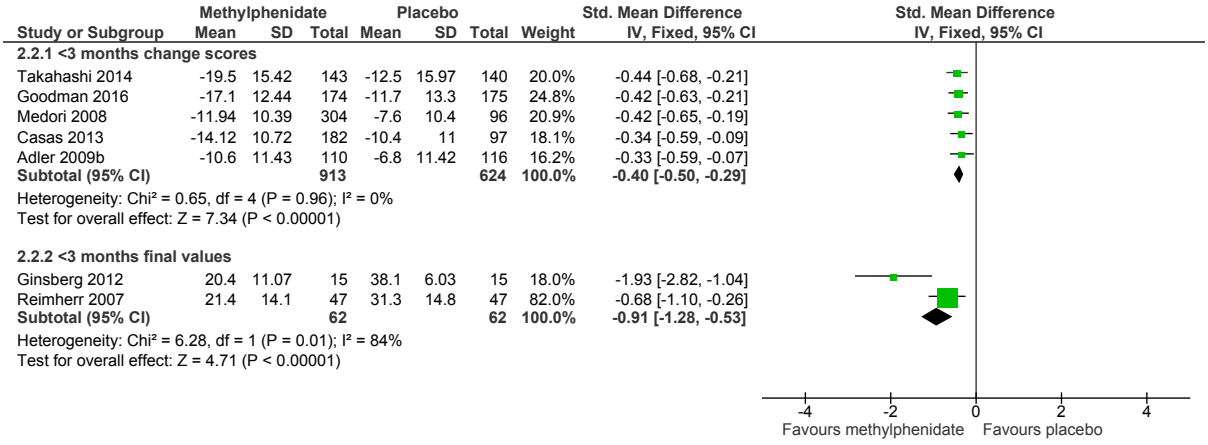



**Figure 187: ADHD total symptoms self rated (CAARS-O:SV total scores and CAARS ADHD index) at 2 to 5 weeks; low values are beneficial, final values reported)**

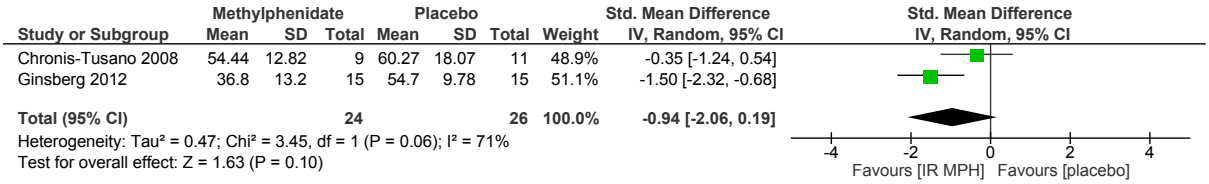



**Figure 188: ADHD total symptoms self rated (CAARS total scores at 5 to 8 weeks; 0-71, low values are beneficial, change scores reported)**

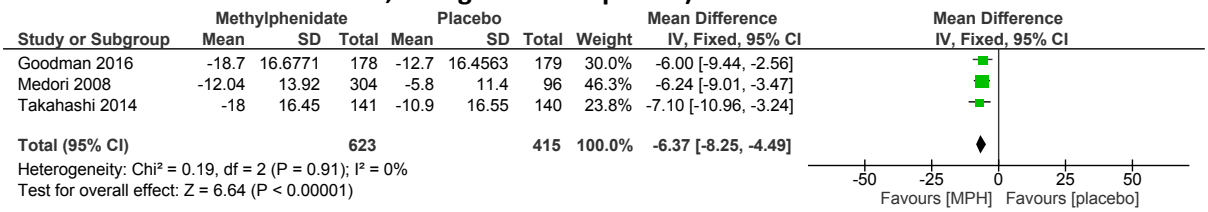


**Figure 189: ADHD total symptoms self rated (CAARS self report form total scores at 13 weeks; 0-54, low values are beneficial, change scores reported)**

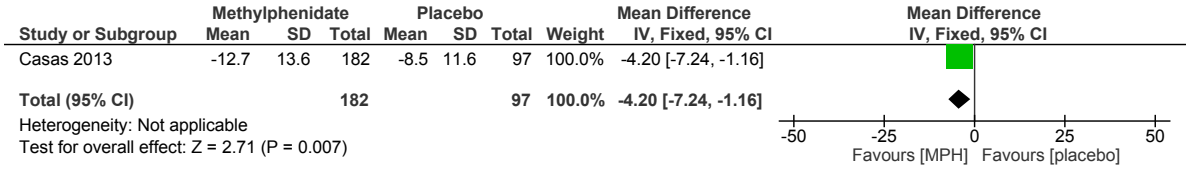



**Figure 190: ADHD inattention symptoms self rated (CAARS inattention subscale at 8 weeks; 0-27, low values are beneficial)**

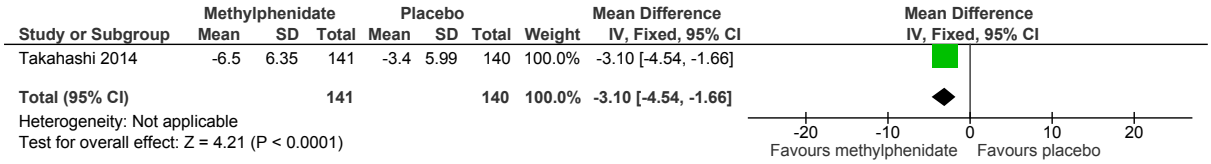



**Figure 191: ADHD inattention symptoms investigator rated (5 to 8 weeks; CAARS inattention subscale; 0-27, low values are beneficial, change scores reported)**

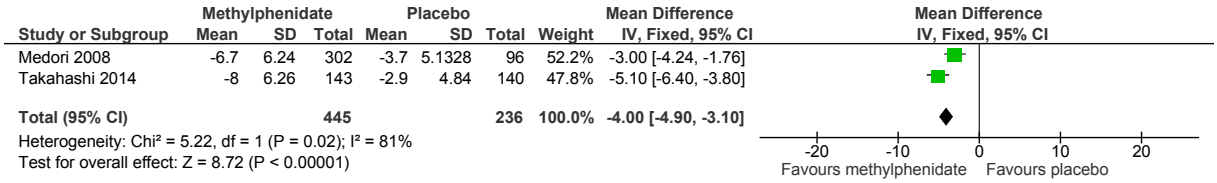



**Figure 192: ADHD inattention symptoms investigator rated (CAARS and ADHD-RS inattention subscales at 3 to 8 weeks; low values are beneficial, final values reported)**

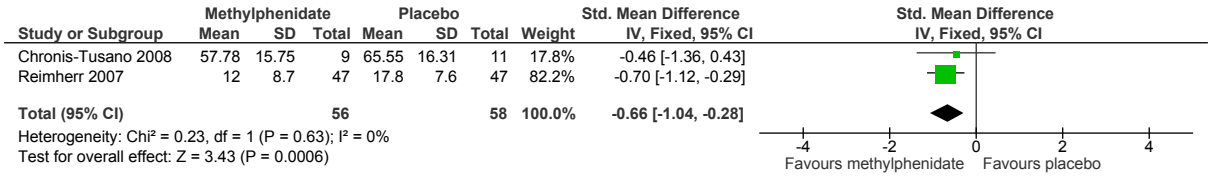



**Figure 193: ADHD inattention symptoms investigator rated (CAARS inattention subscale scores at 13 weeks; 0-27, low values are beneficial, change scores reported)**

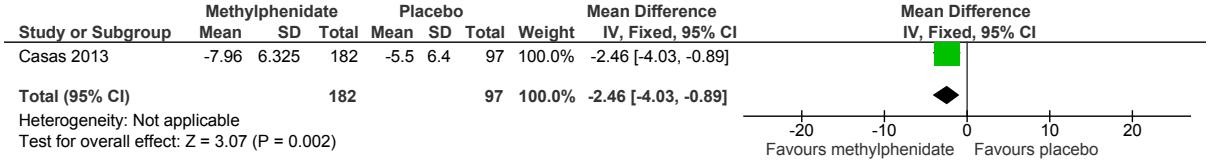



**Figure 194: ADHD hyperactivity symptoms self rated (CAARS hyperactive subscale at 8 weeks; 0-27, low values are beneficial, change scores reported)**

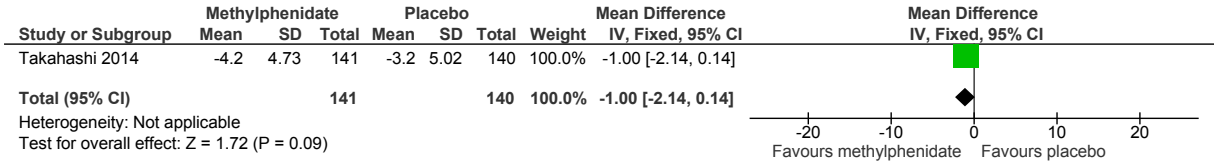


**Figure 195: ADHD hyperactivity symptoms investigator rated (CAARS hyperactive subscale at 5 to 8 weeks; 0-27, low values are beneficial, change scores reported)**

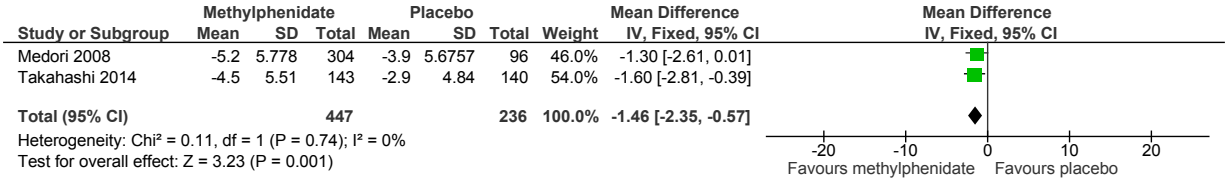



**Figure 196: ADHD hyperactivity symptoms investigator rated (ADHD-RS and CAARS hyperactivity subscale) at 2 to 8 weeks; low values are beneficial, final values reported)**

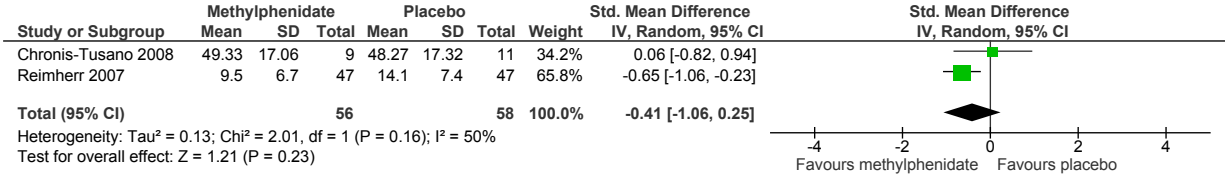



**Figure 197: ADHD hyperactivity symptoms investigator rated (CAARS hyperactivity subscale) at 13 weeks; 0-27; low values are beneficial, change scores reported)**

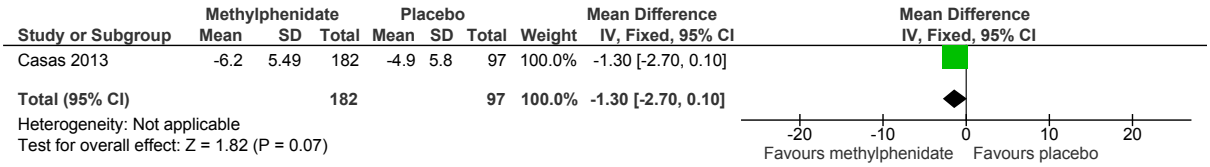



**Figure 198: CGI-I score of 1 or 2 at 7-13 weeks**

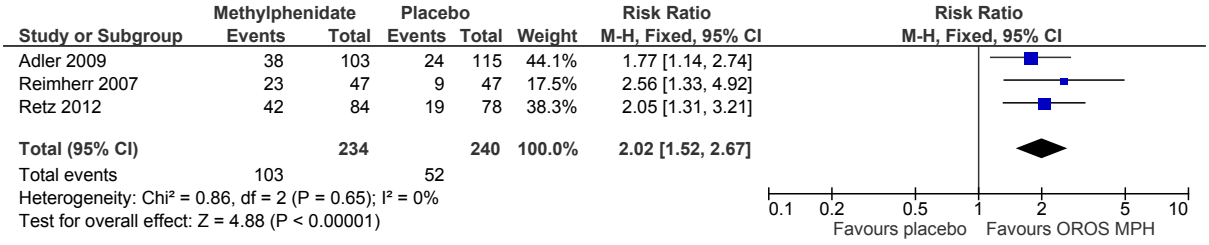



**Figure 199: Behaviour outcome (Global Assessment of Functioning) at 5 weeks; 0-100; high values are beneficial**

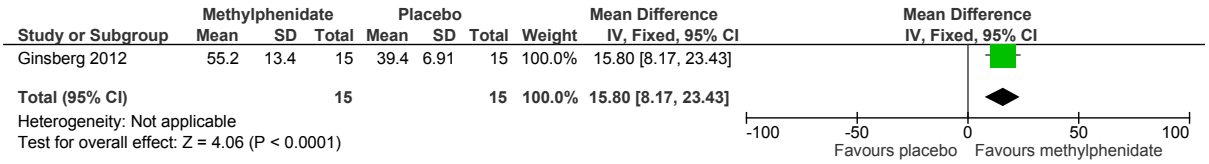


**Figure 200: Emotional dysregulation (PT; CAARS-S:L Emotional lability scale) at 5 weeks; 0-12, low values are beneficial, final values reported**

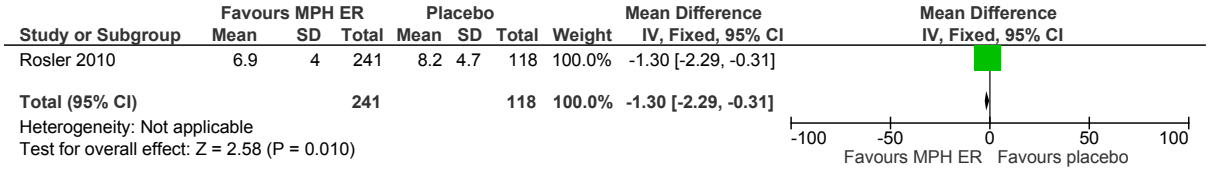



**Figure 201: Emotional dysregulation at 4 weeks (Crossover trial; WRAADS emotional dysregulation score; 0-28; lower values are beneficial)**

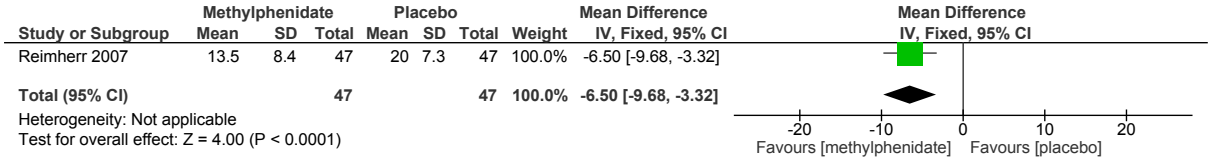
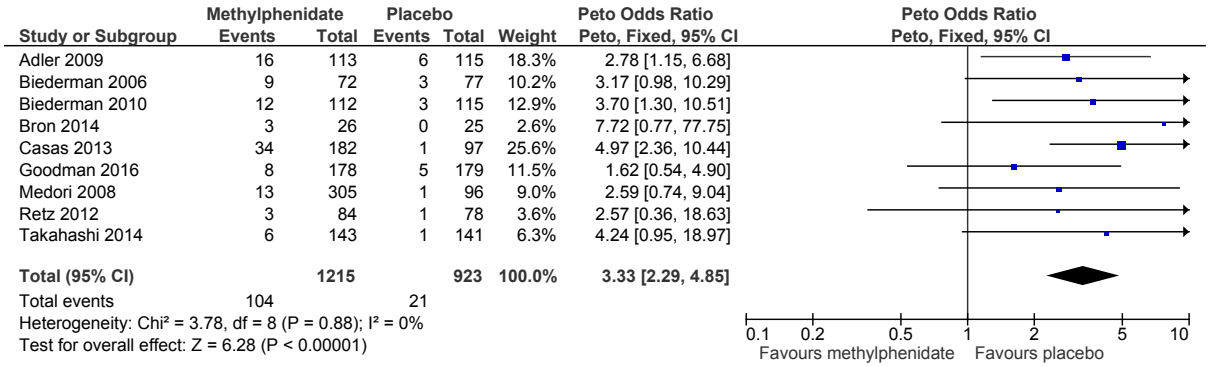



**Figure 202: Discontinuation due to adverse events at 6 to 13 weeks**




## Dexamfetamine versus placebo

**Figure 203: ADHD total symptoms investigator rated at 2 weeks (DSM-IV RS total scores); 0-54, lower values are beneficial, final values reported**

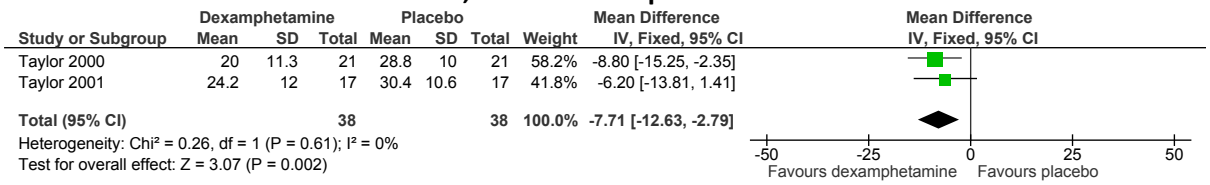


**Figure 204: ADHD inattention symptoms investigator rated at 2 weeks (DSM-IV RS Inattentive subscale); 0-27, lower values are beneficial, final values reported**

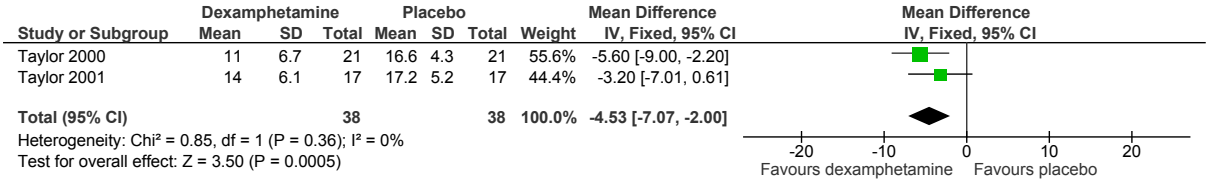



**Figure 205: ADHD hyperactivity symptoms investigator rated (DSM-IV RS Hyperactive subscale) at 2 weeks; 0-27, lower values are beneficial, final values reported**

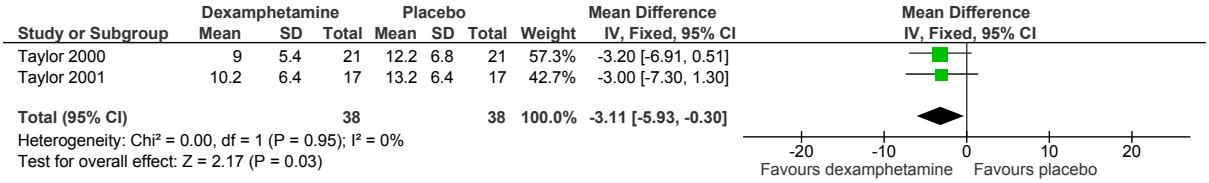
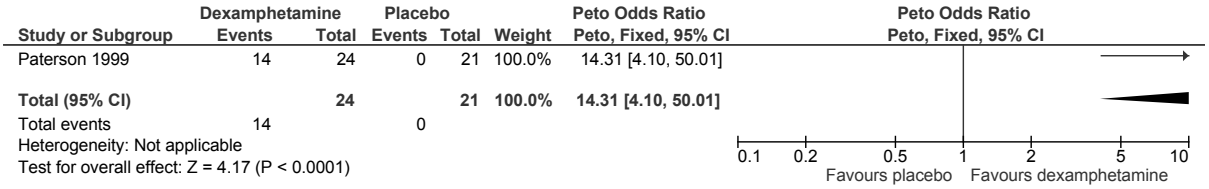



**Figure 206: Treatment response at 6 weeks (CGI-I score of 1 or 2)**




## Lisdexamfetamine dimesylate versus placebo

**Figure 207: Quality of life at 10 weeks (AAQoL), 0-100, high values are beneficial, change scores reported**

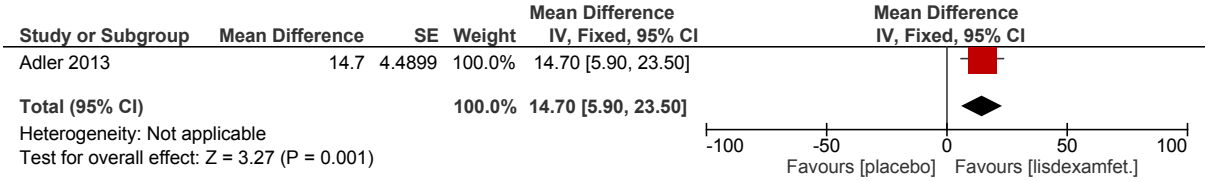



**Figure 208: ADHD total symptoms investigator rated at 4 to 10 weeks (ADHD-RS total scores); 0-54, lower values are beneficial, change scores reported**

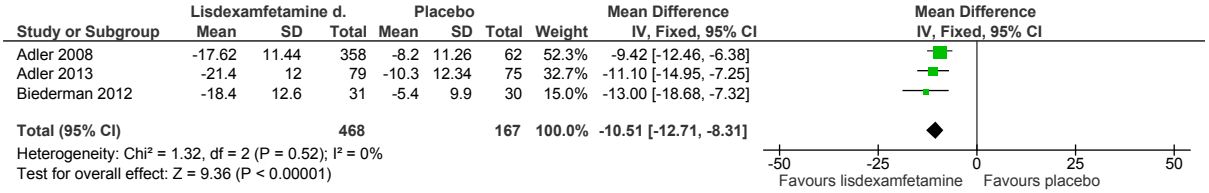


**Figure 209: ADHD inattention symptoms investigator rated at 10 weeks (ADHD-RS inattention subscale); 0-27, lower values are beneficial, change scores reported**

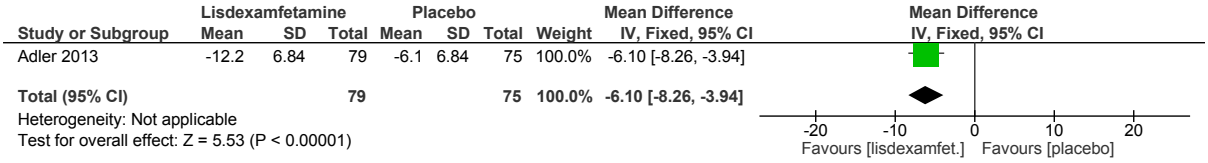



**Figure 210: ADHD hyperactivity symptoms investigator rated at 10 weeks (ADHD-RS hyperactivity subscale); 0-27, lower values are beneficial, change scores reported**

