National Institute for Health and Care Excellence

Final

# Attention deficit hyperactivity disorder (update)

## [D] Evidence review for safety of pharmacological treatment

*NICE guideline CG72*

*Intervention evidence review*

*March 2018*

*Final*

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

## Update information

**September 2019:** The evidence review was updated to clarify why the committee agreed that an ECG is not needed before starting stimulants, atomoxetine or guanfacine if cardiovascular history and examination are normal and the person is not on medicine that poses an increased cardiovascular risk.

See the related updated recommendation at www.nice.org.uk/guidance/NG87

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# 1 Safety of pharmacological treatment

## 1.1 Review question: What are the adverse events associated with pharmacological treatment for people with ADHD?

## 1.2 Introduction

There are key unanswered questions for clinicians treating all age groups of people with ADHD and these concern the best medication to use, the sequence of medication, the optimum duration of treatment, when it is appropriate to consider drug discontinuation, which drug treatments to use in the presence of co-occurring conditions and these questions are addressed in other reviews evaluating the clinical effectiveness of the medication and their impact on ADHD symptoms (for more information, see evidence report F on combination treatment). There is much presumption and hearsay around the potential harmful effects of ADHD medication and this is unhelpful in supporting clinicians and people with ADHD to make and review treatment choices. The aim of this review is to evaluate the evidence identifying the adverse events that are key in considering which medication to choose, the appropriate baseline assessments, how it should be initiated and what review and monitoring process should be in place to ensure that medication of the treatment ADHD is safely and effectively delivered.

## 1.3 PICO table

For full details see the review protocol in appendix A.

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

| | |
|---|---|
| **Population** | Children, young people and adults with ADHD<br>Stratification: Children (<5 years), children and young people (5-17 years) and adults (≥18 years) |
| **Intervention(s)** | The following treatments (all doses), received for a minimum of 2-weeks:<br>• CNS stimulants<br>  ○ methylphenidate<br>  ○ methylphenidate modified release<br>  ○ dexamphetamine<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<br>  ○ Quetiapine<br>  ○ Aripriprazole |

| | |
|---|---|
| | • 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<br>• pharmacological treatments used to treat Parkinson's Disease |
| **Comparison(s)** | Placebo<br>Compared against each other |
| **Outcomes** | All outcomes to be measured at short term (up to 12 weeks) and long-term (≥12 weeks) timepoints<br>**Critical outcomes:**<br>• Adverse events<br>  ○ Total number of participants with an adverse event<br>  ○ All-cause mortality<br>  ○ Suicide or suicidal ideation<br>  ○ Cardiac mortality<br>  ○ Cardiac events including tachycardia/palpitations (defined by >/120bpm) or systolic or diastolic blood pressure changes<br>  ○ Substance misuse<br>  ○ Abnormal growth ( height and weight)<br>  ○ Increase in seizures in people with epilepsy<br>  ○ Psychotic symptoms<br>  ○ Disturbed sleep<br>  ○ Liver damage (defined by deranged LFTs)<br>  ○ Increased tics<br>  ○ Tremors<br>  ○ Congenital defects amongst patients who are pregnant<br>  ○ Sexual dysfunction |
| **Study design** | RCTs<br>Open label RCTs and non-randomised studies only for long term outcomes (≥3 months) |

This review sought to evaluate the adverse events of pharmacological treatments to support discussions about medication choice and to enable appropriate monitoring. The population of this review was stratified by age (children aged <5 years, children and young people (5-18 years), and adults (over 18). The guideline committee felt that adverse effects could differ between these populations, which could indicate the need for different events to be monitored.

The committee agreed that where outcomes were relevant but did not match the protocol exactly (e.g. appetite changes reported in the study with weight loss specified in the protocol) these outcomes would be extracted but downgraded for indirectness."

Quality assessments were conducted for all outcomes. GRADE was completed for outcomes of comparative studies, and quality assessments for outcomes of non-comparative studies were reported narratively.

## 1.4 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[479] 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.

## 1.5 Clinical evidence

### 1.5.1 Included studies (pre-school children under the age of 5)

Three RCTs were included in the review that evaluated the adverse events of pharmacological treatments in preschool age children (<5 years of age);[41, 283, 297] these are summarised in Table 2 below. Evidence from these studies is summarised in Table 7 and Table 8.

Two of these studies compared methylphenidate with placebo[283, 297], while the other study compared risperidone to methylphenidate.[41]

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.

### 1.5.2 Excluded studies

See the excluded studies list in appendix I.

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

**Table 2: Summary of studies included in the evidence review (RCTs)**

| 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) | Preschool children aged 3-6 years who met DSM-IV-TR criteria for ADHD. (n=38) | • Weight changes at 6 weeks<br>• Sleep 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.<br><br>Unclear line of treatment<br><br>(Total scores parent ADHD-RS approx. 28). |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Ghuman 2009[283] | (n=17) Crossover<br>Intervention 1: CNS stimulants – Methylphenidate initiated at 1.25mg t.i.d. and titrated based on response and tolerance<br>Comparison: Placebo | 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 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. | • Systolic blood pressure at 4 weeks<br>• Weight changes at 4 weeks<br>• Height changes at 4 weeks | Mixed line. 8 children were drug naïve and 6 had received previous psychotropic medication.<br><br>No clinically important changes in ECG parameters.<br><br>Unclear line of treatment |
| Greenhill 2006[297](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 | • Tachycardia at 1 weeks | Children were stimulant naive |

See appendix D for full evidence tables.

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

Sixty RCTs were included in the review, which evaluated the adverse events of pharmacological treatments in children and young people (5-18 years of age); these are summarised in Table 3 below:

- ten RCTs compared immediate release methylphenidate versus placebo[183, 211, 265, 292, 299, 465, 495, 579, 635, 698]
- three RCTs compared osmotic-release oral system methylphenidate versus placebo [174, 247, 481]
- nineteen RCTs compared atomoxetine with placebo [24, 47, 66, 208, 274, 279, 323(322) 374(93) 377, 435, 457, 459, 466, 481, 614(613) 618, 649, 658, 659]
- two RCTs compared atomoxetine versus methylphenidate [481, 649]
- one RCT compared atomoxetine with lisdexamfetamine [213]
- seven RCTs compared guanfacine versus placebo [96, 187, 349, 483, 556, 691]
- one RCT compared atomoxetine with guanfacine [349]
- two RCTs compared lisdexamfetamine with placebo [174, 242]
- one RCT compared lisdexamfetamine with methylphenidate [174].
- three RCTs compared clonidine versus placebo [359, 495, 635]
- two RCTs compared clonidine versus methylphenidate [495, 635]
- one RCT compared clonidine versus desipramine [580]

- one RCT compared desipramine versus placebo [594]
- one RCT compared venlafaxine versus methylphenidate [710]
- two RCTs compared risperidone versus placebo [134, 476]
- two RCTs compared bupropion with placebo [145, 182]
- two RCTs compared buproprion versus methylphenidate [71, 355]
- four RCTs compared modafinil versus placebo [103, 298, 371, 615]
- one RCT compared modafinil versus methylphenidate [35].

Seven non-randomised studies were included in the review that reported the adverse events of pharmacological treatments in children and young people (6-18 years of age)[95, #514, #532, #1130, #1134, #575, #1108]. One study compared atomoxetine to methylphenidate and two studies compared stimulants to no treatment. The other four studies were open label non comparative studies; one study evaluated lisdexamfetamine dimesylate, one study atomoxetine, one study guanfacine, and one study melatonin.

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.

### 1.5.5 Excluded studies

See the excluded studies list in appendix I.

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

**Table 3: Summary of studies included in the evidence review (RCTs)**

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Allen 2005 [24] | Intervention: Atomoxetine 0.5mg/kg per day to 1.5mg/kg per day (n=76)<br><br>Comparison: Placebo (n=72) | Children aged 7 to 17 years that met DSM-IV criteria for ADHD and had concurrent Tourette's syndrome or chronic motor tic disorder. (n=148) | • Tachycardia at 18 weeks<br>• Weight changes at 18 weeks<br>• Tics at 18 weeks | 68.2% had previous stimulant 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 OROS (20-30mg per day) (n=30) | Children aged 6 to 15 years that met DSM-IV criteria for ADHD (n=60) | • Weight change at 6 weeks | ADHD-RS-IV score at least 1.5 standard deviations above norms for age and gender (ADHD-RS-IV baseline score of 40)<br>Unclear line of treatment |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | | All patients combined subtype and newly diagnosed, drug naïve |
| Anon 2002 (Tourette's Syndrome Study Group) [635] | Interventions:<br>Methylphenidate (n=37)<br>Clonidine (n=34)<br>Combination (n=33)<br>Comparison:<br>Placebo (n=32) | Children and adolescents 7-14 meeting DSM-IV-TR ADHD and Tourette disorder, chronic motor tic disorder or chronic vocal tic disorder criteria (n=136) | • Increase in tics at 16 weeks | All tic disorder ( 95% Tourette's, 4% chronic motor tic disorder, 1% chronic vocal tic disorder)<br><br>Unclear line of treatment and subtype |
| Arnold 2006[47] | Crossover trial (n=16)<br><br>Intervention:<br>Atomoxetine: maximum dose 1.4mg/kg per day<br><br>Comparison:<br>Placebo | Children aged 5 to 15 years meeting DSM-IV criteria for ADHD | • Sleep at 6 weeks<br>• Tics at 6 weeks<br>• Tremor at 6 weeks | Subtypes not specified<br>43.8% Autism spectrum disorder<br><br>Unclear line of treatment and subtype |
| Bangs 2007 [66] | Intervention:<br>Atomoxetine. target dose was 1.2mg/kg per day which could be increased to 1.8mg/kg (n=72)<br><br>Comparison:<br>Placebo (N=70) | Children and adolescents aged 12-18 who met DSM-IV criteria for ADHD<br>(n=142) | • Decreased weight at 9 weeks and 9 months<br>• Sleep (insomnia) at 9 months (non-comparative | 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[71] | Intervention:<br>Bupropion 50-200mg/day | Children aged 7-16 with a diagnosis of ADHD according to DSM-III-R | • Total participants with adverse events at 5 | 10 of 15 had previously taken Methylphenidate up to two weeks before |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | Comparison: Methylphenidate 20-60mg/day<br><br>Crossover trial (n=18) | | weeks<br>• Weight changes at 5 weeks<br>• Sleep at 5 weeks<br>• Tremor at 5 weeks | enrolling. Results at seven weeks. Subtype status not stated. Subjects' CGI was "severe" in 12 and "moderate" in three. |
| Biederman 1989[88 87, 89] | Intervention: Desipramine 30, 50 and 70mg (n=31)<br><br>Comparison: Placebo. (n=31) | Children 13 to 17 years with ADHD according to DSM-IV-TR criteria (n=62) | • Decreased appetite at 9 weeks<br>• Sleep at 9 weeks | Unclear line of treatment |
| Biederman 2006[103] | 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) | • Systolic blood pressure at 9 weeks<br>• Weight change at 9 weeks<br>• Decreased appetite at 9 weeks<br>• Sleep 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[94] (Childress 2014[160], Lopez 2008[423], Jain 2011[357]) | Lisdexamfetamine dimesylate 30, 50 and 70 mg/ day(n=235)<br><br>Placebo (n=79) | Children 13 to 17 years with ADHD according to DSM-IV-TR criteria (n=314) | • Total participants with adverse events<br>• Weight decrease at 4 weeks<br>• Sleep at 4 weeks | ADHD Rating Scale of (ADHD-RS-IV) score >28<br><br>Unclear line of treatment |
| Biederman 2008[96] | Interventions: Extended release guanfacine 2mg/d (n=87) Extended release | Children aged 6-17 who met DSM-IV criteria for a primary diagnosis of ADHD combined | • Total adverse events at 5 weeks<br>• All-cause mortality at 5 | All/mixed subtypes (Inattentive 26.1%, Hyperactive-impulsive 2%, Combined 71.9%) |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | guanfacine 3mg/d (n=86)<br>Extended release guanfacine 4mg/d (n=86)<br>Total (n=138)<br><br>Comparison: Placebo (n=86) | subtype, predominantly inattentive subtype, or predominantly hyperactive-impulsive subtype (n=345) | weeks<br>• Appetite changes at 5 weeks<br>• Sleep at 5 weeks | Baseline scores of ADHD-RS show the majority of the population had severe ADHD.<br><br>Unclear line of treatment |
| Brown 1989 [124] | Crossover trial (n=11)<br><br>Intervention: Methylphenidate 0.15mg/kg per day, 0.3mg/kg per day and 0.5mg/kg per day (2 weeks)<br><br>Comparison: Placebo (2 weeks) | Boys aged 12 to 15 years diagnosed with ADHD according to DSM-III criteria | • Systolic blood pressure at 2 weeks | Comorbid ASD<br>Unclear line of treatment<br>Subtypes not specified |
| Buitelaar 2001 [134] | (n=19) Intervention 1: Antipsychotics – Risperidone (maximum 5mg/day)<br><br>(n=19) Intervention 2: No treatment - Placebo | (n=38) Children aged 12 to 18 years with a formal diagnosis of ADHD with subaverage cognitive abilities (IQ of 60 to 90 on the WISC-R for children). | • Total participants with adverse events at 6 weeks<br>• Tremor at 6 weeks | Subtype not specified<br><br>70% stimulant naive |
| NCT00763971 trial: Coghill 2013 [174] (Coghill 2014 [177], Banaschewski 2013 [64], Coghill 2014 [176]) | Intervention: Lisdexamfetamine dimesylate 30-70mg/day (n=113)<br><br>Comparison: Methylphenidate 18-54mg per day (n=112)<br><br>Comparison: placebo (n-111) | Children 6 to 16 years with ADHD according to DSM-IV-TR criteria (n=336) | • Systolic blood pressure at 7 weeks<br>• Weight changes at 7 weeks<br>• Sleep at 7 weeks<br>• | ADHD-RS-IV score of 28 or higher<br><br>Unclear line of treatment<br>. |
| Connor 2010 [187] | (n=138) Guanfacine. Guanfacine modified release (maximum dose 4mg/day)<br><br>(n=79) Comparison: placebo | (n=217) Children aged 6 to 12 years who met the DSM-IV criteria for ADHD | • Total participants with adverse events at 8 weeks<br>• Mortality at 8 weeks<br>• Psychotic symptoms at 8 weeks | ADHD-RS-IV score of 24 or more<br><br>Inattentive subtype(12.6%), hyperactive subtype(3.3%), combined subtype (84.1%) |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | | Unclear line of treatment |
| Conners 1980[183] | Intervention: Methylphenidate mean dose 22mg/day (maximum 60mg/day) (n=20)<br><br>Comparison: Placebo (n=21) | Children diagnosed with ADHD between 6 and 11 years old (n=41) | • Palpitations at 8 weeks<br>• Appetite problems at 8 weeks<br>• Sleep (insomnia) at 8 weeks | Line of treatment unclear<br>Subtypes unclear |
| Dell'agnello 2009[208] | Intervention: Atomoxetine 1.2mg/kg/d(n=105)<br><br>Comparison: Placebo (n=32) | Children aged 6-15 years who met DSM-IV diagnostic criteria for ADHD and oppositional defiant disorder. (n=137) | • Diastolic blood pressure at 8 weeks<br>• Decreased weight at 8 weeks<br>• Sleep (insomnia) at 8 weeks | 20% of the atomoxetine group and 12.5% of the placebo group had previous therapy.<br><br>89% of the population diagnosed with combined subtype. |
| Dittmann 2014[213] (Nagy 2015[477], Dittmann 2013[214]) | Intervention: Lisdexamfetamine dimesylate (n=133)<br>Intervention: Atomoxetine (n=134) | Children with ADHD according to DSM-IV criteria (n=267) | • Total participants with any adverse events at 9 weeks<br>• Systolic blood pressure at 9 weeks<br>• Decreased weight at 9 weeks<br>• Decreased appetite at 9 weeks<br>• Sleep at 9 weeks | Mean baseline scores of ADHD-RS-IV total scores were 42.6(6.14).<br><br>Unclear line of treatment |
| Findling 2006[247] | Intervention 1: IR-Methylphenidate (n=133)<br><br>Intervention 2: OROS-MPH (n=139)<br><br>Comparison: Placebo (n=46) | Children 6 to 12 years with ADHD according to DSM-IV-TR criteria (n=318) | • Decreased weight (anorexia) at 3 weeks<br>• Sleep (insomnia) at 3 weeks<br>• Tics at 3 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. |
| Findling 2011[242] | Intervention: Lisdexamfetamine | Children 13 to 17 years with ADHD | • Total participants | Moderate severity on ADHD-RS (28 or |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | 30, 50 and 70mg (n=235)<br><br>Comparison: Placebo. (n=79) | according to DSM-IV-TR criteria (n=314) | with any adverse events at 4 weeks<br>• All-cause mortality at 4 weeks<br>• Systolic blood pressure at 4 weeks<br>• Weight decrease at 4 weeks<br>• Sleep at 4 weeks | higher). 3 week titration period and 1 week maintenance<br><br>Unclear line of treatment |
| Gadow 2008[265](Gadow 2007[266];Gadow 1995[267]) | Crossover (n=31)<br>Interventions: CNS stimulants – Methylphenidate 0.1mg/kg per day, 0.3mg/kg per day and 0.5mg/kg per day<br><br>Comparison: placebo | Children meeting the DSM-III or IV criteria for ADHD and either chronic motor tic disorder or Tourette's syndrome. | • Systolic blood pressure at 2 weeks<br>• Weight change at 2 weeks<br>• Tic severity at 2 weeks | Line of treatment not specified<br>Subtype not specified |
| Gau 2007[274] | 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) | • Weight changes at 6 weeks<br>• Sleep at 6 weeks | 64% drug naïve.<br><br>Baseline scores of CGI-S show the majority of the population had moderate ADHD. 73% combined subtype, 27% combined subtype, and no participants had the predominantly hyperactive subtype. |
| Geller 2007[279] | 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) | • Weight loss 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 . |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | | |
| Gonzalez;Heydrich [292] | Intervention: Methylphenidate<br>Comparison: placebo<br>Crossover trial (n=33) | Children and adolescents 6-18 meeting DSM-IV-TR ADHD criteria and epilepsy | Seizures at 3 weeks | Adaptive RCTs; those with seizures were kept on current dose, those without increased their dose up to 54mg<br><br>Unclear line of treatment |
| Greenhill 2006[298] | Intervention: Modafinil (n=133)<br><br>Comparison: placebo (n=67) | Children aged 6 to 16 diagnosed with ADHD and ASD according to the DSM-IV. (n=198) | • Systolic blood pressure at 9 weeks<br>• Weight loss at 9 weeks<br>• Decreased appetite at 9 weeks<br>• Sleep at 9 weeks | ADHD-RS score at least 1.5 SDs above normal values for age and gender<br>23.7% of the population were of Inattentive subtype of ADHD, 5.05% were hyperactive/impulsive subtype and 70.2% were of the combined subtype.<br>. |
| Greenhill 2002[299] | (n=155) Intervention 1: CNS stimulants – Methylphenidate (maximum 60mg/day)<br><br>(n=159) Intervention 2: No treatment - Placebo. | (n=311) Children aged 6 to 16 years diagnosed with ADHD according to DSM-IV criteria | • Total participants with adverse events at 3 weeks | Combined and predominantly hyperactive/impulsive subtypes only<br>64% had been previously treated for ADHD<br><br>Unclear line of treatment |
| Harfterkamp 2012[323] (Harfterkamp 2014[322]) | Intervention: Atomoxetine, fixed dose of 1.2mg/kg/day (n=48)<br><br>Comparison: Placebo (n=49) | Children aged 6 to 17 diagnosed with ADHD and ASD according to the DSM-IV. (n=97) | • Sleep (insomnia) at 8 weeks | 37% received no previous drug treatment<br>All subjects scored over 1.5 SD above age-standard norms for ADHD-RS. Sub-type not stated. Baseline scores of CGI-S show the majority of the population had moderate ADHD.<br><br>Comorbid autism spectrum disorder |
| Huss 2015 [349] | Intervention: Guanfacine 4- | Children aged 6 to 17 years who met | • Total participants | 85% combined, 12% inattentive and 3% |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | 7mg/day (n=115)<br><br>Intervention: Atomoxetine (n=112)<br><br>Comparison: Placebo (n=111) | the DSM-IV criteria for ADHD (n=338) | with adverse events at 10 to 13 weeks<br>• All-cause mortality at 10 to 13 weeks<br>• Blood pressure at 10 to 13 weeks<br>• Sleep (insomnia) at 10 to 13 weeks | hyperactive impulsive<br><br>Moderate severity (ADHD-RS score of 32 or higher at baseline)<br><br>Unclear line of treatment |
| Jafarinia 2012[355] | Intervention: Bupropion 100mg/d if <30kg, 150mg/d if >30kg(n=22)<br><br>Comparison: Methylphenidate 20mg if <30kg, 30mg is >30kg (n=22) | Children and adolescents aged 6-17 who met the DSM-IV-TR diagnostic criteria for ADHD (n=44) | • Tachycardia at 8 weeks<br>• Decreased appetite<br>• Sleep at 8 weeks | All patients were drug naïve.<br><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 majority of the population had severe ADHD. |
| Jain 2011[359] | 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) | • Total participants with adverse events<br>• All- cause mortality at 8 weeks<br>• Sleep at 8 weeks | Minimum score of 26 on ADHD-RS<br><br>Unclear line of treatment |
| Kahbazi 2009[371] | (n=23) Intervention 1: CNS stimulants - Modafinil. Once daily 200-300mg per day depending on weight (200mg/day for <30kg and 300mg/day for >30kg).<br><br>(n=23) Intervention 2: No treatment - Placebo. | (n=46) Children aged 6 to 15 years with ADHD according to DSM-IV criteria | • Weight loss at 5 weeks | ADHD-RS-IV score at least 1.5 SDs above norms.<br>All combined subtype (mean baseline ADHD-RS score of 36)<br><br>Unclear line of treatment |
| Kaplan 2004[374] (Biederman 2002[93]) | Intervention: Atomoxetine (n=53) | Children 7 to 13 years with ADHD according to DSM-IV-TR criteria (n=98) | • Decreased appetite at 9 weeks<br>• Sleep at 9 | Unclear line of treatment and subtype. |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | Comparison: Placebo (n=45) | | weeks | |
| Kelsey 2004 [377] | 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) | • Systolic blood pressure at 8 weeks<br>• Sleep 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. |
| Kollins 2011[387] | 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) | • Sleep at 8 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[435] | 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) | • Total participants with adverse events<br>• All-cause mortality at 6 weeks<br>• Suicide at 6 weeks<br>• Systolic blood pressure at 6 weeks<br>• Weight changes at 6 weeks<br>• Height changes at 6 weeks | All participants were stimulant naive, however 40% were on nortropics (n=30) or psychotropics (n=14) before the trial, and 10% continued another medication during the trial. All ADHD subtypes were included, 72.4% combined, 24% inattentive, 5% hyperactive. Baseline scores of ADHD-RS show the majority of the population had severe ADHD. |
| Mohammadi 2012[463] | (n=23) Intervention 1: CNS stimulants – Methylphenidate (20-30mg/day depending on weight) | (n=46) Children aged 6-14 years who met the DSM-IV criteria for ADHD | • Decreased appetite at 6 weeks<br>• Sleep (insomnia) at | ADHD-RS-IV score of at least 1.5 standard deviations above norms for patient's age and gender |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | (n=23) Intervention 2: No treatment - Standard treatment. Buspirone tablets 20-30mg doses depending on weight | | 6 weeks<br>• Tics at 6 weeks | All combined subtype and drug naive |
| Michelson 2001[459] | Intervention: Atomoxetine 0.5-1.8mg/kg per day (n=213)<br><br>Placebo (n=84) | Children aged 8 to 18 years with ADHD according to DSM-IV-TR criteria (n=297) | • Systolic blood pressure at 13 weeks<br>• Decreased weight at 13 weeks<br>• Decreased appetite 13 weeks<br>• Sleep (Sleep (insomnia)) at 13 weeks | Required to be at least 1.5 SD above the age and gender norms as assessed by ADHD-RS-IV<br><br>.<br><br>Unclear line of treatment |
| Michelson 2002[457] | Intervention: Atomoxetine 1.2mg/kg/d (n=84)<br><br>Comparison: Placebo (n=84) | Children and adolescents aged 8-18 who met the DSM-IV diagnostic criteria for ADHD (n=168) | • Systolic blood pressure at 6 weeks<br>• Decreased appetite at 6 weeks | Unclear line of therapy.<br><br>All/mixed subtypes. 57.6% combined, 40.6% inattentive, 1.8% hyperactive impulsive.<br>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. |
| Montoya 2009[466] | 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) | • Total participants with adverse events at 12 weeks<br>• Decreased appetite 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. |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Nagaraj 2006[476] | (n=19) Intervention: Antipsychotics – Risperidone<br><br>(n=21) Comparison: placebo. | (n=40) children aged 6 to 12 years diagnosed with autism according to DSM-IV criteria, who were referred to outpatients clinics due to symptoms of hyperactivity, aggression and language difficulties. | • Weight at 6 months | 20% have had previous treatment (n=20) |
| Newcorn 2008[481] | 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: Placebo (n=27) | Children aged 6-16 diagnosed with ADHD as per the DSM-IV criteria (n=191) | • Total participants with adverse events at 6 weeks<br>• Systolic blood pressure at 6 weeks<br>• Weight changes at 6 weeks | Subpopulation of stimulant naïve subjects. |
| Newcorn 2013[483] (Stein 2015[601]; Young 2014[707] | Intervention: Extended release guanfacine maximum dose 4mg/d (n=227)<br><br>Comparison: Placebo (n=113) | Children aged 6-12 years diagnosed with ADHD as per the DSM-IV criteria (n=340) | • Total participants with adverse events at 8 weeks<br>• Suicidal ideation at 8 weeks<br>• Increased appetite at 8 weeks<br>• Sleep 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[495] (Daviss 2008[206], Cannon 2009[141]) | Intervention: Methylphenidate (n=29)<br>Intervention 2: Clonidine (n=31)<br>Intervention 3: Methylphenidate and clonidine combination (n=32)<br><br>Comparison: placebo (n=30) | Children and adolescents 7-12 meeting DSM-IV-TR ADHD criteria (n=122) | • Heart palpitations at 16 weeks<br>• Systolic blood pressure at 16 weeks<br>• Weight changes at 16 weeks<br>• Sleep at 16 weeks<br>• Psychotic symptoms at 16 weeks | Unclear line of treatment |
| Sallee 2009 [549] | Intervention: Guanfacine | Children and adolescents 6-17 | • Total participants | 73% combined, 26% inattentive, 2% |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | (n=256) All doses – 1, 2, 3 and 4mg/day.<br>Comparison: Placebo (n=66) | meeting DSM-IV-TR ADHD criteria (n=182) | with adverse events at 9 weeks<br>• Cardiovascular events at 9 weeks | hyperactive/impulse<br>Severity: Mixed (Mean ADHD-RS-IV score of 40.1 (SD 8.65))<br><br>Unclear line of treatment |
| Scahill 2015[557] | 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) | • Sleep at 8 weeks<br>• Psychotic symptoms 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 IQ of 35 (or mental age of 18 months) or greater. Baseline scores of ADHD-RS show the majority of the population had severe ADHD. |
| Simonoff 2013[579] | 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) | • Systolic blood pressure at 16 weeks<br>• Weight change at 16 weeks<br>• Decreased appetite at 16 weeks<br>• Sleep at 16 weeks | Unclear line of treatment<br><br>Mean baseline scores of Teacher Conners ADHD Index of 20.6 (SD9.5) |
| Singer 1995[580] | Crossover (n=34)<br><br>Intervention 1: Tricyclic antidepressants - Desipramine 25mg-100mg per day<br><br>Intervention 2: Clonidine. total daily dose of clonidine, 0.2mg/day | Children aged 7 to 14with who met the DSM-III criteria for ADHD and Tourette's syndrome or other tic disorders | • Total participants with adverse events at 6 weeks | Unclear line of treatment and subtype. |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | Comparison: No treatment - Placebo | | | |
| Spencer 2002[594] | (n=21) Intervention 1: Tricyclic antidepressants - Amitriptyline (50mg/day; titrated up to 3.5mg/kg per day unless adverse effects developed)<br><br>(n=20) Intervention 2: No treatment - Placebo | (n-41) Children aged 5 to 17 years with a diagnosis of ADHD ascertained from clinical referrals to a paediatric psychopharmacology unit. All subjects had a history of Tourette disorder or non-Tourette disorder chronic tic disorders. | • Decreased appetite at 6 weeks<br>• Disturbed sleeping at 6 weeks<br>• Improvement to tics at 6 weeks | Combined subtype<br><br>22/41 participants had been previously treated with stimulants.<br><br>. |
| Spencer 2008[600] | 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 (n=41) | • Decreased appetite at 8 weeks<br>• Tics at 8 weeks | Unclear line of treatment<br><br>53.6% had received previous stimulants. Baseline scores of ADHD-RS show the majority of the population had severe ADHD. |
| Svanborg 2009[614] (Svanborg 2009[613]) | Intervention: Atomoxetine 1.2mg/kg or 80mg/day (n=49)<br><br>Comparison: Placebo (n=50) | Children aged 6-15 diagnosed with ADHD as per the DSM-IV criteria (n=99) | • Decreased appetite at 10 weeks | All patients stimulant naïve. All/mixed subtypes (77.8% combined, 4% hyperactive, 18.2% inattentive). Baseline mean total ADHD-RS-IV = 39<br><br>Baseline scores of ADHD-RS show the majority of the population had severe ADHD. |
| Swanson 2006[615] | Intervention: Modafinil (n=120)<br><br>Comparison: Placebo (n=63) | Children and adolescents (6 to 17 years) meeting DSM-IV-TR ADHD criteria (n=183) | • Tachycardia at 7 weeks<br>• Systolic blood pressure at 7 weeks<br>• Weight change at 7 weeks<br>• Sleep at 7 weeks<br>• Psychotic symptoms at | Severity of 1.5 SDs above the US age and gender norms on the ADHD-RS-Parent Version<br><br>Unclear line of treatment |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | 7 weeks | |
| Takahashi 2009[618] | (n=62) Intervention 1: CNS stimulants - Atomoxetine. 0.5mg/kg per day<br><br>(n=60) Intervention 2: CNS stimulants - Atomoxetine. 1.2mg/kg<br><br>(n=61) Intervention 3: CNS stimulants - Atomoxetine. 1.8mg/kg per day<br><br>(n=62) Intervention 4: No treatment - Placebo. | (n=245) children aged 6 to 17 years who met the DSM-IV criteria for ADHD | • Total adverse events at 8 weeks<br>• Weight changes at 8 weeks | At least 1.5SDs above norm on ADHD-RS<br><br>61.2% inattentive, 4.5% hyperactive/impulsive, 34.2% combined<br><br>46% stimulant naïve |
| Trzepacz 2011[636] | Intervention: Atomoxetine. Mixed dosage (n=281)<br><br>Comparison: placebo (n=113) | (n=394) children aged 6 to 15 years with a diagnosis of ADHD according to DSM-IV-TR | • Sexual dysfunction at 15 months | Line of treatment unclear<br><br>73% combined subtype, 22% inattentive and 5% hyperactive |
| Van der heijden 2007[642] ; Hoebert 2008[337] | 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_ | • Sleep at 4 year follow up | 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 2007[649] | 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) | • Weight change at 8 weeks<br>• Appetite changes at 8 weeks<br>• Sleep 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 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | | hyperactive/impulsive subtype). Baseline scores of CGI-S show the majority of the population had moderate ADHD.<br><br>Unclear line of treatment |
| Wehmeier 2012[658] (Wehmeier 2015[657], Wehmeier 2014[655]) | (n=63) Intervention 1: CNS stimulants – Atomoxetine (1.2mg/kg per day)<br><br>(n=62) Intervention 2: No treatment - Placebo. | (n=125) children aged 6 to 12 years old who met the DSM-IV criteria for ADHD | • Total participants with adverse events at 8 weeks | 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><br>75.2% of the study population were stimulant naive, previous treatment with atomoxetine was an exclusion criteria<br><br>Unclear line of treatment |
| Wehmeier 2011[659] | (n=64) Intervention: Atomoxetine (1.2mg/kg per day)<br><br>(n=64) Comparison: placebo | (n=128) children aged 6 to 12 years who met the DSM-IV criteria for ADHD | • Total participants with adverse events at 8 weeks | Exclusion criteria: previous treatment with atomoxetine or other psychotropic medication other than the study drug<br><br>Unclear line of treatment |
| Weiss 2005[664] | (n=101) Intervention: Atomoxetine (1.2mg/kg per day; maximum 1.6mg/kg per day)<br><br>(n=52) Comparison: Placebo | (n=153) children aged 8 to 12 years with a diagnosis of ADHD confirmed using a structured interview and clinical assessment. | • Weight change at 7 weeks<br>• Sleep at 7 weeks | ADHD Index score at least 1.5 SDs above age and sex norms.<br><br>Hyperactive/impulsive 0.7%, Inattentive 26.8%, 72.5% combined<br><br>Unclear line of treatment |
| Wilens 2015[691] | Intervention: Extended release guanfacine, max | Children aged 13-17 who met DSM-IV criteria for ADHD | • Total participants with any | Around 75% of the population had previously used |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | dose 4-7mg depending on weight (n=157)<br><br>Comparison: Placebo (n=155) | (n=312) | adverse events at 15 weeks<br>• All-cause mortality at 15 weeks<br>• Decreased appetite at 15 weeks<br>• Sleep at 15 weeks | stimulant medication Baseline scores of CGI-S show the majority of the population had moderate ADHD. 68% combined subtype, 29% inattentive subtype, and 3% hyperactive subtype.<br><br>Unclear line of treatment |
| Wolraich 2001[698] | Intervention: Methylphenidate 18-54mg/day (n=189; 94 OROS-MPH, 94 IR MPH<br>Comparison: placebo (n=89) | Children and adolescents 6-12 meeting DSM-IV-TR ADHD criteria (n=278) | • Total participants with adverse events at 4 weeks<br>• Increase in tics 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<br><br>Unclear line of treatment |
| Zarinara 2010[710] | (n=19) Intervention 1: Venlafaxine . Patients were randomised to receive 50-75 mg/day depending on weight<br>(n=19) Intervention 2: CNS stimulants – Methylphenidate(20-30mg per day depending on weight) | (n=38) Children aged 6 to 12 years who met the DSM-IV criteria for ADHD | • Decreased appetite at 6 weeks<br>• Sleep at 6 weeks | Baseline ADHD-RS-IV scores were ~ 30 (teacher rated)<br><br>Unclear line of treatment<br>All combined subtype |

**Table 4: Summary of studies included in the evidence review (Non-randomised)**

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Biederman 2008 [95] | (n=240) Intervention: Guanfacine 2mg/day | Children aged 5 to 17 years diagnosed with ADHD according to DSM-IV criteria | • Cardiovascular events at 24 months<br>• Weight at 24 months | Unclear line of treatment<br>Subtypes not specified |
| Dittmann 2009 [215] | (n=159) Intervention: Atomoxetine 0.5-1.2mg/kg per day | Children aged 12-17 years who met DSM-IV diagnostic criteria for ADHD | • Liver function at 24 weeks | Combined and inattentive subtypes.<br>Moderate severity.<br>86.2% previously treated for ADHD. |
| Findling 2008 [243] | (n=274) Intervention: Lisdexamfetamine 30-70mg per day | Children 6 to 12 years with ADHD according to DSM-IV-TR criteria (n=318) | • Weight at 11 months<br>• Blood pressure at 11 months | Combined and hyperactive subtypes |
| Germanario 2013 [280] | (n=296) Intervention: Methylphenidate<br>(n=294) Intervention: Atomoxetine | Children aged 6 to 18 years with ADHD according to DSM-IV criteria (n=590) | • Height at 24 months<br>• Weight at 24 months | All participants drug naïve prior to the study<br>90% combined subtype, 5.6% inattentive subtype, 4.4% hyperactive subtype |
| Groenman 2013 [305] | (n=327) Intervention: Stimulants<br>(n=61) Comparison: No stimulants | (n=388) Children aged 5-17 years with a formal diagnosis of ADHD | • Substance use disorder at 4.4 years | Subtype and line of treatment not specified |
| Hoebert 2009 [337] | (n=105) Intervention: Melatonin (dose of 3mg per day if weight was less than 40kg, 6mg per day if weight was more than 40kg) | Children aged 6-12 years who met DSM-IV criteria for ADHD | • Insomnia at 4 years | All participants had chronic onset sleep insomnia |
| Shin 2016 [571] | (n=114,647) Intervention: Methylphenidate. Exposure was defined by submitted prescriptions, mean duration of 0.5 months for | Children aged 17 years or younger with an ADHD diagnosis according to ICD-10 | • Cardiovascular events at 6 months<br>• All-cause mortality at 6 months | Subtype, line of treatment and severity unclear. |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | each period of drug use<br><br>Comparison: No treatment (same population; defined as non exposed periods where drugs were not used) | | | |

See appendix D for full evidence tables.

### 1.5.7 Included studies (adults)

Thirty-six RCTs [8, 10, 11, 15, 20, 34, 52, 92, 97, 98, 139, 144, 222, 293, 294, 360, 394, 399, 406, 410, 452, 456, 498, 527, 529, 532, 540, 595, 596, 612, 619, 623, 683, 686, 696, 708] were included in the review that evaluated the adverse events of pharmacological treatments in adults and these are summarised in **Table 5** below:

- thirteen RCTs compared controlled release methylphenidate versus placebo[20, 97, 98, 144, 293, 360, 410, 452, 527, 529, 538, 619, 696]
- three RCTs compared immediate release methylphenidate versus placebo[394, 399, 595].
- three RCTs compared dexamphetamine versus placebo[498, 596, 623]
- four RCTs compared lisdexamphetamine versus placebo[8, 10, 92, 683]
- nine RCTs compared atomoxetine versus placebo[11, 15, 222, 294, 406, 456, 612, 686, 708]
- one RCT compared guanfacine versus placebo[139]
- one RCT compared venlafaxine versus placebo[34]
- one RCT compared reboxetine versus placebo[532]
- two RCTs compared modafinil versus placebo[52, 623]
- one RCT compared buproprion SR versus placebo[399]
- one RCT compared modafinil versus dexamphetamine[623]
- one RCT compared buproprion SR versus methylphenidate[399].

Six open label non-comparative studies were included in the review that reported the long term adverse events of pharmacological treatments in adults. Three studies reported the adverse events of methylphenidate, one study on lisdexamphetamine and two studies on atomoxetine.

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.

### 1.5.8 Excluded studies

See the excluded studies list in appendix I.

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

**Table 5: Summary of studies included in the evidence review (RCTs)**

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Adler 2008[10] (Mattingly 2013[440], Adler 2009[9], Kollins 2011[389])<br>Adler [19]<br>Babcock 2012 [55] | 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 with moderate to severe ( >28) ADHD according to DSM-IV (n=420) | • Total number of participants with adverse events at 4 weeks<br>• Decreased appetite at 4 weeks<br>• Anorexia at 4 weeks<br>• Weight change at 4 weeks<br>• Sleep (insomnia) at 4 weeks | Unclear line of treatment.<br>All subjects had moderate to severe ADHD as rated by a clinician on ADHD-RS (scores 28 or above).<br><br>Doses have been combined as there no difference was reported. The highest number of adverse events were reported in the first week on the 30mg dose. |
| Adler 2009 [11] | 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) | • Total numbers of participants with adverse events at 16 weeks<br>• Sleep (insomnia) at 16 weeks<br>• Sexual dysfunction at 16 weeks<br>• Decreased appetite 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 [15] (Brown 2011 [126]) | Intervention: Atomoxetine 80mg/d (n=250)<br><br>Comparison: Placebo (n=251) | Adults aged 18-65 who met DSM-IV criteria for ADHD (n=501) | • Sleep (insomnia) at 10 and 24 weeks<br>• Sexual dysfunction at 10 and 24 weeks | 72% combined subtype<br><br>Unclear line of treatment; exclusion criteria: failure to respond to an adequate trial of ADHD stimulant medication, buproprion or other nonstimulant medications. |
| Adler 2009 [20] | Intervention: Methylphenidate titrated -max 108mg (n=113)<br><br>Comparison: Placebo (n=116) | Adults aged 18-65 years with ADHD according to DSM-IV<br>Chronic from childhood (n=229) | • Total numbers of participants with adverse events at 7 weeks<br>• Blood pressure at 7 | Severity: AISRS score of 24 or higher<br><br>Unclear line of treatment; known non-responders were excluded from the |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | weeks<br>• Decreased appetite at 7 weeks<br>• Weight change at 7 weeks<br>• Sleep (insomnia) at 7 weeks | study<br><br>80% combined subtype<br><br>. |
| Adler 2013 [8, 7] | Intervention: Lisdexamfetamine, max dose 70mg/day (n=80)<br><br>Comparison: Placebo (n=81) | Adults aged 18-26 years with ADHD according to DSM-IV (n=161) | • Total numbers of participants with adverse events at 10 weeks<br>• Decreased appetite at 10 weeks<br>• Sleep (insomnia) 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<br>No reported deaths or serious adverse events |
| 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) | • Sexual dysfunction at 6 weeks | All participants were drug naïve.<br>The participants were parents or siblings of children diagnosed to have ADHD. |
| Arnold 2014[52] | 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: Placebo (n = 74) | Adults aged 18 and over diagnosed with ADHD according to DSM-IV criteria. (n = 338) | • Total numbers of participants with adverse events at 9 weeks<br>• Suicidal ideation at 9 weeks<br>• Tachycardia at 9 weeks<br>• Anorexia at 9 weeks<br>• Psychotic symptoms at 9 weeks<br>• Sleep (insomnia) 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 |
|---|---|---|---|---|
| | | | | |
| Biederman 2006[97] | 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) | • Cardiac events at 6 weeks<br>• Decreased appetite at 6 weeks<br>• Sleep (insomnia) at 6 weeks<br>• Sexual dysfunction at 6 weeks | Unclear line of treatment.<br>Baseline CGI-S scores show the majority of the population had moderate ADHD. |
| Biederman 2010 [98] | 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) | • Sleep (insomnia) at 6 weeks<br>• Cardiac events at 6 weeks | Unclear line of treatment.<br><br>Subjects had to endorse a moderate or severe level of impairment attributed to the ADHD symptoms. Baseline scores of CGI-S show the majority of the population had moderate ADHD.<br><br>. |
| Biederman 2012[92] | 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) | • Cardiac events at 6 weeks<br>• Decreased appetite at 6 weeks<br>• Sleep (insomnia) at 6 weeks | Unclear line of treatment. |
| Butterfield 2016 [139] | Intervention: Guanfacine (n=13)<br><br>Comparison: 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).<br>Mean age: 37.5. | • Increased appetite at 9 weeks | 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.<br><br>Unclear line of |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | | treatment |
| Casas 2013 [144] | Intervention 1: OROS methylphenidate 54mg (n=90)<br><br>Intervention 2: OROS methylphenidate 72mg (n=92)<br><br>Comparison: Placebo (n=97) | Adults 18-65 with ADHD diagnosed by DSM-IV (n=279) | • Palpitations at 13 weeks<br>• Decreased appetite at 13 weeks<br>• Weight loss at 13 weeks<br>• Sleep (insomnia) at 13 weeks | 70% combined 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. |
| Durrell 2013[222] (Adler 2014 [6]) | 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) | • Decreased appetite at 12 weeks<br>• Sleep (insomnia) at 12 weeks | 64% of subjects were drug naïve. 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. |
| Goodman 2016 [293] | Intervention: Methylphenidate modified release long acting Max 72 mg (n=178)<br><br>Comparison: Placebo (n=179) | Adults aged 18 – 65 who met DSM-IV criteria for ADHD (n=357) | • Total numbers of participants with adverse events at 6 weeks<br>• Palpitations at 6 weeks<br>• Decreased appetite at 6 weeks<br>• Sleep (insomnia) 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 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | | use disorder. Baseline scores on CAARS-O:SV, ASRS, CGI-S and GAF show participants had severe ADHD |
| Goto 2012 [294] | Intervention: Atomoxetine 40-120mg/day (n=195) Comparison: Placebo (n=196) | Adults aged 18 and over who met DSM-IV criteria for ADHD (n=391) | • Weight loss at 10 weeks • Decreased appetite at 10 weeks • Sleep (insomnia) at 10 weeks | 22% had prior stimulant exposure All participants were required to have a CGI-S score of 4 or more. |
| Jain 2007 [360] | Intervention: Methylphenidate OROS 80mg/d Comparison: Placebo Crossover trial (n=50) | Adults 18-60 who met DSM-IV criteria for ADHD | • Sleep (insomnia) at 3 weeks | Exclusion of known non-responders Unclear line of treatment |
| Kooij 2004 [394] LAMDA-II | Intervention: Methylphenidate IR, titrated up to 1mg/kg/day Comparison: Placebo Crossover trial: (n=45) | Adults aged 20-56 who met DSM-IV criteria for ADHD | • Palpitations at 3 weeks • Sleep (insomnia) at 3 weeks • Tics at 3 weeks | Stimulant naïve population. All subtypes were included. Baseline scores of CGI-S show the majority of the population had moderate ADHD. the placebo group. |
| Kuperman 2001 [399] | Intervention 1: Bupropion SR, maximum dose 300mg/day (n=11) Intervention 2: Methylphenidate IR, max dose 0.9mg/kg/day (n=8) Comparison: Placebo (n=11) | Adults aged 18-60 years who met DSM-IV criteria for ADHD (n=30) | • Total numbers of participants with adverse events at 7 weeks | Unclear line of treatment. Baseline scores of CGI-S show the majority of the population had mild ADHD. |
| Lee 2014 [406] | Intervention: Atomoxetine, maximum dose | Adults aged 18 and over who met DSM-IV criteria for ADHD | • Blood pressure at 10 weeks | 19.2% had previous treatment with stimulants. |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | 120mg daily (n=37)<br><br>Comparison: Placebo (n=37) | (n=74) | • Weight change at 10 weeks<br>• Weight loss at 10 weeks<br>• Sleep (insomnia) at 10 weeks | 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 scores of CGI-S show the majority of the population had moderate ADHD. |
| Levin 2007 [410] | Intervention: Methylphenidate max 60mg/d (n=53)<br>Comparison: Placebo (n=53) | Adults aged 18 to 65 years who met DSM-IV criteria for ADHD and met criteria for cocaine dependence (n=106) | • Sleep (insomnia) at 14 weeks | Unclear line of treatment |
| Medori 2008 [452]<br>Rosler 2013 [539] | Intervention: Methylphenidate CR, maximum dose 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)<br><br>Exclusion criteria included responders | • Weight loss at 5 weeks<br>• Sleep (insomnia) 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 [456] | 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) | • Decreased appetite at 8 weeks<br>• Sleep (insomnia) at 8 weeks<br>• Sexual dysfunction 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 |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | | CGI-S score of 4.7 |
| Paterson 1999[498] | Intervention: Dexamphetamine, 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) | • Weight changes 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. |
| Reimherr 2007 [527] | Intervention: OROS Methylphenidate, up to maximum dose 90mg daily<br>Comparison: Placebo<br>Crossover trial: (n=47) | Adults aged 19-57 who met DSM-IV criteria for ADHD | • Weight change at 4 weeks<br>• Sleep (insomnia) at 4 weeks | Line of treatment not specified<br>Subtype not specified<br>Baseline ADHD-RS scores of 36.2 |
| Retz 2012[529] | Intervention: Methylphenidate 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) | • Palpitations at 8 weeks | Unclear line of treatment.<br>Baseline scores of CGI-S show the majority of the population had moderate ADHD. |
| Riahi 2010 [532] | Intervention: Reboxetine 8mg twice a day (n=23)<br><br>Comparison: Placebo (n=17) | Adults age 18 and over diagnosed with ADHD (n=40) | • Sleep (insomnia) at 4 weeks | Unclear line of treatment.<br><br>. |
| Rosler 2009[538] (Rosler 2010[540]) | 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) | • Blood pressure at 24 weeks | 38% of the population had previous treatment for ADHD. |
| Spencer 2005[595] | 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) | • Sleep (insomnia) 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. |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | | |
| Spencer 2007 [59616] | Intervention 1: Dexamphetamine ER 20mg/d ( n=58)<br><br>Intervention 2: Dexamphetamine ER 40mg/d ( n=55)<br><br>Intervention 3: Dexamphetamine ER 60mg/d( n=55)<br><br>Comparison: Placebo (n=53) | Adults 18-60 years diagnosed with ADHD according to DSM-IV criteria with childhood onset (n=221)<br><br>ADHD-RS score > 24 | • Sleep (insomnia) at 5 weeks | Unclear line of treatment<br><br>No dose related effects. |
| Sutherland 2012[612] | Intervention: Atomoxetine 80-100mg/d (n=97)<br><br>Comparison: Placebo (n=47) | Adults aged 18-60 years with ADHD according to DSM-IV-TR criteria and AISRS (n=144) | • Sleep (insomnia) at 8 weeks<br>• Sexual dysfunction at 8 weeks | Unclear line of treatment.<br>A third group were randomised to atomoxetine plus buspirone; this data will be included in the pharmacological combination review.<br>All subjects had to have a score of 24 or more on the AISRS scale, Mean scores AISRS = 36 |
| Takahashi 2014 [619] | Intervention: OROS Methylphenidate (n= 143)<br>Comparison: Placebo (n= 141) | Adults aged 18-64 years with ADHD according to DSM-IV-TR criteria (n=284) | • Palpitations at 9 weeks<br>• Decreased appetite at 9 weeks<br>• Psychotic symptoms at 9 weeks<br>• Sleep (insomnia) at 9 weeks | Drug exposure for 54 days<br><br>Unclear line of treatment |
| Taylor 2000 [623] | Intervention 1<br>Dexamphetamine, max dose 40 mg/day<br><br>Intervention<br>Modafinil, max dose 400 mg/day<br><br>Comparison: | Adults aged 18-59 years with ADHD according to DSM-IV | • Sleep (insomnia) at 2 weeks | Crossover trial of three, 2 week drug treatment comparisons.<br><br>Unclear line of treatment.<br>Subjects had to meet full DSM-IV criteria for the disorder by |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | Placebo<br><br>Crossover trial: (n=22) | | | 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 |
| Wigal 2010 [683]<br>Wigal 2011 [682] | Early dose optimisation and then 2 week RCT<br>Intervention: Lisdexamfetamine, max dose 70mg/day (n=115)<br><br>Comparison: Placebo (n=117) | Adult ADHD<br>Known responders and then optimised (n=132) | • Total numbers of participants with adverse events at 2 weeks<br>• Sleep (insomnia) at 2 weeks | Unclear line of treatment |
| Wilens 2008[686] | 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 symptom severity score >20 on the AISRS. (n=147) | • Decreased appetite at 13 weeks<br>• Weight change 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. |
| Winhusen 2010 [696] | Intervention: OROS Methylphenidate (n= 127)<br>Comparison: Placebo (n= 128) | Adults over the age of 18, who met DSM-IV-TR criteria for adult ADHD | • Total number of participants with adverse events at 24 weeks<br>• Palpitations at 24 weeks<br>• Blood pressure at 24 weeks<br>• Decreased appetite at 24 weeks<br>• Sleep (insomnia) at 24 weeks | Unclear line of treatment<br>. |
| Young 2011[708] | Intervention: Atomoxetine 60- | Adults over the age of 18, who met | • Decreased appetite at 8 | 84% of the subjects were stimulant naïve. |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| (Wietecha 2012[669]) | 100mg/d (n=268)<br><br>Comparison: Placebo (n=234) | DSM-IV-TR criteria for adult ADHD, had a historical diagnosis during childhood and a CGI-ADHD-S score of 4+. (n=502) | and 24 weeks<br>• Sleep (insomnia) at 8 and 24 weeks<br>• Sexual dysfunction at 8 and 24 weeks | 68.7% of the study population were of the combined subtype of ADHD, 31.1% of inattentive subtype, 0.2% of the hyperactive/ impulsive subtype. No co-morbid conditions reported. Participants randomised to the intervention arm were initiated to treatment during an assessment stage prior to the trial. Participants who were unable to tolerate the drug were excluded from the trial. Baseline scores of CGI-S show the majority of the population had moderate ADHD. |

**Table 6: Summary of studies included in the evidence review (non-randomised)**

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Adler 2008[18] | Intervention: Atomoxetine 80mg/d (n=384) | Adults aged 18 and over who met DSM-IV criteria for ADHD | • Insomnia at 221 weeks<br>• Erectile dysfunction at 221 weeks | Long term open label extension of Michelson 2003 [456] |
| Adler 2011 [13] | Intervention: Methylphenidate 36-108mg/day (mean dose 67.7mg/day) (n=550) | Adults aged 18 to 65 years who met the DSM-IV criteria for ADHD | • Total numbers of participants with adverse events at 52 weeks<br>• Blood pressure at 52 weeks<br>• Weight change at 52 weeks<br>• Decreased appetite at 52 weeks<br>• Insomnia at 52 weeks | |
| Buitelaar | Intervention: OROS | Adults aged 18 to | • Total numbers | 52 week open label |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| 2012 [133] | methylphenidate max 90mg per day (n=155) | 65 years who met DSM-IV criteria for ADHD and completed the Medori 2008 [452] trial | of participants with adverse events at 52 weeks<br>• Discontinuation due to adverse event at 52 weeks<br>• Insomnia at 52 weeks<br>• Hypertension at 52 weeks | non comparative extension of Medori 2008 [452]<br>Rosler 2013 [539] |
| Ginsberg 2014 [287] | Intervention: Methylphenidate modified release long acting<br>Max >60 mg<br>(n=298)<br><br>Open label extension of Huss 2014 [348] | Adults aged 18 – 60 who met DSM-IV criteria for ADHD childhood onset<br>Known responders | • Tachycardia at 52 weeks<br>• Decreased appetite at 52 weeks | No changes were reported in blood pressure, pulse rate or body weight.<br>No deaths were reported. |
| Hirata 2014 [336] | Intervention: Atomoxetine, 40-120mg/day (n=233) | Adults aged 18 and over who met DSM-IV criteria for ADHD | • Palpitations at 52 weeks<br>• Decreased appetite at 52 weeks<br>• Weight decreased at 52 weeks | 52 week open label non comparative extension of Goto 2012 [294] |
| Weisler 2009 (Mattingly 2013) [660(440)] | Intervention Lisdexamfetamine, max dose 70mg/day (n=349) | Adults aged 18-55 years with moderate to severe ( >28) ADHD according to DSM-IV | • Total numbers of participants with adverse events at 52 weeks<br>• Decreased appetite at 52 weeks<br>• Decreased weight at 52 weeks<br>• Insomnia at 52 weeks | 52 week open label non comparative extension of Adler 2008[10] |

See appendix D for full evidence tables.

## 1.5.10 Quality assessment of clinical studies included in the evidence review

### 1.5.10.1 Clinical evidence (pre-school children under the age of 5)

**Table 7: 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 (pre-schoolers) (95% CI) |
| Tachycardia | 325 (1 study)[c] 1 week | LOW[a] due to risk of bias | RD 0 (-0.01 to 0.01) | 0 events in the control group | 0 events in both arms |
| Systolic blood pressure (mmHg) | 35 (1 study)[c] 4 weeks | VERY LOW[a,b] due to risk of bias, imprecision | | The mean systolic blood pressure in the control group was 91mmHg | Mean systolic blood pressure in the intervention groups was 5mmHg higher (3.17 lower to 13.17 higher) |
| Diastolic blood pressure (mmHg) | 35 (1 study)[c] 4 weeks | VERY LOW[a,b] due to risk of bias, imprecision | | The mean diastolic blood pressure in the control group was 63mmHg | Mean diastolic blood pressure in the intervention groups was 1mmHg higher (5.18 lower to 7.18 higher) |
| Weight (kg) | 35 (1 study) 4 weeks | LOW[a] due to risk of bias | | See comment[d] | The mean weight in the intervention group was 1.9kg lower (from 5.94 lower to 2.14 higher) |
| Height (cm) | 35 (1 study)[c] 4 weeks | VERY LOW[a,b]due to risk of bias, imprecision | | The mean height in the control group was 109.2cm | Mean height in the intervention groups was 0.2cm higher (5.41 lower to 5.81 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.*

*(c) To note: this was a crossover study of 1 week on placebo and 1 week on each of 4 doses of methylphenidate (n=165). Risk was calculated by pooling number of events in*

*each dose, and number of participants that took each dose.*
*(d) Control group risk not reported*

**Table 8: Methylphenidate versus risperidone**

| 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 risperidone (pre-schoolers) (95% CI) |
| Sleep (sedation) | 38 (1 study) 6 weeks | VERY LOW[a,b] due to risk of bias, imprecision | OR 0.15 (0 to 7.58) | 32 per 1000 | 42 fewer per 1000 (from 50 fewer to 235 more) |
| Decreased appetite | 38 (1 study) 6 weeks | VERY LOW[a,b,c] due to risk of bias, imprecision, indirectness | OR 8.26 (0.16 to 418.42) | 0 events in control arm | 60 more 1000 (from 80 fewer to 190 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 if the majority of the evidence had indirect outcomes.*

### 1.5.10.2 Clinical evidence (children aged 5 to 18)

**Table 9: IR 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) |
| Total participants with | 316 | VERY LOW[a,b] due to risk of | RR 1.36 | 379 per 1000 | 136 more per 1000 |

| | | | | | |
|---|---|---|---|---|---|
| adverse events | (1 study)<br>3 weeks | bias, imprecision | (1.06 to 1.75) | | (from 23 more to 284 more) |
| Total participants with adverse events | 69<br>(1 study)<br>16 weeks | LOW [a,b]<br>due to risk of bias, imprecision | RR 1.95<br>(1.11 to 3.43) | 300 per 1000 | 285 more per 1000<br>(from 33 more to 729 more) |
| Tachycardia | 40<br>(1 study)<br>8 weeks | VERY LOW [a,b]<br>due to risk of bias, imprecision | OR 7.39 (0.15 to 372.38) | 0 events in control arm | 50 more per 1000 (from 80 less to 100 more) |
| Tachycardia | 49<br>(1 study)<br>16 weeks | VERY LOW [a,b]<br>due to risk of bias, imprecision | OR 7.65 (0.15 to 385.67) | 0 events in control arm | 30 more per 1000 (from 60 less to 120 more) |
| Systolic blood pressure (mmHg) | 84<br>(2 studies)<br>2 weeks | MODERATE[a]<br>due to risk of bias | | The mean systolic blood pressure in the control group was 95mmHg | Systolic blood pressure in the intervention groups was 3.18mmHg higher<br>(0.76 to 5.6 higher) |
| Systolic blood pressure (mmHg) | 181<br>(2 studies)<br>16 weeks | MODERATE[a]<br>due to risk of bias | | The mean systolic blood pressure in the control group was 102mmHg | Systolic blood pressure in the intervention groups was 1.05mmHg higher<br>(1.75 lower to 3.84 higher) |
| Diastolic blood pressure (mmHg) | 22<br>(1 studies)<br>2 weeks | LOW[a,b]<br>due to risk of bias, imprecision | | The mean diastolic blood pressure in the control group was 94.7mmHg | Diastolic blood pressure in the intervention groups was 2.90 higher (from 0.37 to 5.43 higher) |
| Diastolic blood pressure (mmHg) | 122<br>(1 study)<br>16 weeks | LOW[a,b]<br>due to risk of bias, imprecision | | The mean diastolic blood pressure in the control group was 64.4mmHg | Diastolic blood pressure in the intervention groups was 3.20 mmHg higher (0.21 lower to 6.61 higher) |
| Decreased weight | 122<br>(1 study)<br>2 weeks | MODERATE[a,b]<br>due to risk of bias | | See comment[c] | Mean weight in the intervention groups was 1.07kg lower<br>(17.03 to14.89 lower) |

| | | | | | |
|---|---|---|---|---|---|
| | | imprecision | | | |
| Decreased weight | 181<br>(2 studies)<br>16 weeks | MODERATE[a,b]<br>due to risk of bias<br>imprecision | | The mean weight change in the control group was +1.4kg | The mean weight in the intervention group was 1.9kg lower (2.61 to 1.18kg) |
| Height (cm) | 34<br>(1 study)<br>6 weeks | VERY LOW[a,b]<br>due to risk of bias,<br>imprecision | | The mean height in the control group was 109.2cm | Height change in the intervention groups was 0.2cm higher<br>(5.41 lower to 5.81 higher) |
| Seizures | 66<br>(1 study)<br>3 weeks | LOW[a,b]<br>due to risk of bias,<br>imprecision | RR 1.33 (0.32 TO 5.5) | 91 per 1000 | 30 more per 1000<br>(from 62 fewer to 409 more) |
| Psychotic symptoms | 59<br>(1 study)<br>16 weeks | MODERATE[a,b]<br>due to risk of bias | RD 0 (-0.06 TO 0.06) | 0 events in control arm | 0 events in both arms |
| Sleep (insomnia) | 523<br>(4 studies)<br>3 weeks-8 weeks | MODERATE[a]<br>due to risk of bias | OR 5.57<br>(2.82 to 11) | 50 per 1000 | 177 more per 1000<br>(from 79 more to 317 more) |
| Sleep (insomnia) | 59<br>(1 study)<br>16 weeks | VERY LOW[a,b]<br>due to risk of bias,<br>imprecision | RR 0.21 (0.03 to 1.67) | 167 per 1000 | 131 fewer per 1000<br>(from 280 fewer to 20 more) |
| Increase in tics | 351<br>(2 studies)<br>16 weeks | VERY LOW[a,b]<br>due to risk of bias,<br>imprecision | RR 0.62<br>(0.29 to 1.34) | 90 per 1000 | 34 fewer per 1000<br>(from 64 fewer to 31 more) |
| YGTSS tics global severity;0-100; lower scores are beneficial | 62<br>(1 study)<br>16 weeks | LOW[a,b]<br>due to risk of bias,<br>imprecision | | The mean YGTSS global severity score in the control group was 28.3 | The mean YGTSS global severity score in the intervention groups was 1.8 higher<br>(6.28 lower to 9.88 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.*
*(c) Control group means not reported.*