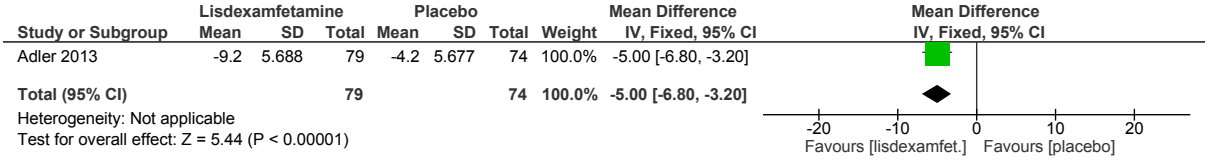



**Figure 211: CGI score of 1 or 2 at 4 weeks**

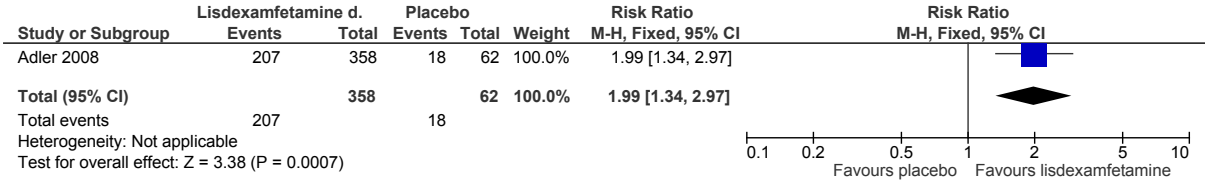



**Figure 212: Behavioural outcomes at 6 weeks (Global assessment of functioning); 0-100, higher values are beneficial, final values reported**

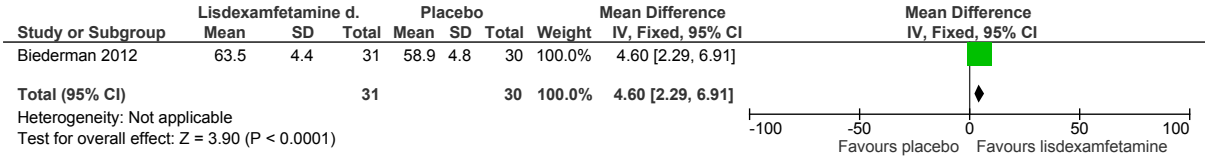
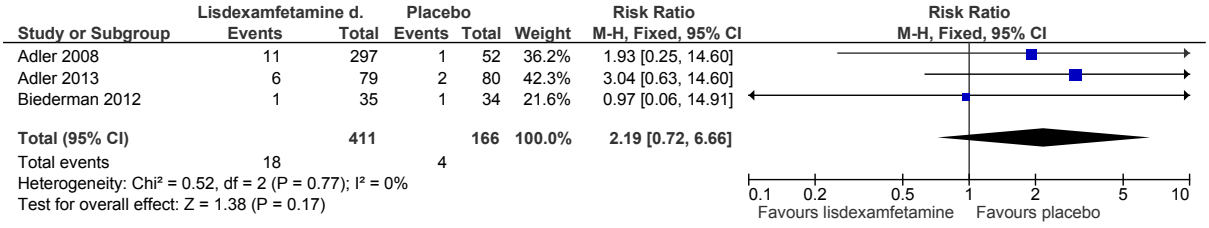
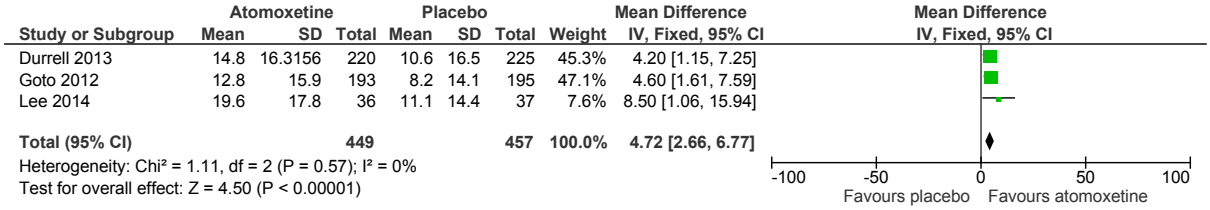



**Figure 213: Discontinuation due to adverse events at 4-10 weeks**

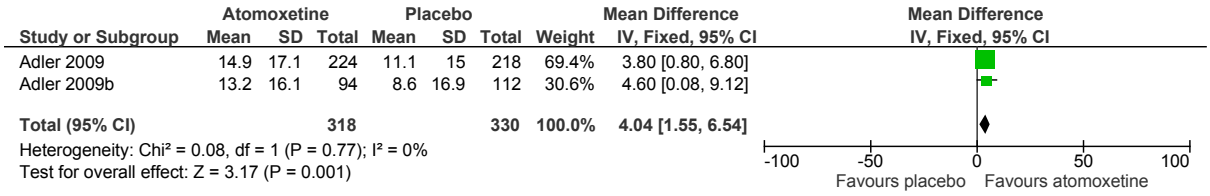


## Atomoxetine versus placebo

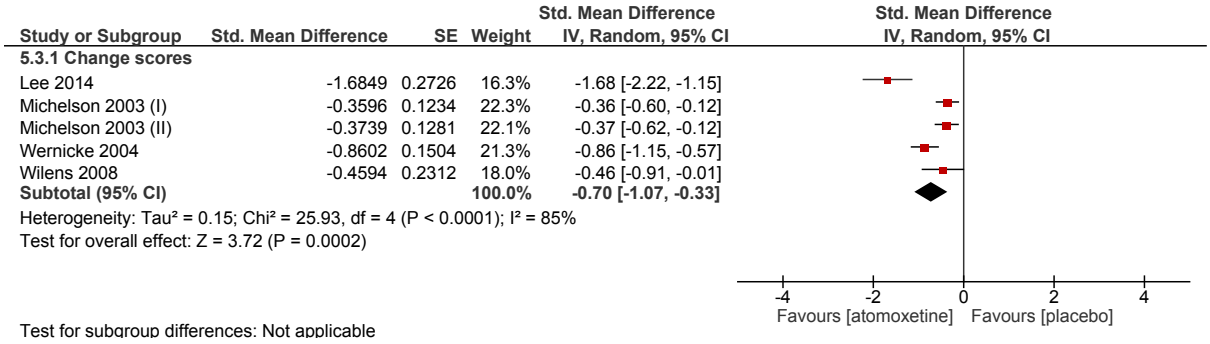
### Figure 214: Quality of Life at 10 to 12 weeks (AAQoL Total Scores); 0-100; high values are beneficial




### Figure 215: Quality of life at 16 to 24 weeks (AAQoL Total Scores); 0-100; high values are beneficial




### Figure 216: 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)




### Figure 217: ADHD total symptoms investigator rated at 8 to 12 weeks (AISRS and CAARS total scores; 0-54; final values reported; low values are beneficial)

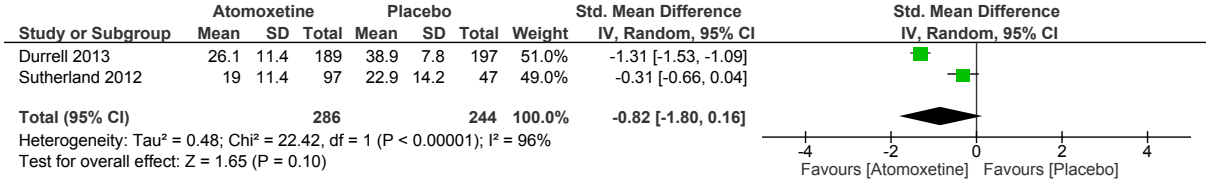


**Figure 218: ADHD total symptoms investigator rated at 16 to 24 weeks (AISRS and CAARS total scores; change scores reported; low values are beneficial)**

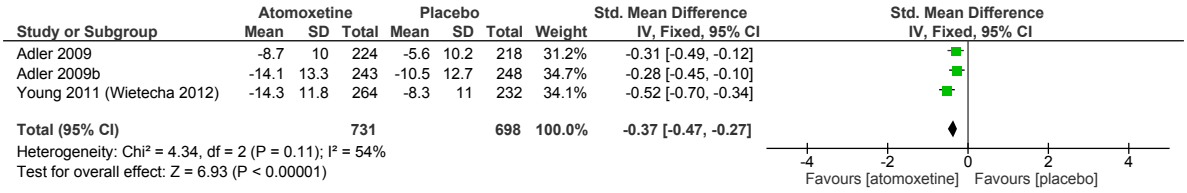



**Figure 219: ADHD total symptoms self rated at 10 to 12 weeks (CAARS total score); 0-84 change scores reported; low values are beneficial**

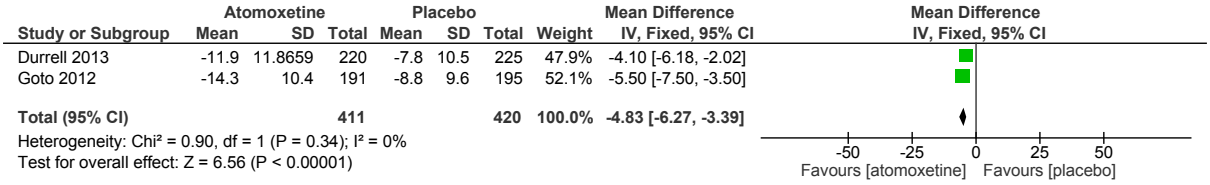



**Figure 220: ADHD inattention symptoms self rated at 10 to 12 weeks (CAARS inattention subscale); 0-28; low values are beneficial; change scores reported**

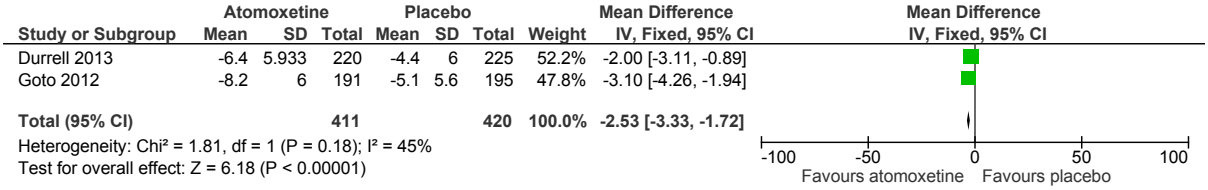



**Figure 221: ADHD inattention symptoms investigator rated at 8 to 12 weeks (multiple scales including CAARS and ADHD-RS inattention subscales); low values are beneficial; change scores reported**

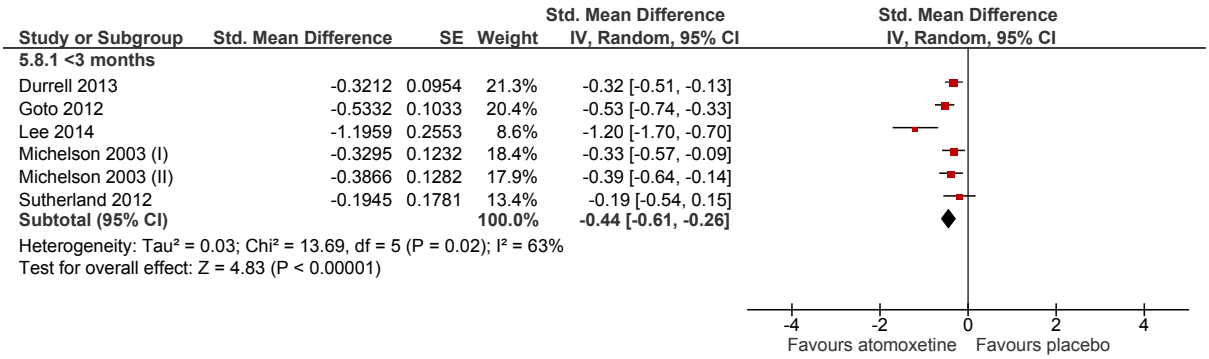


**Figure 222: ADHD inattention symptoms investigator rated at 16 to 24 weeks (multiple scales including AISRS and CAARS inattention subscale scores; change scores reported; low values are beneficial)**

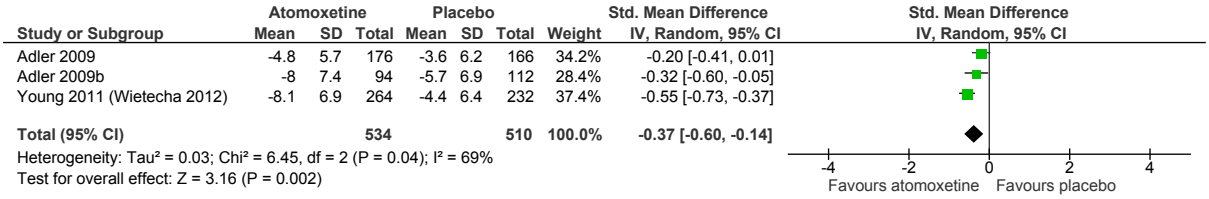



**Figure 223: ADHD hyperactivity symptoms investigator rated at 8 to 12 weeks(multiple scales including AISRS and CAARS hyperactivity/impulsivity subscale); low values are beneficial; change scores reported**

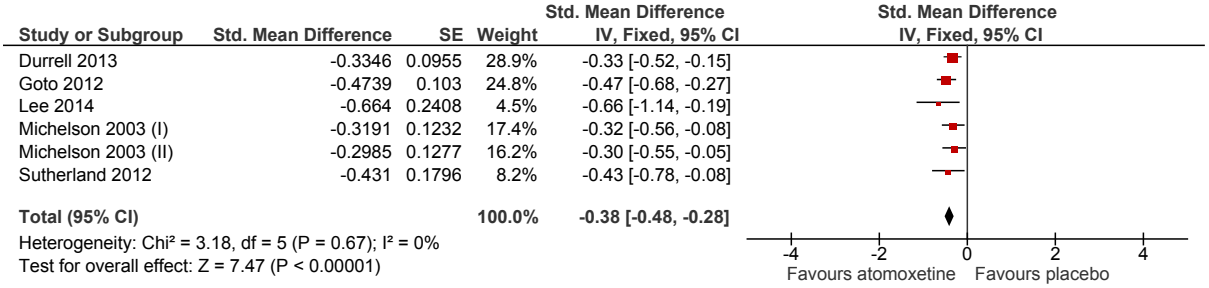



**Figure 224: ADHD hyperactivity symptoms self rated at 10 to 12 weeks (CAARS hyperactivity subscales; 0-27; low values are beneficial; change scores reported)**

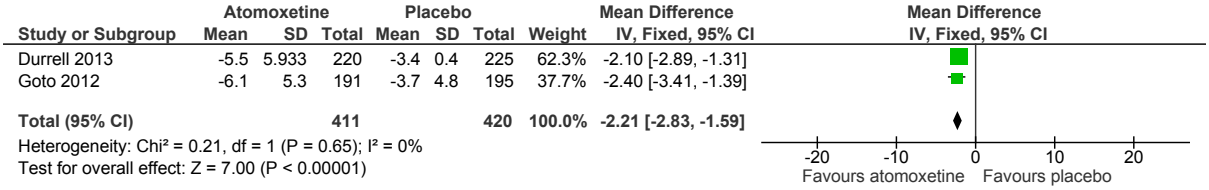



**Figure 225: ADHD hyperactivity symptoms at 16 to 24 weeks investigator rated (CAARS and AISRS hyperactivity subscales); 0-27; change scores reported; low values are beneficial**

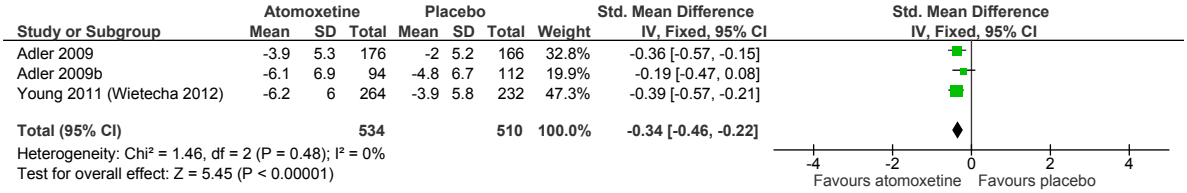


**Figure 226: Behaviour outcome at 10 to 12 weeks (BRIEF-A self report total score); 0-100, low values are beneficial, change scores reported**

| Study or Subgroup | Atomoxetine Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Durrell 2013 | -19.78 | 25.59 | 161 | -13.41 | 21.76 | 167 | 18.0% | -6.37 [-11.52, -1.22] |
| Goto 2012 | -10.7 | 13.6 | 193 | -6.1 | 10.4 | 195 | 82.0% | -4.60 [-7.01, -2.19] |
| **Total (95% CI)** | | | **354** | | | **362** | **100.0%** | **-4.92 [-7.10, -2.73]** |

Heterogeneity: Chi² = 0.37, df = 1 (P = 0.54); I² = 0%
Test for overall effect: Z = 4.41 (P < 0.0001)

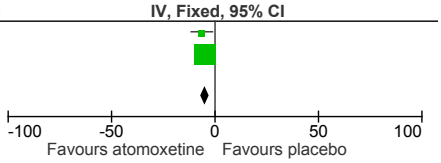



**Figure 227: Discontinuation due to adverse events at 8 to 12 weeks**

| Study or Subgroup | Atomoxetine Events | Total | Placebo Events | Total | Weight | Peto Odds Ratio Peto, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Biederman 2012 | 0 | 0 | 0 | 0 | | Not estimable |
| Durrell 2013 | 21 | 220 | 6 | 225 | 27.7% | 3.33 [1.53, 7.26] |
| Goto 2012 | 10 | 195 | 3 | 196 | 13.8% | 3.05 [1.01, 9.21] |
| Lee 2014 | 0 | 36 | 1 | 37 | 1.1% | 0.14 [0.00, 7.01] |
| Michelson 2003 (I) | 11 | 141 | 6 | 139 | 17.5% | 1.84 [0.69, 4.89] |
| Michelson 2003 (II) | 12 | 129 | 3 | 127 | 15.5% | 3.50 [1.24, 9.92] |
| Sutherland 2012 | 11 | 97 | 7 | 47 | 15.2% | 0.72 [0.25, 2.07] |
| Wilens 2008 | 7 | 67 | 2 | 73 | 9.2% | 3.57 [0.93, 13.73] |
| **Total (95% CI)** | | **885** | | **844** | **100.0%** | **2.30 [1.53, 3.47]** |
| Total events | 72 | | 28 | | | |

Heterogeneity: Chi² = 8.99, df = 6 (P = 0.17); I² = 33%
Test for overall effect: Z = 4.00 (P < 0.0001)

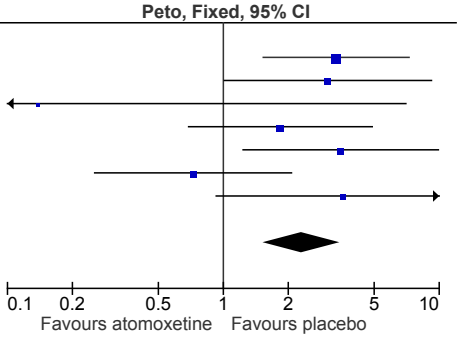
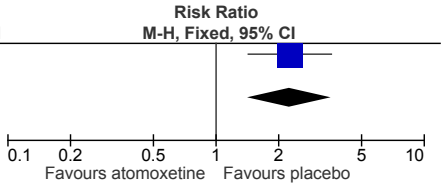



**Figure 228: Discontinuation due to adverse events at 24 weeks**

| Study or Subgroup | Atomoxetine Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Young 2011 (Wietecha 2012) | 57 | 268 | 22 | 234 | 100.0% | 2.26 [1.43, 3.58] |
| **Total (95% CI)** | | **268** | | **234** | **100.0%** | **2.26 [1.43, 3.58]** |
| Total events | 57 | | 22 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 3.48 (P = 0.0005)




## Guanfacine versus placebo

**Figure 229: ADHD total symptoms investigator rated (DSM-IV RS total scores); 0-54; low values are beneficial; 6 weeks**

| Study or Subgroup | Guanfacine Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Taylor 2001 | 22.3 | 8.2 | 17 | 30.4 | 10.6 | 17 | 100.0% | -8.10 [-14.47, -1.73] |
| **Total (95% CI)** | | | **17** | | | **17** | **100.0%** | **-8.10 [-14.47, -1.73]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 2.49 (P = 0.01)

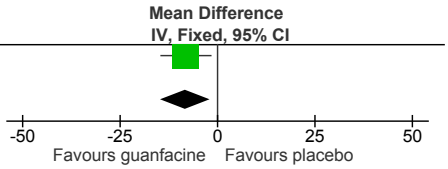



**Figure 230: ADHD inattention symptoms investigator rated (DSM-IV RS inattentive subscale); 0-27; low values are beneficial; 6 weeks**

| Study or Subgroup | Guanfacine Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Taylor 2001 | 12.8 | 4.1 | 17 | 17.2 | 5.2 | 17 | 100.0% | -4.40 [-7.55, -1.25] |
| **Total (95% CI)** | | | **17** | | | **17** | **100.0%** | **-4.40 [-7.55, -1.25]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 2.74 (P = 0.006)

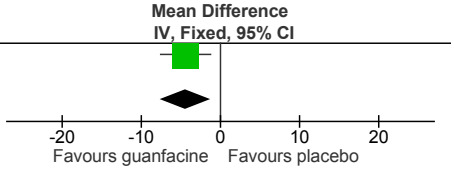
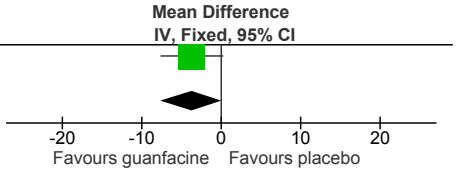


**Figure 231: ADHD hyperactivity symptoms investigator rated (DSM-IV RS hyperactive subscale); 0-27; low values are beneficial; 6 weeks**

| Study or Subgroup | Guanfacine Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Taylor 2001 | 9.5 | 5 | 17 | 13.2 | 6.4 | 17 | 100.0% | -3.70 [-7.56, 0.16] |
| **Total (95% CI)** | | | **17** | | | **17** | **100.0%** | **-3.70 [-7.56, 0.16]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.88 (P = 0.06)




## Guanfacine versus dexmethamphetamine

**Figure 232: ADHD total symptoms investigator rated (DSM-IV RS total scores); 0-54; low values are beneficial; 6 weeks**

| Study or Subgroup | Guanfacine Mean | SD | Total | Dexamphetamine Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Taylor 2001 | 22.3 | 8.2 | 17 | 24.2 | 12 | 17 | 100.0% | -1.90 [-8.81, 5.01] |
| **Total (95% CI)** | | | **17** | | | **17** | **100.0%** | **-1.90 [-8.81, 5.01]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.54 (P = 0.59)

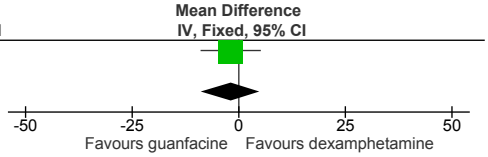



**Figure 233: ADHD inattention symptoms investigator rated (DSM-IV RS inattentive subscale); 0-27; low values are beneficial; 6 weeks**

| Study or Subgroup | Favours guanfacine Mean | SD | Total | Dexamphetamine Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Taylor 2001 | 12.8 | 4.1 | 17 | 14 | 6.1 | 17 | 100.0% | -1.20 [-4.69, 2.29] |
| **Total (95% CI)** | | | **17** | | | **17** | **100.0%** | **-1.20 [-4.69, 2.29]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.67 (P = 0.50)

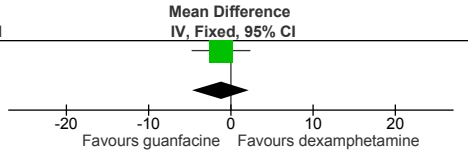
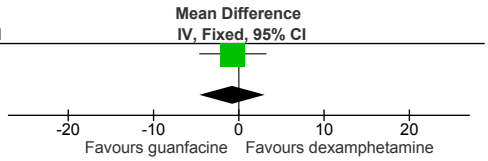



**Figure 234: ADHD hyperactivity symptoms investigator rated (DSM-IV RS hyperactive subscale); 0-27; low values are beneficial; 6 weeks**

| Study or Subgroup | Guanfacine Mean | SD | Total | Dexamphetamine Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Taylor 2001 | 9.5 | 5 | 17 | 10.2 | 6.4 | 17 | 100.0% | -0.70 [-4.56, 3.16] |
| **Total (95% CI)** | | | **17** | | | **17** | **100.0%** | **-0.70 [-4.56, 3.16]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.36 (P = 0.72)