**Table 10: 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) |
| Total participants with adverse events | 293 (1 study) 6 weeks | LOW[a,b] due to risk of bias, imprecision | RR 1.23 (0.98 to 1.55) | 541 per 1000 | 124 per 1000 (from 11 fewer to 297 more) |
| Systolic blood pressure | 514 (2 studies) 6-7 weeks | MODERATE[a] due to risk of bias | | The mean systolic blood pressure increase in the control group was 1mmHg | Mean systolic blood pressure in the intervention groups was 1.98mmHg lower (2.32 to 1.64 lower) |
| Diastolic blood pressure | 514 (2 studies) 6-7 weeks | MODERATE[a] due to risk of bias | | The mean diastolic blood pressure increase in the control group was 1.3mmHg | Mean diastolic blood pressure in the intervention groups was 0.83mmHg lower (0.82 lower to 3.33 higher) |
| Decreased weight | 514 (2 studies) 6-7 weeks | MODERATE[a] due to risk of bias | | The mean weight gain in the control group was 1.1kg | Mean weight in the intervention groups was 2kg lower (2.23 to 1.77 lower) |
| Sleep (insomnia) | 221 (1 studies) 7 weeks | LOW[a,b] due to risk of bias, imprecision | OR 3.93 (0.6 to 25.66) | 0 per 1000 | 40 more per 1000 (from 0 to 90 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: Methylphenidate versus no treatment (non-randomised)**

| 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) |
| Cardiovascular events | 114,647 (1 study) Mean follow up 6 months | VERY LOW[a,c] due to risk of bias, indirectness | RR 3.07 (2.72 to 3.46) | 3 per 1000 | 6 more events per 1000 (5 more to7 more) |
| Substance misuse | 388 (1 study) Mean follow up 4.4 years | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.71 (0.45 to 1.13) | 279 per 1000 | 81 fewer per 1000 (from 156 more to 36 fewer) |

*(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 for indirect outcomes*

**Table 12: 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 Methylphenidate IR versus OROS methylphenidate (95% CI) |
| Total participants with adverse events | 189 (1 study) 4 weeks | LOW[a,b] due to risk of bias, imprecision | RR 1.09 (0.79 to 1.5) | 426 per 1000 | 38 more per 1000 (from 89 fewer to 213 more) |
| Decreased appetite | 272 (1 study) 3 weeks | VERY LOW[a,b,c] due to risk of bias, imprecision, indirectness | RR 0.46 (0.15 to 1.47) | 65 per 1000 | 35 fewer per 1000 (from 55 fewer to 30 more) |
| Sleep (insomnia) | 272 (1 study) | VERY LOW[a,b] due to risk of | RR 0.87 (0.27 to 2.79) | 43 per 1000 | 6 fewer per 1000 (from 32 fewer to 77 more) |

| | | | | | |
|---|---|---|---|---|---|
| | 3 weeks | bias, imprecision | | | |
| Increase in tics | 189 (1 study) 4 weeks | VERY LOW[a,b] due to risk of bias, imprecision | OR 7.31 (0.15-368.51) | 0 per 1000 | 10 more per 1000 (from 20 fewer to 40 more) |

*(d) 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.*
*(e) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.*
*(f) Downgraded by 1 increment because the majority of the evidence had indirect outcomes.*

**Table 13: 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) |
| Total participants with any adverse event | 600 (2 studies) 4-7 weeks | MODERATE[a] due to risk of bias | OR 2.2 (1.5 to 3.21) | 530 per 1000 | 183 more per 1000 (from 98 more to 253 more) |
| All-cause mortality | 314 (1 study) 4 weeks | MODERATE[a] due to risk of bias | RD 0 (-0.02 to 0.02) | 0 events in control arm | 0 events in both arms |
| Systolic blood pressure | 535 (2 studies) 4-7 weeks | MODERATE[a] due to risk of bias | | The mean systolic blood pressure change in the control group was 1.6mmHg | The mean systolic blood pressure change in the intervention group was 1.78mmHg lower (2.08 to 1.48 lower) |
| Diastolic blood pressure | 535 (2 studies) 4-7 weeks | MODERATE[a] due to risk of bias | | The mean diastolic blood pressure change in the control group was 0.8mmHg | The mean diastolic blood pressure change in the intervention group was 0.57mmHg lower (0.25 to 0.89 lower) |

| | | | | | |
|---|---|---|---|---|---|
| Weight change | 221 (1 study)<br>7 weeks | MODERATE[a] due to risk of bias | | The mean weight change in the control group was 0.7kg | The mean weight change in the intervention groups was 2.8kg lower (3.2 to 2.4 lower) |
| Decreased weight | 604<br>(2 studies)<br>4-7 weeks | MODERATE[a] due to risk of bias | OR 3.66<br>(1.79 to 7.48) | 7 per 1000 | 17 more per 1000<br>(from 5 more to 41 more) |
| Sleep (insomnia) | 825<br>(3 studies)<br>4-7 weeks | MODERATE[a] due to risk of bias | OR 3.84<br>(2.34 to 6.31) | 19 per 1000 | 51 more per 1000<br>(from 25 more to 91 more) |

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

### Non-comparative long-term studies: lisdexamfetamine dimesylate

In one study[243] with 272 participants, there was at least one adverse event reported by 78% (213/272) of participants taking lisdexamfetamine dimesylate, with a mean follow up of 259 days. The most common adverse events (reported in >10% of participants) were decreased appetite, headache, decreased weight, insomnia, upper abdominal pain, upper respiratory tract infection, irritability and nasopharyngitis. In particular 17.6% (48/272) had weight decreases. There was a very high risk of bias due to selection bias and attrition bias. There were no serious concerns related to indirectness. Imprecision and inconsistency were not applicable.

**Table 14: Lisdexamfetamine dimesylate 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 Lisdexamfetamine versus methylphenidate (95% CI) |
| Systolic blood pressure | 222<br>(1 study)<br>7 weeks | MODERATE[a] due to risk of bias | | The mean systolic blood pressure change in the control group was 0.3mmHg | The mean systolic blood pressure change in the intervention group was 0.7mmHg higher (2.05 lower to 3.45 higher) |
| Diastolic blood pressure | 222<br>(1 study) | MODERATE[a] due to risk of | | The mean diastolic blood | The mean diastolic blood pressure change in the intervention group was 1.5mmHg lower (4.07 lower to |

| | | | | | |
|---|---|---|---|---|---|
| | 7 weeks | bias | | pressure change in the control group was 1.7mmHg | 1.07 higher) |
| Weight change | 222 (1 study) 7 weeks | MODERATE[a] due to risk of bias | | The mean weight change in the control groups was 1.3kg | The mean weight change in the intervention groups was 0.8kg lower (1.24 to 0.36 lower) |
| Sleep (insomnia) | 222 (1 study) 7 weeks | LOW[a,b] due to risk of bias, imprecision | RR 1.78 (0.82 to 3.85) | 81 per 1000 | 63 more per 1000 (from 15 fewer to 231 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 15: 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) |
| Overall participants with adverse events | 993 (5 studies) 6-10 weeks | LOW[a,b] due to risk of bias, imprecision | RR 1.18 (1.06, 1.32) | 567 per 1000 | 102 more per 1000 (from 34 more to 173 fewer) |
| Overall participants with adverse events | 84 (1 study) 12 weeks | LOW[a,b] due to risk of bias, imprecision | RR 1.75 (1.19, 2.56) | 373 per 1000 | 276 more per 1000 (from 71 more to 581 more) |
| All-cause mortality | 105 (1 study) 6 weeks | HIGH | RD 0 (-0.04 to 0.04) | 0 events in control arm | 0 events in both arms |
| Suicidal ideation | 105 (1 study) 6 weeks | HIGH | RD 0 (-0.04 to 0.04) | 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 Atomoxetine versus placebo (95% CI) |
| Systolic blood pressure | 1216 (6 studies) 6-13 weeks | MODERATE[a] due to risk of bias | | The mean systolic blood pressure change in the control group was 1.8mmHg | The mean systolic blood pressure in the intervention group was 1.62mmHg lower (1.87 to 1.37 lower) |
| Diastolic blood pressure | 944 (5 studies) 6-13 weeks | LOW[a,b] due to risk of bias, imprecision | | The mean diastolic blood pressure change in the control group was 0.3mmHg | The mean diastolic blood pressure in the intervention group was 2.8mmHg higher (1.67 to 3.93 higher) |
| Change in height | 754 (4 studies) 6-8 weeks | MODERATE[a] due to risk of bias | | Mean height change in the control group was 2.46cm | The mean height change in the intervention groups was 0.99cm lower (1.78 to 0.2 lower) |
| Change in weight | 754 (4 studies) 6-12 weeks | MODERATE[a] due to risk of bias | | The mean weight change in the control group was 1.1kg | The mean weight was 1.61kg lower in the intervention group (1.73 to 1.48 lower) |
| Change in weight | 709 (3 studies) 12-18 weeks | MODERATE[a] due to risk of bias | | The mean weight change in the control group was 2.65kg | The mean weight was 2.11kg lower in the intervention group (2.46 to 1.76 lower) |
| Change in weight at high risk (anxiety disorders) | 176 (1 study) 12 weeks | MODERATE[a] due to risk of bias | | The mean weight change in the control group was 1.39kg | The mean weight in the intervention groups was 1.94kg lower (2.5 lower to 1.38 lower) |
| Decreased weight | 492 (4 studies) 6-9 weeks | LOW[a,b] due to risk of bias, imprecision | OR 2.13 (0.93 to 4.91) | 30 per 1000 | 31 more per 1000 (from 2 to 101 more) |
| Sleep (Insomnia) | 640 (5 studies) 6-13 weeks | LOW[a,b] due to risk of bias, imprecision | RR 1.71 (1.04 to 2.81) | 68 per 1000 | 49 more per 1000 (from 3 more to 124 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 Atomoxetine versus placebo (95% CI) |
| Sleep (Insomnia) | 315 (2 studies) 13-16 weeks | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.85 (0.32 to 2.29) | 52 per 1000 | 8 fewer per 1000 (from 35 fewer to 67 more) |
| Tic severity (YGTSS); 0-100; lower scores are beneficial | 265 (2 studies) 8-16 weeks | MODERATE[a] due to risk of bias | | The mean tic severity score in the control group was -2.5 | The mean tic severity score was 7.9 lower in the intervention group (9.35 to 4.85 lower) |
| Tics | 32 (1 study) 6 weeks | VERY LOW[a,b] due to risk of bias, imprecision | RR 3 (0.71 to 12.69) | 125 per 1000 | 250 more per 1000 (36 more to 1000 more) |
| Tremor | 32 (1 study) 6 weeks | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.5 (0.05 to 4.98) | 125 per 1000 | 62 more pre 1000 (6 more to 623 more) |
| Sexual dysfunction | 394 (1 study) 70 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.*

### Non-comparative long-term studies: Atomoxetine

In one study with a follow up of 24 weeks all liver function tests were within normal ranges (n=159).[215]. There was a high risk of bias due to selection bias and attrition bias. There were no serious concerns related to indirectness. Imprecision and inconsistency were not applicable.

**Table 16: Methylphenidate versus 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 atomoxetine (95% CI) |
| Total participants with adverse events | 440<br>(1 study)<br>6 weeks | MODERATE[a] due to risk of bias | RR 0.99 (0.87 to 1.13) | 675 per 1000 | 7 fewer per 1000 (from 88 fewer to 88 more) |
| Systolic blood pressure | 440<br>(1 study)<br>6 weeks | MODERATE[a] due to risk of bias | | The mean systolic blood pressure change in the control group was -0.6mmHg | The mean systolic blood pressure change in the intervention groups was 0.3mmHg lower (0.55 to 0.05 lower) |
| Diastolic blood pressure | 440<br>(1 study)<br>6 weeks | MODERATE[a] due to risk of bias | | The mean diastolic blood pressure change in the control group was -3.8mmHg | The mean diastolic blood pressure change in the intervention groups was 0.7 lower (2.84 lower to 1.44 higher) |
| Decreased weight | 770<br>(2 studies)<br>6 to 8 weeks | MODERATE[a] due to risk of bias | | The mean weight loss in the control group was 0.8kg | The mean weight change in the intervention groups was 0.37kg lower<br>(0.6 to 0.14 lower) |
| Sleep (insomnia) | 330<br>(1 study)<br>8 weeks | LOW[b] due to imprecision | RR 0.56<br>(0.19 to 1.64) | 54 per 1000 | 24 fewer per 1000<br>(from 44 fewer to 35 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 17: Methylphenidate versus atomoxetine (non-randomised)**

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

| | Participants (studies) Follow up | evidence (GRADE) | (95% CI) | Risk with Control | Risk difference with Methylphenidate versus atomoxetine (95% CI) |
|---|---|---|---|---|---|
| Weight (kg; final values) | 83 (1 study) 24 months | VERY LOW[a,b] risk of bias, imprecision | | The mean weight in the control group was 49.11kg | The mean weight in the intervention groups was 2.31kg lower (9.97 to 5.35 lower) |
| Height (Z scores; change scores) | 83 (1 study) 24 months | VERY LOW[a,b] risk of bias, imprecision | | The mean height z score in the control group was 0.441 | The mean height in the intervention groups was 0.48 lower (0.77 to 0.19 lower) |

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

**Table 18: Atomoxetine versus lisdexamfetamine dimesylate**

| 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 lisdexamfetamine (95% CI) |
| Total adverse events | 267 (1 study) 9 weeks | HIGH | RR 0.99 (0.85 to 1.15) | | 7 fewer per 1000 (from 108 fewer to 108 more) |
| Systolic blood pressure | 267 (1 study) 9 weeks | HIGH | | The mean systolic blood pressure change in the control group was 0.7mmHg | The mean systolic blood pressure in the intervention groups was 0.1mmHg lower (2.15 lower to 1.95 higher) |
| Diastolic blood pressure | 267 (1 study) 9 weeks | HIGH | | The mean diastolic blood pressure change in the control group was 0.1mmHg | The mean diastolic blood pressure in the intervention groups was 1.2mmHg higher (0.79 lower to 3.19 higher) |
| Decreased weight | 267 (1 study) | HIGH | RR 0.32 (0.16 to 0.65) | 211 per 1000 | 143 fewer per 1000 (from 74 fewer to 177 fewer) |

| 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 lisdexamfetamine (95% CI) |
| | 9 weeks | | | | |
| Sleep (insomnia) | 267<br>(1 study)<br>9 weeks | MODERATE[a]<br>due to imprecision | RR 0.53<br>(0.23 to 1.21) | 113 per 1000 | 53 fewer per 1000<br>(from 87 fewer to 24 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 19: Atomoxetine versus guanfacine**

| 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 guanfacine (95% CI) |
| Total participants with adverse events | 226<br>(1 study)<br>10-13 weeks | MODERATE[a]<br>due to risk of bias | RR 0.88<br>(0.75 to 1.03) | 772 per 1000 | 93 fewer per 1000<br>(from 193 fewer to 23 more) |
| Decreased appetite | 226<br>(1 study)<br>10-13 weeks | VERY LOW[a,b,c]<br>due to risk of bias, indirectness, imprecision | RR 2.1<br>(1.2 to 3.68) | 132 per 1000 | 145 more per 1000<br>(from 26 more to 353 more) |
| Sleep (insomnia) | 226<br>(1 study)<br>10-13 weeks | VERY LOW[a,b]<br>due to risk of bias, imprecision | RR 0.63<br>(0.27 to 1.45) | 114 per 1000 | 42 fewer per 1000<br>(from 83 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.*
*(c) Downgraded by 1 increment if the majority of evidence had indirect outcomes.*

**Table 20: 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) |

| 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) |
| Total participants with adverse events | 1438 (5 studies)<br>5-13 weeks | VERY LOW[a,b,d] due to risk of bias, imprecision, inconsistency | RR 1.26 (1.07 to 1.48) | 634 per 1000 | 171 more per 1000 (from 114 more to 234 more) |
| Total participants with adverse events | 312 (1 study)<br>15 weeks | LOW[1,b] due to risk of bias, imprecision | RR 1.21 (1.1 to 1.33) | 774 per 1000 | 163 more per 1000 (from 77 more to 255 more) |
| All-cause mortality | 754<br>(3 studies)<br>8-15 weeks | LOW due to risk of bias | RD 0 (-0.01 to 0.01) | 0 events in control arm | 0 events in both arms |
| Cardiovascular events | 322<br>(1 study)<br>9 weeks | MODERATE[a] due to risk of bias | RD 0 (-0.02 to 0.02) | 0 events in control arm | 0 events in both arms |
| Systolic blood pressure | 34<br>(1 study)<br>8 weeks | LOW[b] due to imprecision | | The mean systolic blood pressure in the control groups was 110.5mmHg | The mean systolic blood pressure change in the intervention group was 0.2mmHg higher (9.43 lower to 9.83 higher) |
| Suicidal ideation | 340<br>(1 study)<br>8 weeks | LOW[b] due to imprecision | OR 1.5<br>(0.06 to 36.53) | 0 per 1000 | 0 more per 1000 (from 10 fewer to 20 more) |
| Decreased appetite | 877<br>(3 studies)<br>8-15 weeks | VERY LOW[a,b,c] due to risk of bias, imprecision, indirectness | RR 1.17<br>(0.77 to 1.77) | 95 per 1000 | 16 more per 1000<br>(from 22 fewer to 73 more) |
| Psychotic symptoms | 62 | LOW[b] due | OR 7.9 | 0 per 1000 | 30 more per 1000 (from 50 fewer to 120 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 versus placebo (95% CI) |
| | (1 study)<br>8 weeks | to imprecision | (0.16 to 398.87) | | |
| Sleep (insomnia) | 877<br>(3 studies)<br>8-15 weeks | VERY LOW[a,b] due to risk of bias, imprecision | RR 1.77<br>(1.02 to 3.08) | 45 per 1000 | 35 more per 1000<br>(from 5 fewer to 96 more) |
| Tic severity; 0 -25; lower scores are beneficial | 17<br>(1 study)<br>8 weeks | LOW[a,b] due to risk of bias, imprecision | | Tic severity in the control arm was 15.4 | Mean tic severity in the intervention groups was 4.7 lower (8.93 lower to 0.47 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.*
*(c) Downgraded by 1 increment because the majority of the evidence had indirect outcome.*
*(d) Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis.*

### Non-comparative long-term studies: guanfacine

In one study[95] (n=240) at least one adverse event was reported by 87.1% (209/240) of participants, with a mean follow up of 8.8 months. The most common adverse events (reported in >10% of participants) included somnolence, headache, fatigue, sedation, abdominal pain, upper respiratory tract infection, cough, pharyngitis and increased weight. In particular, 21/240 participants reported weight increase as an adverse event. No weight decreases were reported. 3 cardiovascular events were reported (3/240; one instance of orthostatic hypotension and 2 events of syncope). All outcomes were at a very high risk of bias due to selection bias and attrition bias. There were no serious concerns related to indirectness. Imprecision and inconsistency were not applicable.

### Table 21: Clonidine 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 Clonidine versus placebo (95% CI) |
|---|---|---|---|---|---|
| Total participants with adverse events | 208 (1 study) 8 weeks | LOW[a,b] due to risk of bias, imprecision | RR 1.16 (0.99 to 1.36) | 718 per 1000 | 115 more per 1000 (from 7 fewer to 258 more) |
| Total participants with adverse events | 71 (1 study) 16 weeks | MODERATE[a] due to risk of bias | RR 2.8 (1.7 to 4.6) | 300 per 1000 | 540 more per 1000 (from 210 more to 1000 more) |
| All-cause mortality | 220 (1 study) 8 weeks | MODERATE[a] due to risk of bias | RD 0 (-0.03 TO 0.03) | 0 events in control arm | 0 events in both arms |
| Tachycardia | 61 (1 study) 16 weeks | MODERATE[a] due to risk of bias | RD 0 (-0.06 to 0.06) | 0 events in control arm | 0 events in both arms |
| Systolic blood pressure (mmHg) | 61 (1 study) 16 weeks | LOW[a,b] due to risk of bias, imprecision | | Mean systolic blood pressure in the control arm was -2mmHg | The mean systolic blood pressure in the intervention groups was 1.1mmHg higher (3.24 lower to 5.44 higher) |
| Diastolic blood pressure (mmHg) | 61 (1 study) 16 weeks | MODERATE[a] due to risk of bias | | Mean systolic blood pressure in the control arm was -1.3mmHg | The mean diastolic blood pressure in the intervention groups was 0.1mmHg higher (3.91 lower to 4.11 higher) |
| Weight changes (kg) | 61 (1 study) 16 weeks | LOW[a,b] due to risk of bias, imprecision | | Mean weight increase in the control group was 1.4kg | The mean weight increase in the intervention groups was 0.6kg higher (0.57 lower to 1.77 higher) |
| Psychotic symptoms | 61 (1 study) 16 weeks | MODERATE[a] due to risk of bias | RD 0 (-0.06 to 0.06) | 0 events in control arm | 0 events in both arms |
| Sleep (insomnia) | 220 (1 study) 8 weeks | VERY LOW[a,b] due to risk of bias, imprecision | RR 2.51 (0.33 to 19.34) | 21 per 1000 | 31 more per 1000 (from 14 fewer to 382 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 Clonidine versus placebo (95% CI) |
| Sleep (insomnia) | 61 (1 study) 16 weeks | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.97 (0.31 to 3.01) | 167 per 1000 | 5 fewer per 1000 (from 115 fewer to 335 more) |
| Increase in tics | 66 (1 study) 16 weeks | VERY LOW[a,b] due to risk of bias, imprecision | RR 1.21 (0.51 to 2.86) | 219 per 1000 | 46 more per 1000 (from 107 fewer to 407 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: Methylphenidate 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 versus Clonidine (95% CI) |
| Total participants with adverse events | 60 (1 study) 16 weeks | LOW[a,b] due to risk of bias, imprecision | RR 0.7 (0.5 to 0.98) | 839 per 100 | 252 less per 1000 (from 17 fewer to 419) |
| Tachycardia | 60 (1 study) 16 weeks | LOW[a,b] due to risk of bias, imprecision | OR 7.92 (0.16 to 399.84) | 0 per 1000 | 30 more (from 50 fewer to 120 more) |
| Systolic blood pressure | 60 (1 study) 16 weeks | LOW[a,b] due to risk of bias, imprecision | | The mean systolic blood pressure change in the control group was -0.9mmHg | The mean systolic blood pressure change in the intervention group was 0.1mmHg lower (4.58 lower to 4.38 higher) |
| Weight change | 60 (1 study) | LOW[a,b] due to risk of bias, | | The mean weight change in the | The mean weight change in the intervention group was 1.7kg lower (3.02 to 0.38 lower) |

| | | | | | |
|---|---|---|---|---|---|
| | 16 weeks | imprecision | | control group was +2kg | |
| Psychotic symptoms (hallucinations) | 60<br>(1 study)<br>16 weeks | MODERATE[a] due to risk of bias | RD 0 (-0.06 to 0.06) | 0 events in control arm | 0 events in both arms |
| Sleep (insomnia) | 60<br>(1 study)<br>16 weeks | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.21<br>(0.03 to 1.72) | 161 per 1000 | 127 fewer per 1000<br>(from 156 fewer to 116 more) |
| Increase in tics | 71<br>(1 study)<br>16 weeks | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.82<br>(0.36 to 1.87) | 265 per 1000 | 48 fewer per 1000<br>(from 169 fewer to 230 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 23: 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) |
| Total Participants with adverse events (<3 months) | 68<br>(1 study)<br>6 weeks | MODERATE[a] due to imprecision | RR 1.08<br>(0.84 to 1.37) | 765 per 1000 | 61 more per 1000<br>(from 122 fewer to 283 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 24: Desipramine 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 Despiramine versus placebo (95% CI) |
|---|---|---|---|---|---|
| Decreased appetite | 41 (1 study) 6 weeks | MODERATE[b] due to indirectness | OR 8.75 (1.38 to 55.58) | 0 per 1000 | 240 more per 1000 (from 50 more to 430 more) |
| Sleep (difficulty sleeping) | 41 (1 study) 6 weeks | LOW[a] due to imprecision | RR 3.81 (0.46 to 31.23) | 50 per 1000 | 140 more per 1000 (from 27 fewer to 1000 more) |
| Improvement of tics | 41 (1 study) 6 weeks | HIGH | RR 10.48 (1.49 to 73.88) | 50 per 1000 | 474 more per 1000 (from 25 more to 1000 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 evidence had indirect outcomes.*

**Table 25: Methylphenidate versus venlafaxine**

| 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 venlafaxine (95% CI) |
| Decreased appetite | 37 (1 study) 6 weeks | LOW[a,b] due to imprecision, indirectness | RR 3.69 (0.88 to 15.49) | 105 per 1000 | 283 more per 1000 (from 13 fewer to 1000 more) |
| Sleep (insomnia) | 37 (1 study) 6 weeks | HIGH | RR 5.28 (1.34 to 20.86) | 105 per 1000 | 451 more per 1000 (from 36 more to 1000 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 because the majority of the evidence had indirect outcomes.*

**Table 26: Risperidone versus placebo**

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

| | Participants (studies) Follow up | the evidence (GRADE) | effect (95% CI) | Risk with Control | Risk difference with Risperidone versus placebo (95% CI) |
|---|---|---|---|---|---|
| Weight change | 40 (1 study) 6 months | LOW[a,b] due to risk of bias, imprecision | | The mean weight change in the control groups was 1.71kg | The mean weight change in the intervention groups was 1.1kg higher (0.04 to 2.16 higher) |
| Sleeping problems | 36 (1 study) 6 weeks | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.36 (0.08 to 1.61) | 294 per 1000 | 188 fewer per 1000 (from 271 fewer to 179 more) |
| Tremor | 36 (1 study) 6 weeks | VERY LOW[a,b] due to risk of bias, imprecision | RR 1.79 (0.37 to 8.57) | 118 per 1000 | 93 more per 1000 (from 74 fewer to 891 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 27: Methylphenidate versus buproprion**

| 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 Buproprion (95% CI) |
| Total participants with adverse events | 30 (1 study) 6 weeks | LOW[a,b] due to risk of bias, imprecision | RR 1.8 (0.79 to 4.11) | 333 per 1000 | 261 more (70 fewer to 1000 more) |
| Tachycardia | 40 (1 study) 6 weeks | LOW[b] due to imprecision | RR 2 (0.2 to 20.33) | 50 per 1000 | 50 more per 1000 (from 40 fewer to 966 more) |

| | | | | | |
|---|---|---|---|---|---|
| Decreased appetite | 70<br>(2 studies)<br>6 weeks | VERY LOW[a,b,c] due to risk of bias, imprecision, indirectness | OR 0.52 (0.17 to 1.59) | 371 per 1000 | 136 fewer per 1000<br>(from 280 fewer to 113 more) |
| Sleep (insomnia) | 70<br>(2 studies)<br>6 weeks | VERY LOW[a,b] due to risk of bias, imprecision | OR 0.7 (0.21 to 2.27) | 286 per 1000 | 67 fewer per 1000<br>(from 208 fewer to 190 more) |
| Tremor | 30<br>(1 study)<br>6 weeks | VERY LOW[a,b] due to risk of bias, imprecision | OR 0.14<br>(0 to 6.82) | 67 per 1000 | 57 fewer per 1000<br>(from 67 fewer to 261 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 the majority of the evidence had indirect outcomes.*

**Table 28: 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) |
| Tachycardia | 183<br>(1 study)<br>7 weeks | VERY LOW[a,b] due to risk of bias, imprecision | OR 4.6<br>(0.07 to 284.33) | 0 per 1000 | 10 more per 1000 (from 20 fewer to 40 more) |
| Systolic blood | 636 | LOW[a,b] due | | The mean systolic | The mean systolic blood pressure in the intervention |

| | | | | | |
|---|---|---|---|---|---|
| pressure | (3 studies)<br>3-9 weeks | to risk of bias, imprecision | | blood pressure in the control group was 103.8mmHg | group was 0.07mmHg higher (1.56 lower to 1.71 higher) |
| Diastolic blood pressure | 248<br>(1 study)<br>9 weeks | MODERATE[a] due to risk of bias | | The mean diastolic blood pressure change in the control group was -0.5mmHg | The mean diastolic blood pressure in the intervention group was 0.03mmHg higher (2.88 lower to 2.95 higher) |
| Weight change | 429<br>(2 studies)<br>7-9 weeks | VERY LOW[a,b] due to risk of bias, imprecision | | The mean weight change in the control group was +0.65kg | The mean weight change in the intervention groups was 1.26kg lower<br>(1.51 lower to 1.63 higher) |
| Decreased weight | 46<br>(1 study)<br>5 weeks | VERY LOW[a,b] due to risk of bias, imprecision | RR 2 (0.19 to 20.55) | 43 per 1000 | 43 more per 1000 (from 36 fewer to 850 more) |
| Psychotic symptoms | 183<br>(1 study)<br>7 weeks | VERY LOW[a,b] due to risk of bias, imprecision | OR 4.6 (0.07 to 284.33) | 0 per 1000 | 10 more per 1000 (from 20 fewer to 40 more) |
| Sleep (insomnia) | 631<br>(3 studies)<br>3-9 weeks | MODERATE[a] due to risk of bias | OR 4.12 (2.57 to 6.61) | 37 per 1000 | 101 more per 1000<br>(from 53 more to 167 more) |
| Sleep (insomnia) | 97<br>(1 study)<br>8 weeks<br>Autism population | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.61 (0.15 to 2.42) | 102 per 1000 | 40 fewer per 1000<br>(from 86 fewer to 121 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 29: Methylphenidate versus modafinil**

| 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 modafinil (95% CI) |
| Decreased weight | 60<br>(1 study)<br>6 weeks | LOW[a]<br>due to imprecision | RR 2.33<br>(0.67 to 8.18) | 100 per 1000 | 133 more per 1000<br>(from 33 fewer to 718 more) |

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

### Non-comparative long-term studies: melatonin

In one study with 94 participants at least one adverse event was reported by 20.2% (n=19/94) participants in the 4-year follow up of children with ADHD and chronic sleep onset insomnia. [337] There were no common adverse events reported. 3.2% of participants (3/94) suffered from sleep maintenance insomnia, nightmares in 2.1% (2/94) and excessive morning sedation in 2.1% (n=2/94). There was very high risk of bias due to selection bias, blinding and attrition bias. There were no serious concerns related to indirectness. Imprecision and inconsistency were not applicable.

## 1.5.10.3 Clinical evidence (adults)

**Table 30: 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) |
| Total participants with adverse events | 1267<br>(6 studies)<br>5-8 weeks | VERY LOW[a,d]<br>due to risk of bias, imprecision | RR 1.31<br>(1.2 to 1.43) | 601 per 1000 | 186 more per 1000<br>(from 120 more to 258 more) |
| Total participants with adverse events - Immediate release | 24<br>(1 study)<br>5-8 weeks | LOW[b,c]<br>due to risk of bias, imprecision | RR 1.12<br>(0.67 to 1.89) | 667 per 1000 | 80 more per 1000<br>(from 220 fewer to 594 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 Methylphenidate versus placebo (95% CI) |
| adverse events - OROS | (5 studies) 5-8 weeks | due to risk of bias, imprecision | (1.2 to 1.44) | 564 per 1000 | 175 more per 1000 (from 113 more to 248 more) |
| Total participants with adverse events | 533 (2 studies) 13-24 weeks | VERY LOW[a,d] due to risk of bias, imprecision | RR 1.16 (1.06 to 1.26) | 763 per 1000 | 122 more per 1000 (from 46 more to 198 more) |
| Cardiac events | 375 (2 studies) 6 weeks | LOW[c,d] due to risk of bias, imprecision | RR 2.6 (0.83 to 8.13) | 20 per 1000 | 32 more per 1000 (from 3 fewer to 143 more) |
| Cardiac events 24 weeks | 96 (1 study) 24 weeks | VERY LOW[b,c] due to risk of bias, imprecision | RR 4.39 (0.57 to 33.62) | 29 per 1000 | 98 more per 1000 (from 12 fewer to 946 more) |
| Systolic blood pressure | 229 (1 study) 7 weeks | MODERATE[c] due to risk of bias | | The mean systolic blood pressure change in the control groups was -0.5 mmHg | The mean systolic blood pressure change was 0.7 lower (3.12 lower to 1.72 higher) |
| Systolic blood pressure | 359 (1 study) 24 weeks | MODERATE[c] due to risk of bias | | The mean systolic blood pressure in the control groups was 123 mmHg | The mean systolic blood pressure - systolic blood pressure in the intervention groups was 1 mmHg higher (2.17 lower to 4.17 higher) |
| Diastolic blood pressure | 229 (1 study) 7 weeks | MODERATE[c] due to risk of bias | | The mean diastolic blood pressure change in the control groups was 0.4 mmHg | The mean diastolic blood pressure - diastolic blood pressure in the intervention groups was 0.7 mmHg higher (1.13 lower to 2.53 higher) |
| Diastolic blood pressure | 359 (1 study) | MODERATE[c] due to risk of | | The mean diastolic blood pressure in the control groups was 78 | The mean diastolic blood pressure - diastolic blood pressure in the |

| 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) |
| | 24 weeks | bias | | mmHg | intervention groups was the same (2.13 lower to 2.13 higher) |
| Palpitations (immediate release and OROS MPH) | 1294 (5 studies) 3-9 weeks | MODERATE[c] due to risk of bias | RR 7.3 (3.68 to 14.46) | 14 per 1000 | 88 more per 1000 (from 38 more to 188 more) |
| Palpitations - Immediate release MPH | 90 (1 study) 3 weeks | VERY LOW[b,c] due to risk of bias, imprecision | RR 4 (0.47 to 34.41) | 22 per 1000 | 66 more per 1000 (from 12 fewer to 735 more) |
| Palpitations- OROS MPH | 1204 (4 studies) 3-9 weeks | HIGH | RR 7.68 (3.73 to 15.82) | 7 per 1000 | 47 more per 1000 (from 19 more to 104 more) |
| Palpitations | 893 (3 studies) 13-24 weeks | LOW[b] due to risk of bias | RR 3.45 (1.97 to 6.06) | 8 per 1000 | 20 more per 1000 (from 8 more to 40 more) |
| Decreased appetite | 1882 (8 studies) 2-9 weeks | VERY LOW[b,e] due to risk of bias, indirectness | RR 4.57 (3.37 to 6.21) | 56 per 1000 | 200 more per 1000 (from 133 more to 292 more) |
| Decreased appetite | 989 (4 studies) 13-24 weeks | VERY LOW[b.e] due to risk of bias, indirectness | RR 3.59 (2.46 to 5.24) | 53 per 1000 | 137 more per 1000 (from 77 more to 225 more) |
| Weight change | 323 (2 studies) 4-7 weeks | LOW[c,d] due to risk of bias, imprecision | | The mean weight change in the control groups was 0.39kgs | The mean weight change in the intervention groups was 2.11 kgs lower (2.77 to 1.44 lower) |
| Weight loss | 401 (1 study) 5 weeks | VERY LOW[b,c] due to risk of bias, | RR 1.38 (0.54 to 3.56) | 52 per 1000 | 20 more per 1000 (from 24 fewer to 133 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 Methylphenidate versus placebo (95% CI) |
| | | imprecision | | | |
| Weight loss | 279 (1 study) 13 weeks | VERY LOW[a,d] due to risk of bias, imprecision | RR 3.46 (1.24 to 9.64) | 41 per 1000 | 101 more per 1000 (from 10 more to 354 more) |
| Anorexia | 100 (1 study) 3 weeks | VERY LOW[a,d] due to risk of bias, imprecision | RR 3.67 (1.09 to 12.36) | 60 per 1000 | 160 more per 1000 (from 5 more to 682 more) |
| Anorexia | 279 (1 study) 13 weeks | VERY LOW[a,d] due to risk of bias, imprecision | RR 2.4 (0.84 to 6.89) | 41 per 1000 | 57 more per 1000 (from 7 fewer to 241 more) |
| Psychotic symptoms | 284 (1 study) 4 weeks | VERY LOW[a,b] due to risk of bias, imprecision | OR 7.29 (0.14 to 367.25) | 0 per 1000 | 10 more per 1000 (from 10 fewer to 30 more) |
| Sleep (insomnia) (immediate release MPH and OROS MPH) | 2076 (10 studies) 2-9 weeks | MODERATE[c] due to risk of bias | RR 1.88 (1.42 to 2.48) | 68 per 1000 | 60 more per 1000 (from 29 more to 101 more) |
| Sleep (insomnia)- Immediate release MPH | 236 (2 studies) 2-9 weeks | VERY LOW[c,d]due to risk of bias, imprecision | RR 1.47 (0.88 to 2.45) | 194 per 1000 | 91 more per 1000 (from 23 fewer to 281 more) |
| Sleep (insomnia) - OROS MPH | 1840 (8 studies) 2-9 weeks | MODERATE[c] due to risk of bias | RR 2.04 (1.47 to 2.84) | 58 per 1000 | 60 more per 1000 (from 27 more to 107 more) |
| Sleep (insomnia) | 736 (4 studies) 13-24 weeks | VERY LOW[a,d] due to risk of bias, | RR 1.47 (0.99 to 2.18) | 116 per 1000 | 55 more per 1000 (from 1 fewer to 137 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 Methylphenidate versus placebo (95% CI) |
| | | imprecision | | | |
| Tics | 90 (1 study) 3 weeks | VERY LOW[b,c] due to risk of bias, imprecision | OR 2.81 (0.38 to 20.67) | 22 per 1000 | 37 more per 1000 (from 14 fewer to 295 more) |
| Tremor | 279 (1 study) 13 weeks | VERY LOW[b,c] due to risk of bias, imprecision | RR 4.8 (0.62 to 37.31) | 10 per 1000 | 38 more per 1000 (from 4 fewer to 363 more) |
| Sexual dysfunction | 359 (1 study) 24 weeks | VERY LOW[a,d] due to risk of bias, imprecision | RR 3.3 (1.18 to 9.23) | 34 per 1000 | 78 more per 1000 (from 6 more to 280 more) |
| | | | | | |

*(a) Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.*
*(b) Downgraded by 2 increments if the confidence interval crossed both MIDs.*
*(c) Downgraded by 1 increment if the majority of the evidence was at high risk of bias.*
*(d) Downgraded by 1 increment if the confidence interval crossed one MID.*
*(e) Downgraded by 1 or 2 increments if the majority of evidence had indirect outcomes.*

**Non-comparative long-term studies: methylphenidate**

In one study at 52 weeks (n=550)[13]:

- At least one adverse event was reported by 91.6% (504/550) of participants.
- The most common adverse events (reported > 10% of the participants) were headache, dry mouth, anxiety, URTI, nausea, pulse rate increased, irritability.
- There was a 10% decrease in weight in 11.2% of the participants (60/550)
- There was a 10% increase in 0.9% of the participants (5/550).
- Systolic blood pressure >140 was reported in 9.6% (52/550)
- Diastolic blood pressure <50 in 0.4% (2/550) and >90 in 12% (65/550)
- Decreased appetite was reported in 26.7% (144/550) of participants and insomnia 20.7 % (112/550).
- All outcomes were at a very high risk of bias due to selection bias, blinding and attrition bias. There were no serious concerns related to indirectness. Imprecision and inconsistency were not applicable.

In one study at 52 weeks (n= 155)[133]:

- At least one adverse event was reported by 81.3% (n=126) of participants
- Twelve participants reported severe adverse events these were not considered to be drug related.
- The most common adverse events (reported >5% of the participants) were headache, nasopharyngitis,influenza, restlessness, back pain, drug effects decreasing, and depressed mood.
- In particular insomnia was reported by 7.1%, (11/155) of the participants and hypertension by 5.8%, (n=9/155).
- All outcomes were at a very high risk of bias due to selection bias, blinding and attrition bias. There were no serious concerns related to indirectness. Imprecision and inconsistency were not applicable.

In one study at 52 weeks (n=298)[287], two participants reported severe adverse events these were not considered to be drug related. The most common adverse events (reported > 5% of the participants) were nasopharyngitis, headache, dry mouth, nausea, URTI, diarrhoea, back pain, fatigue, anxiety, gastroenteritis, oropharyngeal pain, and influenza. In particular tachycardia was reported by 3.7%, (11/298) of the participants and decreased appetite by 8.7%, (26/298). All outcomes were at a very high risk of bias due to selection bias, blinding and attrition bias. There were no serious concerns related to indirectness. Imprecision and inconsistency were not applicable.

**Table 31 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) |
| Total participants with adverse events | 811 (3 studies) 2-10 weeks | VERY LOW[a,b,c] due to risk of bias, inconsistency, imprecision | RR 1.17 (0.87 to 1.56) | 581 per 1000 | 99 more per 1000 (from 76 fewer to 325 more) |
| Cardiac events | 69 (1 study) 6 weeks | VERY LOW[a,e] due to risk of bias, imprecision | RR 0.97 (0.06 to 14.91) | 29 per 1000 | 1 fewer per 1000 (from 27 fewer to 403 more) |
| Decreased appetite | 880 (4 studies) 2-10 weeks | VERY LOW[a,f] due to risk of bias, indirectness | RR 7.2 (3.64 to 14.26) | 38 per 1000 | 236 more per 1000 (from 100 more to 504 more) |
| Weight change - 30mg | 181 (1 study) 4 weeks | MODERATE[d] due to risk of bias | | The mean weight change in the control groups was 0.5 kg | The mean weight change - 30mg in the intervention groups was 3.3kg lower (4.63 to 1.97 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 versus Placebo (95% CI) |
| Weight change - 50mg | 179 (1 study) 4 weeks | MODERATE[d] due to risk of bias | | The mean weight change in the control groups was 0.5 kg | The mean weight change - 50mg in the intervention groups was 3.6kg lower (4.92 to 2.28 lower) |
| Weight change - 70mg | 184 (1 study) 4 weeks | MODERATE[d] due to risk of bias | | The mean weight change in the control groups was 0.5 kg | The mean weight change - 70mg in the intervention groups was 4.8kg lower (6.12 to 3.48 lower) |
| Weight loss | 159 (1 study) 10 weeks | LOW[a] due to risk of bias | OR 8.21 (1.99 to 33.91) | 0 per 1000 | 100 more per 1000 (from 30 more to 170 more) |
| Anorexia 4-10 weeks | 579 (2 studies) 4-10 weeks | MODERATE[d] due to risk of bias | OR 4.4 (1.46 to 13.25) | 0 per 1000 | 50 more per 1000 (from 20 more to 80 more) |
| Sleep (insomnia) | 880 (4 studies) 2-10 weeks | LOW[a] due to risk of bias | RR 3.73 (1.84 to 7.57) | 34 per 1000 | 93 more per 1000 (from 29 more to 223 more) |
| Sexual dysfunction | 159 (1 study) 10 weeks | VERY LOW[a,c] due to risk of bias, imprecision | OR 7.78 (1.08 to 56.29) | 0 per 1000 | 50 more per 1000 (from 0 more to 100 more) |

*(a) Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.*
*(b) Downgraded due to heterogeneity, unexplained by subgroup analysis.*
*(c) Downgraded by 1 increment if the confidence interval crossed one MID.*
*(d) Downgraded by 1 increment if the majority of the evidence was at high risk of bias.*
*(e) Downgraded by 2 increments if the confidence interval crossed two MIDs.*
*(f) Downgraded by 1 or 2 increments if the majority of evidence had indirect outcomes*

**Non-comparative long-term studies: lisdexamfetamine dimesylate**

In one study at 52 weeks (n= 349)[660], 87.7% (306/349) reported an adverse event. The most common adverse events (reported > 5% of the participants) were anxiety, back pain, dry mouth, headache, irritability, muscle spasm, nasopharyngitis, sinusitis, URTI. In particular decreased appetite was reported in 14.3% (50/349) of the participants, weight decreased in 6% (21/349) and insomnia in 19.5% (68/349). All outcomes were at a very high risk of bias due to selection bias, blinding and attrition bias. There were no serious concerns related to indirectness. Imprecision and inconsistency were not applicable.

**Table 32 Dexamphetamine 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 Dexamphetamine ER versus placebo (95% CI) |
| Weight change (kg) | 45<br>(1 study)<br>6 weeks | HIGH | | The mean weight change in the control group was 0.286kg | The mean weight change in the intervention groups was<br>3.31kg higher<br>(2.05 to 4.58 higher) |
| Decreased appetite | 262<br>(2 studies)<br>2-5 weeks | VERY LOW[a,b,c]<br>due to risk of bias, imprecision, indirectness | OR 2.08<br>(0.96 to 4.49) | 57 per 1000 | 56 more per 1000<br>(from 4 fewer to 188 more) |
| Sleep (insomnia) | 262<br>(2 studies)<br>2-5 weeks | VERY LOW[a,b]<br>due to risk of bias, imprecision | RR 1.62<br>(0.84 to 3.09) | 148 per 1000 | 92 more per 1000<br>(from 24 fewer to 309 more) |

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

**Table 33 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) |
| Total participants with adverse events | 1115<br>(3 studies) | VERY LOW[a,b,c]<br>due to risk of bias, inconsistency, | RR 1.31<br>(1.03 to | 649 per 1000 | 201 more per 1000<br>(from 19 more to 422 more) |

| | | | | | |
|---|---|---|---|---|---|
| | 8-10 weeks | imprecision | 1.65) | | |
| Total participants with adverse events | 1387<br>(3 studies)<br>12-25 weeks | LOW[d]<br>due to risk of bias | RR 1.13<br>(1.06 to 1.19) | 773 per 1000 | 100 more per 1000<br>(from 46 more to 147 more) |
| Palpitations | 74<br>(1 study) | VERY LOW[a,e]<br>due to risk of bias, imprecision | RR 1.5<br>(0.27 to 8.46) | 54 per 1000 | 27 more per 1000<br>(from 39 fewer to 403 more) |
| Systolic blood pressure | 71<br>(1 study)<br>10 weeks | LOW[a,c]<br>due to risk of bias, imprecision | | The mean systolic blood pressure change in the control groups was -1.2mmHg | The mean systolic blood pressure in the intervention groups was 4.5 higher<br>(0.77 lower to 9.77 higher) |
| Diastolic blood pressure | 71<br>(1 study)<br>10 weeks | LOW[a,c]<br>due to risk of bias, imprecision | | The mean diastolic blood pressure change in the control groups was -1.4mmHg | The mean diastolic blood pressure in the intervention groups was<br>2.7 higher<br>(1.74 lower to 7.14 higher) |
| Weight change | 71<br>(1 study)<br>10 weeks | VERY LOW[a,b,c]<br>due to risk of bias, inconsistency, imprecision | | The mean weight change in the control groups was 0.3kg | The mean weight change in the intervention groups was<br>2.4 lower<br>(3.65 to 1.15 lower) |
| Weight change | 147<br>(1 study)<br>13 weeks | VERY LOW[a,d]<br>due to risk of bias, imprecision | | The mean weight change in the control groups was 0.42kg | The mean weight change in the intervention groups was<br>1.33 lower<br>(1.98 to 0.68 lower) |
| Weight loss | 465<br>(2 studies)<br>10 weeks | MODERATE[a]<br>due to risk of bias | OR 6.34<br>(2.47 to 16.23) | 3 per 1000 | 16 more per 1000<br>(from 4 more to 44 more) |
| Decreased appetite | 2537<br>(6 studies)<br>8-10 weeks | LOW[a,f]<br>due to risk of bias, indirectness | RR 4.92<br>(3.52 to 6.87) | 31 per 1000 | 122 more per 1000<br>(from 78 more to 182 more) |
| Decreased appetite | 2017<br>(5 studies)<br>12-24 weeks | VERY LOW[d,f]<br>due to risk of bias, indirectness | RR 4.19<br>(2.95 to 5.96) | 28 per 1000 | 89 more per 1000<br>(from 55 more to 139 more) |
| Sleep (insomnia) | 1757<br>(5 studies) | MODERATE[a]<br>due to risk of bias | RR 2<br>(1.29 to | 84 per 1000 | 84 more per 1000<br>(from 24 more to 176 more) |

| | | | | | |
|---|---|---|---|---|---|
| | 8-10 weeks | | 3.1) | | |
| Sleep (insomnia) | 1890<br>(4 studies)<br>12-24 weeks | LOW[d]<br>due to risk of bias | RR 1.75<br>(1.3 to 2.34) | 71 per 1000 | 53 more per 1000<br>(from 21 more to 95 more) |
| Sexual dysfunction | 1655<br>(4 studies)<br>8-10 weeks | MODERATE[a]<br>due to risk of bias | RR 4.73<br>(2.36 to 9.49) | 12 per 1000 | 45 more per 1000<br>(from 16 more to 102 more) |
| Sexual dsyfunction | 1890<br>(4 studies)<br>12-24 weeks | LOW[d]<br>due to risk of bias | RR 5.43<br>(2.36 to 12.5) | 4 per 1000 | 18 more per 1000<br>(from 5 more to 46 more) |

*(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias.*
*(b) Downgraded due to heterogeneity, unexplained by subgroup analysis.*
*(c) Downgraded by 1 increment if the confidence interval crossed one MID.*
*(d) Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.*
*(e) Downgraded by 2 increments if the confidence interval crossed both MIDs.*
*(f) Downgraded by 1 or 2 increments if the majority of evidence had indirect outcomes.*

### Non-comparative long-term studies: atomoxetine

In one study at 48 weeks (n= 233)[336], at least one adverse event was reported by 93.6% (n=218) of participants and the discontinuation rate at 48 weeks was 65%. The most common adverse events (reported > 5% of the participants) were nausea, nasopharyngitis, thirst, headache, somnolence, constipation, vomiting, dysuria. In particular palpitations was reported by 7.3 %, (17/233) of the participants decreased appetite by 16.3%, (38/233), weight decreased by 6.4% (15/233). All outcomes were at a very high risk of bias due to selection bias, blinding and attrition bias. There were no serious concerns related to indirectness. Imprecision and inconsistency were not applicable.

In one study at 221 weeks (n= 384)[18], the most common adverse events (reported > 5% of the participants) were dry mouth, headache, nausea, constipation, URTI, nasopharyngitis, urinary hesitation, irritability, back pain, influenza, sinusitis, dysmenorrhea, anxiety, fatigue, dizziness, dyspepsia, arthralgia, cough, depression, libido decreased, abnormal dreams, decreased appetite, nasal congestion, pharyngolaryngeal pain, dyspepsia, sleep disorder, diarrhoea, hyperhidrosis, initial insomnia and middle insomnia. In particular insomnia was reported by 19.3 %, (74/384) of the participants and erectile dysfunction by 11.5% (44/384) and decreased appetite by 6%, (23/384). All outcomes were at a very high risk of bias due to selection bias, blinding and attrition bias. There were no serious concerns related to indirectness. Imprecision and inconsistency were not applicable.

**Table 34 Guanfacine versus placebo**

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

| | Participants (studies) Follow up | (GRADE) | effect (95% CI) | Risk with Control | Risk difference with Guanfacine versus Placebo (95% CI) |
|---|---|---|---|---|---|
| Increased appetite | 26 (1 study) 9 weeks | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.5 (0.05 to 4.86) | 154 per 1000 | 77 fewer per 1000 (from 146 fewer to 594 more) |

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

**Table 35 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) |
| Sexual dysfunction | 44 (1 study) 6 weeks | LOW[a] due to imprecision | OR 7.75 (0.47 to 128.03) | 0 events in control group | 90 more per 1000 (from 50 fewer to 230 more) |

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

**Table 36 Buproprion SR 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 SR versus Placebo (95% CI) |
| Total participants with adverse events | 25 (1 study) 7 weeks | VERY LOW[a,b] due to risk of bias, imprecision | RR 1.04 (0.61 to 1.78) | 667 per 1000 | 27 more per 1000 (from 260 fewer to 520 more) |

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

**Table 37 Buproprion SR 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 SR versus methylphenidate (95% CI) |
| Total participants with adverse events | 25<br>(1 study)<br>7 weeks | VERY LOW[a,b]<br>due to risk of bias, imprecision | RR 0.92<br>(0.57 to 1.5) | 750 per 1000 | 60 fewer per 1000<br>(from 322 fewer to 375 more) |

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

**Table 38 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) |
| Total participants with adverse events | 338<br>(1 study)<br>9 weeks | LOW[a]<br>due to risk of bias | RR 1.01<br>(0.91 to 1.12) | 851 per 1000 | 9 more per 1000<br>(from 77 fewer to 102 more) |
| Suicidal ideation | 338<br>(1 study)<br>9 weeks | VERY LOW[a,b]<br>due to risk of bias, imprecision | OR 3.6<br>(0.03 to 411.56) | 0 per 1000 | 0 more per 1000 (from 20 less to 20 more) |
| Tachycardia | 338<br>(1 study)<br>9 weeks | VERY LOW[a,b]<br>due to risk of bias, imprecision | OR 3.6<br>(0.03 to 411.56) | 0 per 1000 | 0 more per 1000 (from 20 less to 20 more) |
| Decreased appetite | 44<br>(1 study)<br>2 weeks | LOW[c,d]<br>due to imprecision, indirectness | OR 8.58<br>(1.13 to 65.51) | 0 events in control arm | 180 more per 1000 (from 10 more to 350 more) |
| Anorexia | 338<br>(1 study)<br>9 weeks | VERY LOW[a,3]<br>due to risk of bias, imprecision | RR 3.55<br>(1.13 to 11.18) | 41 per 1000 | 105 more per 1000<br>(from 5 more to 417 more) |
| Psychotic symptoms | 338<br>(1 study)<br>9 weeks | VERY LOW[a,b]<br>due to risk of bias, imprecision | OR 3.6<br>(0.03 to 411.56) | 0 events in control arm | 0 more per 1000 (from 20 fewer to 20 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 Modafinil versus Placebo (95% CI) |
| | (2 studies)<br>2-9 weeks | due to risk of bias, imprecision | (1.18 to 3.91) | 145 per 1000 | 167 more per 1000<br>(from 26 more to 422 more) |
| | | | | | |

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

**Table 39 Modafinil versus dexamphetamine**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with Modafinil versus Dexamphetamine (95% CI) |
| Sleep (insomnia) | 44<br>(1 study)<br>2 weeks | LOW[a]<br>due to imprecision | RR 0.5<br>(0.18 to 1.42) | 364 per 1000 | 182 fewer per 1000<br>(from 298 fewer to 153 more) |

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

**Table 40 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) |
| Sleep (insomnia) | 40<br>(1 study)<br>4 weeks | VERY LOW[a,b]<br>due to risk of bias, imprecision | RR 5.91<br>(0.81 to 42.92) | 59 per 1000 | 290 more per 1000<br>(from 11 fewer to 1000 more) |

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

*(b) Downgraded by 1 increment if the confidence interval crossed1 MID.*

See appendix F for full GRADE tables.

# 1.6 Economic evidence

## 1.6.1 Included studies

No relevant health economic studies were identified.

## 1.6.2 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.

# 1.7 Resource impact

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

# 1.8 Evidence statements

## 1.8.1 Clinical evidence statements

### 1.8.1.1 Pre-school children (under the age of 5)

**Methylphenidate versus placebo**

- No evidence was identified for total number of participants with adverse events, all-cause mortality, cardiac mortality, suicide or suicidal ideation, substance misuse, increase in seizures, disturbed sleep, liver damage, tics, tremors, congenital defects and psychotic symptoms for follow up of 12 weeks. There was no evidence for follow up over 12 weeks.
- Weight change was higher at 4 weeks in the methylphenidate group compared to the placebo group (1 study, low quality), this was considered clinically important.
- Differences in tachycardia, systolic blood pressure, diastolic blood pressure and height at 4 weeks were not clinically important between the groups (1 study, low to very low quality)

**Methylphenidate versus risperidone**

- No evidence was identified for total number of participants with adverse events, all-cause mortality, suicide or suicidal ideation, cardiac mortality, cardiac events, substance misuse, increase in seizures, liver damage, increased tics, tremor, congenital defects and psychotic symptoms for follow up to 12 weeks. There was no evidence for follow up over 12 weeks.
- A higher number of pre-schoolers had a decreased appetite at 6 weeks in the methylphenidate group compared to the risperidone group (1 study, very low quality), and this was considered clinically important.
- Differences in sleep outcomes at 6 weeks were not clinically important between the groups (1 study, very low quality)

### 1.8.1.2 Children and young people (aged 5 to 18)

**IR methylphenidate versus placebo**

- No evidence was identified for all-cause mortality, suicide or suicidal ideation, cardiac mortality, substance misuse, increase in seizures, liver damage, tremor, congenital defects and psychotic symptoms for follow up to 12 weeks. No evidence was identified for all-cause mortality, suicide or suicidal ideation, cardiac mortality, increase in seizures, liver damage, tremor, congenital defects for follow up over 12 weeks.
- At both time points the total number of children reporting any adverse event was higher for methylphenidate compared to placebo (2 studies, low to very low quality). The following outcomes had a higher number of children reporting adverse events in the methylphenidate group; Tachycardia at 8 and 16 weeks (2 studies very low quality), decreased weight at 2 and 16 weeks (3 studies moderate quality), seizures at 3 weeks (1 study low quality), substance misuse at 4.4 years (1 study very low quality; non-randomised). and sleep (insomnia) at 3-8 weeks and 16 weeks (4 studies moderate quality; 1 study very low quality) These were all considered clinically important.
- Differences in systolic blood pressure at 2 and 16 weeks (4 studies, moderate quality), diastolic blood pressure at 2 and 16 weeks (2 studies, low quality), cardiovascular events at 6 months (1 study very low quality non-randomised), height at 6 weeks (1 study, very low quality), psychotic symptoms at 16 weeks (1 study moderate quality),tics at 16 weeks (2 studies low to very low quality) and tics severity (1 study low quality) were not clinically important between the groups.

**OROS methylphenidate versus placebo**

- No evidence was identified for all-cause mortality, suicide or suicidal ideation, cardiac mortality, substance misuse, increase in seizures, liver damage, tics, tremor, congenital defects, sexual dysfunction and psychotic symptoms for follow up to 12 weeks. No evidence was identified for follow up over 12 weeks.
- At 6 weeks the total number of children reporting any adverse event was higher for methylphenidate compared to placebo (1 study, low quality). Children in in the methylphenidate group had larger weight decreases compared to placebo at 6 to 7 weeks (2 studies, moderate quality). This was considered clinically important.
- Differences in systolic blood pressure at 6-7 weeks (2 studies, moderate quality), diastolic blood pressure at 6-7 weeks (2 studies, moderate quality) and sleep (1 study low quality) were not clinically important between the groups.

**IR methylphenidate versus OROS methylphenidate**

- No evidence was identified for all-cause mortality, suicide or suicidal ideation, cardiac mortality, cardiac events, substance misuse, increase in seizures, liver damage, tremor, congenital defects, sexual dysfunction and psychotic symptoms for follow up to 12 weeks. No evidence was identified for follow up over 12 weeks.
- At 4 weeks the total number of children reporting any adverse event was not clinically different between the groups (1 study, low quality). Differences in appetite, insomnia and tics at 3-4 weeks (1 study very low quality) were not clinically important between the groups.

**Lisdexamfetamine dimesylate versus placebo**

- No evidence was identified for suicide or suicidal ideation, cardiac mortality, substance misuse, increase in seizures, liver damage, tics, tremor, congenital defects, sexual dysfunction and psychotic symptoms for follow up to 12 weeks. No evidence was identified for all-cause mortality, cardiac mortality, blood pressure, suicidal ideation, substance misuse, increase in seizures, liver damage, tremor, congenital defects, sexual dysfunction, psychotic symptoms and sleep for follow up over 12 weeks.
- 
- At 4-7 weeks the total number of children reporting any adverse event was higher for lisdexamfetamine compared to placebo (2 studies, moderate quality). The following outcomes had a higher number of children reporting adverse events in the

lisdexamfetamine group compared to placebo: weight change at 7 weeks (1 study moderate quality), decreased weight at 4-7 weeks (2 studies moderate quality) and sleep at 4-7 weeks (3 studies moderate quality). These were all considered clinically important.

- Differences in all-cause mortality at 4 weeks (1 study moderate quality), systolic blood pressure at 4-7 weeks (2 studies, moderate quality) and diastolic blood pressure at 4-7 weeks (2 studies, moderate quality) were not clinically important between the groups.
- In one non-comparative long-term study on lisdexamfetamine with 272 participants, there was at least one adverse event reported by 78% (213/272) of participants taking lisdexamfetamine dimesylate, with a mean follow up of 259 days. The most common adverse events (reported in >10% of participants) were decreased appetite, headache, decreased weight, insomnia, upper abdominal pain, upper respiratory tract infection, irritability and nasopharyngitis. In particular 17.6% (48/272) had weight decreases. There was a very high risk of bias due to selection bias and attrition bias. There were no serious concerns related to indirectness. Imprecision and inconsistency were not applicable.

**Lisdexamfetamine dimesylate versus methylphenidate**

- No evidence was identified for total number of participants with adverse events, all-cause mortality, suicide or suicidal ideation, cardiac mortality, substance misuse, increase in seizures, liver damage, tics, tremor, congenital defects, sexual dysfunction and psychotic symptoms for follow up to 12 weeks. No evidence was identified for follow up over 12 weeks.
- A higher number of children in the methylphenidate group reported Sleep (insomnia) compared to methylphenidate 7 weeks (1 study low quality). This was considered clinically important.
- Differences in systolic blood pressure, diastolic blood pressure and weight change at 7 weeks (1 study moderate quality) were not clinically important between the groups.