## Reboxetine versus placebo

**Figure 235: ADHD total symptoms investigator rated (CAARS total scores); 0-54; low values are beneficial; 6 weeks**

| Study or Subgroup | Reboxetine Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Riahi 2010 | 21.89 | 9.63 | 22 | 27.47 | 8.18 | 17 | 100.0% | -5.58 [-11.18, 0.02] |
| **Total (95% CI)** | | | **22** | | | **17** | **100.0%** | **-5.58 [-11.18, 0.02]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.95 (P = 0.05)

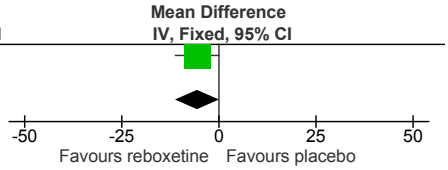


**Figure 236: ADHD inattention symptoms investigator rated (CAARS inattentive subscale) ; 0-27; low values are beneficial; 6 weeks**

| Study or Subgroup | Reboxetine Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Riahi 2010 | 11.31 | 5.17 | 22 | 16.05 | 4.65 | 17 | 100.0% | -4.74 [-7.83, -1.65] |
| **Total (95% CI)** | | | **22** | | | **17** | **100.0%** | **-4.74 [-7.83, -1.65]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 3.01 (P = 0.003)

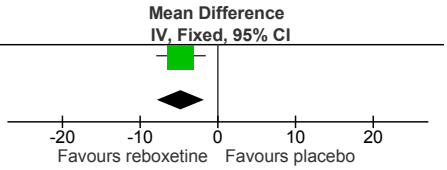



**Figure 237: ADHD hyperactivity symptoms investigator rated (CAARS hyperactive subscale); 0-27; low values are beneficial; 6 weeks**

| Study or Subgroup | Reboxetine Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Riahi 2010 | 10.54 | 4.89 | 22 | 11.47 | 5.14 | 17 | 100.0% | -0.93 [-4.12, 2.26] |
| **Total (95% CI)** | | | **22** | | | **17** | **100.0%** | **-0.93 [-4.12, 2.26]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.57 (P = 0.57)

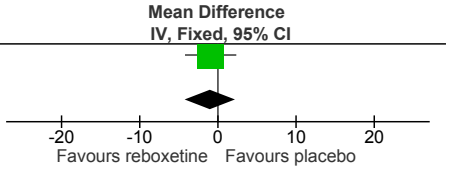



**Figure 238: Behavioural outcomes (Global assessment of functioning); 0-100; high values are beneficial; 6 weeks**

| Study or Subgroup | Reboxetine Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Riahi 2010 | 6.13 | 0.83 | 22 | 5.05 | 0.42 | 17 | 100.0% | 1.08 [0.68, 1.48] |
| **Total (95% CI)** | | | **22** | | | **17** | **100.0%** | **1.08 [0.68, 1.48]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 5.29 (P < 0.00001)

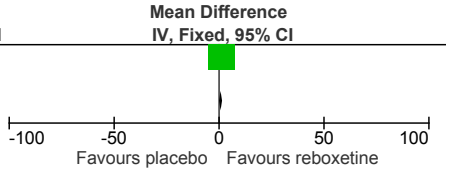
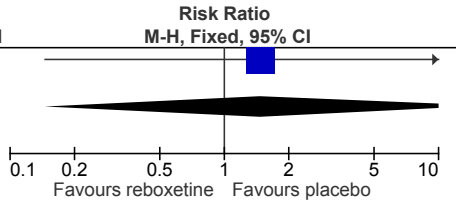



**Figure 239: Discontinuation due to adverse events at 6 weeks**

| Study or Subgroup | Reboxetine Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Riahi 2010 | 2 | 23 | 1 | 17 | 100.0% | 1.48 [0.15, 15.00] |
| **Total (95% CI)** | | **23** | | **17** | **100.0%** | **1.48 [0.15, 15.00]** |
| Total events | 2 | | 1 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.33 (P = 0.74)




## Venlafaxine versus placebo

**Figure 240: ADHD total symptoms self rated at 6 weeks (CAARS ADHD index); 0-27; low values are beneficial**

| Study or Subgroup | Venlafaxine Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Amiri 2012 | -25.35 | 12.47 | 20 | -12.05 | 6.01 | 21 | 100.0% | -13.30 [-19.34, -7.26] |
| **Total (95% CI)** | | | **20** | | | **21** | **100.0%** | **-13.30 [-19.34, -7.26]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 4.32 (P < 0.0001)

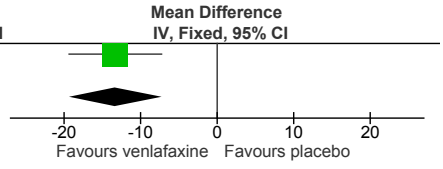


**Figure 241: ADHD inattention symptoms self rated (CAARS inattentive subscale); 0-27; low values are beneficial; 6 weeks**

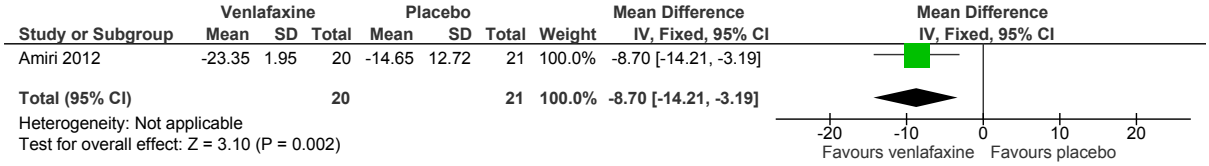



**Figure 242: ADHD hyperactivity symptoms self rated at 6 weeks (CAARS hyperactive/impulsive subscale); 0-27; low values are beneficial**

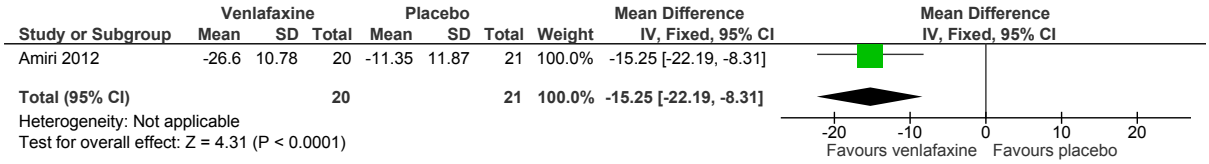



**Figure 243: Discontinuation due to adverse events at 6 weeks**

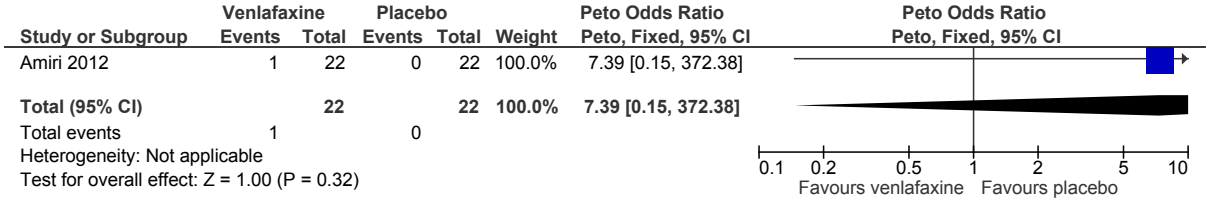
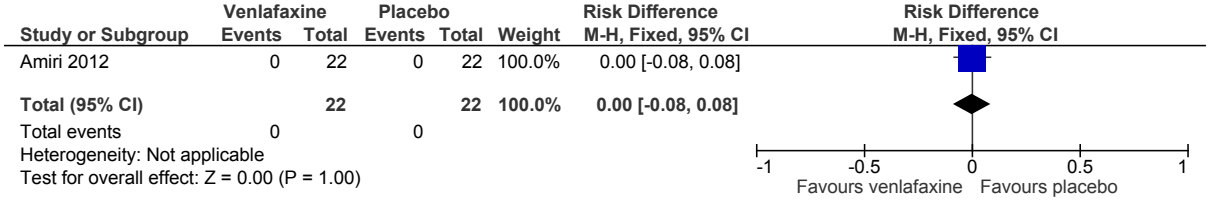



**Figure 244: Serious adverse events at 6 weeks**




## Bupropion versus placebo

**Figure 245: ADHD total symptoms investigator rated at 7 weeks (ADHD-RS total score); 0-54; low values are beneficial; change scores reported**

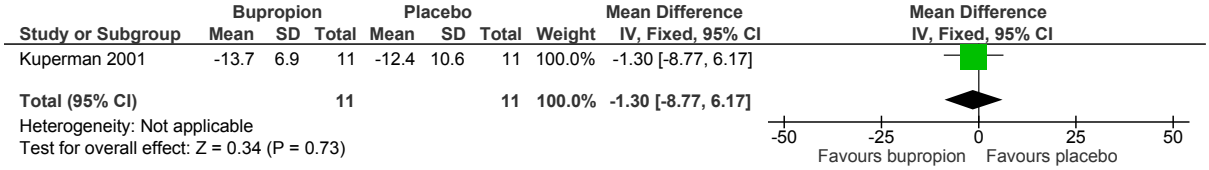


**Figure 246: ADHD total symptoms investigator rated at 6 weeks (CAARStotal score); 0-54; low values are beneficial; final values reported**

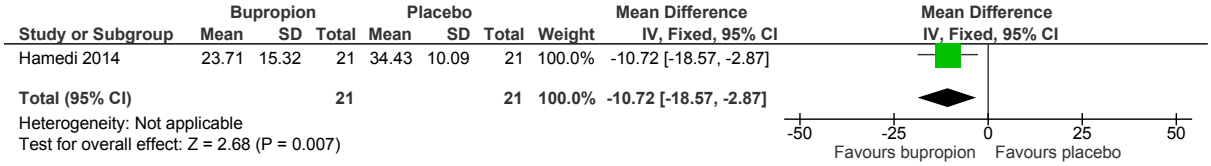



**Figure 247: CGI-I score of 1 or 2 at 7 weeks**

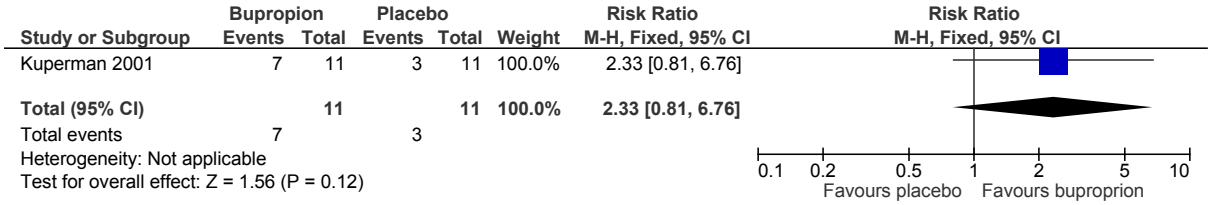
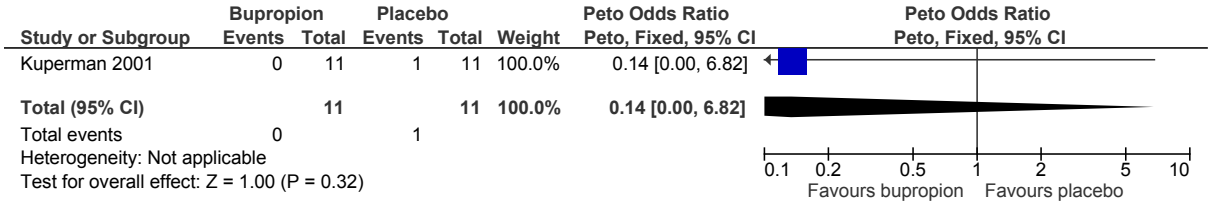



**Figure 248: Discontinuation due to adverse events at 7 weeks**




## Bupropion versus methylphenidate

**Figure 249: ADHD total symptoms investigator rated at 7 weeks (ADHD-RS total score); 0-54, low values are beneficial**

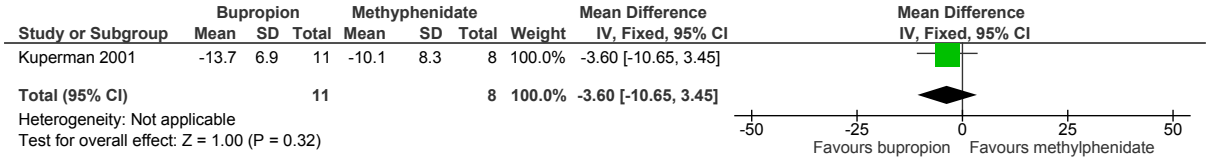



**Figure 250: CGI-I score of 1 or 2 at 7 weeks**

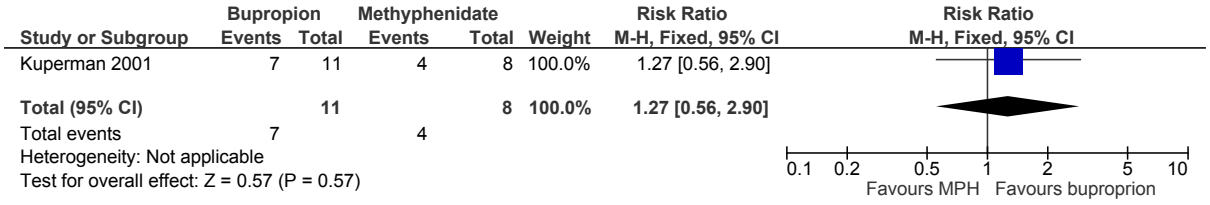
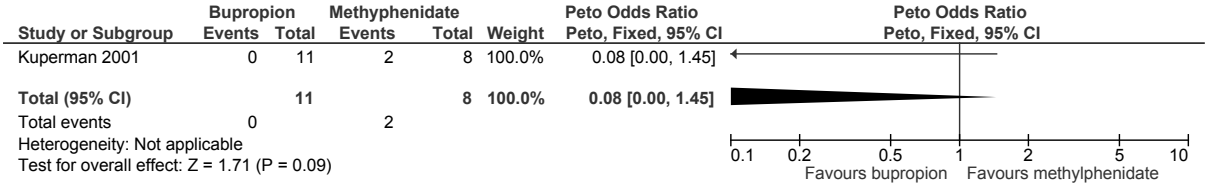


**Figure 251: Discontinuation due to adverse events at 7 weeks**




## Modafinil versus placebo

**Figure 252: Quality of life at 9 weeks (Quality of life enjoyment and satisfaction questionnaire); 0-10, higher values are beneficial**

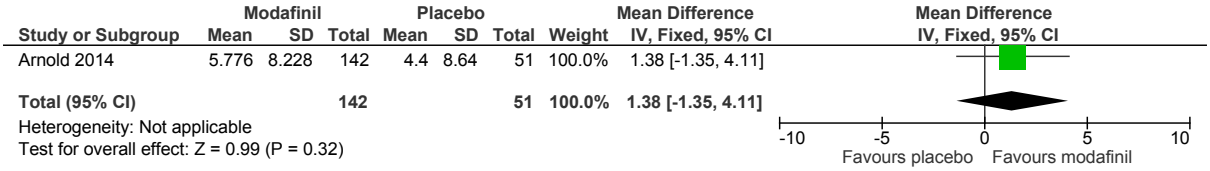



**Figure 253: ADHD total symptoms self rated at 9 weeks (Adult ADHD Self report scores; 0-54, lower values are beneficial**

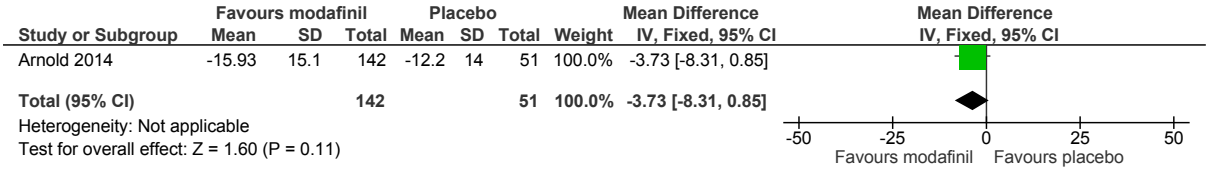



**Figure 254: ADHD total symptoms investigator rated at 2 weeks (DSM-IV RS total scores); 0-54, lower values are beneficial**

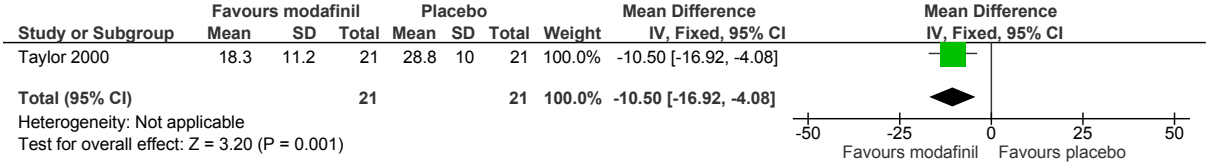



**Figure 255: ADHD inattention symptoms investigator rated at 2 weeks (DSM-IV RS Inattentive subscale); 0-27 lower values are beneficial, final values reported**

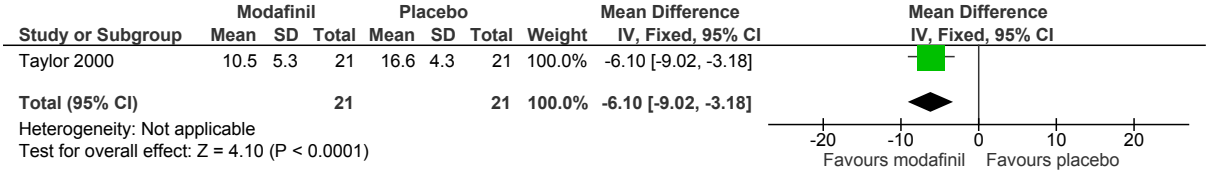


**Figure 256: ADHD hyperactivity symptoms investigator rated at 2 weeks (DSM-IV RS Hyperactive subscale); 0-27, lower values are beneficial**

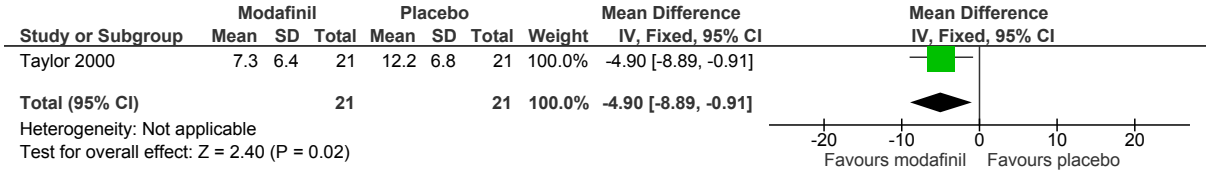



**Figure 257: Behavioural outcomes at 9 weeks (BRIEF-A); 0-100, lower values are beneficial**

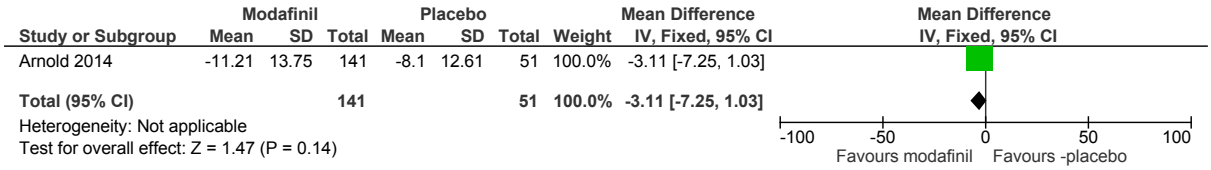
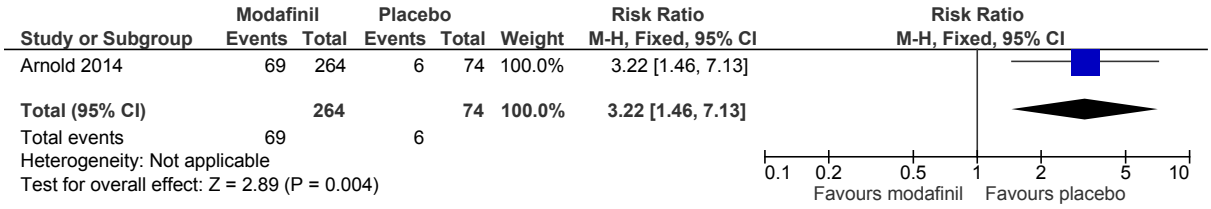



**Figure 258: Discontinuation due to adverse events at 7 weeks**




## Modafinil versus dexamfetamine

**Figure 259: ADHD total symptoms investigator rated (DSM-IV RS total scores) at 2 weeks; 0-54; lower values are beneficial**

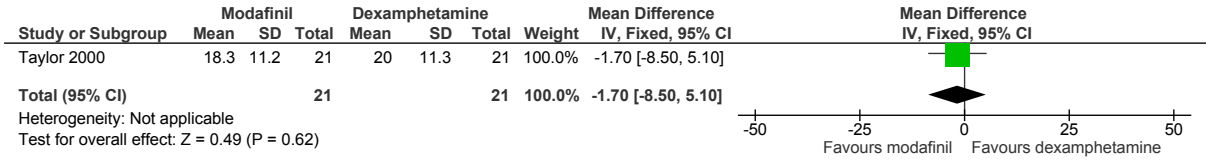



**Figure 260: ADHD inattention symptoms investigator rated (DSM-IV RS Inattentive subscale) at 2 weeks; 0-27, lower values are beneficial**

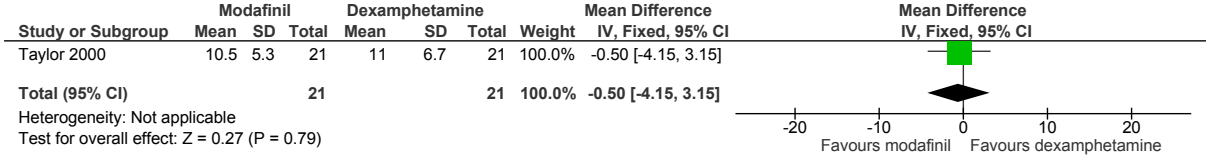
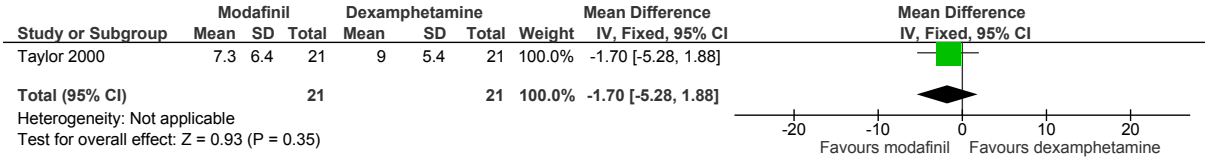


**Figure 261: ADHD hyperactivity symptoms investigator rated (DSM-IV Hyperactive subscale) at 2 weeks; 0-27, lower values are beneficial**




## Atomoxetine and buspirone versus placebo

**Figure 262: ADHD total symptoms investigator rated at 8 weeks (AISRS total scores); 0-54; lower values are beneficial**

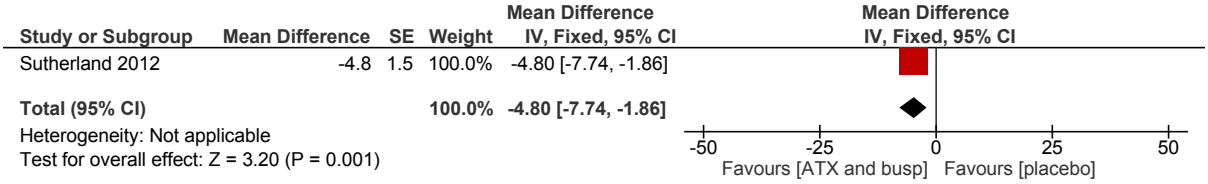



**Figure 263: ADHD inattention symptoms investigator rated at 8 weeks (AISRS inattention subscale); 0-27; lower values are beneficial**