**Atomoxetine versus placebo**

- No evidence was identified for cardiac mortality, substance misuse, increase in seizures, liver damage, congenital defects and psychotic symptoms for follow up to 12 weeks. No evidence was identified for all-cause mortality, cardiac mortality, cardiac events, substance misuse, increase in seizures, increase in tremors, congenital defects and psychotic symptoms for follow up over 12 weeks.
- At both time points the total number of adults reporting any adverse event was higher for atomoxetine compared to placebo (6 studies, low quality). The following outcomes had a higher number of children reporting adverse events in the atomoxetine group; weight at 6-12 weeks and 13-18 weeks (8 studies moderate quality), Sleep (insomnia) at 6-12 weeks and 13-16 weeks (7 studies, low to very low quality), tics at 6 weeks (1 study very low quality) and tremor at 6 weeks (1 study very low quality). There was a clinical benefit of atomoxetine compared to placebo at 8 to 16 weeks for tic severity (2 studies moderate quality). These were all considered clinically important.
- Differences in all-cause mortality at 6 weeks (1 study high quality), suicidal ideation at 6 weeks (1 study high quality), systolic blood pressure at 6-13 weeks (6 studies moderate quality), diastolic blood pressure at 6-13 weeks (5 studies low quality), height at 5 weeks (4 studies moderate quality), number of participants with decreased weight at 6-9 weeks (4 studies low quality), sleep at 13-16 weeks (2 studies very low quality) and sexual dysfunction at 70 weeks (1 study moderate quality) were not clinically important between the groups.
- In one long-term non-comparative study on atomoxetine with a follow up of 24 weeks all liver function tests were within normal ranges (n=159). There was a high risk of bias due to selection bias and attrition bias. There were no serious concerns related to indirectness. Imprecision and inconsistency were not applicable.

**Methylphenidate versus atomoxetine**

- No evidence was identified for all-cause mortality, cardiac mortality, suicide or suicidal ideation, substance misuse, increase in seizures, liver damage, tics, tremor, congenital defects, sexual dysfunction and psychotic symptoms for follow up to 12 weeks. No evidence was identified for total number of participants with adverse events, all-cause mortality, cardiac mortality, suicide or suicidal ideation, substance misuse, increase in seizures, blood pressure, liver damage, sleep, tics, tremor, congenital defects, sexual dysfunction and psychotic symptoms weeks for follow up over 12 weeks.
- At 6 weeks the total number of children reporting any adverse events was not different between the groups (1 study moderate quality).
- Differences in systolic and diastolic blood pressure at 6 weeks (1 study moderate quality), weight at 6-8 weeks (2 studies moderate quality) and 24 months (1 study very low quality; non-randomised), height at 24 months (1 study very low quality; non-randomised) and sleep at 8 weeks (1 study low quality) were not clinically important between the groups.

**Atomoxetine versus lisdexamfetamine dimesylate**

- No evidence was identified for all-cause mortality, cardiac mortality, suicide or suicidal ideation, substance misuse, increase in seizures, liver damage, tics, tremor, congenital defects, sexual dysfunction and psychotic symptoms for follow up to 12 weeks. No evidence was identified for follow up over 12 weeks
- At 9 weeks the total number of children reporting any adverse events was not different between the groups (1 study high quality). The following outcomes had a higher number of children reporting adverse events in the lisdexamfetamine group compared to the atomoxetine group: decreased weight at 9 weeks (1 study high quality) and sleep (insomnia) at 9 weeks (1 study moderate quality). These were all considered clinically important.
- Differences in systolic and diastolic blood pressure at 9 weeks (1 study high quality) were not clinically important between the groups.

**Atomoxetine versus guanfacine**

- No evidence was identified for all-cause mortality, cardiac mortality, cardiac events, suicide or suicidal ideation, substance misuse, increase in seizures, liver damage, tics, tremor, congenital defects, sexual dysfunction and psychotic symptoms for follow up to 12 weeks. No evidence was identified for follow up of over 12 weeks
- At 10-13 weeks the total number of children reporting any adverse events was higher in the guanfacine group compared to the atomoxetine group (1 study moderate quality). A higher number of children had decreased appetite in the atomoxetine group compared to the guanfacine group at 10-13 weeks (1 study very low quality). These were all considered clinically important.
- Differences in sleep (insomnia) at 10-13 weeks (1 study, very low quality) were not clinically important between the groups.

**Guanfacine versus placebo**

- No evidence was identified for cardiac mortality, substance misuse, increase in seizures, liver damage, tremor, congenital defects and sexual dysfunction for follow up to 12 weeks. No evidence was identified for cardiac mortality, suicidal ideation, increase in seizures, liver damage, tics, tremor, congenital defects, sexual dysfunction and psychotic symptoms for follow up over 12 weeks.
- At both time points the total number of children reporting any adverse event was higher in the guanfacine group compared to placebo (6 studies, very low to low quality). The number of psychotic symptoms in the guanfacine group was higher compared to placebo at 8 weeks (1 study low quality). There was a benefit of atomoxetine compared to placebo at 8 weeks for tic severity (1 study low quality). These were all considered clinically important.

- Differences in all-cause mortality at 8-15 weeks (3 studies low quality), cardiac events at 9 weeks (1 study moderate quality), systolic blood pressure at 8 weeks (1 study low quality), suicidal ideation at 8 weeks (1 study low quality), decreased appetite at 8-15 weeks (3 studies low quality) and insomnia at 8-15 weeks (3 studies very low quality) were not clinically important between the groups.
- In one non-comparative long-term study of guanfacine (n=240) at least one adverse event was reported by 87.1% (209/240) of participants, with a mean follow up of 8.8 months. The most common adverse events (reported in >10% of participants) included somnolence, headache, fatigue, sedation, abdominal pain, upper respiratory tract infection, cough, pharyngitis and increased weight. In particular, 21/240 participants reported weight increase as an adverse event. No weight decreases were reported. 3 cardiovascular events were reported (3/240; one instance of orthostatic hypotension and 2 events of syncope). All outcomes were at a very high risk of bias due to selection bias and attrition bias. There were no serious concerns related to indirectness. Imprecision and inconsistency were not applicable.
-

**Clonidine versus placebo**

- No evidence was identified for cardiac mortality, cardiac events, substance misuse, abnormal growth, increase in seizures, liver damage, tics, tremor, congenital defects, sexual dysfunction and psychotic symptoms for follow up to 12 weeks. No evidence was identified for all-cause mortality, cardiac mortality, suicidal ideation, substance misuse, increase in seizures, liver damage, tremor, congenital defects and sexual dysfunction for follow up over 12 weeks.
- At both time points the total number of children reporting any adverse event was higher in the clonidine group compared to placebo (2 studies, low to moderate quality). This was considered clinically important.
- Differences in all-cause mortality at 8 weeks (1 study moderate quality), tachycardia at 16 weeks (1 study moderate quality) systolic and diastolic blood pressure at 16 weeks (1 study low to moderate quality), weight changes at 16 weeks (1 study low quality), psychotic symptoms at 16 weeks (1 study moderate quality), sleep (insomnia) at 8 and 16 weeks (2 studies very low quality) and tics at 16 weeks (1 study very low quality) were not clinically important between the groups.

**Methylphenidate versus clonidine**

- No evidence was identified for follow up to 12 weeks. No evidence was identified for all-cause mortality, cardiac mortality, substance misuse, seizures, liver damage, tremors, congenital defects and sexual dysfunction for follow up over 12 weeks.
- At 16 weeks the total number of children reporting any adverse events was higher in the clonidine group compared to methylphenidate (1 study low quality, 16 weeks). A higher number of children reported tachycardia and weight loss in the methylphenidate group compared to clonidine at 16 weeks (1 study low quality). A higher number of children reported sleep (insomnia) in the clonidine group compared to methylphenidate at 16 weeks (1 study very low quality). These were all considered clinically important.
- Differences in systolic blood pressure, psychotic symptoms and tics at 16 weeks (1 study moderate to very low quality) were not clinically important between the groups.

**Clonidine versus desipramine**

- No evidence was identified except for total participants with any adverse event at 6 weeks.
- At 6 weeks the total number of children reporting any adverse event was higher in the clonidine group compared to desipramine (1 study moderate quality). This was considered clinically important.

**Desipramine versus placebo**

- No evidence identified except for decreased appetite, disturbed sleep and improvement of tics at 6 weeks.
- A higher number of children reported adverse events in the desipramine group compared to the placebo group at 6 weeks for decreased appetite (1 study moderate quality) and difficulty sleeping (1 study low quality). There was an improvement in tics in the desipramine group compared to the placebo group at 6 weeks (1 study high quality). These were all considered clinically important.

**Methylphenidate versus venlafaxine**

- The only evidence identified was for decreased appetite and sleep at 6 weeks.
- A higher number of children reported adverse events in the methylphenidate group compared to the placebo group at 6 weeks for decreased appetite (1 study low quality) and sleep (1 study high quality). These were both considered clinically important.

**Risperidone versus placebo**

- No evidence identified except for disturbed sleep and tremor at 6 weeks, and weight changes at 6 months.
- A higher number of children reported adverse events in the risperidone group compared to the placebo group at 6 weeks for sleeping problems (1 study very low quality) and tremor (1 study very low quality). These were both considered clinically important.
- Differences in weight at 6 months (1 study low quality) were not clinically important between the groups.

**Methylphenidate versus buproprion**

- No evidence was identified for all-cause mortality, cardiac mortality, suicide or suicidal ideation, substance misuse, increase in seizures, liver damage, tics, tremor, congenital defects, sexual dysfunction and psychotic symptoms for follow up to 12 weeks. No evidence was identified at follow up over 12 weeks.
- At 6 weeks the total number of adults reporting any adverse event was higher for methylphenidate compared to buproprion (1 study low quality). A higher number of children reported tachycardia in the methylphenidate group compared to buproprion at 6 weeks (1 study low quality). A higher number of children reported sleep (insomnia), decreased appetite and tremor in the buproprion group compared to methylphenidate at 6 weeks (1-2 studies very low quality). These were all considered clinically important.

**Modafinil versus placebo**

- No evidence was identified for total participants with adverse events, all-cause mortality, cardiac mortality, suicide or suicidal ideation, substance misuse, increase in seizures, liver damage, tics, tremor, congenital defects and sexual dysfunction for follow up to 12 weeks. No evidence was identified for follow up over 12 weeks.
- A higher number of children reported tachycardia at 7 weeks (1 study very low quality), psychotic symptoms at 3-9 weeks (1 study very low quality), and sleep (insomnia) at 3-9 weeks (3 studies moderate quality) in the modafinil group compared to placebo. These were all considered clinically important.
- Differences in systolic blood pressure at 3-9 weeks (3 studies low quality), diastolic blood pressure at 9 weeks (1 study moderate quality), weight at 5-9 weeks (3 studies very low quality) and sleep at 8 weeks in participants with autism (1 study very low quality) were not clinically important between the groups.

**Methylphenidate versus modafinil**

No evidence identified except for decreased weight at 6 weeks.

- A higher number of children had weight decreases in the methylphenidate group compared to modafinil at 6 weeks (1 study low quality). This was considered clinically important.

**Melatonin**

- No evidence identified except for sleep at 4 years
- In one non-comparative long-term study with 94 participants at least one adverse event was reported by 20.2% (n=19/94) participants in the 4-year follow up of children with ADHD and chronic sleep onset insomnia. There were no common adverse events reported. 3.2% of participants (3/94) suffered from sleep maintenance insomnia, nightmares in 2.1% (2/94) and excessive morning sedation in 2.1% (n=2/94). There was very high risk of bias due to selection bias, blinding and attrition bias. There were no serious concerns related to indirectness. Imprecision and inconsistency were not applicable.

#### 1.8.1.3 Adults

**Methylphenidate versus placebo**

- No evidence was identified for all-cause mortality, cardiac mortality, suicide or suicidal ideation, substance misuse, increase in seizures, liver damage, tremor, congenital defects, sexual dysfunction for follow up to 12 weeks. No evidence was identified for all-cause mortality, cardiac mortality, substance misuse, increase in seizures, liver damage, increase in tics, congenital defects and psychotic symptoms for follow up over 12 weeks.
- At both time points the total number of adults reporting any adverse event was higher for methylphenidate compared to placebo (8 studies, very low quality). The following outcomes had a higher number of adults reporting adverse events in the methylphenidate group; cardiac events at 6 and 24 weeks (2 studies, low quality;1 study very low quality), palpitations at 9 weeks (5 studies, moderate quality), decreased appetite at 9 and 24 weeks (8 studies, very low quality; 4 studies very low quality), weight loss at 13 weeks (1 study, very low quality), anorexia at 3 and 13 weeks ( both 1 study, very low quality), sleep (insomnia) at 9 and 24 weeks (10 studies, moderate quality;4 studies very low quality), tics at 3 weeks (1 study very low quality), tremor at 13 weeks (1 study very low quality), sexual dysfunction at 24 weeks (1 study very low quality). These were all clinically important, any differences identified between modified release and immediate release were not considered clinically important.
- Differences in systolic and diastolic blood pressure measures at both 7 and 24 weeks (1 study, moderate quality), palpitations at 24 weeks (3 studies low quality) weight changes at 7 weeks (2 studies, low quality), weight loss at 5 weeks (1 study, very low quality) and psychotic symptoms (1 study, very low quality) were not clinically important between the groups.
- In one long-term non-comparative study of methylphenidate at 52 weeks, at least one adverse event was reported by 91.6% (504/550) of participants. The most common adverse events (reported > 10% of the participants) were headache, dry mouth, anxiety, URTI, nausea, pulse rate increased, irritability. There was a 10% decrease in weight in 11.2% of the participants (60/550. There was a 10% increase in 0.9% of the participants (5/550). Systolic blood pressure >140mmHg was reported in 9.6% (52/550). Diastolic blood pressure <50mmHg in 0.4% (2/550) and >90mmHg in 12% (65/550). Decreased appetite was reported in 26.7% (144/550) of participants and insomnia 20.7 % (112/550). All outcomes were at a very high risk of bias due to selection bias, blinding and attrition bias. There were no serious concerns related to indirectness. Imprecision and inconsistency were not applicable.
- In one long-term non-comparative study of methylphenidate at 52 weeks, at least one adverse event was reported by 81.3% (n=126) of participants. Twelve participants reported severe adverse events these were not considered to be drug related.The most

common adverse events (reported >5% of the participants) were headache, nasopharyngitis ,influenza, restlessness, back pain, drug effects decreasing, and depressed mood. In particular insomnia was reported by 7.1%, (11/155) of the participants and hypertension by 5.8%, (n=9/155). All outcomes were at a very high risk of bias due to selection bias, blinding and attrition bias. There were no serious concerns related to indirectness. Imprecision and inconsistency were not applicable.

- In one long-term non-comparative study of methylphenidate at 52 weeks (n=298) two participants reported severe adverse events these were not considered to be drug related. The most common adverse events (reported > 5% of the participants) were nasopharyngitis, headache, dry mouth, nausea, URTI, diarrhoea, back pain, fatigue, anxiety, gastroenteritis, oropharyngeal pain, and influenza. In particular tachycardia was reported by 3.7%, (11/298) of the participants and decreased appetite by 8.7%, (26/298). All outcomes were at a very high risk of bias due to selection bias, blinding and attrition bias. There were no serious concerns related to indirectness. Imprecision and inconsistency were not applicable.

**Lisdexamfetamine versus placebo**

- No evidence was identified for all-cause mortality, suicide or suicidal ideation, cardiac mortality, substance misuse, increase in seizures, liver damage, increased tics, tremor, congenital defects and psychotic symptoms for follow up to 12 weeks. No evidence was identified for all-cause mortality, suicide or suicidal ideation cardiac mortality, cardiac events ,substance misuse, increase in seizures, liver damage, increase in tics, tremors, congenital defects sexual dysfunction and psychotic symptoms for follow up over 12 weeks.
- The following outcomes had a higher number of adults reporting adverse events in the lisdexamfetamine group; total participants with adverse events at 10 weeks (3 studies, very low quality), decreased appetite at 10 weeks (4 studies, very low quality), weight loss (1 study, low quality), anorexia at 10 weeks (2 studies, moderate quality) and sleep (insomnia) at 10 weeks (4 studies, low quality). These were all clinically important.
- Differences in cardiac events at 6 weeks (1 study, very low quality), weight change at 4 weeks (1 study, moderate quality), and sexual dysfunction (1 study, very low quality) were not clinically important between the groups.
- In one non-comparative long-term study of lisdexamfetamine at 52 weeks (n= 349) 87.7% (306/349) reported an adverse event. The most common adverse events (reported > 5% of the participants) were anxiety, back pain, dry mouth, headache, irritability, muscle spasm, nasopharyngitis, sinusitis, URTI. In particular, decreased appetite was reported in 14.3% (50/349) of the participants, weight decreased in 6% (21/349) and insomnia in 19.5% (68/349). All outcomes were at a very high risk of bias due to selection bias, blinding and attrition bias. There were no serious concerns related to indirectness. Imprecision and inconsistency were not applicable.

**Dexamphetamine versus placebo**

- No evidence was identified for total number of participants with adverse events, all-cause mortality, suicide or suicidal ideation, cardiac mortality, substance misuse, increase in seizures, liver damage, increased tics, tremor, congenital defects, sexual dysfunction and psychotic symptoms for follow up to 12 weeks. No evidence was identified for total number of participants with adverse events, all-cause mortality, suicide or suicidal ideation, cardiac mortality, substance misuse, abnormal growth, increase in seizures, disturbed sleep, liver damage, increased tics, tremor, congenital defects, sexual dysfunction and psychotic symptoms for follow up over 12 weeks
- A higher number of adults reported sleep (insomnia) at 5 weeks in the dexamphetamine group compared to the placebo group (2 studies, very low quality), this was considered clinically important.

- Differences in weight change at 6 weeks (1 study, high quality) and decreased appetite at 5 weeks (2 studies, very low quality) were not clinically important between the groups.

**Atomoxetine versus placebo**

- No evidence was identified for all-cause mortality, suicide or suicidal ideation, cardiac mortality, substance misuse, increase in seizures, liver damage, increased tics, tremor, congenital defects, and psychotic symptoms for follow up to 12 weeks. No evidence was identified for all-cause mortality, suicide or suicidal ideation, cardiac mortality, cardiac events, substance misuse, increase in seizures, liver damage, increased tics, tremor, congenital defects, and psychotic symptoms for follow up over 12 weeks.
- The following outcomes had a higher number of adults reporting adverse events in the atomoxetine group; total participants with adverse events at 10 and 25 weeks (3 studies, very low quality; 3 studies, low quality), decreased appetite at 10 weeks (4 studies, moderate), weight loss (1 study, low quality), anorexia at 10 weeks (2 studies, moderate quality) and sleep (insomnia) at 10 and 24 weeks (5 studies, moderate quality; 4 studies, low quality). These were all clinically important.
- Differences in palpitations at 10 weeks (1 study, very low quality), blood pressure (1 study, low quality), weight change at 10 and 13 weeks (1 study, very low quality; 1 study, very low quality), weight loss ( 2 studies, moderate quality) and sexual dysfunction at 10 and 24 weeks were not clinically important between the groups.
- In one non-comparative long-term study of atomoxetine at 48 weeks (n= 233), at least one adverse event was reported by 93.6% (n=218) of participants. The most common adverse events (reported > 5% of the participants) were nausea, nasopharyngitis, thirst, headache, somnolence, constipation, vomiting, dysuria. In particular palpitations was reported by 7.3 %, (17/233) of the participants decreased appetite by 16.3%, (38/233), weight decreased by 6.4% (15/233). All outcomes were at a very high risk of bias due to selection bias, blinding and attrition bias. There were no serious concerns related to indirectness. Imprecision and inconsistency were not applicable.
- In one non-comparative long-term study of atomoxetine at 221 weeks (n= 384), the most common adverse events (reported > 5% of the participants) were dry mouth, headache, nausea, constipation, URTI, nasopharyngitis, urinary hesitation, irritability, back pain, influenza, sinusitis, dysmenorrhea, anxiety, fatigue, dizziness, dyspepsia, arthralgia, cough, depression, libido decreased, abnormal dreams, decreased appetite, nasal congestion, pharyngolaryngeal pain, dyspepsia, sleep disorder, diarrhoea, hyperhidrosis, initial insomnia and middle insomnia. In particular insomnia was reported by 19.3 %, (74/384) of the participants and erectile dysfunction by 11.5% (44/384) and decreased appetite by 6%, (23/384). All outcomes were at a very high risk of bias due to selection bias, blinding and attrition bias. There were no serious concerns related to indirectness. Imprecision and inconsistency were not applicable.

**Guanfacine versus placebo**

- No evidence was identified for total number of participants with adverse events, all-cause mortality, suicide or suicidal ideation, cardiac mortality, cardiac events, substance misuse, increase in seizures, disturbed sleep, liver damage, increased tics, tremor, congenital defects, sexual dysfunction and psychotic symptoms for follow up to 12 weeks. No evidence was identified for total number of participants with adverse events, all-cause mortality, suicide or suicidal ideation, cardiac mortality, , cardiac events, substance misuse, abnormal growth ,increase in seizures, disturbed sleep, liver damage, increased tics, tremor, congenital defects, sexual dysfunction and psychotic symptoms for follow up over 12 weeks
- A higher number of adults reported an increase in appetite at 9 weeks (1 study, low quality) in the placebo group compared to the guanfacine group, this was considered clinically important.

**Venlafaxine versus placebo**

- No evidence was identified for total number of participants with adverse events, all-cause mortality, suicide or suicidal ideation, cardiac mortality, cardiac events, substance misuse, increase in seizures, disturbed sleep, liver damage, increased tics, tremor, congenital defects, and psychotic symptoms for follow up to 12 weeks. No evidence was identified for total number of participants with adverse events, all-cause mortality, suicide or suicidal ideation, cardiac mortality, cardiac events, substance misuse, abnormal growth ,increase in seizures, disturbed sleep, liver damage, increased tics, tremor, congenital defects, sexual dysfunction and psychotic symptoms for follow up over 12 weeks
- A higher number of adults reported sexual dysfunction at 6 weeks in the venlafaxine group (1 study, moderate quality) this was not considered clinically important.

**Bupropion SR versus placebo**

- No evidence was identified for all-cause mortality, suicide or suicidal ideation, cardiac mortality, cardiac events, substance misuse, increase in seizures, disturbed sleep, liver damage, increased tics, tremor, congenital defects, sexual dysfunction, and psychotic symptoms for follow up to 12 weeks. No evidence was identified for total number of participants with adverse events, all-cause mortality, suicide or suicidal ideation, cardiac mortality, cardiac events, substance misuse, abnormal growth ,increase in seizures, disturbed sleep, liver damage, increased tics, tremor, congenital defects, sexual dysfunction and psychotic symptoms for follow up over 12 weeks
- A higher number of adults reported adverse events at 7 weeks in the bupropion SR group (1 study, very low quality) this was not considered clinically important.

**Bupropion SR versus methylphenidate**

- No evidence was identified for all-cause mortality, suicide or suicidal ideation, cardiac mortality, cardiac events, substance misuse, increase in seizures, disturbed sleep, liver damage, increased tics, tremor, congenital defects, sexual dysfunction, and psychotic symptoms for follow up to 12 weeks. No evidence was identified for total number of participants with adverse events, all-cause mortality, suicide or suicidal ideation, cardiac mortality, cardiac events, substance misuse, abnormal growth ,increase in seizures, disturbed sleep, liver damage, increased tics, tremor, congenital defects, sexual dysfunction and psychotic symptoms for follow up over 12 weeks.
- A lower number of adults reported adverse events at 7 weeks in the bupropion SR group compared to the methylphenidate group (1 study, very low quality) this was considered clinically important.

**Modafinil versus placebo**

- No evidence was identified for all-cause mortality, cardiac mortality, substance misuse, increase in seizures, liver damage, increased tics, tremor, congenital defects and sexual dysfunction follow up to 12 weeks.
- No evidence was identified for total number of participants with adverse events, all-cause mortality, suicide or suicidal ideation, cardiac mortality, cardiac events, substance misuse, abnormal growth ,increase in seizures, disturbed sleep, liver damage, increased tics, tremor, congenital defects, sexual dysfunction and psychotic symptoms for follow up over 12 weeks
- The following outcomes had a higher number of adults reporting adverse events in the modafinil group; anorexia at 9 weeks (1 study, very low quality), decreased appetite (1 study low quality) and sleep (insomnia) ( 2 studies, very low quality). These were clinically important.

**Modafinil versus dexamphetamine**

- No evidence was identified for all-cause mortality, suicide or suicidal ideation, cardiac mortality, cardiac events, substance misuse, increase in seizures, disturbed sleep, liver damage, increased tics, tremor, congenital defects, sexual dysfunction, and psychotic

symptoms for follow up to 12 weeks. No evidence was identified for total number of participants with adverse events, all-cause mortality, suicide or suicidal ideation, cardiac mortality, cardiac events, substance misuse, abnormal growth ,increase in seizures, disturbed sleep, liver damage, increased tics, tremor, congenital defects, sexual dysfunction and psychotic symptoms for follow up over 12 weeks.

- A lower number of adults reported sleep (insomnia) at 2 weeks in the modafinil group compared to the dexamphetamine group (1 study, low quality), this was considered clinically important.

**Reboxetine versus placebo**

- No evidence was identified for all-cause mortality, suicide or suicidal ideation, cardiac mortality, cardiac events, substance misuse, increase in seizures, disturbed sleep, liver damage, increased tics, tremor, congenital defects, sexual dysfunction, and psychotic symptoms for follow up to 12 weeks. No evidence was identified for total number of participants with adverse events, all-cause mortality, suicide or suicidal ideation, cardiac mortality, cardiac events, substance misuse, abnormal growth ,increase in seizures, disturbed sleep, liver damage, increased tics, tremor, congenital defects, sexual dysfunction and psychotic symptoms for follow up over 12 weeks.
- A lower number of adults reported sleep (insomnia) at 2 weeks in the reboxetine group (1 study, very low quality), this was considered clinically important.

### 1.8.2 Health economic evidence statements

- No relevant economic evaluations were identified.

## 1.9 The committee's discussion of the evidence

### 1.9.1 Interpreting the evidence

#### 1.9.1.1 The outcomes that matter most

The committee considered all the outcomes to be critical for considering the evidence on safety. The outcomes for both short and long term 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. They were all considered equally as they would be critical in determining if someone would start on a drug or the choice of medication.

#### 1.9.1.2 The quality of the evidence

The quality of the evidence ranged from very low to high, with the majority of the evidence very low to moderate quality in all the age ranges.

In children under the age of 5 there was very little evidence (only comparisons between methylphenidate and placebo, methylphenidate and risperidone) and only growth, sleep and cardiovascular (systolic blood pressure and tachycardia) outcomes were reported.

There was a greater breadth of evidence in children and young people 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. The

outcomes not reported or rarely reported were all-cause mortality, suicide ideation, cardiac mortality, substance misuse, liver damage, tremor and congenital defects.

For all age groups, there was a lack of long term RCT data and most studies were 12 weeks or less. Overall the RCTs reported a median follow up time of 8 weeks. In the under 5s age group the median follow up time was 4 weeks (range 1-6), in the 5-18 age group the median follow up was 8 weeks (range 2-208) and in the adult group the median follow up was 8 weeks (range 2-24). No other studies were identified in the under 5 years, in the 5-18 age group 8 non comparative studies were identified and had a median follow up time of 40 weeks ( range 24-220) and in the adults 6 non comparative studies were identified with a median follow time of 52 weeks ( range 52-221).

Studies also used a variety of methods to report adverse effects, which led to concerns about meta-analysing this data. For example some used standard side effect scales whereas others only reported adverse effects that occurred in a minimum percentage of the population.

#### 1.9.1.3 Benefits and harms

The evidence showed that all of the medication for ADHD included in this review appears to be safe at least in the short term with very few serious adverse events reported. However a high number of participants taking the active drug in trials reported experiencing at least one adverse event (with rates of up to 90% in some trials). The reported rates in the placebo arms were also high (with rates up to 70%) and the committee noted this to be a recognised placebo effect finding in trials on ADHD. The majority of the adverse events reported were categorised as minor by the authors and these are summarised earlier in this report under the specific drugs according to frequency of their occurrence. The committee discussed that it is likely there is a connection with the high discontinuation rates reported in the pharmacological efficacy review and the number of the adverse events reported.

The committee agreed that effective strategies for reviewing treatment, monitoring behaviour response and managing adverse events were critical when deciding on treatment options and improving adherence to treatment in people with ADHD. To ensure the consistency of recording and monitoring the committee agreed that is important to use standard symptom and side effect rating scales.

The committee discussed that the key to maintaining a successful treatment plan was the careful initiation of ADHD medication. This includes the starting and titrating medication according to the BNF and the person's tolerance and specific circumstances until dose optimisation (reduced symptoms, positive behaviour change, improvements in education, employment and relationships and tolerable adverse effects) is achieved. The committee discussed the definition of response or non-response and agreed that this had to considered on an individual basis. Response is measured by the individual and how they feel medication has reduced the impact of their ADHD symptoms, this could be quite different depending on the individual's circumstances at that point in time. The committee noted it is important to have an open dialogue with people during titration as some people develop doubts or become disillusioned about the efficacy of the medication simply because they do not understand or misunderstand the titration process. When they start on the low dose, they feel disappointed that it doesn't seem to work, and then begin to doubt that any medication will help. Explaining this can help adherence,

The committee updated the recommendations on initiation and titration reminding clinicians that they should be aware of the pharmacokinetic profiles of ADHD medication as different preparations can vary in their profiles and this is important when considering which drug or formulations of drugs to prescribe.

The committee noted the importance of discussing treatment choices with women trying to conceive or during pregnancy and whilst breastfeeding.

The committee had hoped evidence would be identified that would augment their experience on the management of drugs in people with ADHD and co-existing co-morbidities. Overall there was very little evidence on any subgroups although there was a small amount of evidence in children with tic disorder that showed an increase in tics in groups taking atomoxetine or clonidine compared to placebo, and some very low quality evidence to suggest that tics were more frequent in clonidine compared to methylphenidate. There was also some low quality evidence to suggest that sleep related adverse events in children with comorbid autism did not differ from the ADHD population. The most common deviation from the standard prescribing pathway currently is to avoid stimulant medication in groups with tic disorders, the committee noted that if anything the evidence supported avoiding non-stimulant ADHD medication but also that the very low quality of the evidence meant that a recommendation along these lines would not be justified. Five studies reported psychotic episodes and these were rare events. The committee noted this lack of evidence was across the ADHD evidence reviews and have made research recommendations to address this gap in the literature (see research recommendations in evidence report C on pharmacological efficacy and sequencing). As a result the committee made consensus recommendations on the initiation and dose titration of medication for people with co-existing conditions. The committee agreed there was not enough evidence and in their experience reason to deviate from the usual pathway for drug choice (see evidence report C on pharmacological efficacy and sequencing for the recommendations on which drug to use) but there should be slower titration and more careful monitoring that included recording of adverse effects and regular weekly contact. The exception to this was to stop ADHD medication in people experiencing a psychotic episode. The committee also recommended that if a person taking medication develops tics or seizures the benefits of the medication should be reassessed and changes to the medication or cessation in the case of seizures should be considered. The committee recommended caution in prescribing simulants to people who are at risk of drug misuse (see evidence report C on pharmacological efficacy and sequencing) to support this they recommended that healthcare professionals and parents should be aware of the potential for stimulant misuse and diversion and to monitor for this (for example, worsening behaviour with apparent medication adherence). The managing treatment review (for more information, see evidence report H on managing treatment) also highlighted that parents may not initiate treatment if they had concerns about treatment misuse, hence the importance of discussing these concerns and exploring all possible treatment options, especially when stimulants might not be appropriate.