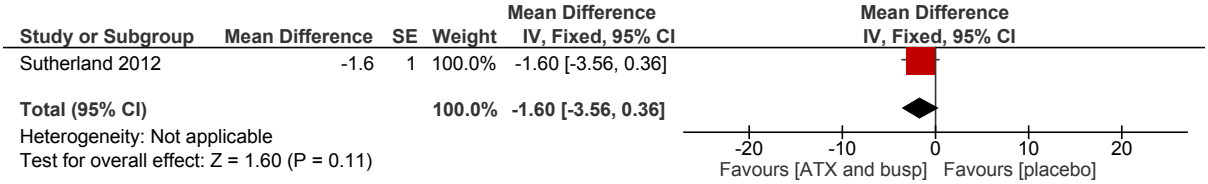



**Figure 264: ADHD hyperactivity symptoms investigator rated at 8 weeks (AISRS hyperactivity subscale); 0-27; lower values are beneficial**

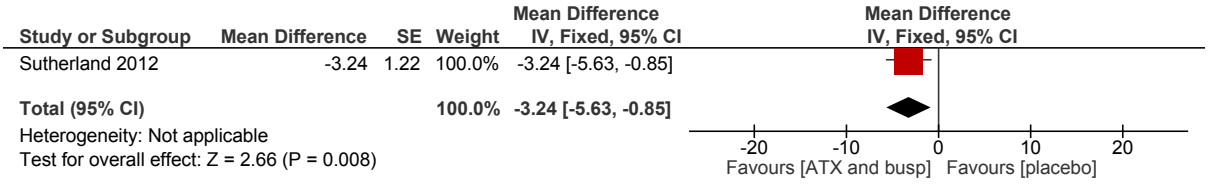
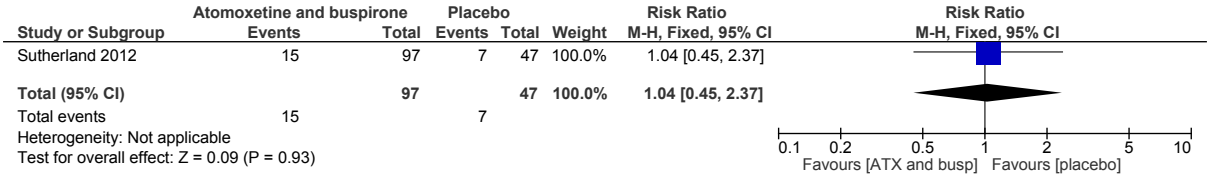



**Figure 265: Discontinuation due to adverse events at 8 weeks**



# E.2 Pharmacological sequencing

## Children

### E.2.1 Methylphenidate versus placebo in children with ADHD not responding to atomoxetine

**Figure 266: Discontinued treatment due to adverse events**

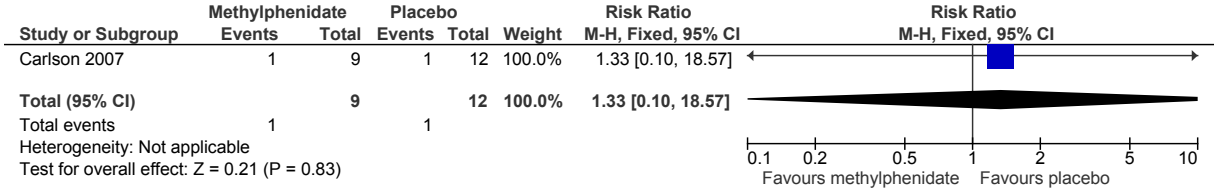
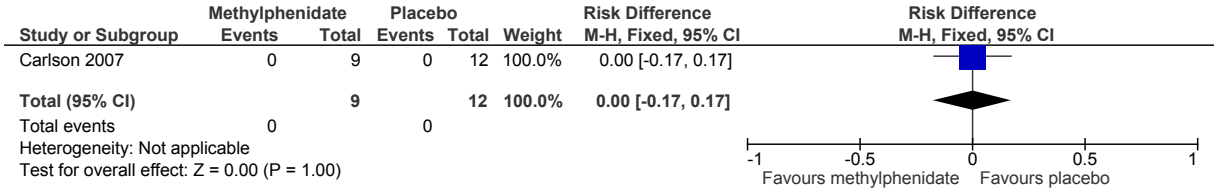



**Figure 267: Adverse events leading to hospitalisation/death/disability**




### E.2.2 Lisdexamfetamine dimesylate versus placebo in children with ADHD who had not responded to previous methylphenidate treatment

**Figure 268: ADHD symptoms (Clinical response: >/= 30% reduction in ADHD-RS-IV total score AND CGI-I 1 or 2)**

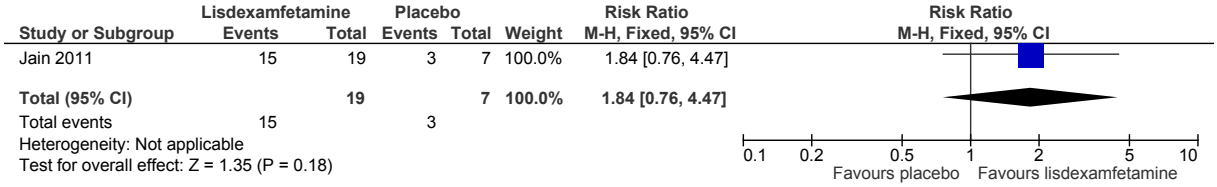
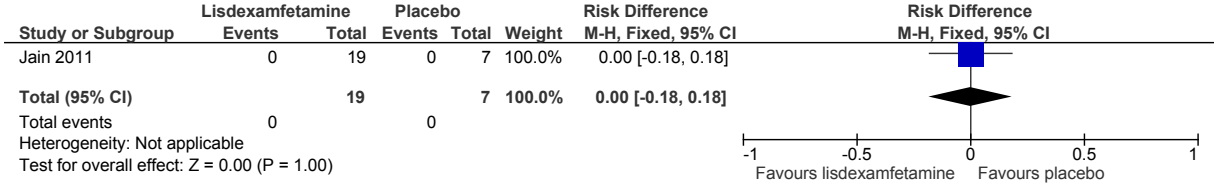
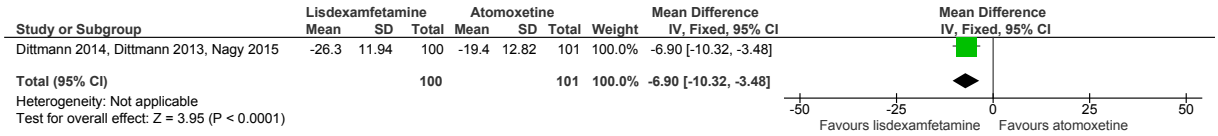



**Figure 269: Adverse events leading to hospitalisation/death/disability**




### E.2.3 Lisdexamfetamine dimesylate versus atomoxetine in children with ADHD who had an inadequate response to previous methylphenidate treatment

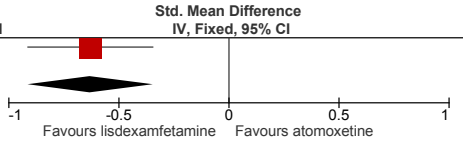
**Figure 270: ADHD total symptoms (investigator rated ADHD-RS-IV, change score, 0-54, high is poor)**



## Figure 271: Hyperactivity/impulsivity (Investigator rated, ADHD-RS-IV, high is poor)

| Study or Subgroup | Std. Mean Difference | SE | Weight | Std. Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|
| Dittmann 2014, Dittmann 2013, Nagy 2015 | -0.6296 | 0.1446 | 100.0% | -0.63 [-0.91, -0.35] |
| **Total (95% CI)** | | | **100.0%** | **-0.63 [-0.91, -0.35]** |

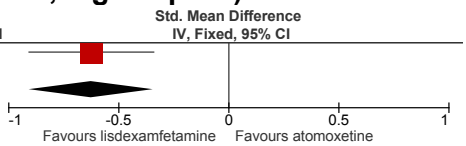
Heterogeneity: Not applicable
Test for overall effect: Z = 4.35 (P < 0.0001)




## Figure 272: Inattention (Investigator rated, ADHD-RS-IV, high is poor)

| Study or Subgroup | Std. Mean Difference | SE | Weight | Std. Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|
| Dittmann 2014, Dittmann 2013, Nagy 2015 | -0.6244 | 0.1445 | 100.0% | -0.62 [-0.91, -0.34] |
| **Total (95% CI)** | | | **100.0%** | **-0.62 [-0.91, -0.34]** |

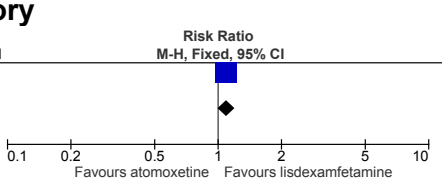
Heterogeneity: Not applicable
Test for overall effect: Z = 4.32 (P < 0.0001)




## Figure 273: CGI-S improvement of at least one category

| Study or Subgroup | Lisdexamfetamine Events | Total | Atomoxetine Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Dittmann 2014, Dittmann 2013, Nagy 2015 | 90 | 95 | 84 | 97 | 100.0% | 1.09 [1.00, 1.20] |
| **Total (95% CI)** | | **95** | | **97** | **100.0%** | **1.09 [1.00, 1.20]** |
| Total events | 90 | | 84 | | | |

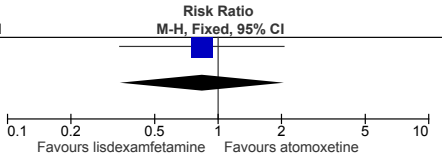
Heterogeneity: Not applicable
Test for overall effect: Z = 1.92 (P = 0.05)




## Figure 274: Discontinued treatment due to adverse event

| Study or Subgroup | Lisdexamfetamine Events | Total | Atomoxetine Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Dittmann 2014, Dittmann 2013, Nagy 2015 | 8 | 128 | 10 | 134 | 100.0% | 0.84 [0.34, 2.05] |
| **Total (95% CI)** | | **128** | | **134** | **100.0%** | **0.84 [0.34, 2.05]** |
| Total events | 8 | | 10 | | | |

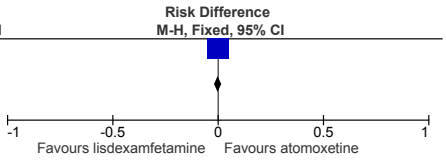
Heterogeneity: Not applicable
Test for overall effect: Z = 0.39 (P = 0.70)




## Figure 275: Serious TEAE

| Study or Subgroup | Lisdexamfetamine Events | Total | Atomoxetine Events | Total | Weight | Risk Difference M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Dittmann 2014, Dittmann 2013, Nagy 2015 | 0 | 128 | 0 | 134 | 100.0% | 0.00 [-0.01, 0.01] |
| **Total (95% CI)** | | **128** | | **134** | **100.0%** | **0.00 [-0.01, 0.01]** |
| Total events | 0 | | 0 | | | |

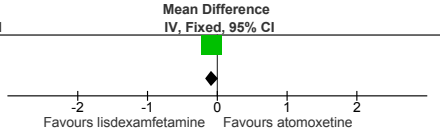
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)




## Figure 276: Function/behaviour (Parent rated, WFIRS-P, 0-3, high is poor)

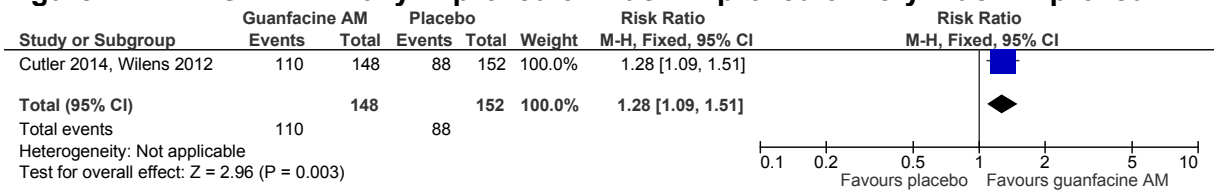
| Study or Subgroup | Lisdexamfetamine Mean | SD | Total | Atomoxetine Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Dittmann 2014, Dittmann 2013, Nagy 2015 | -0.35 | 0.3652 | 107 | -0.27 | 0.3234 | 113 | 100.0% | -0.08 [-0.17, 0.01] |
| **Total (95% CI)** | | | **107** | | | **113** | **100.0%** | **-0.08 [-0.17, 0.01]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.72 (P = 0.09)

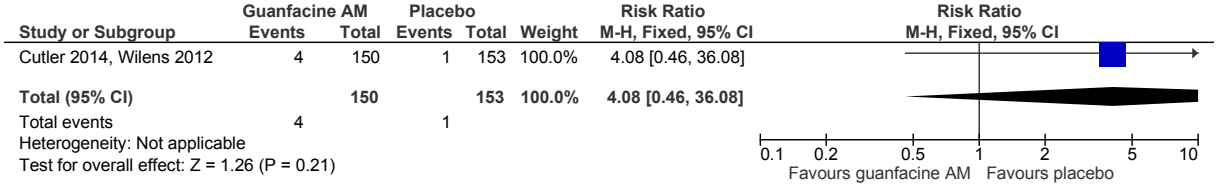


## E.2.4 Guanfacine AM versus placebo in children with ADHD are taking CNS stimulants but have a partial or suboptimal response

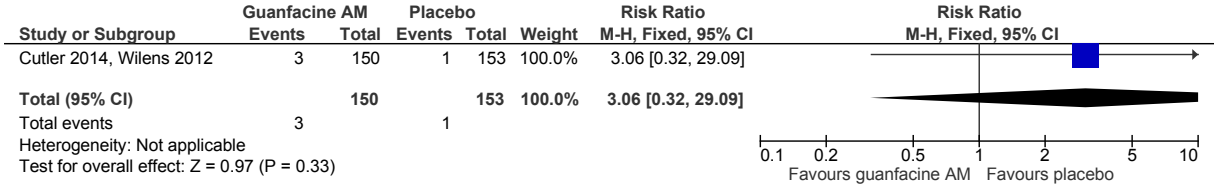
### Figure 277: CGI-I minimally improved or much improved or very much improved



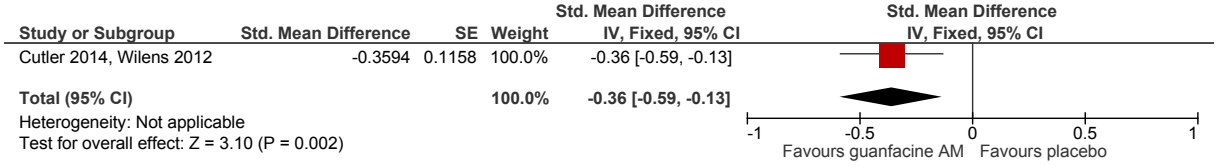

### Figure 278: Early discontinuation of treatment due to adverse events



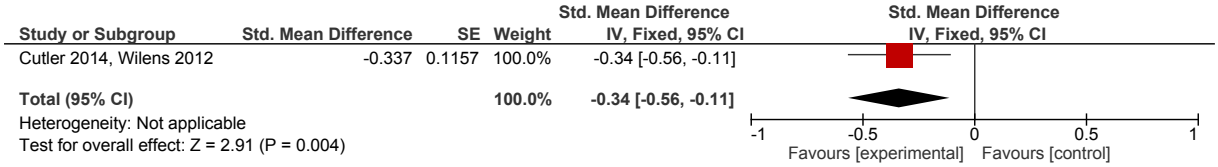

### Figure 279: Adverse events leading to hospitalisation/death/disability (severe TEAEs)



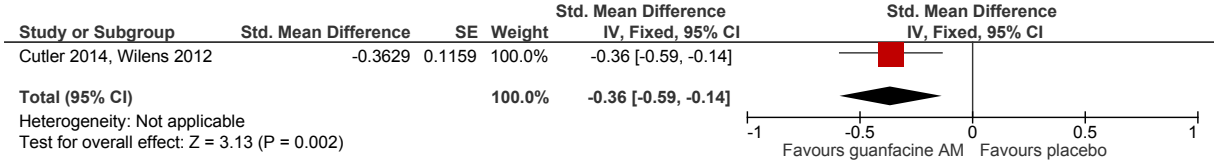

### Figure 280: ADHD symptoms (ADHD-RS-IV inattention subscale)




### Figure 281: ADHD symptoms (ADHD-RS-IV)

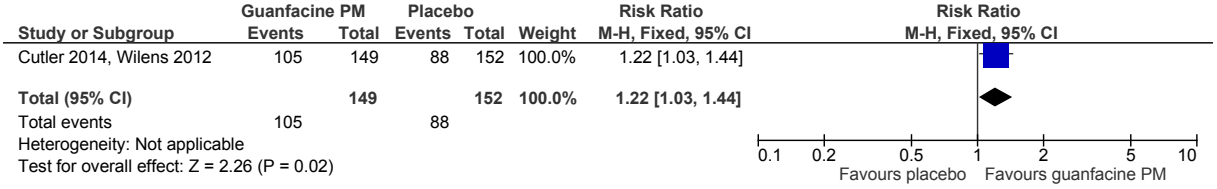



### Figure 282: ADHD symptoms (ADHD-RS-IV hyperactivity/impulsivity subscale)

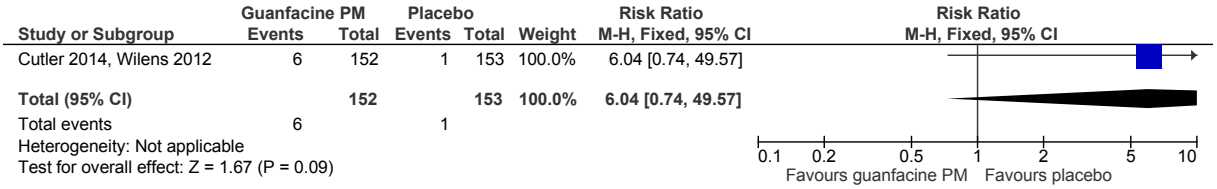


## E.2.5 Guanfacine PM versus placebo in children with ADHD are taking CNS stimulants but have a partial or suboptimal response

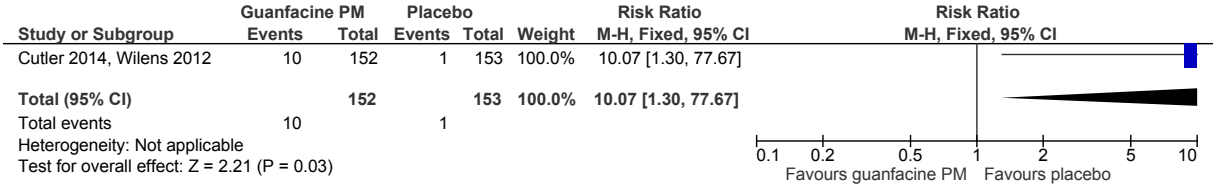
### Figure 283: CGI-I minimally improved or much improved or very much improved



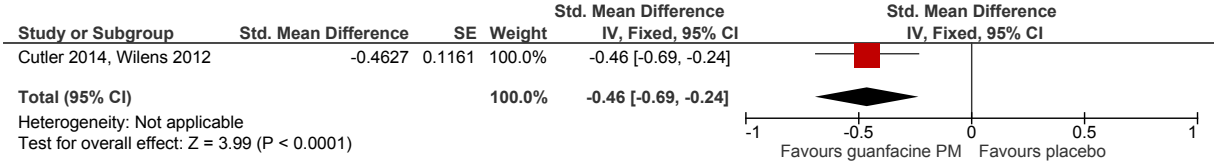

### Figure 284: Early discontinuation of treatment due to adverse events



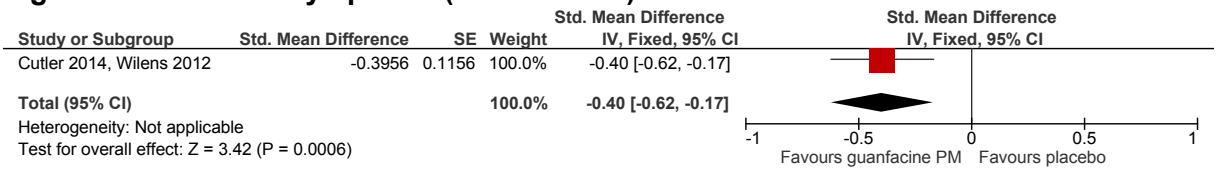

### Figure 285: Adverse events leading to hospitalisation/death/disability (severe TEAEs)



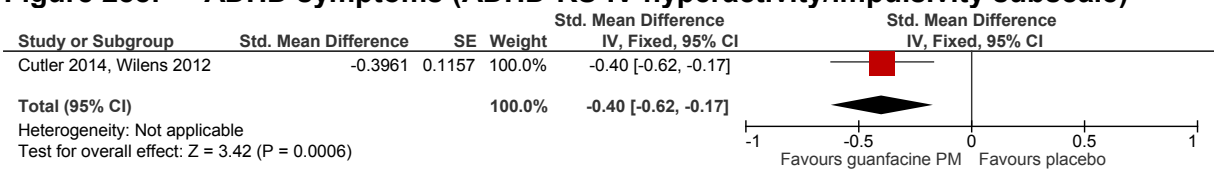

### Figure 286: ADHD symptoms (ADHD-RS-IV inattention subscale)




### Figure 287: ADHD symptoms (ADHD-RS-IV)

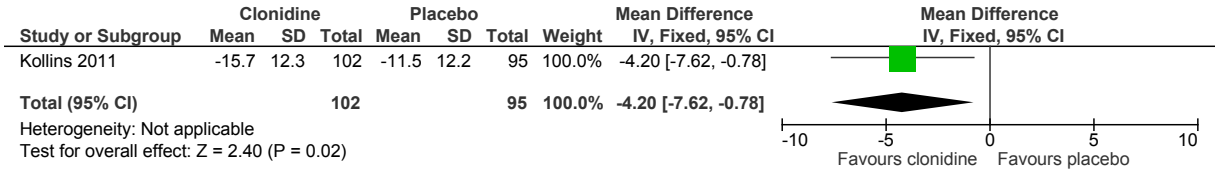



### Figure 288: ADHD symptoms (ADHD-RS-IV hyperactivity/impulsivity subscale)

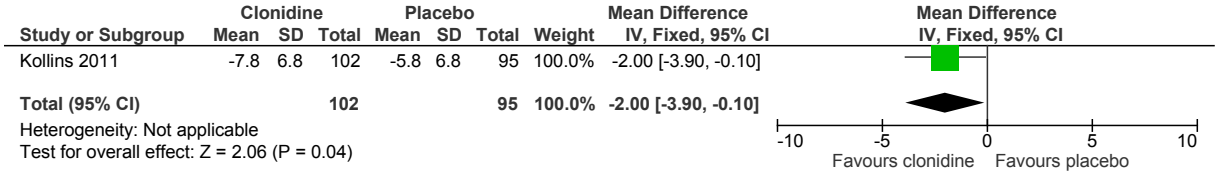


## E.2.6 Clonidine versus placebo in children with ADHD and insufficient response to stimulant treatment

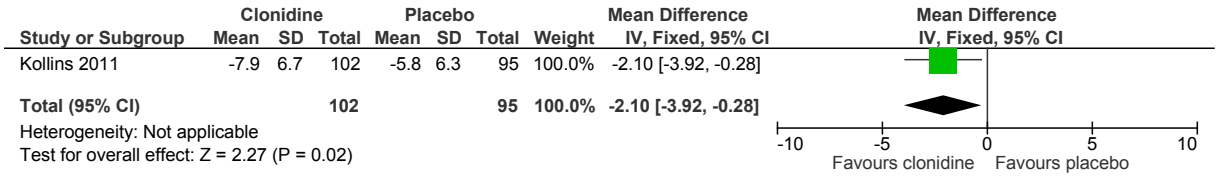
### Figure 289: ADHD total symptoms (ADHD-RS-IV improvement, high is poor)



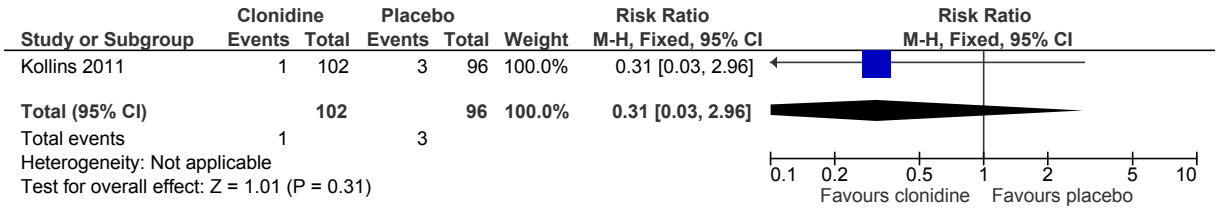

### Figure 290: Inattention (ADHD-RS-IV, high is poor)




### Figure 291: Hyperactivity/impulsivity (ADHD-RS-IV, high is poor)

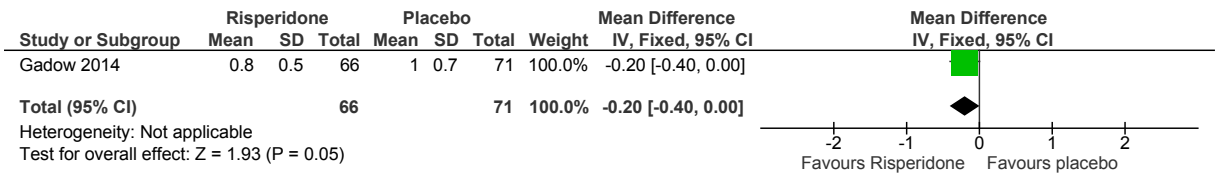



### Figure 292: Discontinued treatment due to TEAE

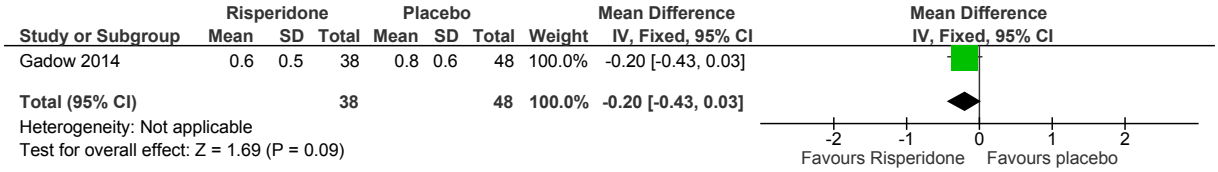



## E.2.7 Risperidone versus placebo in children with ADHD who do not show sufficient clinical response to methylphenidate

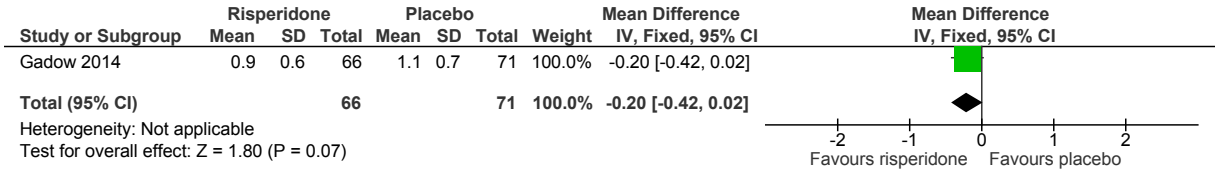
### Figure 293: ADHD total symptoms (parent rated ADHD-SC4, Severity Score, 0-3, high is poor)



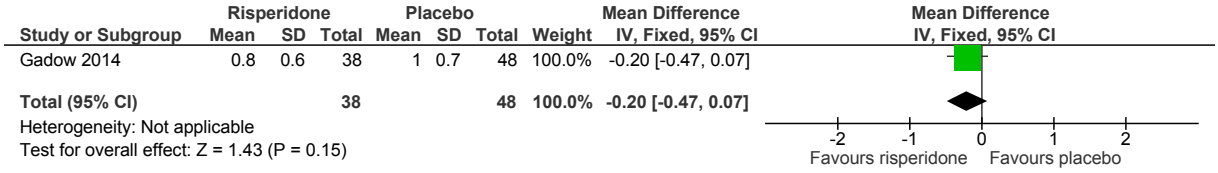

### Figure 294: ADHD total symptoms (teacher rated ADHD-SC4, Severity Score, 0-3, high is poor)



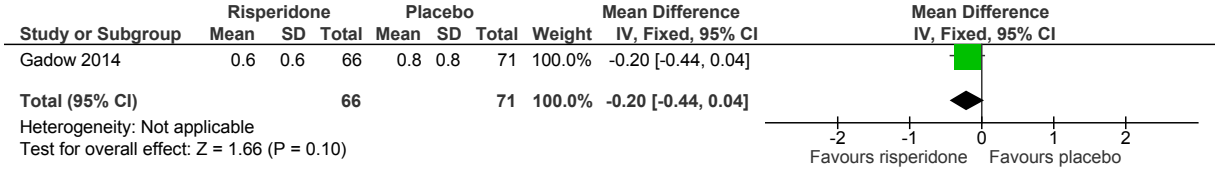

## Figure 295: Inattention (parent rated ADHD-SC4 Severity, 0-3, high is poor)



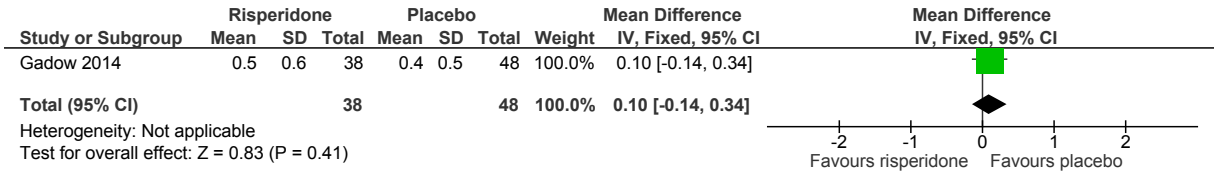

## Figure 296: Inattention (teacher rated ADHD-SC4 Severity, 0-3, high is poor)



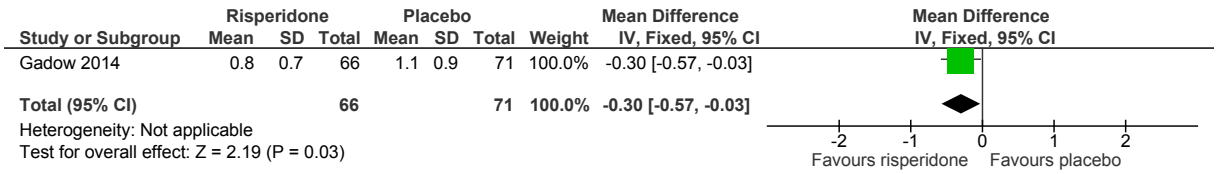

## Figure 297: Hyperactivity (parent rated ADHD-SC4 Severity Subscore, 0-3, high is poor)



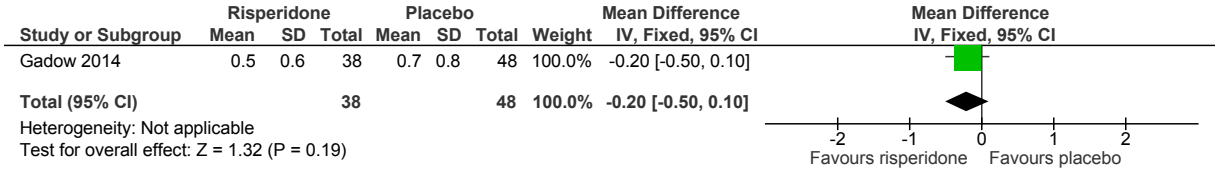

## Figure 298: Hyperactivity (teacher rated ADHD-SC4 Severity Subscore, 0-3, high is poor)



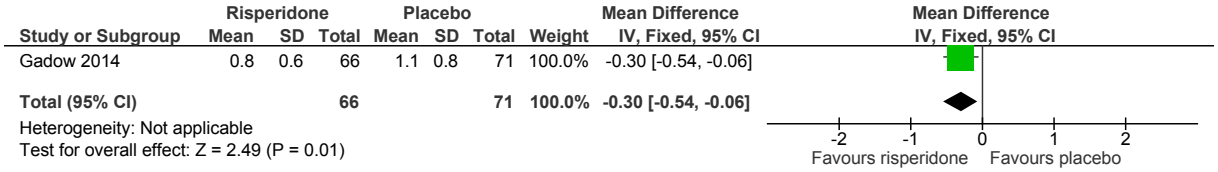

## Figure 299: Impulsivity (parent rated ADHD-SC4 Severity Subscore, 0-3, high is poor)



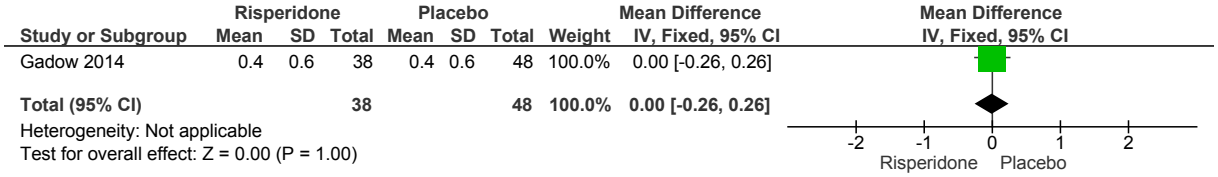
## Figure 300: Impulsivity (teacher rated ADHD-SC4 Severity Subscore, 0-3, high is poor)



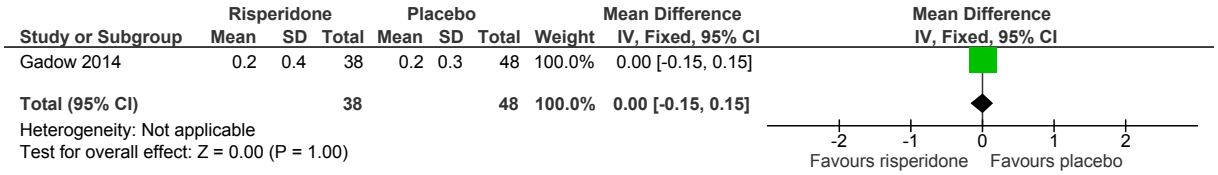

## Figure 301: Function/behaviour (parent rated ODD DSM-IV, 0-3, high is poor)



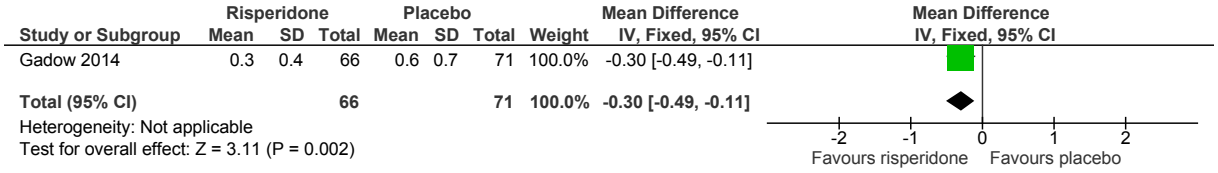

## Figure 302: Function/behaviour (teacher rated ODD DSM-IV, 0-3, high is poor)



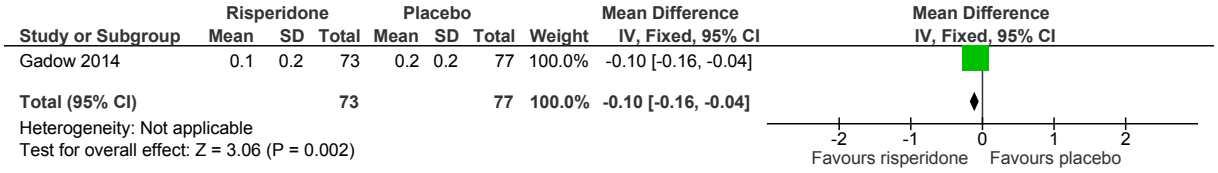

## Figure 303: Function/behaviour (teacher rated Peer Conflict Scale, 0-3, high is poor)




## Figure 304: Function/behaviour (parent rated Peer Conflict Scale, 0-3, high is poor)



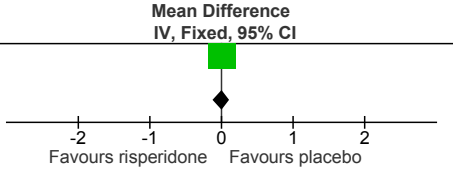

## Figure 305: Function/behaviour (parent rated CD DSM-IV, 0-3, high is poor)



### Figure 306: Function/behaviour (teacher rated CD DSM-IV, 0-3, high is poor)

| Study or Subgroup | Risperidone Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Gadow 2014 | 0.1 | 0.3 | 30 | 0.1 | 0.2 | 39 | 100.0% | 0.00 [-0.12, 0.12] |
| **Total (95% CI)** | | | **30** | | | **39** | **100.0%** | **0.00 [-0.12, 0.12]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



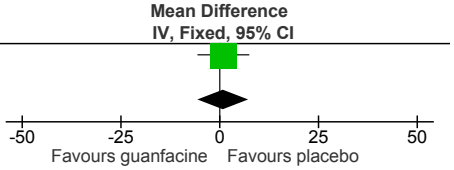

## Adults

## E.2.8 Guanfacine versus placebo in adults with a sub-optimal response to CNS stimulants

### Figure 307: ADHD total symptoms (ADHD-RS, 0-54, high is poor)

| Study or Subgroup | Guanfacine Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Butterfield 2016 | 11.85 | 7.62 | 13 | 10.92 | 8.9 | 13 | 100.0% | 0.93 [-5.44, 7.30] |
| **Total (95% CI)** | | | **13** | | | **13** | **100.0%** | **0.93 [-5.44, 7.30]** |

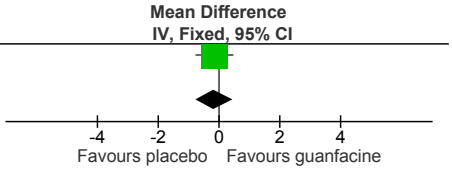
Heterogeneity: Not applicable
Test for overall effect: Z = 0.29 (P = 0.77)




### Figure 308: CGI-S (change score, 0-7, high scores are beneficial)

| Study or Subgroup | Guanfacine Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Butterfield 2016 | 0.85 | 0.8 | 13 | 1 | 0.76 | 13 | 100.0% | -0.15 [-0.75, 0.45] |
| **Total (95% CI)** | | | **13** | | | **13** | **100.0%** | **-0.15 [-0.75, 0.45]** |

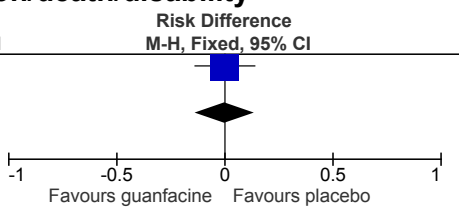
Heterogeneity: Not applicable
Test for overall effect: Z = 0.49 (P = 0.62)




### Figure 309: Adverse events leading to hospitalisation/death/disability

| Study or Subgroup | Guanfacine Events | Total | Placebo Events | Total | Weight | Risk Difference M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Butterfield 2016 | 0 | 13 | 0 | 13 | 100.0% | 0.00 [-0.14, 0.14] |
| **Total (95% CI)** | | **13** | | **13** | **100.0%** | **0.00 [-0.14, 0.14]** |
| Total events | 0 | | 0 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



# Appendix F: GRADE tables

## F.1 Pharmacological efficacy

### F.1.1 Pre-school children (under the age of 5)

**Table 80: 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 81: 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 82: Clinical evidence profile: Methylphenidate and risperidone versus methylphenidate**

| Quality assessment | No of patients | Effect | Quality | Importance |
|---|---|---|---|---|

| 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.

## F.1.2 Children and young people (aged 5 to 18)

**Table 83: 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 84: 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 | 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 85: 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 86: 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..

[3]Downgraded due to heterogeneity, unexplained by subgroup analysis

**Table 87: 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 88: 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 89: 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 |

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias.

**Table 90: 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 91: 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 92: 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 |

[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 93: 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 benficial; 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 94: 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 95: 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 96: 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 97: 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 98: 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 99: Clinical evidence profile: Risperidone versus placebo**

| 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 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 100: Clinical evidence profile: Ariprazole 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 101: 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 102: Clinical evidence profile: Buproprion 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 103: Clinical evidence profile: Buproprion 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 104: 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 105: 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 106: 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 verses 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 107: 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 108: 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) | | |

[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 109: 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 110: 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.

**Table 111: 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 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 112: 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.

[3]Downgraded due to heterogeneity, unexplained by subgroup analysis

**Table 113: 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 | Controlled release methylphenidate versus placebo | Control | Relative (95% CI) | Absolute | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Quality of life (Q-LES-Q, 0-80, high scores are good)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 141 | 140 | RR 2.03 (1.64 to 2.51) | MD 1.6 higher (from 1.52 lower to 4.72 higher) | HIGH | CRITICAL |
| **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** | | | | | | | | | | | | |
| 5 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | Serious[3] | none | 913 | 624 | - | SMD 0.4 lower (0.5 to 0.29 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, change scores reported; 5-8 weeks** | | | | | | | | | | | | |
| 3 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | Serious[3] | none | 623 | 415 | - | MD 6.37 lower (8.25 to 4.49 lower) | LOW | CRITICAL |
| **ADHD total symptoms self rated (CAARS total scores); 0-54, lower values are beneficial, change scores reported; 13 weeks** | | | | | | | | | | | | |
| 1 | randomised | serious | no serious | no serious | Serious[3] | none | 182 | 97 | | MD 4.2 lower | LOW | CRITICAL |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | trials | | inconsistency | indirectness | | | | | | (7.24 lower to 1.16 lower) | | |
| **ADHD inattention symptoms self-rated (CAARS inattention subscale at 8 weeks; 0-27, low values are beneficial)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | Serious[3] | none | 141 | 140 | - | MD 3.1 lower (4.54 to 1.66 lower) | MODERATE | CRITICAL |
| **ADHD inattention symptoms investigator rated (CAARS Inattention subscale); lower values are beneficial, change scores reported; 5-8 weeks** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | Serious[3] | none | 445 | 236 | - | MD 4 lower (4.9 to 3.1 lower) | LOW | CRITICAL |
| **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; 5-8 weeks** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | Serious[3] | none | 447 | 236 | - | MD 1.46 lower (2.35 lower to 0.57 higher) | LOW | CRITICAL |
| **ADHD hyperactivity symptoms self rated (CAARS hyperactivity subscale at 8 weeks; 0-27, low values are beneficial)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | Serious[3] | none | 304 | 96 | - | MD 1 lower (2.14 lower to 0.14 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 Lability 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 | 104/1215 | 21/923 | OR 3.33 (2.29 to 4.85) | 72 more per 1000 (from 51 more to 101 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 114: Clinical evidence profile: Dexamfetamine versus placebo

| Quality assessment | | | | | | No of patients | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|

| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Dexamfetamine 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 115: Clinical evidence profile: Lisdexamfetamine dimesylate versus placebo**

| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Lisdexamfetamine dimesylate versus placebo | Control | Relative (95% CI) | Absolute | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **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.

**Table 116: 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; Investigater 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; Investigater 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.

[5]Downgraded by 2 increments if the confidence interval crossed two MIDs.

**Table 117: 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 118: Clinical evidence profile: Guanfacine versus dexamfetamine**

| Quality assessment | No of patients | Effect | Quality | Importance |
|---|---|---|---|---|

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Guanfacine versus dexamfetamine** | **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 icnrements if the confidence interval crossed two MIDs.

**Table 119: 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 trials | very serious[2] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 22 | 17 | - | MD 1.08 lower (0.68 to 1.48 lower) | LOW | IMPORTANT |
| **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 120: 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 | serious[1] | no serious | no serious | serious[2] | none | 20 | 21 | - | MD 8.7 lower (14.21 | LOW | IMPORTANT |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | trials | | inconsistency | indirectness | | | | | | to 3.19 lower) | | |
| **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 121: 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 122: 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 123: 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 | very | no serious | no serious | no serious | none | 69/264 | 6/74 | RR 3.22 | 180 more per 1000 | LOW | CRITICAL |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | trials | serious[1] | inconsistency | indirectness | imprecision | | (26.1%) | | (1.46 to 7.13) | (from 110 more to 260 more) | | |

[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 124: Clinical evidence profile: Modafinil versus dexamfetamine**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Modafinil versus dexamfetamine** | | **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 125: Clinical evidence profile: Atomoxetine and buspirone versus placebo**

| Quality assessment | No of patients | Effect | Quality | Importance |
|---|---|---|---|---|

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Modafinil versus dexamfetamine** | | **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 126: 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 127: 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 TEAEs** | | | | | | | | | | | | |
| 1 | randomised | serious[1] | no serious | serious[2] | very | none | 3/150 | 0.7% | RR 3.06 (0.32 | 14 more per 1000 (from | VERY | CRITICAL |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | trials | | inconsistency | | serious[3] | | (2%) | | to 29.09) | 5 fewer to 197 more) | LOW | |
| **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 128: 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 | serious[1] | no serious | serious[2] | serious[3] | none | 10/152 | 0.7% | RR 10.07 (1.3 | 63 more per 1000 (from | VERY | CRITICAL |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | trials | | inconsistency | | | | (6.6%) | | to 77.67) | 2 more to 537 more) | LOW | |
| **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 129: 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 trials | serious[2] | no serious inconsistency | no serious indirectness | serious[1] | none | 38 | 48 | - | MD 0.20 lower (0.47 lower to 0.07 higher) | ⊕⊕OO LOW | CRITICAL |
| **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) | ⊕⊕⊕O 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) | ⊕⊕OO 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) | ⊕⊕⊕O 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) | ⊕⊕OO 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) | ⊕⊕⊕O 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) | ⊕⊕⊕O 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) | ⊕⊕⊕O 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) | ⊕⊕⊕O 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) | ⊕⊕⊕O 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) | ⊕OOO 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 130: 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 131: 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) | ⊕OOO 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) | ⊕OOO 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) | ⊕OOO 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) | ⊕OOO 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) | ⊕OOO VERY LOW | CRITICAL |

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

**Table 132: Clinical evidence profile: Lisdexamfetamine dimesylate versus atomoxetine for ADHD in children and young people**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | 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) | ⊕⊕⊕O 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) | ⊕⊕⊕O 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) | ⊕⊕⊕O 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) | ⊕⊕⊕O 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) | ⊕⊕OO 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 | ⊕⊕OO 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) | ⊕⊕⊕O MODERATE | 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] Absolute effect calculated from risk difference