The committee noted the importance of a baseline assessment before commencing any treatment and listed key areas to evaluate. Assessment is fundamental and the discussion of considerations with the person with ADHD is also covered in evidence report H on managing treatment. The committee had hoped that the review on adverse events would be able to support them in determining what it is important to assess clinically before starting ADHD medication. In particular there was uncertainty around the importance of cardiac tests and which ones to do. The evidence was limited in answering this as cardiac disease, cardiac conditions, or any ECG abnormalities were exclusion criteria for most of the studies. Serious cardiovascular outcomes such as tachycardia were rarely reported and reported changes in blood pressure and pulse rate were small. To support the committee a consultant cardiologist was co-opted to the guideline to provide expert advice on what tests should be done and when to refer for a cardiology opinion before starting treatment.

The expert advice concurred with the limited evidence base that serious cardiovascular events are uncommon in people prescribed methylphenidate, atomoxetine or guanfacine for the treatment of ADHD. The committee considered the additional time and resources needed to perform and report on a baseline ECG as well as the likely harm or benefit of such routine testing. Expert cardiological advice emphasised the importance of a normal cardiovascular examination and history prior to commencing medication and advised that a routine ECG before commencing stimulants, atomoxetine or guanfacine, if history and examination were normal, was not needed. The committee agreed with this view. However, the committee noted it was common for people with ADHD to be diagnosed with coexisting condition(s) and

polypharmacy is not unusual. Taking this into account and based on the expert advice the committee agreed it was important to make a consensus recommendation that a baseline ECG is required before commencing medication in particular or coexisting conditions where, for example, tricyclics and monoamine oxidase inhibitors may be used or any other medication that may affect the QT interval.

The committee agreed that it was important to monitor heart rate and blood pressure every 6 months and if there were important clinical changes the dose should be reduced and referral to a cardiologist may be necessary. The committee noted that checking BP and heart rates may be difficult in some people with severe ADHD symptoms and Intellectual disability due to their severe hyperactivity and inability to tolerate the process. However in the committee's experience it is rarely impossible and the individual circumstances of the person should be taken into account when deciding on treatment.

The committee noted that clinically important differences in sleep disturbance, decreased appetite and weight changes were reported compared to placebo at both under and over 12 weeks for all age groups. The evidence comparing drugs was limited and of mostly very low to low quality and the committee found it difficult based on the evidence to conclude that any one drug appears to have a higher rate of adverse events than another.

There was some moderate quality short term evidence that showed increased insomnia and greater weight loss in children taking methylphenidate compared to atomoxetine and this was supported by the committee's experience. The evidence reported that children taking guanfacine had lower rates of appetite loss compared to atomoxetine, although the evidence comparing guanfacine to placebo did not show a clinically important difference in appetite loss. However, this evidence was of very low quality and the impact on growth rates remained unclear.

#### 1.9.1.4 Long term adverse events

The committee discussed the absence of good long term data reporting adverse events on the drugs commonly used to treat ADHD symptoms in both children and adults. They agreed it was difficult to confidently comment on the impact of taking medication for ADHD for a long period of time. However they did note that in the identified evidence weight decreases were reported at up 9 months in children when taking stimulants. One study comparing methylphenidate and atomoxetine reported lower weight and height at 2 years in the children taking methylphenidate. These results are mirrored in the studies evaluating the impact of ADHD medication on adults.

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.

Sleep difficulties and appetite loss are the adverse events that are commonly reported in both the long and short term and in the committee's experience most troublesome to people taking medication.

Drawing on their experience the committee discussed how untreated ADHD could have long lasting negative impacts on a person's life. 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.

The committee were clear that anyone prescribed stimulants should have regular follow up and that includes the close monitoring of weight and height and updated the recommendations on monitoring height and weight advising at least 6 monthly height checks, 3 monthly weight checks in children 10 years and under, at 3 and 6 months in children over 10 years and young people after starting treatment and every 6 months thereafter, or more often if concerns arise and also 6 monthly checks in adults. This is an important when weighing up the benefits of a drug holiday when it may be an opportunity for a child to catch up on growth rates (for more information, see evidence report I on withdrawal and drug holidays).

The committee noted that dietary advice in the case of weight loss should be obtained from an appropriate healthcare professional, ideally a dietitian if available. As evidence was not assessed for the impact of the specific provider of dietary advice the committee was unable to make recommendations on exactly who advice should be obtained from.

The committee recommended that changes in sleep pattern should be recorded and medication adjusted accordingly. They noted it was important to refer back to sleep pattern information gained from patient prior to initiation medication to ensure reported poor sleep is related to medication and not patient reflecting on a longer term problem.

There was some evidence that sexual dysfunction, in particular erectile dysfunction, was experienced by people on atomoxetine and the committee recommended that this should be monitored for.

The committee noted that aspects of baseline assessment (for example checking blood pressure or heart rate) may be challenging in people with severe ADHD and intellectual disability or other co-existing conditions affecting compliance. However baseline assessments are still important in these situations and all necessary measures (for example longer appointments) should be considered to achieve them.

In summary the evidence on adverse events is lacking; the quality of the evidence is mostly 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 many of their recommendations on their experience of the benefits and harms of treatment and through consensus.

### 1.9.2 Cost effectiveness and resource use

No economic evidence has been identified for this question.

Most of the recommendations made around safety are consensus based from the experience of the committee. The adverse events from a treatment can be serious and have an impact on quality of life, not just of the person with ADHD but also of their families and carers. Treating adverse effects can also accrue resource use, and so strategies to minimise these are likely to be cost effective.

The previous recommendations have been updated, however still include the main components of what a baseline assessment should involve. Some specific changes to note; some changes have been made to this such as a review to confirm whether the child (or adult) continues to meet the criteria for ADHD. This would be done as part of the assessment by the individual who is already undertaking the pre-drug assessment, and would not involve any additional staff. Some additional detail has been added such as when to refer for a further opinion. This may lead to more referrals, however such referrals are rare.

Follow up and monitoring frequency was also based on committee consensus and they agreed the safety profile of the drugs require initial close monitoring, particularly in younger

children. Most of the drugs used (e.g. stimulants) have been used for a long time and the (short term) safety profiles are well known. The potential impact on height, weight and cardiovascular effects require careful monitoring for drug titration. The frequencies referred to in the recommendations may not be current practice for the whole country; for example measuring weight every 3 months in children 10 years and under. Practice is variable and it might currently be every 6 months in some areas. It is also variable how this might be undertaken, as weight measurement could be undertaken by GP's under shared care arrangements, and some community paediatric or CAMHS services have a clinic nurse that can chase up weight information from the GP. Where a service does not have a nurse as part of the service organisation, then the consultant may have to request weight measurements to ensure appropriate prescribing, so more frequent monitoring may place a burden on their time. Other service models discussed by the committee include parents/carers/schools monitoring weight and liaising with nurses in the community paediatric or CAMHS services. Therefore although increasing the frequency of weight measurement to 3 months may be a change in practice in some areas, there are service models where this happens and could be reflected in places where this is not current practice. Additionally the population between 5 and 10 years that are on medication is likely to be small, therefore the committee did not consider this was likely to have a significant resource impact.

### 1.9.3 Other considerations

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.

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.

The committee discussed the importance of people with ADHD having regular reminders abut monitoring their general health, such as dental check-ups. When people come for checks this would be a good opportunity to ask about this.

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# Appendices

# Appendix A: Review protocols

**Table 41: Review protocol: Adverse events**

| Field | Content |
|---|---|
| Review question | What are the adverse events issues associated with pharmacological treatment for people 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 adverse events that may be associated with pharmacological treatments for ADHD so that clinicians can use this information to (a) inform the appropriate choice of treatment in people with contra-indications to treatment and (b) to inform a recommendation on what potential adverse events clinicians should consider monitoring for in people receiving treatment for ADHD |
| 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>Dexamphetamine<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 |
| Eligibility criteria – comparator(s) / control or | Placebo<br>Each other |

| | |
|---|---|
| reference (gold) standard | |
| Outcomes and prioritisation | **Critical**<br>• Total number of participants with an adverse event<br>• All-cause mortality<br>• Suicide or suicidal ideation<br>• Cardiac mortality<br>• Cardiac events including tachycardia/palpitations (defined by >/120bpm), and systolic and diastolic blood pressure changes<br>• Substance abuse<br>• Abnormal growth ( height and weight)<br>• Appetite changes<br>• Increase in seizures in people with epilepsy<br>• Psychotic symptoms<br>• Sleep including insomnia<br>• Liver damage (defined by deranged LFTs)<br>• Increased tics<br>• Tremors<br>• Congenital defects amongst patients who are pregnant<br>• Sexual dysfunction<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>This review will be looking at specified adverse events and will not include data on the overall number of serious adverse events; these are included in the efficacy review.<br>This review will include a narrative summary of the common adverse events reported in the studies for information. Adverse events have been categorised as very common (≥ 1 in 10), common (1 in 100 to 1 in 10), uncommon (1 in 1000 to 1 in 100), rare (1 in 10,000 to 1 in 1000) and very rare (< 1 in 10,000). |
| Eligibility criteria – study design | We will extract data according to the following hierarchy:<br><br>1. Comparative data<br>a. RCTs included in other pharmacological reviews or excluded from other pharmacological reviews for having no relevant outcomes<br>b. RCTs excluded from other reviews for excluding participants based on previous response/tolerance of medication only for long term outcomes (≥3 months)<br>c. Open label RCTs and non-randomised studies only for long term outcomes (≥3 months)<br>2. Non-comparative data for long term outcomes (≥3 months)<br><br>The purpose of including non-randomised studies is to supplement the evidence from randomised studies, particularly for outcomes that require long observation periods with large numbers of participants (which are challenges in randomised study design). |
| 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. |

| | |
|---|---|
| | Crossover trials will be excluded if there is an inappropriate washout period (specific to pharmacokinetics of drug involved) |
| 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>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/ces [X] 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/<br>[Please document any deviations/alternative approach when GRADE isn't used or if a modified GRADE approach has been used for non-intervention or non-comparative studies.] |
| 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 | For details please see sections 6.4 and 9.1 of Developing NICE |

| | |
|---|---|
| evidence | 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.<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 and the methods section of this guideline. |
| 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 42: 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 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).[479]<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. |

| Review question | All questions – health economic evidence |
|---|---|
| | 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).<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

*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 indexed and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

**Table 43: Database date parameters for search**

| Database | Dates searched | Search filter used |
|---|---|---|
| Medline (Ovid) | 01 October 2007 – 28 April 2017 | Exclusions<br>Observational<br>Randomised controlled trials<br>Systematic review studies |
| Embase (Ovid) | 01 October 2007 – 28 April 2017 | Exclusions<br>Observational<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>Observational<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. | Epidemiologic studies/ |
| 63. | exp Case control studies/ |
| 64. | exp Cohort studies/ |
| 65. | Cross-sectional studies/ |
| 66. | case control.ti,ab. |
| 67. | (cohort adj (study or studies or analys*)).ti,ab. |
| 68. | ((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab. |
| 69. | ((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab. |
| 70. | or/62-69 |
| 71. | 38 and (50 or 61 or 70) |

**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. | Clinical study/ |
| 60. | exp Case control study/ |
| 61. | Family study/ |
| 62. | Longitudinal study/ |
| 63. | Retrospective study/ |

| | |
|---|---|
| 64. | Prospective study/ |
| 65. | Cross-sectional study/ |
| 66. | Cohort analysis/ |
| 67. | Follow-up/ |
| 68. | cohort*.ti,ab. |
| 69. | 45 and 46 |
| 70. | case control.ti,ab. |
| 71. | (cohort adj (study or studies or analys*)).ti,ab. |
| 72. | ((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab. |
| 73. | ((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab. |
| 74. | or/59-66, 47-73 |
| 75. | 37 and (47 or 58 or 74) |

**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 #18 |

**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. | (su.exact.explode("longitudinal studies") or su.exact.explode("followup studies") OR SU.EXACT("Cohort Analysis") or ti,ab(case-control*) or ti,ab(cohort near/1 (study or studies or analys*)) or ti,ab((follow-up or observational or uncontrolled or non-randomi?ed or nonrandomi?ed or epidemiologic*) near/1 (study or studies)) or ti,ab((longitudinal or retrospective or prospective or cross-section) and (study or studies or review or analys* or cohort*))) |
| 5. | 1 AND (2 OR 3 OR 4) |
| 6. | Limit to English |
| 7. | 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 44: Database date parameters and filters used**

| Database | Dates searched | Search filter used |
|---|---|---|
| Medline | 2014 – 28 April 2017 | Exclusions<br>Health economics<br>Economic modelling |
| Embase | 2014 – 28 April 2017 | Exclusions<br>Health economics<br>Economic modelling |
| Centre for Research and Dissemination (CRD) | HTA - 2008 – 28 April 2017<br>NHSEED - 2008 to March 2015 | None |

**Medline (Ovid) search terms**

| | |
|---|---|
| 1. | "attention deficit and disruptive behavior disorders"/ or attention deficit disorder with hyperactivity/ |
| 2. | ((attenti* or disrupt*) adj3 (adolescent* or adult* or behav* or child* or class or classes or classroom* or condition* or difficult* or disorder* or learn* or people or person* or poor or problem* or process* or youngster*)).ti. |
| 3. | ((attenti* or disrupt*) adj3 disorder*).ab. |
| 4. | (adhd or addh or ad hd or ad??hd).ti,ab. |
| 5. | (attenti* adj3 deficit*).ti,ab. |

| | |
|---|---|
| 6. | (((hyperkin* or hyper kin*) adj1 (syndrome* or disorder*)) or hkd).ti,ab. |
| 7. | (minimal brain adj2 (dysfunct* or disorder*)).ti,ab. |
| 8. | or/1-7 |
| 9. | limit 8 to English language |
| 10. | letter/ |
| 11. | editorial/ |
| 12. | news/ |
| 13. | exp historical article/ |
| 14. | Anecdotes as Topic/ |
| 15. | comment/ |
| 16. | case report/ |
| 17. | (letter or comment*).ti. |
| 18. | or/10-17 |
| 19. | randomized controlled trial/ or random*.ti,ab. |
| 20. | 18 not 19 |
| 21. | animals/ not humans/ |
| 22. | Animals, Laboratory/ |
| 23. | exp animal experiment/ |
| 24. | exp animal model/ |
| 25. | exp Rodentia/ |
| 26. | (rat or rats or mouse or mice).ti. |
| 27. | or/20-26 |
| 28. | 9 not 27 |
| 29. | Economics/ |
| 30. | Value of life/ |
| 31. | exp "Costs and Cost Analysis"/ |
| 32. | exp Economics, Hospital/ |
| 33. | exp Economics, Medical/ |
| 34. | Economics, Nursing/ |
| 35. | Economics, Pharmaceutical/ |
| 36. | exp "Fees and Charges"/ |
| 37. | exp Budgets/ |
| 38. | budget*.ti,ab. |
| 39. | cost*.ti. |
| 40. | (economic* or pharmaco?economic*).ti. |
| 41. | (price* or pricing*).ti,ab. |
| 42. | (cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab. |
| 43. | (financ* or fee or fees).ti,ab. |
| 44. | (value adj2 (money or monetary)).ti,ab. |
| 45. | or/29-44 |
| 46. | exp models, economic/ |
| 47. | *Models, Theoretical/ |
| 48. | *Models, Organizational/ |
| 49. | markov chains/ |

| | |
|---|---|
| 50. | monte carlo method/ |
| 51. | exp Decision Theory/ |
| 52. | (markov* or monte carlo).ti,ab. |
| 53. | econom* model*.ti,ab. |
| 54. | (decision* adj2 (tree* or analy* or model*)).ti,ab. |
| 55. | or/46-54 |
| 56. | 28 and (45 or 55) |

**Embase (Ovid) search terms**

| | |
|---|---|
| 1. | attention deficit disorder/ |
| 2. | ((attenti* or disrupt*) adj3 (adolescent* or adult* or behav* or child* or class or classes or classroom* or condition* or difficult* or disorder* or learn* or people or person* or poor or problem* or process* or youngster*)).ti. |
| 3. | ((attenti* or disrupt*) adj3 disorder*).ab. |
| 4. | (adhd or addh or ad hd or ad??hd).ti,ab. |
| 5. | (attenti* adj3 deficit*).ti,ab. |
| 6. | (((hyperkin* or hyper kin*) adj1 (syndrome* or disorder*)) or hkd).ti,ab. |
| 7. | (minimal brain adj2 (dysfunct* or disorder*)).ti,ab. |
| 8. | or/1-7 |
| 9. | limit 8 to English language |
| 10. | letter.pt. or letter/ |
| 11. | note.pt. |
| 12. | editorial.pt. |
| 13. | case report/ or case study/ |
| 14. | (letter or comment*).ti. |
| 15. | or/10-14 |
| 16. | randomized controlled trial/ or random*.ti,ab. |
| 17. | 15 not 16 |
| 18. | animal/ not human/ |
| 19. | nonhuman/ |
| 20. | exp Animal Experiment/ |
| 21. | exp Experimental Animal/ |
| 22. | animal model/ |
| 23. | exp Rodent/ |
| 24. | (rat or rats or mouse or mice).ti. |
| 25. | or/17-24 |
| 26. | 9 not 25 |
| 27. | statistical model/ |
| 28. | exp economic aspect/ |
| 29. | 27 and 28 |
| 30. | *theoretical model/ |
| 31. | *nonbiological model/ |
| 32. | stochastic model/ |
| 33. | decision theory/ |

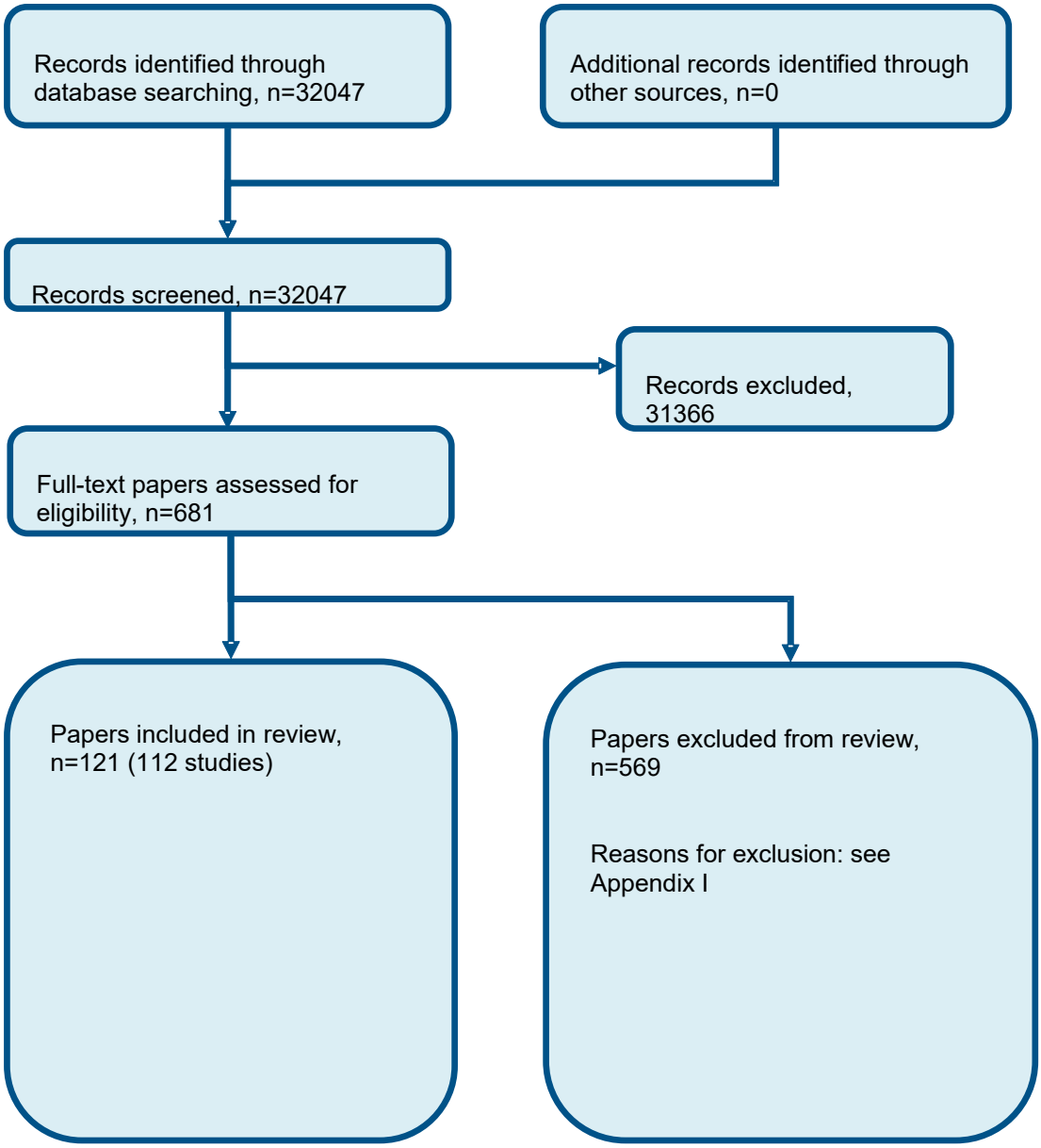
| | |
|---|---|
| 34. | decision tree/ |
| 35. | monte carlo method/ |
| 36. | (markov* or monte carlo).ti,ab. |
| 37. | econom* model*.ti,ab. |
| 38. | (decision* adj2 (tree* or analy* or model*)).ti,ab. |
| 39. | or/29-38 |
| 40. | *health economics/ |
| 41. | exp *economic evaluation/ |
| 42. | exp *health care cost/ |
| 43. | exp *fee/ |
| 44. | budget/ |
| 45. | funding/ |
| 46. | budget*.ti,ab. |
| 47. | cost*.ti. |
| 48. | (economic* or pharmaco?economic*).ti. |
| 49. | (price* or pricing*).ti,ab. |
| 50. | (cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab. |
| 51. | (financ* or fee or fees).ti,ab. |
| 52. | (value adj2 (money or monetary)).ti,ab. |
| 53. | or/40-52 |
| 54. | 26 and (39 or 53) |

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

| | |
|---|---|
| #1. | MeSH DESCRIPTOR Attention Deficit and Disruptive Behavior Disorders |
| #2. | MeSH DESCRIPTOR Attention Deficit Disorder with Hyperactivity |
| #3. | (((attenti* or disrupt*) adj3 (adolescent* or adult* or behav* or child* or class or classes or classroom* or condition* or difficult* or disorder* or learn* or people or person* or poor or problem* or process* or youngster*))):TI |
| #4. | (((attenti* or disrupt*) adj3 disorder*)) |
| #5. | ((adhd or addh or ad hd or ad??hd)) |
| #6. | ((attenti* adj3 deficit*)) |
| #7. | ((((hyperkin* or hyper kin*) adj1 (syndrome* or disorder*)) or hkd)) |
| #8. | ((minimal brain adj2 (dysfunct* or disorder*))) |
| #9. | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 |
| #10. | (#9) IN NHSEED, HTA |

# Appendix C: Clinical evidence selection

**Figure 1: Flow chart of clinical study selection for the review of adverse events of pharmacological treatment for people with ADHD?**



# Appendix D: Clinical evidence tables

| Study (subsidiary papers) | Adler 2013[8] (Adler 2013[7]) |
|---|---|
| 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 |
| 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 |

| Study (subsidiary papers) | Adler 2013[8] (Adler 2013[7]) |
|---|---|
| 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
- Actual outcome: ADHD-RS-IV with adult prompts inattention subscale LS mean change scores (adjusted for baseline) at 10 weeks; Group 1: mean -21.4 (SD 12.34); n=79,
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Previous treatments not stated; Group 1 Number missing: 18, Reason: adverse events, protocol violation, withdrawn consent, lost to follow up, other reasons (3 participants). 1 not stated; Group 2 Number missing: 28, Reason: adverse events, protocol violation, withdrawn consent, lost to follow up, lack of efficacy, other reasons (3). 1 not stated
- Actual outcome: ADHD-RS-IV with adult prompts hyperactivity/impulsivity subscale LS mean change scores (adjusted for baseline) at 10 weeks;
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Previous treatments not stated; Group 1 Number missing: 18, Reason: adverse events, protocol violation, withdrawn consent, lost to follow up, other reasons (3 participants). 1 not stated; Group 2 Number missing: 28, Reason:

| Study (subsidiary papers) | Adler 2013[8] (Adler 2013[7]) |
|---|---|
| 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 | Adler 2008[18] |
|---|---|
| Study type | Open label non comparative |
| Number of studies (number of participants) | 1 (n=384) |
| Countries and setting | Conducted in USA; Setting: Multicentre study conducted at 31 centres in the USA |
| Line of therapy | Unclear |
| Duration of study | Intervention time: 4 years |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis: DMS-IV |
| Stratum | Adults |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Meet DSM-IV criteria at interview (CAARS-Inv:SV)) with moderate disability, confirmed by informant. |
| Exclusion criteria | 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 |

| Study | Adler 2008[18] |
|---|---|
| | within the year preceding visit 1 (3) current diagnosis of alcohol, drug misuse, or prescription medication misuse. |
| Recruitment/selection of patients | From clinics and advertisements |
| Age, gender and ethnicity | Age - Mean (SD): 42.4 . Gender (M): 64%. Ethnicity: White 92.2% |
| 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) 46.9% had prior drug exposure 7. Severity: Moderate (moderate and above). |
| Indirectness of population | No indirectness |
| Interventions | Intervention 1: CNS stimulants - Atomoxetine. Atomoxetine, flexible dose 30-160mg twice a day. Duration 4 years .<br>2. Method of titration: Titrated to optimum dose |
| Funding | Study funded by industry (Eli Lilly and Company) |
| RESULTS (NUMBERS ANALYSED) n=384<br>Insomnia 74/384<br>Erectile dysfunction 44/384<br>High risk of bias due to selection and attrition bias | |
| Protocol outcomes not reported by the study | 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), and systolic and diastolic blood pressure changes, Substance abuse, Abnormal growth ( height and weight), Appetite changes, Increase in seizures in people with epilepsy, Liver damage (defined by deranged LFTs),Increased tics ,Tremors, Congenital defects amongst patients who are pregnant, Psychotic symptoms. |

| Study (subsidiary papers) | Adler 2008[10] (Mattingly 2013[440], Adler 2009[9], Kollins 2011[389]) |
|---|---|
| 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 |
| Line of therapy | Unclear |

| Study (subsidiary papers) | Adler 2008[10] (Mattingly 2013[440], Adler 2009[9], Kollins 2011[389]) |
|---|---|
| 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 pulse 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 period, patients were assigned to 30mg/day for 1 week with a forced dose escalation to 50mg/day from |

| Study (subsidiary papers) | Adler 2008[10] (Mattingly 2013[440], Adler 2009[9], Kollins 2011[389]) |
|---|---|
| | 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<br>- 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 | |

| Study (subsidiary papers) | Adler 2008[10] (Mattingly 2013[440], Adler 2009[9], Kollins 2011[389]) |
|---|---|

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
- 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:

| Study (subsidiary papers) | Adler 2008[10] (Mattingly 2013[440], Adler 2009[9], Kollins 2011[389]) |
|---|---|
| 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[11] |
|---|---|
| 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 |

| Study | Adler 2009[11] |
|---|---|
| | than a 30% decrease by visit 2 (4) CGI-O-S score of 4 or greater (5) dysthymia comorbidity was also 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<br><br>Protocol outcome 1: Quality of life at <3- or >6-months | |

| Study | Adler 2009[11] |
|---|---|
| - 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; 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 |

| Study | Adler 2009[11] |
|---|---|
| | estimated (2) selection bias; only participants that didn't respond to 2 weeks of placebo treatment were included in the analysis and (3) outcome reporting bias; number of participants included in the outcome was not specified.<br>CGI-I-S: high risk of bias due to attrition bias |

| Study (subsidiary papers) | NCT00190736 trial: Adler 2009[15] (Brown 2011[126]) |
|---|---|
| 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 nonstimulants 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 |

| Study (subsidiary papers) | NCT00190736 trial: Adler 2009[15] (Brown 2011[126]) |
|---|---|
| | 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. 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,

| Study (subsidiary papers) | NCT00190736 trial: Adler 2009[15] (Brown 2011[126]) |
|---|---|
| | 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: Conners Adult ADHD Rating scale -Investigator rated (CAARS-Inv:SV)Evening total - change score at 6 months; Group 1: mean -7.3 (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 |

| Study (subsidiary papers) | NCT00190736 trial: Adler 2009[15] (Brown 2011[126]) |
|---|---|
| | <3- or >6-months; Emotional dysregulation at <3- or >6-months |

| Study | CR011560 trial: Adler 2009[20] |
|---|---|
| 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 |

| Study | CR011560 trial: Adler 2009[20] |
|---|---|
| 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 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

| Study | CR011560 trial: Adler 2009[20] |
|---|---|
| unknown reasons, 4 lost to follow up<br>- 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;<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: comparable for age, sex, ADHD subscale, mean body mass index and mean 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[24] |
|---|---|
| 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); high risk for tics |
| 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- |

| Study | Allen 2005[24] |
|---|---|
| | 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. |
| 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 1mg/kg/day, at visits 4 and 5 this could be titrated upward or downward or maintained within the range of 0.5 to 1.5mg/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

YGTSS tic severity -5.5 (6.9); -3(8.3)
Insomnia 2;3
Body weight -0.9kg(1.9); +1.6kg(2.3). However incidence of weight decrease reported: 2;0
BPM >110 10;2

| Study | Allen 2005[24] |
|---|---|
| Low risk of bias | |
| 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 | 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 | Met the DSM-IV-TR diagnostic criteria for ADHD. All patients were newly diagnosed and had a 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 | History or current diagnosis of pervasive developmental disorders, schizophrenia or other psychiatric comorbidity that required pharmacotherapy. Any evidence of suicide risk and mental retardation. Clinically significant chronic medical condition (such as seizures, dependence on drugs, hyper/hypo-tension). 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: 6-15 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 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. ADHD-RS-IV scores at baseline approx. 40 (parent) and35 (teacher)). |

| Study | Amiri 2008[35] |
|---|---|
| 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). modafinil was titrated up during the trial according to the following schedule: week 1 100 mg/day, week 2: 200 mg/day (capsule of modafinil in the morning and capsule of placebo in the afternoon) and week 3: 300 mg/day for children >30 kg (capsule of modafinil in the morning, capsule of placebo at midday and capsule of placebo 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 (200-300mg/day (once daily), depending on weight (200mg/day for <30kg and 300mg/day for >30kg)).<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 (20-30mg/day depending on weight ( 20mg/day for <30 kg and 30mg/day for >30kg)). |
| 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>Low risk of bias<br>Weight loss 3/30 (Modafinil) ; 7/30 (MPH) | |
| 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 | Amiri 2012[34] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |

| Study | Amiri 2012[34] |
|---|---|
| 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 |
| 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). |

| Study | Amiri 2012[34] |
|---|---|
| | (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