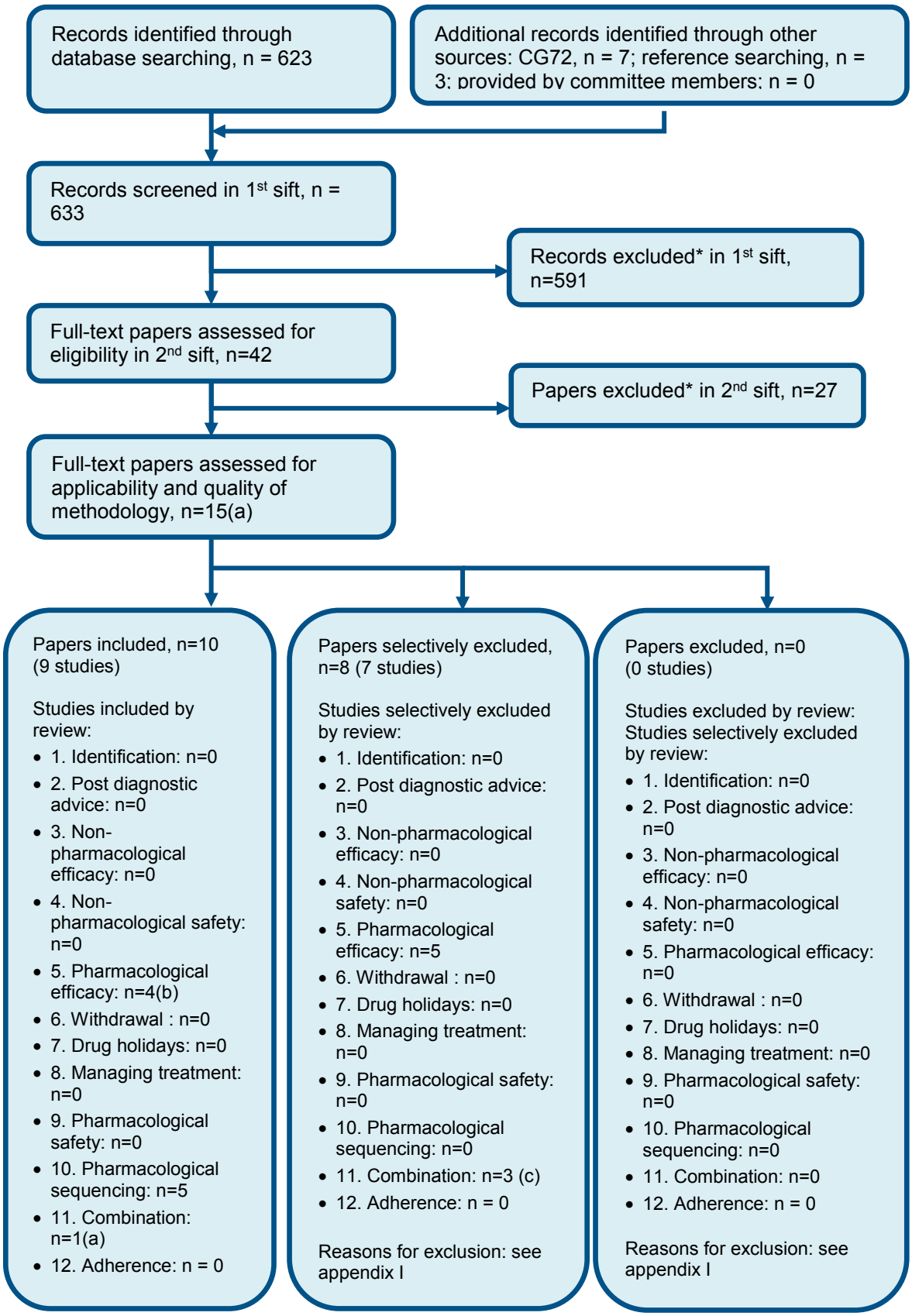
## F.2.3 Adults

### Table 133: 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) | ⊕OOO 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) | ⊕OOO 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 | ⊕⊕OO LOW | CRITICAL |

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

# Appendix G: Health economic evidence selection




** Non-relevant population, intervention, comparison, design or setting; non-English language*
*(a) note that there were 2 original models from the previous guideline (either included or excluded) which is why the numbers add to more than 15.*
*(b) Two articles identified were applicable to Q5 and Q10, for the purposes of this diagram it has been included under Q5 only.*
*(c) One of these is a model from the previous guideline that was exclude. Two articles identified were applicable to both Q5 and Q11 and have only been included here under Q11. One paper here was selectively excluded in Q11 but included in Q5 and so is double counted in*

*this flowchart*

# Appendix H: Health economic evidence tables

## H.1 Pharmacological efficacy

| Study | [King 2006[372]] | | | |
|---|---|---|---|---|
| **Study details** | **Population & interventions** | **Costs** | **Health outcomes** | **Cost-effectiveness** |
| **Economic analysis:**<br>CUA (health outcome: QALY)<br><br>**Study design:**<br>Probabilistic decision analytic model<br><br>**Approach to analysis:**<br>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 | **Population:**<br>Children aged 6 years<br><br>**Cohort settings:**<br>Start age: NR<br>Male: NR<br><br>**Strategies include:**<br>1. IR-MPH – ATX – DEX – NT<br>2. ER-MPH8 – ATX – DEX – NT<br>3. ER-MPH12 – ATX – DEX – NT<br>4. ATX – IR-MPH – DEX – NT<br>5. ATX – ER-MPH8 – DEX – NT<br>6. ATX – ER-MPH12 – DEX – NT<br>7. IR-MPH – DEX – ATX – NT<br>8. ER-MPH8 – DEX – ATX – NT<br>9. ER-MPH12 – DEX – ATX – NT | **Total costs (mean per patient):**<br>1. £1,233<br>2. £1,470<br>3. £1,479<br>4. £1,480<br>5. £1,550<br>6. £1,563<br>7. £1,140<br>8. £1,336<br>9. £1,410<br>10. £1,466<br>11. £1,485<br>12. £1,488<br>13. £1,098<br>14. £1,157<br>15. £1,159<br>16. £1,158<br>17. £1,177<br>18. £1,180<br>19. £1,223<br><br>**Currency & cost year:**<br>UK pounds 2003/4 | **QALYs (mean per patient):**<br>1. 0.8279<br>2. 0.8273<br>3. 0.8278<br>4. 0.8278<br>5. 0.8277<br>6. 0.8274<br>7. 0.8283<br>8. 0.8277<br>9. 0.8284<br>10. 0.8281<br>11. 0.8281<br>12. 0.8278<br>13. 0.8289<br>14. 0.8287<br>15. 0.8287<br>16. 0.8288<br>17. 0.8288<br>18. 0.8285<br>19. 0.7727 | **ICER:**<br>Strategy 13 is dominant<br>95% CI: NR<br>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.<br><br>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.<br><br>**Analysis of uncertainty:**<br>States that a probabilistic analysis was undertaken (does not state the number of simulations used).<br><br><u>Utility value sensitivity analysis:</u><br>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 |

| | | | | |
|---|---|---|---|---|
| but 3 llines of treatment was found to be cost effective so only these atrategies 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.<br><br>**Perspective:** UK NHS<br>**Time horizon/Follow-up:** 1 year<br>**Treatment effect duration:**[(a)] 1 year<br>**Discounting:** Costs: NA ; Outcomes: NA | 10. ATX – DEX – IR-MPH – NT<br>11. ATX – DEX – ER-MPH8 – NT<br>12. ATX – DEX – ER-MPH12 – NT<br>13. DEX – IR-MPH – ATX – NT<br>14. DEX – ER-MPH8 – ATX – NT<br>15. DEX – ER-MPH12 – ATX – NT<br>16. DEX – ATX – IR-MPH – NT<br>17. DEX– ATX – ER-MPH8 – NT<br>18. DEX– ATX – ER-MPH12 – NT<br>19. No Treatment | **Cost components incorporated:**<br>- Drug costs<br>- Resource use associated with responders (psychiatrist, paediatrician, and GP consultations, and a blood test).<br>- Resource use associated non responders (psychiatrist, paediatrician, and GP consultations, blood test, ECG, EEG, allergy test) | | 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<br><br><u>Co-morbid conditions sensitivity analysis:</u><br>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.<br><br><u>Time horizon sensitivity analysis:</u><br>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.<br><br><u>Resource use sensitivity analysis:</u><br>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.<br><br><u>Sensitivity to structural assumption</u> |

| | | | | |
|---|---|---|---|---|
| | | | | regarding MPH:<br>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 mediciation 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.<br><br>Sensitivity to estimated response rates:<br>- Using all clinician rated response (CGI-S) – strategy 13 is optimal. If DEX is not used first line then strategy 7 is optimal.<br>- 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 |
| **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.<br>Adverse events data: data was inlcuded from 10 trials that measured withdrawal rates. The withdrawal rates were calculated to include all reported wirhdrwal 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.<br>**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: dexamfetamine; 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]]** | | | |
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| **Study details** | **Population & interventions** | **Costs** | **Health outcomes** | **Cost-effectiveness** |
| **Economic analysis:** CUA (health outcome: QALY)<br><br>**Study design:** Probabilistic decision analytic model<br><br>**Approach to analysis:** Markov model of 1 year | **Population:** Children with ADHD<br>**Subgroup 1:** Stimulant naïve patients with no history of pharmacotherapy use and no contraindications to stimulants.<br>**Subgroup 2:** stimulant-contraindicated patients | **Total costs (mean per patient):**<br>**Subgroup 1 (a):**<br>Strategy 1: £125.76<br>Strategy 2: £534.09<br>Incremental (2−1): £408.34<br>(95% CI: NR; p=NR)<br><br>**Subgroup 1 (b):** | **QALYs (mean per patient):**<br><br>**Subgroup 1 (a):**<br>Strategy 1: 0.9040<br>Strategy 2: 0.9308<br>Incremental (2−1): 0.0268<br>(95% CI: NR; p=NR) | **ICER (Intervention 2 versus Intervention 1):**<br>**Subgroup 1 (a):**<br>£15,224 per QALY gained (pa)<br>95% CI: NR<br>Probability strategy 2 cost-effective (£20K/30K threshold): NR<br><br>**Subgroup 1 (b):**<br>£13,241 per QALY gained (pa) |

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| 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.<br><br>**Perspective:** UK NHS<br><br>**Time horizon/Follow-up:** 1 year<br><br>**Treatment effect duration:**[(a)] 1 year<br><br>**Discounting:** Costs: NA ; Outcomes: NA | (naïve) with no history of pharmacotherapy use but are precluded from using stimulants for because of pre-existing conditions.<br><br>**Cohort settings:**<br>Start age: NR<br>Male: NR<br><br>**Subgroup 1 (a):**<br>**Strategy 1:**<br>IR-MPH →IR-DEX→no treatment<br>**Strategy 2:**<br>Atomoxetine →IR-MPH→IR-DEX →no treatment<br><br>**Subgroup 1 (b):**<br>**Strategy 1:**<br>XR-MPH→IR-DEX→no treatment<br>**Strategy 2:**<br>Atomoxetine→XR-MPH→ IR-DEX→no treatment<br><br>**Subgroup 2:**<br>**Strategy 1:**<br>No treatment<br>**Strategy 2:**<br>Atomoxetine→ no treatment | Strategy 1: £334.07<br>Strategy 2: £599.78<br>Incremental (2−1): £265.71<br>(95% CI: NR; p=NR)<br><br>**Subgroup 2:**<br>Strategy 1: £0<br>Strategy 2: £480.94<br>Incremental (2−1): £480.94<br>(95% CI: NR; p=NR)<br><br>**Currency & cost year:**<br>2004 UK pounds<br><br>**Cost components incorporated:**<br>Only study drug costs are included. | **Subgroup 1 (b):**<br>Strategy 1: 0.9140<br>Strategy 2: 0.9341<br>Incremental (2−1): 0.0201<br>(95% CI: NR; p=NR)<br><br>**Subgroup 2:**<br>Strategy 1: 0.8800<br>Strategy 2: 0.9217<br>Incremental (2−1): 0.0417<br>(95% CI: NR; p=NR) | 95% CI: NR<br>Probability strategy 2 cost-effective (£20K/30K threshold): NR<br><br>**Subgroup 2:**<br>£11,523 per QALY gained (pa)<br>95% CI: NR<br>Probability strategy 2 cost-effective (£20K/30K threshold): NR<br><br>**Analysis of uncertainty:**<br>Probabilistic sensitivity analysis stated as being done with 20,000 simulations. However it is unclear if the base case results are probabilistic.<br><br>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).<br>- 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.<br>- When the difference was decreased to |

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| | | | | 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 (naive) 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.[562] 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**(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 dexamfetamine 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[332]] | | | |
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| **Study details** | **Population & interventions** | **Costs** | **Health outcomes** | **Cost-effectiveness** |
| **Economic analysis:** CUA (health outcome: QALY)<br><br>**Study design:** Probabilistic decision analytic model<br>**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 contraindicated group | **Population:** Children with ADHD<br><br>**Subgroup 1:** Stimulant naïve patients with no history of pharmacotherapy use and no contraindications to stimulants.<br>**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.<br><br>**Cohort settings:**<br>Start age: NR<br>Male: NR<br><br>**Subgroup 1 (a)**<br>**Strategy 1:** IR-MPH→Atomoxetine→no treatment<br>**Strategy 2:** | **Total costs (mean per patient):**<br>**Subgroup 1 (a):**<br>Strategy 1: £331<br>Strategy 2: £946<br>Incremental (2−1): £615<br>(95% CI: NR; p=NR)<br><br>**Subgroup 1 (b):**<br>Strategy 1: £815<br>Strategy 2: £1,092<br>Incremental (2−1): £277<br>(95% CI: NR; p=NR)<br><br>**Subgroup 2:**<br>Strategy 1: £0<br>Strategy 2: £876<br>Incremental (2−1): £876<br>(95% CI: NR; p=NR)<br><br>**Currency & cost year:**<br>[2008 Spanish Euros reported here as 2008 UK pounds[(b)]]<br>**Cost components incorporated:**<br>Only the pharmaceutical cost of treatment was | **QALYs (mean per patient):**<br>**Subgroup 1 (a):**<br>Strategy 1: 0.910<br>Strategy 2: 0.930<br>Incremental (2−1): 0.02<br>(95% CI: NR; p=NR)<br><br>**Subgroup 1 (b):**<br>Strategy 1: 0.920<br>Strategy 2: 0.933<br>Incremental (2−1): 0.013<br>(95% CI: NR; p=NR)<br><br>**Subgroup 2:**<br>Strategy 1: 0.880<br>Strategy 2: 0.922<br>Incremental (2−1): 0.042<br>(95% CI: NR; p=NR) | **ICER (Intervention 2 versus Intervention 1):**<br>**Subgroup 1 (a):**<br>£31,007 per QALY gained (pa)<br>95% CI: NR<br>Probability strategy 2 cost-effective (£20K/30K threshold): NR<br><br>**Subgroup 1 (b):**<br>£21,971 per QALY gained (pa)<br>95% CI: NR<br>Probability strategy 2 cost-effective (£20K/30K threshold): NR<br><br>**Subgroup 2:**<br>£21,079 per QALY gained (pa)<br>95% CI: NR<br>Probability strategy 2 cost-effective (£20K/30K threshold): NR<br><br>**Analysis of uncertainty:**<br>Probabilistic sensitivity analysis stated as being done with 20,000 simulations. However it is unclear if the base case results are probabilistic.<br><br>A range of sensitivity analyses were performed (results not reported in paper |

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| there are no stimulants in the algorithm.<br><br>**Perspective:** Spanish national health service<br>**Time horizon/Follow-up:** 1 year<br>**Treatment effect duration:**[(a)] 1 year<br>**Discounting:** Costs: NA ; Outcomes: NA | Atomoxetine→IR-MPH→no treatment<br><br>**Subgroup 1 (b)**<br>**Strategy 1:**<br>XR-MPH→Atomoxetine→no treatment<br>**Strategy 2:**<br>Atomoxetine→XR-MPH→no treatment<br><br>**Subgroup 2:**<br>**Strategy 1:**<br>No treatment<br>**Strategy 2:**<br>Atomoxetine | included | | 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).<br>The smaller the differences in utilities between the treatments then the higher the ICER. |
| **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.<br>**Quality-of-life weights:** The utilities are also the same as those used in the Cottrell paper. [562]<br>**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<br>**Limitations:** Population quite vague. Does not use EQ-5D and valuations of the states are based on parents not the general public.<br>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?<br>**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**[(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 dexamfetamine 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 parities[487]. 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[715]]** | | | |
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| **Study details** | **Population & interventions** | **Costs** | **Health outcomes** | **Cost-effectiveness** |
| **Economic analysis:** CUA (health outcome: QALYs)<br><br>**Study design:** Decision analytic model<br>**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-responders. An NMA | **Population:**<br>Adults with ADHD<br><br>**Cohort settings:**<br>Start age: NR<br>Male: NR<br><br>**Intervention 1:**<br>Methylphenidate ER (MPH-ER)<br><br>**Intervention 2:**<br>Atomoxetine (ATX)<br><br>**Intervention 3:**<br>Lisdexamfetamine (LDX)<br><br>(average doses not specified and taken from a weighted average of the NMA informing the | **Total costs (mean per patient):**<br>Intervention 1: £3387<br>Intervention 2: £3573<br>Intervention 3: £3378*<br><br>Incremental (3−1): - £9<br>(95% CI: NR; p=NR)<br>Incremental (3−2): - £195<br>(95% CI: NR; p=NR)<br><br>**Currency & cost year:**<br>2015 UK pounds<br><br>**Cost components incorporated:**<br>Drug costs, other healthcare resource use such as; appointments with clinicians | **QALYs (mean per patient):**<br>Intervention 1: 0.718<br>Intervention 2: 0.714<br>Intervention 3: 0.724*<br><br>Incremental (3−1): 0.005<br>(95% CI: NR; p=NR)<br>Incremental (3−2): 0.009<br>(95% CI: NR; p=NR) | **ICER (Intervention 3 versus Intervention 1):**<br>Intervention 3 dominant (pa)<br>95% CI: NR<br>Probability Intervention 3 cost-effective (£20K): 61%<br>**ICER (Intervention 3 versus Intervention 2):**<br>Intervention 3 dominant (pa)<br>95% CI: NR<br>Probability Intervention 3 cost-effective (£20K): 80%<br><br>**Analysis of uncertainty:**<br>For the PSA 5000 simulations were performed.<br><br>Additional sensitivity analyses were conducted on the following parameters;<br>• Efficacy; taking the upper and lower intervals of the relative risks of effect.<br>• Discontinuation rates; upper and lower bounds based on +/- 1 SD.<br>• Utilities; a different source was used which |

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| informs treatment effect and discontinuation risks. Costs also include resource use associated with response and non-response.<br><br>**Perspective:** UK NHS<br>**Time horizon/Follow-up:** 1 year<br>**Treatment effect duration:**[(a)] 1 year<br>**Discounting:** Costs: NA ; Outcomes: NA | treatment effect) | (psychiatrists, psychologists, nurses, GP's), measuring blood pressure and weight and having ECG, EEG and allergy test.<br><br>*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. | | had a higher response utility but the same non-response utility.<br>• Resource use; cost of responders increased by one more visit to a GP and psychiatrist.<br>• Time horizon; extended to 5 years with all assumptions the same<br>• Drug costing; applied drug costs to 'real world drug utilisation' from IMS.<br>• Length of titration period; length of titration for ATX extended to 84 days<br><br>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.<br><br>Scenario analyses;<br>• 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.<br>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.<br>• Patients who discontinue are assumed to have same utility during titration period as responders and then the same as non-responders.<br>Results were very similar to the base case. |

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| | | | | • An analysis comparing LDX to MPH-IR, assuming same efficacy and titration dose as MPH-ER but different cost and maintenance dose.<br>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 n 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. The fact that there is a potential conflict of interest and the authors undertook both their own NMA as well and because particularly the results of the MPH and LDX comparators are so close together then it is likely that small changes could change the results, and so for that reason the study has been rated as having very serious limitations.**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]]** | | | |
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| **Study details** | **Population & interventions** | **Costs** | **Health outcomes** | **Cost-effectiveness** |
| **Economic analysis:**<br>CUA (health outcome: QALY)<br><br>**Study design:**<br>Probabilistic decision analytic model<br><br>**Approach to analysis:**<br>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 | **Population:**<br>Children with ADHD<br>Subgroup 1: Stimulant failed patients; previously used methylphenidate but it was intolerable or ineffective.<br>Subgroup 2: stimulant-averse (exposed) patients; have responded successfully to stimulants but would like to stop if other medication was available.<br>Subgroup 3: stimulant contraindicated (exposed) patients; have previously been treated with stimulants but are now precluded from using them.<br><br>**Cohort settings:**<br>Start age: NR<br>Male: NR | **Total costs (mean per patient):**<br>Subgroup 1:<br>Intervention 1: £39.48<br>Intervention 2: £488.26<br>Incremental (2−1): £448.78<br>(95% CI: NR; p=NR)<br><br>Subgroup 2 (a):<br>Intervention 1: £119.27<br>Intervention 2: £493.05<br>Incremental (2−1): £373.79<br>(95% CI: NR; p=NR)<br><br>Subgroup 2 (b):<br>Intervention 1: £312.23<br>Intervention 2: £568.96<br>Incremental (2−1): £256.3<br>(95% CI: NR; p=NR)<br><br>Subgroup 3:<br>Intervention 1: £0 | **QALYs (mean per patient):**<br><br>Subgroup 1:<br>Intervention 1: 0.8967<br>Intervention 2: 0.9268<br>Incremental (2−1): 0.03<br>(95% CI: NR; p=NR)<br><br>Subgroup 2 (a):<br>Intervention 1: 0.9028<br>Intervention 2: 0.9263<br>Incremental (2−1): 0.0235<br>(95% CI: NR; p=NR)<br><br>Subgroup 2 (b):<br>Intervention 1: 0.9120<br>Intervention 2: 0.9301<br>Incremental (2−1): 0.0181<br>(95% CI: NR; p=NR)<br><br>Subgroup 3:<br>Intervention 1: 0.88<br>Intervention 2: 0.9120 | **ICER (Intervention 2 versus Intervention 1):**<br>Subgroup 1:<br>£14,945 per QALY gained (pa)<br>95% CI: NR<br>Probability Intervention 2 cost-effective (£20K/30K threshold): NR<br><br>Subgroup 2 (a):<br>£15,878 per QALY gained (pa)<br>95% CI: NR<br>Probability Intervention 2 cost-effective (£20K/30K threshold): NR<br><br>Subgroup 2 (b):<br>£14,169 per QALY gained (pa)<br>95% CI: NR<br>Probability Intervention 2 cost-effective (£20K/30K threshold): NR<br><br>Subgroup 3:<br>£12,370 per QALY gained (pa)<br>95% CI: NR<br>Probability Intervention 2 cost-effective (£20K/30K threshold): NR |