Protocol outcome 1: ADHD symptoms at <3- or >6-months
- Actual outcome for Adult: Conners Adult ADHD Rating Scale(Self-report)-ADHD symptoms total at 6 weeks; Group 1: mean 28.8  (SD 12.21); n=20, Group 2: mean 13.55  (SD 12.83); n=21;  Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adult: Conners Adult ADHD Rating Scale(Self-report)-Inattentive symptoms at 6 weeks; Group 1: mean 25.35  (SD 1.95); n=20, Group 2: mean 14.65  (SD 12.72); n=21;  Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adult: Conners Adult ADHD Rating Scale(Self-report)-Hyperactive/impulsive symptoms at 6 weeks; Group 1: mean 26.6  (SD 10.78); n=20, Group 2: mean 11.35  (SD 11.87); n=21;  Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adult: Conners Adult ADHD Rating Scale(Self-report)-ADHD index at 6 weeks; Group 1: mean 25.35  (SD 12.47); n=20, Group 2: mean 12.05  (SD 6.01); n=21;  CAARS 0-84 Top=High is poor outcome;  Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adult: Treatment response (defined as 25% drop in ADHD index of the CAARS) at 6 weeks; Group 1: 15/22, Group 2: 4/22;  Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Serious adverse events at All
- Actual outcome for Adult: Serious adverse events at 6 weeks; Group 1: 0/22, Group 2: 0/22;  Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months
- Actual outcome for Adult: Drop out due to adverse events at 6 weeks; Group 1: 1/22, Group 2: 0/22;  Risk of bias: High; Indirectness of outcome: No indirectness

| | |
|---|---|
| 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 | Anon 2002[635] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |

| Study | Anon 2002[635] |
|---|---|
| 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). |
| 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 adverse effects. An 8 week maintenance dosage period followed, during the first 6 weeks dosage changes were permitted in cases of adverse effects.. Duration 16 weeks. Concurrent medication/care: Not specified Further details: 1. Dose: Mixed (Mean 25.7mg/day). 2. Method of titration: Titrated to optimum dose |

| Study | Anon 2002[635] |
|---|---|
| | (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 adverse effects. An 8 week maintenance dosage period followed, during the first 6 weeks dosage changes were permitted in cases of adverse 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 adverse effects. An 8 week maintenance dosage period followed, during the first 6 weeks dosage changes were permitted in cases of adverse 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<br><br>Tics at 16 weeks; high risk due to attrition bias | |
| 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 | Arabgol 2015[41] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |

| Study | Arabgol 2015[41] |
|---|---|
| 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 disease, mental retardation and any psychiatric co-morbid 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 scores parent ADHD-RS approx. 28). |
| Extra comments | ADHD |
| Indirectness of population | No indirectness |
| Interventions | (n=18) Intervention 1: CNS stimulants - Methylphenidate (including modified-release preparations) . Dose started at 2.5mg per day and increased every week based on therapeutic response and the patient's tolerance. The optimal dose of methylphenidate was 20mg/day in two divided doses. The dose was chosen according to prior studies. The mean dose was 12.83 +/- 0.56mg/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 2.5mg/day and gradually increased based on the therapeutic response and patients tolerance).<br><br>(n=20) Intervention 2: Antipsychotics - Risperidone. Starting dose of 0.25mg per day in one dose, increased |

| Study | Arabgol 2015[41] |
|---|---|
| | 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 +/- 0.48mg/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 0.25mg/day and gradually increased based on therapeutic response and the patient's tolerance). |
| Funding | Academic or government funding (Behavioural Sciences Research Center (Shahid Beheshti Medical University)) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS) versus RISPERIDONE<br><br>Sedation 0;1<br>Anorexia 1;0<br>Low risk of bias | |
| 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 | Arnold 2006[47] |
|---|---|
| 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) |

| Study | Arnold 2006[47] |
|---|---|
| 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 |
| 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>High risk of bias due to attrition bias<br>Insomnia: 12/16; 7/16<br>Tics: 6/16: 5/16<br>Tremor:1/16;2/16 | |
| Protocol outcomes not reported by the | Quality of life at <3- or >6-months; CGI at <3- or >6-months; Serious adverse events at All; Dropped out due |

| Study | Arnold 2006[47] |
|---|---|
| study | 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 | Arnold 2014[52] |
|---|---|
| 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 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: |

| Study | Arnold 2014[52] |
|---|---|
| | 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 stated / Unclear |
| Funding | Study funded by industry (Cephalon Inc (now owned by Teva Pharmaceuticals Industries Ltd)) |

| Study | Arnold 2014[52] |
|---|---|
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MODAFANIL 255MG/DAY versus PLACEBO<br><br>Protocol outcome 1: Quality of life at <3- or >6-months<br>- 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<br><br>Protocol outcome 2: ADHD symptoms at <3- or >6-months<br>- 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<br><br>Protocol outcome 3: Behavioural outcomes at <3- or >6-months<br>- 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<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 < 3 months (9 weeks); Group 1: 19/73, Group 2: 6/74; Risk of bias: High; Indirectness of outcome: No indirectness<br><br>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MODAFANIL 340MG/DAY versus PLACEBO<br><br>Protocol outcome 1: Quality of life at <3- or >6-months<br>- 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<br><br>Protocol outcome 2: ADHD symptoms at <3- or >6-months<br>- 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<br><br>Protocol outcome 3: Behavioural outcomes at <3- or >6-months<br>- 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<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 < 3 months (9 weeks); Group 1: 19/73, Group 2: 6/74; Risk of bias: High; Indirectness of outcome: No indirectness | |

| Study | Arnold 2014[52] |
|---|---|
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MODAFANIL 425MG/DAY versus PLACEBO<br><br>Protocol outcome 1: Quality of life at <3- or >6-months<br>- 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<br><br>Protocol outcome 2: ADHD symptoms at <3- or >6-months<br>- 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<br><br>Protocol outcome 3: Behavioural outcomes at <3- or >6-months<br>- 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<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 < 3 months (9 weeks); Group 1: 22/74, Group 2: 6/74; Risk of bias: High; Indirectness of outcome: No indirectness<br><br>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MODAFANIL 510MG/DAY versus PLACEBO<br><br>Protocol outcome 1: Quality of life at <3- or >6-months<br>- 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<br><br>Protocol outcome 2: ADHD symptoms at <3- or >6-months<br>- 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<br><br>Protocol outcome 3: Behavioural outcomes at <3- or >6-months<br>- 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<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 < 3 months (9 weeks); Group 1: 9/44, Group 2: 6/74; Risk of bias: High; Indirectness of outcome: No indirectness | |

| Study | Arnold 2014[52] |
|---|---|
| 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[66] |
|---|---|
| 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); high risk (Major Depression) |
| 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 |
| 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 |

| Study | Bangs 2007[66] |
|---|---|
| | 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 9 weeks<br>decreased appetite 9;0<br>Weight decreased  6;1<br>Weight increased 1;4<br>Irritability 4;1<br><br>Open label phase (9 months – no comparison) (n=120)<br>Weight decreased 14<br>Insomnia 6<br>Weight increased 6<br>Irritability 8<br><br>High risk of bias | |
| 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 | Barrickman 1995[71] |
|---|---|
| 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=18) 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:<br><br>(n=18) 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: |

| Study | Barrickman 1995[71] |
|---|---|
| Funding | Funding not stated |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BUPROPION versus METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS)<br><br>Anorexia 0;2<br>Anxiety 1;0<br>Tremor 0;1<br>Insomnia 1;0<br>Total AEs: 9/15; 5/15<br>Low risk of bias | |
| 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 2006[97] |
|---|---|
| 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 |
| 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. |

| Study | Biederman 2006[97] |
|---|---|
| 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<br>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 |

| Study | Biederman 2006[97] |
|---|---|
| | 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 | Biederman 2008[96] |
|---|---|
| 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 |

| Study | Biederman 2008[96] |
|---|---|
| | 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 >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 pulse 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 |

| Study | Biederman 2008[96] |
|---|---|
| | 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 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 (258) versus PLACEBO (86)<br>Total adverse events 147/258; 9/86<br>Appetite decreased 2 vs. 18<br>Sedation 33;3<br>Somnolence 83;3<br>Deaths 0<br><br>Low risk of bias | |
| 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 |

| Study | Biederman 2008 [95] |
|---|---|
| Study type | NRS (Open-label single arm) |
| Number of studies (number of participants) | (n=240) |

| | |
|---|---|
| Countries and setting | USA |
| Line of therapy | Unclear |
| Duration of study | Intervention time: 24 weeks |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis: DSM-IV |
| Stratum | Children; low/normal risk |
| Subgroup analysis within study | None specified |
| Inclusion criteria | (1) Age appropriate IQ levels |
| Exclusion criteria | (1) any acute or chronic condition or medication that would confound results or be contraindicated for medication (2) weight less than 25kg or morbid obesity |
| Recruitment/selection of patients | Subjects recruited from preceding RCT if they competed at least 2 weeks of the trail without any clinically significant adverse events (originally from 45 outpatient clinics across the US) |
| Age, gender and ethnicity | Age - Range: 5 to 17 years<br>Gender: 184 male, 56 female<br>Ethnicity: 69.6% white, 12.5% black, 10.4% Hispanic, 7.5% other |
| Further population details | 1. ADHD subtype: 26.3% inattentive, 1.3% hyperactive, 72.5% combined<br>2. Age: Children and young people 5 to 17 years<br>3. At risk population: Not applicable / Not stated / Unclear<br>4. Comorbidities: Not specified<br>5. Diagnostic method: DSM-IV<br>6. Line of treatment: Unclear |

| | |
|---|---|
| | 7. Severity: Mixed; baseline ADHD-RS-IV score mean 37.4 |
| Extra comments | |
| Indirectness of population | No indirectness |
| Interventions | (n=240) Intervention: Guanfacine 2mg/day |
| Funding | Shire Development Inc |
| OUTCOMES AT 24 WEEKS; GUNFACINE<br>• Cardiovascular events at 24 months<br>• Weight at 24 months | |
| Risk of bias details | Very high risk of bias due to (1) selection bias (2) attrition bias |
| 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** | **Biederman 2010[98]** |
|---|---|
| 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 |

| Study | Biederman 2010[98] |
|---|---|
| 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:<br><br>(n=115) Intervention 2: No treatment - Placebo. Mean daily dose 96.6+/-26.5mg. Duration 6 weeks. 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

Protocol outcome 1: ADHD symptoms at <3- or >6-months
- Actual outcome for Adult: Treatment response at 6 week; Group 1: 67/109, Group 2: 41/114;  Risk of bias: High; Indirectness of outcome: No indirectness

| Study | Biederman 2010[98] |
|---|---|
| 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[91] (Biederman 2012[92]) |
|---|---|
| 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 condition | Adequate method of assessment/diagnosis: A psychiatric evaluation and Structured Clinical Interview for 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 |

| Study (subsidiary papers) | Biederman 2012[91] (Biederman 2012[92]) |
|---|---|
| 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<br><br>Insomnia<br>Decreased appetite<br>Cardiac events<br>High risk of bias | |
| 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 | Buitelaar 2001[134] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |

| Study | Buitelaar 2001[134] |
|---|---|
| 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); high risk for psychiatric outcomes and sleep |
| 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 baseline phase; 2) their aggressive behaviour failed to respond to behavioural treatment approaches (typically6 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 |

| Study | Buitelaar 2001[134] |
|---|---|
| | 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<br><br>Total adverse events: 17/19; 11/19<br>Tremors: 4/19;2/17<br>Low risk of bias | |
| 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 |

| Study | Buitelaar 2012<br>52 week open label non comparative extension of Medori 2008<br>Rosler 2013 [133] |
|---|---|
| Study type | Open label non comparative |
| Number of studies (number of participants) | 1 (n=155) |
| Countries and setting | Conducted in Europe and USA; Setting: Multicentre study conducted at 23 of the 51 LAMADA study sites (7/13 European) |
| Line of therapy | Unclear |
| Duration of study | Intervention time: - 6 month to 1 year |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis: DMS-IV |

| Study | Buitelaar 2012<br>52 week open label non comparative extension of Medori 2008<br>Rosler 2013 [133] |
|---|---|
| Stratum | Adults |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Meet DSM-IV criteria at interview (Adult ADHD Clinical Diagnostic Scale) , Conners 'Adult ADHD Diagnostic interview for DSM-IV (CAADID) Score > 24 |
| Exclusion criteria | (1) Lifetime diagnosis of OCD, bipolar affective disorder, psychosis, factitious disorder, or somatoform disorders (2) current diagnosis of seizures, tics, panic disorder, suicidal ideation, posttraumatic stress disorder, or an eating disorder within the year preceding visit 1 (3) current diagnosis of alcohol, drug misuse, or prescription medication misuse. (4) known non response to methylphenidate (5) known cardiac problems, untreated hypertension. (6) treatment gap of >30 days after the end of the 7 week open label extension of the LAMDA study. |
| Recruitment/selection of patients | From clinics and advertisements |
| Age, gender and ethnicity | Age - Mean (SD): 35(10.6). Gender (M): 54.2%. Ethnicity: unclear |
| Further population details | 1. ADHD subtype: All/mixed subtypes (106combined, 43inattentive, 5 hyperactive/impulsive). 2. Age: Adults 18-65 years) . 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear (Nil). 5. Diagnostic method: DSM IV. Line of treatment: Mixed line (including drug naive) 100% had prior drug exposure 7. Severity: Moderate (moderate and above). |
| Indirectness of population | No indirectness |
| Interventions | Methylphenidate maximum 90mg/day |
| Funding | Study funded by industry (Janssen-Cilag EMEA) |
| RESULTS (NUMBERS ANALYSED) n=155<br>Total numbers of participants with adverse events 126/155<br>Discontinuation due to adverse event 15/155<br>Insomnia 11/155<br>Hypertension 9/155<br><br>High risk of bias<br>Dropout rate 56/155 | |
| Protocol outcomes not reported by the study | All-cause mortality, Suicide or suicidal ideation , Cardiac mortality, Substance abuse, Increase in seizures in people with epilepsy, Liver damage (defined by deranged LFTs),Increased tics ,Tremors, Congenital defects amongst patients who are pregnant, Psychotic symptoms. Sexual dysfunction |

| Study | Biederman 2010[98] |
|---|---|
| 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: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose<br><br>(n=115) Intervention 2: No treatment - Placebo. Mean daily dose 96.6+/-26.5mg. Duration 6 weeks. Concurrent medication/care: Not stated<br>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not |

| Study | Biederman 2010[98] |
|---|---|
| | stated / Unclear |
| 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>High risk of bias due to attrition bias<br>Insomnia 12/109; 4/144<br>Decreased appetite 26/109; 6/114 | |
| 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) | Biederman 2007[94] (Childress 2014[160], Lopez 2008[423]) |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 2 (n=314) |
| Countries and setting | Conducted in USA; Setting: 40 centres across the US |
| Line of therapy | Mixed line |
| 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 |

| Study (subsidiary papers) | Biederman 2007[94] (Childress 2014[160], Lopez 2008[423]) |
|---|---|
| | 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 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=79) 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. |

| Study (subsidiary papers) | Biederman 2007[94] (Childress 2014[160], Lopez 2008[423]) |
|---|---|
| | Concurrent medication/care: None reported<br>Further details: 1. Dose: 2. Method of titration:<br><br>(n=235) 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 |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ALL LDX GROUPS COMBINED versus PLACEBO<br><br>All outcomes low risk of bias; 4 weeks<br>Any adverse event 162/218 vs. 34/72 (incidence of at least 5% of participants)<br>Insomnia 41/218 vs. 2/72<br>Weight decreased 20/218 vs. 1/72 | |
| 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 2005[104] (Biederman 2006 [103]) |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=246) |
| Countries and setting | Conducted in USA; Setting: 24 sites in the USA |
| 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 |

| Study | Biederman 2005[104] (Biederman 2006 [103]) |
|---|---|
| Inclusion criteria | Patients were 6 to 17 years of age and had a diagnosis of ADHD on the basis of criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)21 for ADHD at screening, as manifested by a psychiatric/clinical evaluation and the Diagnostic Interview Schedule for Children, Fourth Edition, with a Clinical Global Impression Severity of Illness (CGI-S) rating of 4 or higher ("moderately ill" or worse).22 In addition, patients were attending full-time school (i.e., they were not being home-schooled); had a teacher-/investigator-rated Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) School Version total and/or subscale score at least 1.5 SDs above normal values for age and gender,23 were between the 5th and 95th percentile for weight and height on the basis of National Center for Health Statistics guidelines, had an IQ of at least 80 as estimated by the Wechsler Intelligence Scale for Children–Third Edition, and had a score of at least 80 on the Wechsler Individual Achievement Test–Second Edition–Abbreviated |
| Exclusion criteria | patients were excluded when they had a history or current diagnosis of pervasive developmental disorder, schizophrenia, or other psychotic disorders (DSM-IV Axis I); evidence of suicide risk; current psychiatric comorbidity that required pharmacotherapy; or other active clinically significant disease. To avoid potential ethical concerns, patients whose ADHD was well controlled and who were satisfied with current ADHD therapy (with low levels of adverse effects) were also excluded, as were those who had failed to respond to 2 or more adequate courses (dose and duration) of stimulant therapy for ADHD. Other exclusion criteria included a clinically significant drug sensitivity to stimulants, a history of alcohol or substance abuse as defined by DSM-IV criteria,21 consumption of >250 mg/day caffeine, absolute neutrophil count <1 × 109/L, hypertension (systolic blood pressure [SBP] of ≥122 mm Hg or diastolic blood pressure [DBP] of ≥78 mm Hg for patients aged 6–9 years; SBP of ≥126 mm Hg or DBP of ≥82 mm Hg for patients aged 10–12 years; SBP of ≥136 mm Hg or DBP of ≥86 mm Hg for patients aged 13–17 years), hypotension (sitting SBP <50 mm Hg for patients younger than 12 years or <80 mm Hg for patients 12 years and older), and resting pulse rate outside the range of 60 to 115 beats per minute. Concomitant use of prescription or non-prescription agents with psychotropic properties, including ADHD treatments and dietary supplements, was prohibited within 1 week of the baseline visit (within 2 weeks for monoamine oxidase inhibitors and selective serotonin reuptake inhibitors) and during the study. |
| Recruitment/selection of patients | Multicentre trial conducted between November 2003 and June 2004 . A screening visit was conducted within 28 days of baseline testing to determine eligibility. Patients who satisfied all entry criteria and discontinued previous medication for ADHD |
| Age, gender and ethnicity | Age - Range: 6-17 years. Gender (M:F): 174/72. Ethnicity: not reported |
| Further population details | 1. ADHD subtype: All/mixed subtypes (38.2% of the population were of Inattentive subtype of ADHD, 2.84% were hyperactive/impulsive subtype and 58.9% were of the combined subtype). 2. Age:  3. At risk population:  4. Comorbidities:  5. Diagnostic method:  6. Line of treatment:  7. Severity: |
| Extra comments | 38.2% of the population were of Inattentive subtype of ADHD, 2.84% were hyperactive/impulsive subtype and 58.9% were of the combined subtype |

| Study | Biederman 2005[104] (Biederman 2006 [103]) |
|---|---|
| Indirectness of population | No indirectness |
| Interventions | (n=164) Intervention 1: CNS stimulants - Modafanil. treatment with modafinil film–coated tablet once daily in the morning. he dose of modafinil or placebo was individually titrated on the basis of tolerability and efficacy using the following schedule: 85 mg (1 tablet) on days 1 and 2, 170 mg (2 tablets) on days 3 to 7, 255 mg (3 tablets) on days 8 to 14, 340 mg (4 tablets) on days 15 to 21, and 425 mg (5 tablets) on day 22. Titration was stopped when any of the following conditions was met: poor tolerability, no additional expected incremental improvement in efficacy, patient's request, or achievement of a Clinical Global Impression of Improvement (CGI-I) rating of 1. The minimum and maximum daily dosages allowed during the study were 170 mg and 425 mg, respectively. . Duration 9 weeks. Concurrent medication/care: No concomitant medication allowed and washout period for previous medication for ADHD over a 1- to 4-week period implemented<br>Further details: 1. Dose: 2. Method of titration:<br><br>(n=82) Intervention 2: No treatment - Placebo. Matching placebo to active treatment. Duration 9 weeks. Concurrent medication/care: No concomitant medication allowed and washout period for previous medication for ADHD over a 1- to 4-week period implemented<br>Further details: 1. Dose: 2. Method of titration: |
| Funding | Study funded by industry (Study was funded by Cephalon) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MODAFANIL GROUP versus PLACEBO GROUP at 9 weeks<br><br>Insomnia 48;3<br>Decreased appetite 26;3<br>Nervousness 7;5<br>Weight change(kg): -1(1.1); +0.7(1.1)<br>Systolic blood pressure changes(mmHg): -0.18(8.67); -0.5(9.6)<br>High risk of bias | |
| 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 | Biederman 1989[88] [87, 89] |
|---|---|

| Study | Biederman 1989[88] [87, 89] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 62 |
| Countries and setting | |
| Line of therapy | Unclear |
| Duration of study | 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 | |
| Exclusion criteria | |
| Recruitment/selection of patients | |
| Age, gender and ethnicity | Age - Range: 13-17 years. Gender (M:F):29.7% females. 14.8% Hispanic/Latino, 79% white, 14.8% African American. |
| Further population details | 1. ADHD subtype: All/mixed subtypes (38.2% of the population were of Inattentive subtype of ADHD, 2. Age: 3. At risk population: 4. Comorbidities: 5. Diagnostic method: 6. Line of treatment: 7. Severity: 37.8(6.88) mean(SD) of ADHD-RS baseline |
| Extra comments | |
| Indirectness of population | No indirectness |
| Interventions | (n=235) Intervention 1: Desipramine.(31)<br><br>(n=79) Intervention 2: No treatment - Placebo. (31) |
| Funding | Study funded by industry (Study was funded by Cephalon) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LISDEX GROUP versus PLACEBO GROUP at 9 weeks<br>Decreased appetite 29% vs. 12.9%<br>Trouble sleeping 22.6% vs. 6.5%<br>Likely low risk of bias | |
| 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 | Biederman 1989[88] [87, 89] |
|---|---|
| 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 | Brown 1989[124] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=11) |
| Countries and setting | USA; setting not specified |
| Line of therapy | Unclear |
| Duration of study | Intervention time: 2 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 | (1) score of at least 15 on the ACTRS |
| Exclusion criteria | Non specified |
| Recruitment/selection of patients | Not specified |
| Age, gender and ethnicity | Age - Other:12 to 15 years. Gender (M:F): All male. Ethnicity: Black |
| 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 | No indirectness |
| Interventions | (n=11) Intervention 1: Methylphenidate 0.15mg/per kg. Duration 2 weeks. Concurrent medication/care: Not specified<br>(n=11) Intervention 2: Methylphenidate 0.3mg/per kg. Duration 2 weeks. Concurrent medication/care: Not specified<br>(n=11) intervention 3: methylphenidate 0.5mg/per kg. Duration 2 weeks. Concurrent medication/care: Not specified<br><br>(n=11) Intervention4 - Placebo. Placebo. Duration 2 weeks. Concurrent medication/care: Not specified |

| Study | Brown 1989[124] |
|---|---|
| | |
| Funding | Funding not stated |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE ALL DOSES versus PLACEBO<br>Systolic blood pressure (mean end point)<br>MPH: 97.6(1.75)<br>Placebo 94.7(3.9)<br>All outcomes at high risk of bias | |
| Protocol outcomes not reported by the study | |

| Study | Butterfield 2016[139] |
|---|---|
| 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 |

| Study | Butterfield 2016[139] |
|---|---|
| | medication, participated in a clinical trial within 30 days, weight less than 30kg or more than 120kg. |
| Recruitment/selection of patients | Recruited from local advertisements and the clinic's existing patient population. |
| Age, gender and ethnicity | Age - Mean (SD): 37.54 (12.22). Gender (M:F): 12/14. Ethnicity: 85.6% Caucasian, 11.5 African-American, 3.8% Other |
| Further population details | 1. ADHD subtype: All/mixed subtypes (All participants had ADHD diagnosis using diagnostic criteria for adult ADHD (inattentive, hyperactive/impulsive, combined subtypes)). 2. Age: Adults 18-65 years) (Age 19-62. ). 3. At risk population: General population (Recruited from local advertisements and the clinic's existing patient population. ). 4. Comorbidities: Not applicable / Not stated / Unclear (Excluded people with Axis 1 disorders, severe Axis 2 disorders, severe substance dependence.). 5. Diagnostic method: DSM (Diagnostic and Statistical Manual of Mental Health Disorders (4th edition)). 6. Line of treatment: Not applicable / Not stated / Unclear (Not first line therapy. Sub-optimal response to various ADHD medications). 7. Severity: Not 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

RESULTS (NUMBERS ANALYSED) n=26

Protocol outcome 1: Increased appetite Guanfacine 1/26 placebo 2/26
Risk of bias: Very high; Indirectness of outcome: No indirectness

| Study | Butterfield 2016[139] |
|---|---|
| Protocol outcomes not reported by the study | Total number of adverse events, All-cause mortality, Suicide or suicidal ideation , Cardiac mortality, Substance abuse, Increase in seizures in people with epilepsy, Liver damage (defined by deranged LFTs),Increased tics ,Tremors, Congenital defects amongst patients who are pregnant, Psychotic symptoms. Sexual dysfunction |

| Study (subsidiary papers) | LAMDA-II (EudraCT number: 2007-002111-82) trial: Casas 2013[144] (Kooij 2013[395]) |
|---|---|
| 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. |
| 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 |

| Study (subsidiary papers) | LAMDA-II (EudraCT number: 2007-002111-82) trial: Casas 2013[144] (Kooij 2013[395]) |
|---|---|
| | 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 careening 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 asigned to placebo recieved palcebo for 13 weeks. Duration 13 weeks. Concurrent medication/care: concomitant medications to be discontiued during the screening period were adrenergic receptor agonists, antipsychotics, theophylline, coumarin anticoagulants or antoconvulsants, any ADHD tteatment , monoamine oxidase inhibitors, herbal and OTC stimulant diet preperations or drugs containing stimulants<br>Further details: 1. Dose: 2. Method of titration: |
| Funding | Study funded by industry (Authors recieved 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

| Study (subsidiary papers) | LAMDA-II (EudraCT number: 2007-002111-82) trial: Casas 2013[144] (Kooij 2013[395]) |
|---|---|
| | 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: 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<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>- 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,<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>- 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);<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>- 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<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>- 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, |

| Study (subsidiary papers) | LAMDA-II (EudraCT number: 2007-002111-82) trial: Casas 2013[144] (Kooij 2013[395]) |
|---|---|
| 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, 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: 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<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 | |

| Study (subsidiary papers) | LAMDA-II (EudraCT number: 2007-002111-82) trial: Casas 2013[144] (Kooij 2013[395]) |
|---|---|