| Study | [Cottrell 2008[188]] | | | |
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| 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.<br><br>**Perspective:** UK NHS<br><br>**Time horizon/Follow-up:** 1 year<br><br>**Treatment effect duration:**[(a)] 1 year<br><br>**Discounting:** Costs: NA ; Outcomes: NA | **Subgroup 1:**<br>**Intervention 1:**<br>IR-DEX→no treatment<br>**Intervention 2:**<br>Atomoxetine →IR-DEX →no treatment<br><br>**Subgroup 2 (a):**<br>**Intervention 1:**<br>IR-MPH→IR-DEX→no treatment<br>**Intervention 2:**<br>Atomoxetine→IR-MPH→ IR-DEX→no treatment<br><br>**Subgroup 2 (b):**<br>**Intervention 1:**<br>XR-MPH→IR-DEX→no treatment<br>**Intervention 2:**<br>Atomoxetine→XR-MPH→ IR-DEX→no treatment<br><br>**Subgroup 3:**<br>**Intervention 1:**<br>No treatment<br>**Intervention 2:**<br>Atomoxetine→ no treatment | Intervention 2: £395.98<br>Incremental (2−1): £395.98<br>(95% CI: NR; p=NR)<br><br>**Currency & cost year:**<br>2004 UK pounds<br><br>**Cost components incorporated:**<br>Only study drug costs are included. | Incremental (2−1): 0.0320<br>(95% CI: NR; p=NR) | **Analysis of uncertainty:**<br>Probabilistic sensitivity analysis stated as being done with 20,000 simulations. However it is unclear if the base case results are probabilistic.<br><br>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. |
| **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]] |
|---|---|
| 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).<br>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.<br>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).<br>**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[562]. 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.<br>**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.<br>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 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 dexamfetamine 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[332]] | | | |
|---|---|---|---|---|
| **Study details** | **Population & interventions** | **Costs** | **Health outcomes** | **Cost-effectiveness** |
| **Economic analysis:** CUA (health outcome: QALY)<br><br>**Study design:** Probabilistic decision analytic model<br>**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.<br><br>**Perspective:** Spanish national health service<br>**Time horizon/Follow-up**: 1 year<br>**Treatment effect duration:**[(a)] 1 year<br>**Discounting:** Costs: NA ; Outcomes: NA | **Population:** Children with ADHD<br><br>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).<br><br>**Cohort settings:** Start age: NR<br>Male: NR<br><br>**Intervention 1:** No treatment<br><br>**Intervention 2:** Atomoxetine | **Total costs (mean per patient):** Intervention 1: £0<br>Intervention 2: £831<br>Incremental (2−1): £831<br>(95% CI: NR; p=NR)<br><br>**Currency & cost year:** [2008 Spanish Euros reported here as 2008 UK pounds[(b)]]<br><br>**Cost components incorporated:** Only the pharmaceutical cost of treatment was included | **QALYs (mean per patient):** Intervention 1: 0.880<br>Intervention 2: 0.919<br>Incremental (2−1): 0.039<br>(95% CI: NR; p=NR) | **ICER (Intervention 2 versus Intervention 1):** £21,528 per QALY gained (pa)<br>95% CI: NR<br>Probability Intervention 2 cost-effective (£20K/30K threshold): NR<br><br>**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.<br><br>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. |
| **Data sources** | | | | |
| **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 2008[476]). 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). | | | | |

| Study | [Hong 2009[332]] |
|---|---|
| **Quality-of-life weights:** The utilities are also the same as those used in the Cottrell paper.<br>**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:** 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. | |
| **Overall applicability**: Partially 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; IR-MPH: immediate release methylphenidate, EX-MPH: extended release methylphenidate, IR-DEX: immediate release dexamfetamine 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.[487] 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 2008[221]] | | | |
|---|---|---|---|---|
| **Study details** | **Population & interventions** | **Costs** | **Health outcomes** | **Cost-effectiveness** |
| **Economic analysis:** CUA (health outcome: QALYs)<br>**Study design:** deterministic decision analytic model<br>**Approach to analysis:** | **Population:**<br>In primary phase: Children and young people who show sub optimal symptom control with IR MPH (assumed 42% of youths starting | **Total costs (mean per patient):**<br>Intervention 1: £7,095<br>Intervention 2: £8,416<br>Incremental (2−1): £1,321 | **QALYs (mean per patient):**<br>Intervention 1: 7.66<br>Intervention 2: 7.79<br>Incremental (2−1): 0.13<br>(95% CI: NR; p=NR) | **ICER (Intervention 2 versus Intervention 1):**<br>£10,161 per QALY gained (pa)<br>95% CI: NR<br>Probability Intervention 2 cost-effective (£20K/30K threshold): NR |

| Study | [Faber 2008[221]] | | | |
|---|---|---|---|---|
| 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).<br><br>**Perspective:** Dutch Societal perspective<br>**Time horizon:** 10 years<br>**Treatment effect duration**:[(a)] 10 years<br>**Discounting:** Costs: 4%; Outcomes: 4% | treatment with IR MPH)<br>Markov phase: children and young people responding sub optimally to IR MPH because of inappropriate intake. (assumed 83% of the 42% above)<br><br>**Cohort settings:**<br>Start age: age of 8<br>Male: NR<br><br>**Intervention 1:**<br>Immediate release methylphenidate (IR MPH)<br><br>**Intervention 2:**<br>Osmotic release methylphenidate (OROS MPH) | (95% CI: NR; p=NR)<br><br>**Currency & cost year:**<br>[2005 Dutch Euros (presented here as 2005 UK pounds[(b)])]<br><br>**Cost components incorporated:**<br>Medication costs<br>Consultation costs (with GP's, specialists, and crisis contact)<br>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.<br><br>Special education costs were subtracted from the total costs shown in this table. | | **Analysis of uncertainty:**<br>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.<br><br>A worst case ICER was around £30,000, and the best case scenario was the OROS pathway being dominant. |
| **Data sources** | | | | |

| Study | [Faber 2008[221]] |
|---|---|
| **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.<br>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.<br>**Quality-of-life weights:** utilities were from a UK study by Secnick 2005[562], 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).<br>**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.<br>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. | |
| **Comments** | |
| **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. | |
| **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 2005 purchasing power parities[487]*

*(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[644]]** | | | |
|---|---|---|---|---|
| **Study details** | **Population & interventions** | **Costs** | **Health outcomes** | **Cost-effectiveness** |
| **Economic analysis:** CUA (health outcome: QALYs)<br><br>**Study design:** probabilistic decision model<br><br>**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 | **Population:**<br>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)<br>Markov phase: children and young people responding sub optimally to IR MPH because of inappropriate intake. (assumed 83% of the 42% above)<br><br>**Cohort settings:**<br>Start age: age of 8<br>Male: NR<br><br>**Intervention 1:**<br>Immediate release | **Total costs (mean per patient):**<br>Intervention 1: £8,862<br>Intervention 2: £9,459<br>Intervention 3: £8,413<br><br>Incremental (2−1): £597<br>(95% CI: NA; p=NA)<br>Incremental (3−1): -£449<br>(95% CI: NA; p=NA)<br><br>**Currency & cost year:**<br>[2013 Dutch Euros (presented here as 2013 UK pounds[(b)])]<br><br>**Cost components incorporated:**<br>Medication costs<br>Consultation costs (with GP's, specialists, and | **QALYs (mean per patient):**<br>Intervention 1: 6.855<br>Intervention 2: 7.173<br>Intervention 3: 7.173<br><br>Incremental (2−1): 0.318<br>(95% CI: 0.053, 1.285; p=NR)<br>Incremental (3−1): 0.318<br>(95% CI: 0.061, 1.313; p=NR) | **ICER (Intervention 2 versus Intervention 1):**<br>£1,879.37 per QALY gained (da)<br>95% CI: NA<br>Probability Intervention 2 cost-effective (£20K/30K threshold): NA<br><br>**ICER (Intervention 3 versus Intervention 1):**<br>Intervention 3 is dominant<br>95% CI: NA<br>Probability Intervention 3 cost-effective (£20K/30K threshold): NA<br><br>(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) |

| Study | [Van der Schans 2015[644]] | | | |
|---|---|---|---|---|
| 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).<br><br>**Perspective:** Dutch Societal perspective<br>**Time horizon:** 10 years<br>**Treatment effect duration:**[(a)] 10 years<br>**Discounting:** Costs: 4%; Outcomes: 1.5% | methylphenidate (IR MPH)<br><br>**Intervention 2:**<br>Extended release methylphenidate: Osmotic release methylphenidate (OROS MPH)<br><br>**Intervention 3:**<br>Extended release methylphenidate: Medikinet CR/Equasym XL | crisis contact)<br>Other intervention costs (e.g. psycho education, parent training, behaviour therapy, teacher training.<br>Indirect costs; direct healthcare costs of mother and productivity losses.<br><br>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) | | **Analysis of uncertainty:**<br>A series of univariate sensitivity analyses were performed on most of the model parameters. This involved varying base case values +/-25%.<br>In addition a multivariate sensitivity analysis was performed where the worst case parameter values were analysed.<br>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. |
| **Data sources** | | | | |
| **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.<br>**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). [415]<br>**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 | | | | |

| Study | [Van der Schans 2015[644]] |
|---|---|
| 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 parities[487]*

*(c) Directly applicable / Partially applicable / Not applicable*

*(d) Minor limitations / Potentially serious limitations / Very serious limitations*

| Study | [Schawo 2015[557]] | | | |
|---|---|---|---|---|
| **Study details** | **Population & interventions** | **Costs** | **Health outcomes** | **Cost-effectiveness** |
| **Economic analysis:** CUA (health outcome: QALYs)<br><br>**Study design:** probabilistic decision model<br><br>**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 | **Population:**<br>Patients who had responded sub-optimally to IR MPH because of incorrect intake of medication.<br><br>**Cohort settings:**<br>Start age: age of 6<br>Male: NR<br><br>**Intervention 1:** | **Total costs (mean per patient):**<br>Intervention 1: NR<br>Intervention 2: NR<br><br>Incremental (2−1): -£4,231<br>(95% CI: NA; p=NA)<br><br>**Currency & cost year:**<br>[2014 Dutch Euros (presented here as 2014 | **QALYs (mean per patient):**<br>Intervention 1: NR<br>Intervention 2: NR<br><br>Incremental (2−1): 0.15<br>(95% CI: NR; p=NR)<br><br>The incremental QALY for the sensitivity analysis that excluded caregiver utility is | **ICER (Intervention 2 versus Intervention 1):**<br>Intervention 2 is dominant.<br>95% CI: NA<br>Probability Intervention 2 cost-effective (£20K/30K threshold): NA<br><br>**Analysis of uncertainty:**<br>1000 monte carlo simulations.<br><br>Four scenarios were tested as |

| Study | [Schawo 2015[557]] | | | |
|---|---|---|---|---|
| OROS MPH. There are 4 states in each arm (the same for both arms).<br><br>**Perspective:** Dutch Societal perspective<br>**Time horizon:** 12 years<br>**Treatment effect duration:** [a] 12 years<br>**Discounting:** Costs: 4%; Outcomes: 1.5% | Immediate release methylphenidate (IR MPH)<br><br>**Intervention 2:**<br>Extended release methylphenidate: Osmotic release methylphenidate (OROS MPH) | UK pounds[b])]<br><br>**Cost components incorporated:**<br>Medication costs<br>Consultation costs (with GP's, specialists, and crisis contact)<br>Other intervention costs (e.g. psycho education, parent training, behaviour therapy, teacher training.<br>Indirect costs; direct healthcare costs of mother and productivity losses.<br><br>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. | 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. | sensitivity analyses;<br>- assuming transition rates are equal for the two interventions.<br>- 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).<br>- excluding medical costs and production losses of the caregiver (incremental costs of this analysis assumed as the base case here)<br>- excluding the utility of caregivers (incremental QALYs of this analysis assumed as the base case here).<br><br>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. |
| **Data sources** | | | | |
| **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. | | | | |

| Study | [Schawo 2015[557]] |
|---|---|
| **Quality-of-life weights:** quality of life was from a study (Van der kolk et al 2014[640]) 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.<br>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.<br>**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). |
| **Comments** |
| **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. |
| **Overall applicability:** partially applicable(c) **Overall quality:** Very serious limitations(d) |

*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 parities[487]*

*(c) Directly applicable / Partially applicable / Not applicable*

*(d) Minor limitations / Potentially serious limitations / Very serious limitations*

| Study | [Lachaine 2016[395]] | | | |
|---|---|---|---|---|
| **Study details** | **Population & interventions** | **Costs** | **Health outcomes** | **Cost effectiveness** |

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|---|---|---|---|---|
| **Economic analysis:** CEA/CUA (health outcome: QALYs, patient weeks with a response)<br><br>**Study design:** **P**robabilistic decision model<br><br>**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.<br><br>**Perspective:** Canadian Ministry of Health<br>**Time horizon/Follow-up:** 1 year<br>**Treatment effect duration:**[(a)] 1 year<br>**Discounting:** Costs: NA; Outcomes: NA | **Population:**<br>Children aged 6-12 with ADHD with a sub-optimal response to stimulants.<br><br>**Cohort settings:**<br>Start age: NR<br>Male: 71.6% (based on trial used for effect)<br>Proportion starting in each state: Normal;0.00 %, Mild; 3.52 %, Moderate; 90.55 %, Severe; 5.93 %<br><br>**Intervention 1:**<br>Long-acting stimulant monotherapy<br><br>**Intervention 2:**<br>Guanfacine extended release (GXR) + long-acting stimulant<br><br>(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). | **Total costs (mean per patient):**<br>Intervention 1: £530<br>Intervention 2: £902<br>Incremental (2−1): £373<br>(95% CI: NR; p=NR)<br><br>**Currency & cost year:**<br>2013 Canadian dollars (presented here as 2013 UK pounds[(b)])<br><br>**Cost components incorporated:**<br>Medication costs, primary care visits, mental health visits, pharmacy fills, emergency department visits and hospitalizations | **QALYs (mean per patient):**<br>Intervention 1: 0.627<br>Intervention 2: 0.655<br>Incremental (2−1): 0.028<br>(95% CI: NR; p=NR)<br><br>**Patient weeks with a response:**<br>Intervention 1: 12.46<br>Intervention 2: 19.03<br>Incremental (2−1): 6.57<br>(95% CI: NR; p=NR) | **ICER (Intervention 2 versus Intervention 1):**<br>£13,321 per QALY gained (pa)<br>95% CI: NR<br>Probability Intervention 2 cost effective: 95% (read off a graph at a point of $CA36,000 which would be around £20,000)<br><br>**Analysis of uncertainty:**<br>Probabilistic sensitivity analysis with 10,000 simulations.<br><br>Several one-way sensitivity analyses were performed by varying a single variable individually within lower and upper bounds of all key parameters.<br>More specifically, sensitivity analysis on;<br>- 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.<br>- 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.<br>- 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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| | | | | stimulants was performed by varying only the stimulant drug costs.<br><br>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.<br><br>In a sensitivity analysis where patients were maintained on treatment and could transition between heath states during the weeks 9-52 period the ICER increased to $47,909 (almost £27,000) from a MoH perspective. |

**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 alone [691]. 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 heath 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 [572].

**Quality-of-life weights:** Lloyd 2011[415]; 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 [572]. 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 parities[487]*

*(c) Directly applicable / Partially applicable / Not applicable*

*(d) Minor limitations / Potentially serious limitations / Very serious limitations*

| **Study** | **[Zimovetz 2016[716]]** | | | |
|---|---|---|---|---|
| **Study details** | **Population & interventions** | **Costs** | **Health outcomes** | **Cost-effectiveness** |
| **Economic analysis:**<br>CUA (health outcome: QALYs)<br><br>**Study design:**<br>Probabilistic decision analytic model<br>**Approach to analysis:**<br>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 | **Population:**<br>Children and adolescents with ADHD in whom a response to methylphenidate was considered clinically inadequate.<br><br>**Cohort settings:**<br>Start age: NR<br>Male: NR<br><br>**Intervention 1:**<br>Atomoxetine<br><br>**Intervention 2:**<br>Lisdexamfetamine<br><br>(doses NR as were based on the doses from the single trial the model is based on). | **Total costs (mean per patient)[(b)]:**<br>Intervention 1: £2,332<br>Intervention 2: £2,352<br><br>Incremental (2−1): £20<br>(95% CI: NR; p=NR)<br><br>**Currency & cost year:**<br>2012 UK pounds<br><br>**Cost components incorporated:**<br>- Drug costs<br>- Other resource use; consultations with psychiatrists/ paediatricians/GP/nurse, blood tests, ECG's. | **QALYs (mean per patient) [(b)]:**<br>Intervention 1: 0.8092<br>Intervention 2: 0.8202<br><br>Incremental (2−1): 0.011<br>(95% CI: NR; p=NR) | **ICER (Intervention 2 versus Intervention 1):**<br>£1,586 per QALY gained (pa)<br>95% CI: NR<br>Probability Intervention 2 cost-effective (£20K threshold): 86%<br><br>**Analysis of uncertainty:**<br>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.<br><br>*One way sensitivity analyses varied;*<br>Response rates:<br>• 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.<br>• Using response rates from an MTC conducted using ADHD trials in a broader |

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| trial of the two drugs. Includes healthcare resource use of responders and non-responders.<br><br>**Perspective:** UK NHS<br>**Time horizon/Follow-up:** 1 year<br>**Treatment effect duration:**[(a)] 1 year<br>**Discounting:** Costs: NA ; Outcomes: NA | | | | group (not just second line studies).<br>Utility values:<br>• Using utilities from Lloyd 2011[415], 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.<br>• Using utilities directly from the head to head trial, using the HUI2 measure.<br>Resource use estimates:<br>• The resource use estimates in the base case were replaced by those from the King HTA model.<br>• Additional sensitivity analyses varying the percentage of visits that were assumed to be consultations with junior doctors instead of psychiatrists/paediatricians.<br>Drug costing method:<br>• Doses were used using real world data from Canada and Brail where LDX was already used.<br><br>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.<br>LDX remained cost effective in all sensitivity analyses and was dominant in two of them; assumptions about drug costs, and using MTC effectiveness. |
| **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 2013 [207] 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 2004[168], 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 HTA[372] 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

**Table 134: Studies excluded from the clinical review**

| Study | Exclusion reason |
|---|---|
| Abbasi 2011[2] | Incorrect interventions |
| Abikoff 2007[4] | Less than minimum duration |
| Adler 2005[22] | Inappropriate design |
| Adler 2008[18] | No usable outcomes |
| Adler 2008[19] | Open label |
| Adler 2009[17] | Wrong population |
| Adler 2009[20] | No relevant outcomes |
| Adler 2011[13] | Incorrect interventions |
| Adler 2011[14] | Open label |
| Adler 2014[5] | No relevant outcomes |
| Adler 2014[6] | Incorrect interventions |
| Adler 2016[15] | Incorrect population |
| Agay 2010[23] | Less than minimum duration |
| Agay 2014[24] | Less than minimum duration |
| Aman 2000[32] | Incorrect study design |
| Aman 2004[27] | Incorrect interventions |
| Aman 2008[29] | Incorrect study design |
| Aman 2009[30] | Inappropriate comparison |
| Aman 2009[33] | No control group |
| Aman 2010[31] | Incorrect population |
| Aman 2014[28] | Incorrect interventions |
| Aman 2015[26] | Incorrect population |
| Amiri 2013[36] | Incorrect study design |
| An 2013[37] | Less than minimum duration |
| Anderson 2007[38] | Not article |
| Anon 1999[1] | Incorrect interventions |
| Anon 2002[632] | Incorrect study design |
| Anonymous 2008[39] | Incorrect study design |
| Anonymous 2009[248] | Not article |
| Anonymous 2016[176] | Not in English |
| Apostol 2012[40] | Incorrect intervention |
| Araki 2015[42] | Inappropriate comparison |
| Armenteros 2007[43] | Incorrect population |
| Armstrong 2012[44] | Incorrect duration |
| Arnold 2007[46] | Incorrect intervention |
| Arnold 2010[47] | Open label |
| Arnold 2010[48] | Incorrect population |
| Arnold 2015[49] | Wrong intervention (combination) |
| Asherson 2015[51] | Systematic review: study designs inappropriate |

| Study | Exclusion reason |
|---|---|
| Ashkenasi 2011[52] | Open label |
| Babcock 2012[53] | Wrong population |
| Babinski 2014[54] | Incorrect interventions |
| Babinski 2014[56] | No relevant outcomes |
| Babinski 2016[55] | Incorrect population |
| Bahcivan saydam 2015[57] | No intervention |
| Bain 2012[58] | Incorrect interventions |
| Bain 2013[59] | Incorrect interventions |
| Banaschewski 2014 [60] | Incorrect population |
| Bangs 2008[63] | Abstract |
| Barbaresi 2014[64] | Incorrect study design |
| Barkley 2007[65] | Incorrect interventions |
| Barnard 2002[66] | Review: references checked |
| Barry 2006[68] | Incorrect study design. Commentary |
| Bart 2010[69] | No relevant outcomes |
| Barton 2006[70] | Incorrect study design |
| Becker 2013[72] | Background info |
| Becker 2016[71] | Incorrect study design |
| Bedard 2008[74] | Incorrect duration |
| Bedard 2015[73] | No relevant outcomes |
| Bendz 2010[75] | Incorrect study design |
| Bental 2008[76] | Incorrect duration |
| Benvenuto 2013[77] | Incorrect study design |
| Berlin 2012[78] | Incorrect interventions |
| Beyer von morgenstern 2014[79] | Incorrect study design |
| Biederman 1989 [82] | Incorrect population |
| Biederman 1989 [81] | Incorrect population |
| Biederman 1993 [80] | Incorrect population |
| Biederman 2002[86] | Subgroup analysis |
| Biederman 2005 [96] | Incorrect population |
| Biederman 2007[94] | Meta-analysis: references checked |
| Biederman 2007[92] | No relevant outcomes |
| Biederman 2007[83] | No relevant outcomes |
| Biederman 2008[93] | Meta-analysis of individual studies included in review |
| Biederman 2008[88] | Open label |
| Biederman 2012[84] | No relevant outcomes |
| Bilder 2016[97] | No relevant outcomes |
| Blader 2009[99] | Incorrect interventions |
| Blader 2013[98] | Inappropriate comparison |
| 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 |
| Boisjoli 2007[106] | Incorrect interventions |

| Study | Exclusion reason |
|---|---|
| Boonstra 2007[107] | No relevant outcomes |
| Borsting 2008[108] | Conference abstract |
| Bottelier 2014[109] | Protocol |
| Brams 2008[113] | Incorrect duration |
| Brams 2010[112] | Review: references checked |
| Brams 2011[111] | Open label |
| Brams 2012[114] | Erratum |
| Brams 2012[115] | Incorrect duration |
| Brams 2012[116] | No washout following open label lead in phase |
| Brown 1989[119] | No relevant outcomes |
| Brown 2010[120] | Open label |
| Brown 2010[122] | Meta-analysis of included studies |
| Bubnik 2015[123] | No relevant outcomes |
| Buchmann 2007[124] | Inappropriate comparison |
| Buitelaar 1996[125] | Incorrect study design |
| Buitelaar 1996[130] | No usable outcomes |
| Buitelaar 2007[126] | Incorrect interventions |
| Buitelaar 2009[127] | Open label |
| Buitelaar 2012[128] | Open label |
| Burton 2015[131] | Incorrect interventions |
| Butter 1983[132] | Less than minimum duration |
| Butter 1984[133] | Less than minimum duration |
| Camporeale 2013 [135] | Incorrect population |
| Cantilena 2012[137] | Incorrect population |
| Cardo 2013[138] | Open label |
| Castellanos-ryan 2013[143] | Incorrect interventions |
| Castells 2011[144] | Systematic review: checked for references |
| Cetin 2015[145] | Open label |
| Chang 2009[147] | Open label |
| Chang 2012[148] | No relevant outcomes |
| Chantiluke 2015[149] | No usable outcomes |
| Chantiluke 2015[150] | Incorrect study design |
| Chavez 2006[151] | Review: references checked |
| Chen 2014[152] | Incorrect population |
| Cheng-shannon 2004[153] | Review: references checked |
| Childress 2009 [158] | Inappropriate intervention |
| Childress 2012[154] | Open label |
| Childress 2014[157] | Incorrect population |
| Childress 2015[156] | Inappropriate intervention |
| Ching 2012[159] | Systematic review checked for references |
| Cho 2011[160] | Open label |
| Chou 2017[161] | Non randomised study |
| Classen 2013[163] | Systematic review: study designs inappropriate |
| Classen 2013[164] | Incorrect study design |
| Classen 2013[165] | Incorrect study design |

| Study | Exclusion reason |
|---|---|
| Coghill 2010[166] | Systematic review checked for references |
| Coghill 2014[169] | Systematic review: study designs inappropriate. open label |
| 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] | Incorrect study design |
| Connor 2014[180] | References checked |
| Corkum 2008[183] | Incorrect duration |
| Cornforth 2010[184] | Review: references checked |
| Correia Filho 2005 [185] | Incorrect method of diagnosis |
| Cortese 2012[186] | No outcomes of interest |
| Costa 2013[187] | Incorrect duration |
| Cottrell 2008[188] | Included in the economic review |
| Covey 2010[191] | Inappropriate comparison |
| Covey 2011[189] | No relevant outcomes |
| Covey 2015[190] | No useable outcomes |
| Cox 2008[193] | No relevant outcomes |
| Cox 2012[192] | Open label |
| Cubillo 2014[194] | Incorrect duration |
| Cubillo 2014[195] | Incorrect duration |
| Cutler 2010[196] | Conference abstract |
| Dean 2011[201] | Incorrect population |
| Deputy 2002[203] | Not article |
| 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 population (diagnosis) |
| Dopfner 2011[213] | Less than minimum duration |
| Dupaul 2012[214] | Incorrect duration |
| Durell 2014[217] | Erratum |
| Epstein 2011[219] | Incorrect duration |
| Fabiano 2007[222] | Incorrect interventions |
| Fabiano 2010[223, 230] | Incorrect interventions |
| Farah 2009[224] | Incorrect population |
| Farah 2009[225] | No relevant outcomes |
| Faraone 2007[230] | Incorrect intervention |
| Faraone 2009[226] | Review: references checked |
| Faraone 2009[228] | No usable outcomes |
| Faraone 2010[227] | Review: references checked |
| Faraone 2012[229] | Incorrect duration |
| Farmer 2015[231] | Incorrect interventions |
| Farmer 2016[232] | No useable outcomes |
| Fernandez-jaen 2013[233] | Incorrect study design |

| Study | Exclusion reason |
|---|---|
| Findling 2006[242] | Incorrect population |
| Findling 2007[243] | Incorrect duration |
| Findling 2008[236] | Not article |
| Findling 2008[238] | Open label |
| Findling 2009[245] | Open label |
| Findling 2010[234] | Open label |
| Findling 2010[240] | Open label |
| Findling 2010[244] | Incorrect intervention |
| Findling 2011[237] | Incorrect population |
| Findling 2013[239] | Incorrect interventions |
| Findling 2014[241] | Incorrect population |
| Fitzpatrick 1990[246] | Incorrect study design |
| Flapper 2008[247] | Open label |
| Fortier 2013[249] | Inappropriate comparison |
| Foster 2007[250] | Incorrect interventions |
| Fox 2014[251] | No relevant outcomes |
| Fredriksen 2014[252] | Open label |
| Froehlich 2011[254] | No usable outcomes |
| Froehlich 2014[253] | Incorrect duration |
| Fuentes 2013[255] | Open label |
| Fung 2016[256] | Review: references checked |
| Gadow 2011[259] | Incorrect study design |
| Gadow 2016[258] | Incorrect population |
| Gallucci 2006[263] | Incorrect study design |
| Garfinkel 1983[264] | Incorrect duration |
| Garg 2014[265] | Open label |
| Garg 2015[266] | Open label |
| Gau 2010[268] | Open label |
| Gawrilow 2016[269] | Incorrect interventions |
| Gehricke 2009[270] | Incorrect study design |
| Gehricke 2011[271] | Incorrect study design |
| Geller 2007[272] | Inappropriate washout prior to study |
| Ghanizadeh 2012[273] | Incorrect intervention |
| Ghanizadeh 2013[274] | Incorrect interventions |
| Ghuman 2007[276] | Incorrect duration |
| Giblin 2011[277] | Less than minimum duration |
| Ginsberg 2011[279] | Open label |
| Ginsberg 2012[281] | Open label |
| Ginsberg 2014[280] | Open label |
| Gittelman-klein 1976[283] | Inappropriate method of diagnosis |
| Goez 2012[284] | Incorrect duration |
| Gonzalez-Carpio Hernandez 2016[285] | Incorrect study design |
| Gonzalez-heydrich 2010[286] | Incorrect duration |
| Grant 2015[289] | Conference abstract |
| Green 2011[290] | Incorrect duration |

| Study | Exclusion reason |
|---|---|
| Greenhill 2003[295] | Incorrect interventions |
| Greenhill 2006[292] | Wrong population |
| Greenhill 2006[294] | Wrong population |
| Grizenko 2010[297] | Incorrect duration |
| Grizenko 2012[298] | Incorrect duration |
| Grizenko 2013[296] | Incorrect duration |
| Groom 2013[299] | Incorrect duration |
| Guardiola 1999[300] | Not in English |
| Gunther 2010[301] | No useable outcomes |
| Guo 2013[302] | Conference abstract |
| Gustafsson 2010[303] | Incorrect interventions |
| Haas 2008[304] | Open label |
| Haghighat 2014[305] | Not article |
| Hammerness 2009[308] | Review: references checked |
| Hammerness 2013[307] | Open label |
| Handen 2000[310] | Incorrect duration |
| Handen 2008[311] | Incorrect duration |
| Handen 2011[312] | Incorrect study design |
| Hardan 2005[313] | Incorrect study design |
| Harfterkamp 2013[314] | Open label |
| Harfterkamp 2015[317] | Post hoc. open label. |
| Hazell 2003[320] | Combination intervention |
| Hazell 2006[319] | Incorrect study design |
| Hazell 2009[318] | Incorrect study design |
| Heffner 2013[321] | No relevant outcomes |
| Hellwig-brida 2011[322] | Incorrect study design |
| Helseth 2015[323] | Incorrect study design |
| Heriot 2008[324] | Incorrect study design |
| Herring 2012[325] | Incorrect interventions |
| Hervas 2014[326] | Inappropriate method of diagnosis |
| Hester 2010[327] | Incorrect population |
| Hilton 2013[328] | Incorrect population |
| Hirata 2014[329] | Open label |
| Hoebert 2009[330] | Incorrect study design |
| Holden 2013[331] | Not guideline condition |
| Hong 2009[332] | Inappropriate comparison |
| Hong 2014[333] | Incorrect study design |
| Hosenbocus 2009[334] | Review: references checked |
| Howard 2015[335] | Incorrect interventions |
| Huizink 2009[336] | Incorrect interventions |
| Hurt 2011[337] | Incorrect population |
| Hurwitz 2012[338] | Systematic review: study designs inappropriate |
| Huss 2014[339] | Post hoc analysis |
| Huss 2014[340] | Incorrect population |
| Ialongo 1994[342] | Incorrect study design |

| Study | Exclusion reason |
|---|---|
| Ironside 2010[343] | No relevant outcomes |
| Ishii-takahashi 2015[344] | Correction |
| Jacobi-polishook 2009[345] | No relevant outcomes |
| Jahromi 2009[348] | Incorrect duration |
| Jain 2007[352] | Incorrect interventions |
| Jain 2013[350] | Systematic review: study designs inappropriate |
| Jans 2012[353] | Inappropriate intervention |
| Jaselskis 1992[354] | Incorrect population |
| Jasinski 2008[355] | No usable outcomes |
| Jasinski 2009[356] | No usable outcomes |
| Jin 2013[358] | Open label |
| Johnston 2014[359] | Incorrect interventions |
| Jordan 2012[360] | Incorrect study design |
| Jucaite 2014[361] | Incorrect interventions |
| Kandemir 2014[363] | Background information |
| Kaplan 2004[364] | Subgroup analysis |
| Kay 2009[365] | Incorrect population |
| Keating 2011[366] | Not article |
| Kent 2013[368] | Open label |
| Keulers 2007[369] | Open label |
| Khodadust 2012[370] | Incorrect interventions |
| Kim 2009[371] | Open label |
| King 2009[373] | Less than minimum duration |
| Koblan 2015[374] | Incorrect interventions |
| Kollins 2006[375] | Protocol only |
| Kollins 2009[376] | Incorrect duration |
| Kollins 2013[380] | Incorrect duration |
| Kollins 2014[377] | Incorrect comparison |
| Konstenius 2010[382] | Incorrect population |
| Konstenius 2013[383] | No useable outcomes |
| Konstenius 2013[385] | No useable outcomes |
| Konstenius 2014[384] | Incorrect interventions |
| Krakowski 1965[388] | Inappropriate method of diagnosis |
| Kratochvil 2007[389] | Incorrect population |
| Kubas 2012[392] | No useable outcomes |
| Kupietz 1988[394] | Incorrect population |
| Lamberti 2016[396] | Open label |
| Law 1999[397] | No usable outcomes |
| Leblanc 2005[398] | Incorrect interventions |
| Leddy 2009[399] | No relevant outcomes |
| Lee 2013[400] | –Open label design |
| Lerer 1977[403] | No usable outcomes |
| Lerer 1979[402] | No usable outcomes |
| Leuchter 2014[404] | No relevant outcomes |
| Levin 2007[405] | Incorrect interventions |

| Study | Exclusion reason |
|---|---|
| Levin 2015[406] | Incorrect interventions |
| Li 2010[409] | Incorrect interventions |
| Li 2011[407] | Incorrect interventions |
| Li 2013[408] | Incorrect interventions |
| Lin 2014[410] | Incorrect interventions |
| Lin 2016[411] | No useable outcomes |
| Lin 2017[412] | No usable outcomes |
| Lion-francois 2014[413] | Incorrect population |
| Liu 2011[414] | Commentary |
| Logemann 2013[416] | Incorrect duration |
| Loo 2016[417] | No useable outcomes |
| Lufi 2007[419] | No useable outcomes |
| Luman 2015[420] | Incorrect duration |
| Lyon 2010[421] | Incorrect study design |
| Lyon 2011[422] | Incorrect interventions |
| Malone 2009[423] | Incorrect study design |
| Manor 2013[424] | Incorrect interventions |
| Manor 2014[425] | Incorrect interventions |
| Manos 2009[426] | Inappropriate comparison |
| Marchant 2010[427] | Open label |
| Marchant 2011[428] | Open label |
| Marchant 2011[429] | Incorrect interventions |
| Martin 2007[431] | Incorrect duration |
| Martin 2014[432] | Incorrect duration |
| Martins 2004[433] | Inappropriate comparison |
| Mattes 1984[434] | Incorrect population |
| Mattingly 2012[435] | Open label |
| Mattos 2013[438] | Open label |
| Mattos 2014[437] | References checked |
| Matza 2004[440] | Incorrect study design |
| Matza 2007[439] | Incorrect study design |
| McCracken 2016[441] | Incorrect study design |
| Mcgough 2006[442] | Incorrect duration |
| Mcgough 2012[443] | Incorrect study design |
| Mcinnes 2007[444] | Less than minimum duration |
| Mcrae-clark 2010[445] | Incorrect interventions |
| Meisel 2013[447] | Incorrect interventions |
| Michelson 2002[448] | Conference abstract |
| Michelson 2004[451] | Incorrect interventions |
| Mikami 2009[453] | No usable outcomes |
| Mikkelsen 1982[454] | Incorrect study design |
| Miller 2007[455] | Incorrect duration |
| Mohammadi 2012[459] | Incorrect interventions (combination) |
| Mohammadi 2015[458] | Incorrect interventions |
| Monuteaux 2007[461] | Incorrect interventions |

| Study | Exclusion reason |
|---|---|
| Moorthy 2015[462] | Incorrect interventions |
| Morash-Conway 2016[463] | Incorrect study design |
| Moriyama 2013[464] | Review: references checked |
| Moshe 2012[465] | Less than minimum duration |
| Muir 2010[466] | No primary research |
| Muniz 2008[467] | Incorrect duration |
| Murray 2011[468] | Incorrect population |
| Nandam 2011[472] | Incorrect population |
| Newcorn 2006[477] | Abstract |
| Newcorn 2010[480] | Open label |
| Newcorn 2016[475] | Incorrect population |
| Ni 2013[482] | No relevant outcomes |
| Ni 2016[481] | Incorrect study design |
| Niederhofer 2012[483] | Incorrect interventions |
| Nunes 2013[484] | Incorrect interventions |
| Ogrim 2013[485] | Inappropriate comparison |
| Olsen 2012[486] | Incorrect interventions |
| Overtoom 2009[488] | Incorrect duration |
| Owen 2009[489] | Incorrect population (not ADHD) |
| Owens 2016[490] | Incorrect study design |
| Parker 2013[492] | Review: references checked |
| Pataki 1993[493] | Inappropriate washout period |
| Pearson 2013[495] | Incorrect duration |
| Pelham 2011[497] | Less than minimum duration |
| Pelham 2014[496] | Open label dose comparison no washout |
| Perez-alvarez 2009[498] | Incorrect interventions |
| Peterson 2008[499] | Review: references checked |
| Philipsen 2014[500] | Protocol only |
| Philipsen 2015[501] | Incorrect interventions |
| Pierce 2010[502] | Open label |
| Pollak 2010[504] | Less than minimum duration. |
| Posey 2007[505] | Inappropriate washout period |
| Potter 2008[507] | Incorrect duration |
| Potter 2014[506] | Incorrect intervention |
| Prada 2015[508] | Incorrect study design |
| Prasad 2007[510] | Open label |
| Prasad 2009[509] | Incorrect study design |
| Prince 2000[511] | Open label design |
| Pringsheim 2011[512] | SR checked for references |
| Punja 2012[513] | Protocol |
| Ramtvedt 2013[515] | Incorrect study design |
| Ramtvedt 2014[514] | Incorrect study design |
| Ramtvedt 2014[516] | Incorrect study design |
| Rapoport 1974[517] | Inappropriate method of diagnosis |
| Rapport 2008[518] | Inappropriate washout period |

| Study | Exclusion reason |
|---|---|
| Ray 2009[519] | Not guideline condition |
| Redman 2014[520] | Protocol |
| Reichow 2013[521] | Review: references checked |
| Research units on pediatric psychopharmacology autism 2005[523] | Incorrect duration |
| Reyes 2006[525] | Incorrect study design |
| Rezaei 2010[526] | Incorrect population |
| Richardson 1988[528] | Incorrect study design |
| Riggs 2011[529] | Incorrect interventions |
| Roesch 2013[531] | Less than minimum duration |
| Roesch 2013[532] | Incorrect population |
| Rosler 2013[534] | No relevant outcomes |
| Rubia 2009[536] | Incorrect study design |
| Rubia 2011[537] | Incorrect duration |
| Rubia 2011[538] | No relevant outcomes |
| Safavi 2016[541] | Incorrect study design |
| Sahin 2014[542] | Incorrect study design |
| Salehi 2010[543] | Incorrect interventions |
| Sallee 2009[545] | Incorrect duration |
| Sallee 2012[544] | Review (not systematic) |
| Sandler 2008[547] | Incorrect study design |
| Sandler 2010[548] | Inappropriate comparison |
| Santisteban 2014[549] | No relevant outcomes |
| Santosh 2006[550] | Incorrect study design |
| Sayer 2016[551] | Incorrect study design |
| Schachar 1997[556] | Incorrect interventions |
| Schachar 2008[555] | Less than minimum duration |
| Schrantee 2016[558] | Incorrect population |
| Schulz 2010[560] | Less than minimum duration. |
| Schulz 2010[559] | Inappropriate comparison |
| Sciberras 2011[561] | Incorrect interventions |
| Shakibaei 2015[563] | Incorrect interventions |
| Shang 2015[564] | Open label |
| Shang 2016[565] | Incorrect study design |
| Sharp 1999[566] | Incorrect study design |
| Shaywitz 2016[567] | Incorrect study design |
| Shea 2004[568] | Incorrect population (not ADHD) |
| Short 2004[569] | Incorrect study design |
| Shytle 2002[570] | Less than minimum duration |
| Sikirica 2013[571] | References checked |
| Silva 2008[575] | Less than minimum duration |
| Silva 2008[573] | Less than minimum duration |
| Silva 2013[574] | Inappropriate comparison |
| Sinzig 2007[578] | No useable outcomes |
| Slama 2015[579] | Incorrect duration |

| Study | Exclusion reason |
|---|---|
| Snyder 2002[580] | Incorrect interventions |
| So 2008[581] | Incorrect interventions |
| Sobanski 2008[583] | Open label |
| Sobanski 2012[582] | Open label |
| Solanto 2009[584] | Crossover no washout. Inappropriate washout period |
| Sonuga-barke 2007[586] | Incorrect duration |
| Sonuga-barke 2008[588] | No usable outcomes |
| Sonuga-barke 2009[585] | Crossover with no washout |
| Sonuga-barke 2009[587] | Incorrect duration |
| Spencer 2007[594] | Incorrect interventions |
| Spencer 2008[595] | Incorrect interventions |
| Spencer 2008[596] | Incorrect intervention |
| Spencer 2009[589] | Incorrect duration |
| Spencer 2011[597] | Incorrect population |
| Stein 2011[600] | Less than minimum duration |
| Steiner 2014[601] | Incorrect interventions |
| Stocks 2012[602] | Open label |
| Strand 2012[603] | No relevant outcomes |
| Stray 2009[604] | No relevant outcomes |
| Su 2016[605] | Incorrect study design |
| Sung 2010[606] | Review: references checked |
| Surman 2010[607] | Incorrect interventions |
| Svanborg 2009[610] | Incorrect intervention (combination) |
| Svanborg 2009[609] | Incorrect intervention (combination) |
| Swanson 2006[612] | Incorrect population |
| Swanson 2006[611] | No relevant outcomes |
| Swearingen 2007[613] | Incorrect population |
| Szobot 2008[614] | No useable outcomes |
| Takahashi 2014[615] | Wrong population |
| Tamm 2007[618] | No relevant outcomes |
| Tamm 2012[617] | Inappropriate comparison |
| Taragin 2013[619] | Incorrect study design |
| Tebartz van Elst 2016[622] | Incorrect study design |
| Tehrani-doost 2008[623] | Inappropriate comparison. Less than minimum duration. Open label |
| Tellechea 1991[624] | Incorrect population |
| Ter-stepanian 2010[626] | Incorrect duration |
| The MTA Cooperative Group 1999[1] | Inappropriate interventions |
| Thomson 2009[627] | Systematic review checked for references |
| Thomson 2009[628] | Systematic review is not relevant to review question or unclear PICO |
| Thurstone 2010[629] | Incorrect interventions (combination) |
| Torrioli 2008[630] | Incorrect interventions |
| Trzepacz 2011[634] | No relevant outcomes |
| Tucha 2011[635] | No relevant outcomes |

| Study | Exclusion reason |
|---|---|
| Upadhyaya 2013[636] | Incorrect population |
| Upadhyaya 2015[637] | No relevant outcomes |
| Van der donk 2013[638] | Incorrect interventions |
| Van der kolk 2014[640] | Incorrect study design |
| Van der meer 2013[641] | Open label |
| Van der oord 2007[643] | Incorrect interventions |
| Van der oord 2008[642] | Review: references checked |
| Verster 2008[645] | No usable outcomes |
| Verster 2010[646] | –Incorrect population |
| Warden 2012[648] | Combination. No relevant outcomes |
| Waxmonsky 2008[649] | Incorrect duration |
| Waxmonsky 2011[650] | Dose comparison |
| Waxmonsky 2014[651] | Incorrect population |
| Weber 2008[652] | Incorrect interventions |
| Wehmeier 2007[654] | Single arm open label |
| Weisler 2009[659] | No usable outcomes |
| Weisler 2012[660] | Incorrect interventions |
| Weiss 2004[664] | Incorrect interventions |
| Weiss 2006[661] | Incorrect interventions |
| Weiss 2012[662] | Incorrect interventions |
| Wender 2011[665] | Open label |
| Werry 1980[668] | Inappropriate method of diagnosis |
| Westover 2013[669] | No relevant outcomes |
| Wigal 2004[673] | Inappropriate intervention |
| Wigal 2005[680] | Inappropriate intervention |
| Wigal 2006[687] | No results reported |
| Wigal 2010[674] | Conference abstract |
| Wigal 2010[678] | Open label |
| Wigal 2010[679] | No usable outcomes |
| Wigal 2010[686] | Less than minimum duration |
| Wigal 2011[683] | Less than minimum duration |
| Wigal 2011[677] | Less than minimum duration |
| Wigal 2011[685] | Less than minimum duration |
| Wigal 2012[684] | Less than minimum duration. Inappropriate comparison |
| Wigal 2013[675] | Less than minimum duration |
| Wigal 2014[676] | Incorrect population |
| Wigal 2015[681] | Less than minimum duration |
| Wigal 2016[682] | Less than minimum duration |
| Wilens 2006[694] | Incorrect population |
| Wilens 2008[690] | Incorrect intervention (wrong drugs) |
| Wilens 2008[693] | Inappropriate intervention |
| Wilens 2010[692] | Incorrect interventions |
| Wilens 2011[688] | No relevant outcomes |
| Williams 2010[696] | Incorrect study design |
| Williamson 2014[697] | Incorrect study design |

| Study | Exclusion reason |
|---|---|
| Winhusen 2010[700] | Inappropriate comparison |
| Winhusen 2010[699] | Inappropriate comparison |
| Winhusen 2011[698] | No outcomes of interest reported |
| Witt 2008[701] | Open label |
| Wolraich 2001[702] | Wrong population |
| Wong 2012[703] | No usable outcomes |
| Yang 2012[704] | Open label |
| Yang 2015[705] | Incorrect interventions |
| Yellin am 1978[706] | Inappropriate method of diagnosis |
| Yepes 1977[707] | Inappropriate method of diagnosis |
| Yildiz 2011[708] | Open label |
| Yilmaz 2013[709] | No relevant outcomes |
| Young 2014[710] | No useable outcomes |
| Zeni 2009[713] | Incorrect design |
| Zheng 2015[714] | Incorrect design |

# I.2 Excluded health economic studies

## I.2.1 Pharmacological efficacy

**Table 135: 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[278] | This study was assessed as not applicable because the cost year is 1997 and it is therefore before the guideline date cut-off.<br>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[250] | 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[473] | 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[718] | 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 |

| Reference | Reason for exclusion |
|---|---|
| | QALYs (Change in Conners' teacher rating scale) |

### I.2.2 Pharmacological sequencing

None

# 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** | Population:<br>• Children, young people and adults with ADHD and tic disorders<br>• Children, young people and adults with ADHD and history of psychosis/mania<br>• Children, young people and adults with ADHD and emotional dysregulation<br>Intervention(s): stimulant medication (methylphenidate, lisdexamfetamine, dexamfetamine)<br>Comparison: non-stimulant medication (atomoxetine, guanfacine), placebo<br>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 |
| **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** | 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<br>There is a lack of evidence measuring the long term effects of treatments for ADHD. As a chronic lifelong condition it is imperative trials have longer follow up measuring the benefits and risks of treatments. |
| **Equality** | Research 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** | • High: the research is essential to inform future updates of key recommendations in the guideline. |

## J.2 Medication choice in people with no previous medication for ADHD

**Research question: What is the clinical and cost effectiveness of ADHD medications in people with ADHD with no previous medication for the condition?**

**Why this is important:**

This guideline makes recommendations for the medication choices for people with ADHD, but most of the evidence to support these recommendations comes from studies in people who have previously received medication. Therefore, these studies often include a population not representative of the people with newly diagnosed ADHD. There may be differing levels of efficacy of the various treatment options in this population.

**Criteria for selecting high-priority research recommendations:**

| | |
|---|---|
| **PICO question** | Population: children, young people and adults with ADHD who have never previously used ADHD medication<br>Intervention(s): methylphenidate, lisdexamfetamine, dexamfetamine, atomoxetine, guanfacine<br>Comparison: placebo and each other<br>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** | • High: the research is essential to inform future updates of key recommendations in the guideline. |

## J.3 Prescribing beyond monotherapy

**Research question: What is the clinical and cost effectiveness of various ADHD prescribing strategies when monotherapy has failed?**

**Why this is important:**

This guideline makes recommendations for the medication choices for people with ADHD up to the point at which common monotherapies are exhausted. There is very little evidence to guide healthcare professionals beyond this point, particularly with regards to whether there is a benefit of prescribing stimulant and non-stimulant medication together.

**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, dexamfetamine) and one non stimulant (e.g. guanfacine, atomoxetine)<br>Intervention(s): stimulant + non-stimulant (e.g. methylphenidate + atomoxetine), stimulant/non-stimulant + placebo<br>Comparison: each other<br>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** | • High: the research is essential to inform future updates of key recommendations in the guideline. |