- 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 , 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
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: groups were matched for age, sex, race BMI, height, ADHD subtype, baseline CARRS-O-SV scores; Group 1 Number missing: 55, Reason: discontinuation, adverse events, lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other; Group 2 Number missing: 68, Reason: discontinuation, adverse events, lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other
- Actual outcome: Self-Report-Short Version(CAARS-S:SS)-difference in least square mean by ANCOVA, comparing each dose with placebo , adjusted for multiplicity using the 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
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,

| Study (subsidiary papers) | LAMDA-II (EudraCT number: 2007-002111-82) trial: Casas 2013[144] (Kooij 2013[395]) |
|---|---|
| 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<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: 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) | NCT00763971 trial: Coghill 2013[174] (Coghill 2014[177], Banaschewski 2013[64], Coghill 2014[176]) |
|---|---|
| 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 |
| 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 |

| Study (subsidiary papers) | NCT00763971 trial: Coghill 2013[174] (Coghill 2014[177], Banaschewski 2013[64], Coghill 2014[176]) |
|---|---|
| | 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 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) |
| All outcomes high risk of bias due to attrition bias<br>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LISDEXAMFETAMINE DIMESYLATE versus METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS)<br>Decreased weight 15/111; 5/111-1.3<br>1.4I1nsomnia 16/111; 9/111<br>Blood pressure change (systolic): +1(9.8); +0.3(11.1)<br>Weight changes(kg): -2.1(1.9); -1.3(1.4)<br><br>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LISDEXAMFETAMINE DIMESYLATE versus PLACEBO<br>Decreased weight 15/111; 0/110<br>Insomnia 16/111; 0/110<br>Blood pressure change (systolic): +1(9.8); +1(9.6) | |

| Study (subsidiary papers) | NCT00763971 trial: Coghill 2013[174] (Coghill 2014[177], Banaschewski 2013[64], Coghill 2014[176]) |
|---|---|
| Weight changes(kg): -2.1(1.9); +0.7(1)<br>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS) versus PLACEBO<br>Decreased weight 5/111; 0/111<br>Insomnia 9/111; 0/110<br>Blood pressure change(systolic): +0.3(11.1); +1(9.6)<br>Weight changes(kg):-1.3(1.4); +0.7(1) | |
| 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 | Connor 2010[187] |
|---|---|
| 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 pulse rate (except for ADH therapies, which were discontinued during the washout period) |
| 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%), |

| Study | Connor 2010[187] |
|---|---|
| | 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 Development Inc.) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GUANFACINE versus PLACEBO<br><br>Psychotic symptoms (affect lability) 2;4<br>Deaths: 0<br>Total adverse events 114/136; 45/78<br>Low risk of bias | |
| 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 | Conners 1980[183] |
|---|---|
| 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 |
| 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 antiseizure 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 phenothiazine 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 |

| Study | Conners 1980[183] |
|---|---|
| | 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 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>Low risk of bias<br>Insomnia 13/20; 5/21<br>Appetite problems 8/20; 5/21<br>Palpitations 1/20; 0/20 | |
| 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 | Dell'agnello 2009[208] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=137) |
| Countries and setting | Conducted in Italy; Setting: Not stated |
| Line of therapy | Unclear |
| Duration of study | Intervention time: 8 weeks |

| Study | Dell'agnello 2009[208] |
|---|---|
| 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 (7) formal individual or family psychotherapy |
| Recruitment/selection of patients | Not specified |
| Age, gender and ethnicity | Age - Mean (SD): 9.7 years, Range : 6-15 years. Gender (M:F): 98;7Ethnicity: Not specified |
| Further population details | 1. ADHD subtype: All/mixed subtypes (89.5% 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% had received previous drug treatment). 7. Severity: Not applicable / Not stated / Unclear (SNAP-IV score >1.5SD above norms for age and gender; CGI-S >/=4). |
| Extra comments | 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 | No indirectness |
| 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.<br><br>(n=32). Comparison: placebo |
| Funding | Study funded by industry (Eli Lilly and Company) |
| | |

| Study | Dell'agnello 2009[208] |
|---|---|
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE GROUP versus PLACEBO GROUP<br>High risk of bias due to estimated standard deviations<br><br>Protocol outcome 1: Sleep<br>5/105; 2/32 Insomnia<br>Systolic BP +1; +5.1 (p=0.0482)1<br>Weight decreased 6/107; 1/32 | |
| Protocol outcomes not reported by the study | |
| Risk of bias details | All outcomes: high risk of bias due to pre-randomisation administration of an intervention to select patients. |

| Study | Dittmann 2009[215] |
|---|---|
| Study type | NRS (open-label single arm) |
| Number of studies (number of participants) | (n=159) |
| Countries and setting | Germany |
| Line of therapy | Unclear |
| Duration of study | Intervention time: 24 weeks |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis: DSM-IV |
| Stratum | Children; low/normal risk |
| Subgroup analysis within study | None |
| Inclusion criteria | (1) IQ above 70 |
| Exclusion criteria | (1) acute of unstable medical conditions (2) cardiovascular disorder, seizures, PDD, psychosis, bipolar, suicidal ideation or any medical condition or treatment that could confound or contraindicate results |
| Recruitment/selection of patients | Recruited from 25 child and adolescent psychiatry and paediatric practices and outpatient clinics throughout Germany |
| Age, gender and ethnicity | Age - Range: 12 to 17 years<br>Gender: 125 male, 34 female<br>Ethnicity: Not specified |

| Study | Dittmann 2009[215] |
|---|---|
| Further population details | 1. ADHD subtype: 50.9% combined subtype, 45.9% inattentive, 3.2% not otherwise specified<br>2. Age: Children 12 to 17 years<br>3. At risk population: Not applicable / Not stated / Unclear<br>4. Comorbidities: Not specified<br>5. Diagnostic method: DSM-IV<br>6. Line of treatment: Mixed<br>7. Severity: Mixed |
| Extra comments | |
| Indirectness of population | No indirectness |
| Interventions | (n=274) Intervention: Atomoxetine 0.5-1.2mg/kg per day |
| Funding | Lilly Deutschland |
| OUTCOMES AT 24 WEEKS: ATOMOXETINE<br>Liver function: no abnormalities | |
| Risk of bias details | High risk of bias due to (1) selection bias (2) attrition bias |
| 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) | NCT01106430 trial: Dittmann 2014[213] (Nagy 2015[477], Dittmann 2013[214]) |
|---|---|
| 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 |

| Study (subsidiary papers) | NCT01106430 trial: Dittmann 2014[213] (Nagy 2015[477], Dittmann 2013[214]) |
|---|---|
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis: DSM-IV-TR criteria |
| Stratum | Overall |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | ADHD-RS-IV total score of 28 or higher at baseline, and an inadequate response to previous or current MPH treatment |
| Exclusion criteria | Intolerable adverse events from previous MPH treatment, previous exposure to amphetamine or ATX, previous treatment with more than one MPH medication, failure to respond to more than one previous course of MPH medication and good control of ADHD symptoms. Comorbid psychiatric diagnosis, conduct disorder, suicide risk, weight below 22.7 kg, suspected substance abuse and history of seizures |
| Recruitment/selection of patients | Study was conducted between June 2010 to July 2012 at the 51 centres in 9 countries |
| Age, gender and ethnicity | Age - Range: 6 - 17 years. Gender (M:F): 197:70. Ethnicity: 80% Hispanic, 20% other |
| Further population details | 1. ADHD subtype: All/mixed subtypes (78.3% of the patients were classified as the combined ADHD subtype, 3.4% as the predominantly hyperactive-impulsive and 16.5% as the predominantly inattentive). 2. Age: Mixed (People aged 6-17 years old). 3. At risk population: Not applicable / Not stated / Unclear 4. Comorbidities: Not applicable / Not stated / Unclear (Comorbid psychiatric diagnosis, conduct disorder, suicide risk, suspected substance abuse and history of seizures excluded. ). 5. Diagnostic method: DSM (Satisfied DSM 4th edition criteria for a primary diagnosis of ADHD). 6. Line of treatment: 2nd line (non-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 adverse 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 |

| Study (subsidiary papers) | NCT01106430 trial: Dittmann 2014[213] (Nagy 2015[477], Dittmann 2013[214]) |
|---|---|
| | and a CGI-I score of 1 or 2 with tolerable adverse 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 adverse 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. 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 adverse 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 (128) versus ATX GROUP (134) at 9 weeks (all low risk of bias)<br>Decreased appetite: 33;14<br>Decreased weight:28;9<br>Insomnia: 15;8<br><br>Risk of bias: low<br>Any adverse event: 92/128; 95/134<br>Systolic blood pressure 107.9(10.43); 106.2(9.91) | |
| Protocol outcomes not reported by the study | Quality of life at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months |

| Study (subsidiary papers) | Durell 2013[222] (Durell 2014[223], Durrell 2014[224]) |
|---|---|

| Study (subsidiary papers) | Durell 2013[222] (Durell 2014[223], Durrell 2014[224]) |
|---|---|
| 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 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 |

| Study (subsidiary papers) | Durell 2013[222] (Durell 2014[223], Durrell 2014[224]) |
|---|---|
| | 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<br><br>Protocol outcome 1: Quality of life at <3- or >6-months<br>- 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<br>- 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<br><br>Protocol outcome 2: ADHD symptoms at <3- or >6-months<br>- 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<br>- 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<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 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 | Findling (2006) [247] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |

| Study | Findling (2006) [247] |
|---|---|
| Number of studies (number of participants) | 1 (n=318) |
| Countries and setting | Conducted in USA, UK, Australia |
| Line of therapy | Unclear |
| Duration of study | Intervention 3 weeks |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis: DSM-IV |
| Stratum | Children (up to 18 years); normal risk |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Had been on a stable dose of MPH for at least 3 weeks |
| Exclusion criteria | |
| Recruitment/selection of patients | |
| Age, gender and ethnicity | Age - Range: 6-12 years. Gender (M:F): . Ethnicity: not reported |
| Further population details | 1. ADHD subtype: All/mixed 2. Age: 3. At risk population: 4. Comorbidities: 5. Diagnostic method: 6. Line of treatment: 7. Severity: |
| Extra comments | |
| Indirectness of population | No indirectness |
| Interventions | Placebo (48)<br>MPH-IR or MP EqXL(172) |
| Funding | Study funded by industry (Study was funded by Cephalon) |
| Anorexia 9;0<br>Insomnia 11;0<br>Tics0;2 (doesn't specify if in those with Tics/ Tourette's)<br><br>High risk of bias due to attrition bias | |
| Protocol outcomes not reported by the study | |

| Study | Findling 2008[243] |
|---|---|

| Study | Findling 2008[243] |
|---|---|
| Study type | NRS (open-label single arm trial) |
| Number of studies (number of participants) | (n=274) |
| Countries and setting | USA |
| Line of therapy | Mixed |
| Duration of study | Intervention time: 11 months |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis: DSM-IV |
| Stratum | Children; low/normal risk |
| Subgroup analysis within study | None |
| Inclusion criteria | (1) combined or hyperactive subtypes (2) age appropriate IQ levels |
| Exclusion criteria | (1) presence of comorbid conditions (psychiatric, seizures, o r any general condition that might confound results) (2) tics (3) ECG abnormalities (4) significant deviation from normal weight (5) concomitant medication that could confound results |
| Recruitment/selection of patients | Not specified |
| Age, gender and ethnicity | Age - Range: 6 to 12 years<br>Gender: 189 male, 83 female<br>Ethnicity: 52.5% white, 25.7% black, 1.9% Hispanic, 1.1& Asian, 3.6% other |
| Further population details | 1. ADHD subtype: 96.3% combined, 3.7% hyperactive<br>2. Age: Children 6-12 years<br>3. At risk population: Not applicable / Not stated / Unclear<br>4. Comorbidities: Not specified<br>5. Diagnostic method: DSM-IV<br>6. Line of treatment: 197/272 had previous treatment (with lisdexamfetamine)<br>7. Severity: Not applicable / Not stated / Unclear |
| Extra comments | |
| Indirectness of population | No indirectness |
| Interventions | (n=274) Intervention: lisdexamfetamine 30-70mg per day |
| Funding | Shire Development Inc |
| | |

| Study | Findling 2008[243] |
|---|---|
| | |
| Risk of bias details | Very high risk of bias due to (1) selection bias (2) attrition bias |
| 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 | Findling 2011[242] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 314 |
| Countries and setting | USA |
| Line of therapy | Unclear |
| Duration of study | 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 | Moderate severity on ADHD-RS (28 or higher). Age-appropriate intellectual functioning and blood pressure. |
| Exclusion criteria | Conduct disorder or a psychiatric condition (other than ODD) requiring medication. History of seizures, Tourette's or tic disorders, family history of cardiac problems or abnormal thyroid function, high risk of suicide |
| Recruitment/selection of patients | |
| Age, gender and ethnicity | Age - Range: 13-17 years. Gender (M:F):29.7% females. 14.8% Hispanic/Latino, 79% white, 14.8% African American. |
| Further population details | 1. ADHD subtype: All/mixed subtypes (38.2% of the population were of Inattentive subtype of ADHD, 2. Age: 3. At risk population: 4. Comorbidities: 5. Diagnostic method: 6. Line of treatment: 7. Severity: 37.8(6.88) mean(SD) of ADHD-RS baseline |
| Extra comments | |
| Indirectness of population | No indirectness |

| Study | Findling 2011[242] |
|---|---|
| Interventions | (n=235) Intervention 1: Lisdex. Randomised to 30, 50 or 70mg (3 weeks titration and 1 week maintenance)<br><br>(n=79) Intervention 2: No treatment - Placebo. |
| Funding | Study funded by industry (Study was funded by Cephalon) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LISDEX GROUP versus PLACEBO GROUP at 9 weeks<br>Decreased appetite 79;2<br>Insomnia 26;3<br>Weight decreased 22;0<br>Irritability 16;3<br>No deaths<br>SBP mean change: +0.4(1.542); +2.2(1.04)<br>Any adverse event: 160/233; 45/77<br>High risk of attrition bias | |
| 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 | Gadow 2008[265](Gadow 2007[266];Gadow 1995[267]) |
|---|---|
| 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 |

| Study | Gadow 2008[265](Gadow 2007[266];Gadow 1995[267]) |
|---|---|
| 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 |
| 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 |

| Study | Gadow 2008[265](Gadow 2007[266];Gadow 1995[267]) |
|---|---|
| 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(all doses) versus PLACEBO (n=31)<br>Very high risk of bias; unclear if randomised trial<br>Systolic blood pressure at endpoint(mmHg) 101.5(14.45); 95.3(18.7)<br>Weight at end point(kg): 79.23(32.51); 80.3(32.6)<br>YGTSS tics global severity score: 30.1(16.57); 28.3;15.9 | |
| 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[274] |
|---|---|
| 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 |

| Study | Gau 2007[274] |
|---|---|
| | 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 |
| 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 psych stimulants (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 psych stimulants<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
Decreased appetite 26;5
Somnolence 16;3
Insomnia 8;1
Weight loss 4;3

| Study | Gau 2007[274] |
|---|---|
| High risk of bias | |
| 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 | Geller 2007[279] |
|---|---|
| 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) |
| 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: |

| Study | Geller 2007[279] |
|---|---|
| | 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 |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE versus PLACEBO<br><br>Weight loss -0.55kg vs. 1.39kg p<.001 (calculate SD?)<br>Decreased appetite 11;3<br><br>Low risk of bias | |
| 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 | Germanario 2013[280] |
|---|---|
| Study type | NRS (prospective cohort) |
| Number of studies (number of participants) | N=590 |
| Countries and setting | Italy |
| Line of therapy | 1st line |
| Duration of study | Intervention time: 24 months |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis: DSM-IV |
| Stratum | Children; low/normal risk |
| Subgroup analysis within study | None |
| Inclusion criteria | (1) 6 to 18 years old |
| Exclusion criteria | (1) ASD |
| Recruitment/selection of patients | From 87 outpatient clinics |
| Age, gender and ethnicity | Age - Range: 6 to 18 years<br>Gender: 514 male, 76 female<br>Ethnicity: Not specified |
| Further population details | 1. ADHD subtype: 90% combined subtype, 5.6% inattentive, 4.4% hyperactive<br>2. Age: Children<br>3. At risk population: Not applicable / Not stated / Unclear<br>4. Comorbidities: 45.6% had learning disorders, 41.9& ODD, 12.4% anxiety<br>5. Diagnostic method: ICD-10<br>6. Line of treatment: 1st line<br>7. Severity: Not stated |
| Extra comments | |
| Indirectness of population | No indirectness |
| Interventions | (n=296) Intervention: Methylphenidate<br>(n=294) Intervention: Atomoxetine |
| Funding | None specified |
| OUTCOMES AT 24 MONTHS; ATX VERSUS MPH<br>Weight (kg) | |

| Study | Germanario 2013[280] |
|---|---|
| Height (z-scores) | |
| Risk of bias details | Very high risk of bias due to (1) selection bias (2) attrition bias |
| 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 | Goodman 2016[293] |
|---|---|
| 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[293] |
|---|---|
| | 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>Low risk of bias<br>Decreased appetite 25/174; 7/175<br>Insomnia 12/174; 4/175<br>Deaths: 0 in both arms | |
| 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[294] |
|---|---|
| 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 |
| Line of therapy | Mixed line |
| Duration of study | Intervention time: 10 weeks |
| Method of assessment of guideline | Adequate method of assessment/diagnosis: DSM-IV |

| Study | Goto 2013[294] |
|---|---|
| condition | |
| 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

Protocol outcome 1: Quality of life at <3- or >6-months
- Actual outcome for Adult: AAQoL at 10 weeks; Group 1: mean 12.8 (SD 15.9); n=193, Risk of bias: High; Indirectness of outcome: No indirectness

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

| Study | Goto 2013[294] |
|---|---|
| - 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 | Ghuman 2009[283] |
|---|---|
| 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 |

| Study | Ghuman 2009[283] |
|---|---|
| | developmental delays defined by intelligence quotient (IQ) and=or Vineland Adaptive Behaviour 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, 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, preschool 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 adverse 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 |

| Study | Ghuman 2009[283] |
|---|---|
| | 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:<br><br>(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<br>(low risk of bias)<br>Weight changes<br>Height changes<br>Systolic blood pressure | |
| 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) | Ginsberg  2014[287] |
|---|---|
| Study type | Open label non comparative<br>Extension of Huss,  2014 #312 |
| Number of studies (number of participants) | (n=298)<br>N=156 responders ,91 treatment non responders |
| Countries and setting | Conducted in six countries; Setting: 48 clinical research sites |

| Study (subsidiary papers) | Ginsberg 2014[287] |
|---|---|
| Line of therapy | Unclear |
| 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 | Met full DSM-IV criteria for ADHD. Adults 18-60 years<br>Studies where response to previous treatment is an inclusion criteria: "Patients with either hypersensitivity or history of poor response or intolerance to stimulants as per the investigator's judgement were excluded….responders [defined as patients with ≥30% improvement compared to baseline score on the DSM-IV ADHD Rating Scale who continued to meet inclusion criteria were re-randomized to enter the double-blind maintenance of effect phase" |
| 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) pregnancy |
| Recruitment/selection of patients | From November 2010 to August 2012 |
| Age, gender and ethnicity | Age – mean 36.6 years (11.40). Gender (M:F): 160 male, 138 female. Ethnicity: 91.3% White |
| Further population details | Unclear |
| Extra comments | ADHD |
| Indirectness of population | No indirectness |
| Interventions | Intervention: methylphenidate max dose 40-80mg<br>Start from 20mg titrated to optimal dose |
| Funding | Industry funded (Novartis Pharma AG) |
| RESULTS (NUMBERS ANALYSED)<br>N=298<br>Tachycardia n= 11/298<br>Decreased appetite n=26/298 | |
| Protocol outcomes not reported by the study | Total number of participants with an adverse event, All-cause mortality<br>Suicide or suicidal ideation ,Cardiac mortality, Substance misuse ,Abnormal growth ( height and weight),Increase in seizures in people with epilepsy, Sleep including insomnia, Liver damage (defined by |

| Study (subsidiary papers) | Ginsberg 2014[287] |
|---|---|
| | deranged LFTs),Increased tics, Tremors, Congenital defects amongst patients who are pregnant, Sexual dysfunction, Psychotic symptoms |

| Study | Greenhill 2002[299] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | (n=311) |
| 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) |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | (1) AADHD combined subtype or predominantly hyperactive-impulsive subtype as defined by DSM-IV (2) Blood pressure, pulse 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, pulse 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 |

| Study | Greenhill 2002[299] |
|---|---|
| | 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 PREPARATIONS)  versus PLACEBO<br><br>Very high risk of bias due to attrition and selection bias<br>Overall adverse events: 80/155; 61/161 | |
| 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 | Greenhill 2006[298] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=198) |
| Countries and setting | Conducted in USA; Setting: 18 centre<br>as in the U.S |
| Line of therapy | Unclear |

| Study | Greenhill 2006[298] |
|---|---|
| Duration of study | Intervention + follow up: 9 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 | Patients were 6 to 17 years of age and had a diagnosis of ADHD on the basis of criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) 21 for ADHD, a Clinical Global Impression Severity of Illness (CGI-S) rating of 4 or higher ("moderately ill" or worse), absence of learning disabilities, In addition, patients were attending full-time school (i.e., they were not being home-schooled); had a teacher-/investigator-rated Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) School Version total and/or subscale score at least 1.5 SDs above normal values for age and gender,23 were between the 5th and 95th percentile for weight and height on the basis of National Center for Health Statistics guidelines, had an IQ of at least 80 as estimated by the Wechsler Intelligence Scale for Children–Third Edition, and had a score of at least 80 on the Wechsler Individual Achievement Test–Second Edition–Abbreviated |
| Exclusion criteria | Patients were excluded when they had a history or current diagnosis of pervasive developmental disorder, schizophrenia, or other psychotic disorders (DSM-IV Axis I); evidence of suicide risk; current psychiatric comorbidity that required pharmacotherapy; or other active clinically significant disease. To avoid potential ethical concerns, patients whose ADHD was well controlled and who were satisfied with current ADHD therapy (with low levels of adverse effects) were also excluded, as were those who had failed to respond to 2 or more adequate courses (dose and duration) of stimulant therapy for ADHD. Other exclusion criteria included a clinically significant drug sensitivity to stimulants, a history of alcohol or substance abuse as defined by DSM-IV criteria,21 consumption of >250 mg/day caffeine, absolute neutrophil count <1 × 109/L, hypertension (systolic blood pressure [SBP] of ≥122 mm Hg or diastolic blood pressure [DBP] of ≥78 mm Hg for patients aged 6–9 years; SBP of ≥126 mm Hg or DBP of ≥82 mm Hg for patients aged 10–12 years; SBP of ≥136 mm Hg or DBP of ≥86 mm Hg for patients aged 13–17 years), hypotension (sitting SBP <50 mm Hg for patients younger than 12 years or <80 mm Hg for patients 12 years and older), and resting pulse rate outside the range of 60 to 115 beats per minute. Concomitant use of prescription or non-prescription agents with psychotropic properties, including ADHD treatments and dietary supplements, was prohibited within 1 week of the baseline visit (within 2 weeks for monoamine oxidase inhibitors and selective serotonin reuptake inhibitors) and during the study. |
| Recruitment/selection of patients | Multicentre trial conducted between November 2003 and May 2004 . A screening visit was conducted within 28 days of baseline testing to determine eligibility. Patients who satisfied all entry criteria and complied with a washout period of 7 days before baseline testing were recruited. |

| Study | Greenhill 2006[298] |
|---|---|
| Age, gender and ethnicity | Age - Range: 6-16 years. Gender (M:F): 144/54. Ethnicity: 71.7% white, 18.18% black and 10.1% other |
| Further population details | 1. ADHD subtype: All/mixed subtypes (23.7% of the population were of Inattentive subtype of ADHD, 5.05% were hyperactive/impulsive subtype and 70.2% were of the combined subtype). 2. Age:  3. At risk population:  4. Comorbidities:  5. Diagnostic method:  6. Line of treatment:  7. Severity: |
| Extra comments | 23.7% of the population were of Inattentive subtype of ADHD, 5.05% were hyperactive/impulsive subtype and 70.2% were of the combined subtype |
| Indirectness of population | No indirectness |
| Interventions | (n=133) Intervention 1: CNS stimulants - Modafanil. Modafinil film–coated tablets once daily in the morning. The dose of modafinil was individually titrated on the basis of tolerability and efficacy using the following schedule: 85 mg (1 tablet) on days 1 and 2, 170 mg (2 tablets) on days 3 to 7, 255 mg (3 tablets) on days 8 to 14, 340 mg (4 tablets) on days 15 to 21, and 425 mg (5 tablets) on day 22. Titration was stopped when any of the following conditions was met: poor tolerability, no additional expected incremental improvement in efficacy, patient's request, or achievement of a Clinical Global Impression of Improvement (CGI-I) rating of 1. . Duration 9 weeks. Concurrent medication/care: No concomitant medication allowed and  7 day washout period for previous medication for ADHD implemented<br>Further details: 1. Dose:  2. Method of titration:<br><br>(n=67) Intervention 2: No treatment - Placebo. Matching placebo to active treatment. Duration 9 weeks. Concurrent medication/care: No concomitant medication allowed and  7 day washout period for previous medication for ADHD implemented<br>Further details: 1. Dose:  2. Method of titration: |
| Funding | Principal author funded by industry (All authors receive research support grants from major pharma companies) |
| Insomnia<br>modafinil; 37 events<br>placebo; 5 events<br><br>Decreased appetite<br>Intervention: 23<br>Comparison:2 | |

| Study | Greenhill 2006[298] |
|---|---|
| weight loss (1.34kg decrease);<br>Intervention 7,<br>Comparison 0<br>Systolic BP endpoint: 104.7(9.8); 104.5(10.1)<br>All very high risk of bias | |
| 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 | Groenman 2013[305] |
|---|---|
| Study type | NRS (case series) |
| Number of studies (number of participants) | N=338 |
| Countries and setting | Belgium, Denmark and Germany |
| Line of therapy | Unclear |
| Duration of study | Intervention time: Mean 4.4 years |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis: formal diagnosis |
| Stratum | Children; low/normal risk |
| Subgroup analysis within study | None |
| Inclusion criteria | (1) White and of Caucasian descent (2) |
| Exclusion criteria | (1) IQ below 70 (2) epilepsy, autism, brain disorders and any genetic or medical disorder associated with externalising behaviours that might mimic ADHD |
| Recruitment/selection of patients | Part of the IMAGE study |
| Age, gender and ethnicity | Age - Range: 5-17 years<br>Gender: 314 males:24 females<br>Ethnicity: White |
| Further population details | 1. ADHD subtype: Not applicable / Not stated / Unclear (Not specified).<br>2. Age: Children |

| Study | Groenman 2013[305] |
|---|---|
| | 3. At risk population: Not applicable / Not stated / Unclear<br>4. Comorbidities: 30% ODD<br>5. Diagnostic method: Formal diagnosis<br>6. Line of treatment: 1st line<br>7. Severity: Not applicable / Not stated / Unclear |
| Extra comments | |
| Indirectness of population | No indirectness |
| Interventions | (n=327) Intervention: Stimulants<br>(n=61) Comparison: No stimulants |
| Funding | Industry; Shire Pharmaceuticals |
| Substance use disorder at 4.4 years; 17/61 in the no stimulant treatment group, 65/327 in the stimulant treatment group | |
| Risk of bias details | Very high risk of bias due to selection bias, lack of blinding |
| 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) | Harfterkamp 2012[323] (Harfterkamp 2014[322]) |
|---|---|
| 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 |

| Study (subsidiary papers) | Harfterkamp 2012[323] (Harfterkamp 2014[322]) |
|---|---|
| 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) on-going 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 |
| 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<br><br>Decreased appetite 13;3 | |

| Study (subsidiary papers) | Harfterkamp 2012[323] (Harfterkamp 2014[322]) |
|---|---|
| Initial insomnia 3;5<br><br>High risk of bias | |
| 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 |

| Study (subsidiary papers) | Hirata 2014 [336] |
|---|---|
| Study type | Open label non comparative<br>52 week open label non comparative extension of Goto 2012 [294] |
| Number of studies (number of participants) | (n=233) |
| Countries and setting | Conducted in Japan; Setting: 45 study sites in Asia |
| Line of therapy | Mixed line |
| Duration of study | Intervention time: 48 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 |

| Study (subsidiary papers) | Hirata 2014 [336] |
|---|---|
| Indirectness of population | No indirectness |
| Interventions | Intervention: Atomoxetine, 40-120mg/day |
| Funding | Industry funded (Novartis Pharma AG) |
| RESULTS (NUMBERS ANALYSED)<br>N=298<br>Tachycardia n= 11/298<br>Decreased appetite n=26/298<br><br>High risk of bias | |
| Protocol outcomes not reported by the study | Total number of participants with an adverse event, All-cause mortality<br>Suicide or suicidal ideation ,Cardiac mortality, Substance misuse ,Abnormal growth ( height and weight),Increase in seizures in people with epilepsy, Sleep including insomnia, Liver damage (defined by deranged LFTs),Increased tics, Tremors, Congenital defects amongst patients who are pregnant, Sexual dysfunction, Psychotic symptoms |

| Study | Hoebert 2009 [337] |
|---|---|
| Study type | NRS (case series) |
| Number of studies (number of participants) | N=105 |
| Countries and setting | Netherlands |
| Line of therapy | Unclear |
| Duration of study | Intervention time: 3.7 years |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis: formal diagnosis |
| Stratum | Children; chronic sleep onset insomnia |
| Subgroup analysis within study | None |
| Inclusion criteria | (1) diagnosis of ADHD and chronic sleep onset insomnia (2) IQ higher than 80 |
| Exclusion criteria | None specified |
| Recruitment/selection of patients | From an RCT |

| Study | Hoebert 2009 [337] |
|---|---|
| Age, gender and ethnicity | Age - Range: 6 to 12 years<br>Gender: Not specified<br>Ethnicity: Not specified |
| Further population details | 1. ADHD subtype: Not applicable / Not stated / Unclear (Not specified).<br>2. Age: Children<br>3. At risk population: Not applicable / Not stated / Unclear<br>4. Comorbidities: Chronic sleep onset insomnia<br>5. Diagnostic method: Unclear<br>6. Line of treatment: Unclear<br>7. Severity: Not applicable / Not stated / Unclear |
| Extra comments | |
| Indirectness of population | No indirectness |
| Interventions | (n=105) Intervention: melatonin (dose of 3mg per day if weight was less than 40kg, 6mg per day if weight was more than 40kg) |
| Funding | None specified |
| Outcome: Insomnia at 4 years | |
| Risk of bias details | Very high risk of bias due to attrition bias, lack of blinding |
| 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 | Huss 2015[349] |
|---|---|
| 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. |

| Study | Huss 2015[349] |
|---|---|
| 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. 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.<br>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 |

| Study | Huss 2015[349] |
|---|---|
| | 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/ GUANFACINE VERSUS PLACEBO/ ATOMOXETINE VERSUS PLACEBO<br>• Total participants with adverse events at 10 to 13 weeks<br>• All-cause mortality at 10 to 13 weeks<br>• Blood pressure at 10 to 13 weeks<br>• Insomnia at 10 to 13 weeks | |

| Study | Jain 2007[360] |
|---|---|
| Study type | RCT, crossover |
| Number of studies (number of participants) | 1 (n=50) |
| Countries and setting | Conducted in Canada |
| Line of therapy | Mixed line |
| Duration of study | Intervention time: 5 weeks |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis: Adults 18-60 years diagnosed with ADHD according to DSM-IV criteria with childhood onset |
| 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 score > 24, 2 Age 18-60 years |
| Exclusion criteria | Known mental health conditions, substance misuse, known poor response to stimulants, cardiac problems |

| Study | Jain 2007[360] |
|---|---|
| | Studies where response to previous treatment is an inclusion criteria: “Patients were excluded from the study if they had a true allergy to methylphenidate or amphetamines; a history of serious adverse reactions to methylphenidate or were known to be non-responders” |
| Recruitment/selection of patients | Unclear |
| Age, gender and ethnicity | Age - Range: 18-60., mean age 37.2 years Gender: Male 30 female 18 . Ethnicity: White n=42 |
| Further population details | unclear |
| Indirectness of population | No indirectness |
| Interventions | Intervention: Methylphenidate OROS 80mg/d<br><br>Comparison: Placebo<br><br>Crossover trial (n=50) |
| Funding | Funding industry ( Novartis pharmaceuticals Corporation) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON:<br>Insomnia<br>Intervention 11 /50 ,placebo 4/50 | |
| Protocol outcomes not reported by the study | Total numbers of participants with adverse events, All-cause mortality, Suicide or suicidal ideation ,Cardiac mortality, Cardiac events including tachycardia/palpitations (defined by >/120bpm), and systolic and diastolic blood pressure changes, Substance abuse, Abnormal growth ( height and weight),Appetite changes, Increase in seizures in people with epilepsy, Liver damage (defined by deranged LFTs),Increased tics ,Tremors, Congenital defects amongst patients who are pregnant, Sexual dysfunction, Psychotic symptoms |
| Risk of bias details | |

| Study | Jain 2011[359] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=236) |
| Countries and setting | Conducted in USA |
| Line of therapy | Unclear |

| Study | Jain 2011[359] |
|---|---|
| Duration of study | Intervention 8 weeks |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis: DSM-IV |
| Stratum | Children (up to 18 years); normal risk |
| 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, syncope 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: 6-17 years. Gender (M:F): . Ethnicity: not reported |
| Further population details | 1. ADHD subtype: All/mixed 2. Age: mean age 9.5 years 3. At risk population: 4. Comorbidities: Not specified 5. Diagnostic method: DSM 6. Line of treatment: Not stated 7. Severity: Minimum score 26 on ADHD-RS |
| Extra comments | Excluding non responders |
| Indirectness of population | No indirectness |
| Interventions | Clonidine 0.2mg/day. Titration of 0.1mg/day per week increase. Patients who warranted dose reductions due to AEs were discontinued<br>Clonidine 0.4mg/day<br>(154 vs. 76)<br>Placebo |
| Funding | Study funded by industry (Study was funded by Cephalon) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CLONIDINE GROUPS versus PLACEBO GROUP<br>High risk<br>Overall adverse events 108/130; 56/78<br>Insomnia 9;1<br>Irritability 13;3 | |

| Study | Jain 2011[359] |
|---|---|
| Deaths 0;0 | |
| 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[355] |
|---|---|
| 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 | Children and adolescents aged 6-17 years who met the DSM-IV-TR diagnostic criteria for ADHD. To be included, the patients should have 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. Prior to entry, a child and adolescent psychiatrist confirmed the diagnosis of ADHD. 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 | psychiatric co-morbidities ( excluding ODD), high risk of suicide, mental retardation, 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 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 naive) (All drug naive). 7. Severity: Not applicable / Not stated / Unclear (Possibly excluding mild? 1.5 |

| Study | Jafarinia 2012[355] |
|---|---|
| | 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 (20 in each group)<br><br>Decreased appetite 9;11<br>Insomnia 7;10<br>Tachycardia 2;1<br><br>Low risk of bias | |
| 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 | Kahbazi 2009[371] |
|---|---|
| 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 | Overall: Children |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | ADHD-RS-IV score at least 1.5 SDs above norms. |
| 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 250mg/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 - Modafanil. Once daily 200-300mg per day depending on weight (200mg/day for <30kg and 300mg/day for >30kg). Titration process: week 1 100mg/day, week 2 200mg/day, week 3 300mg/day (for children weighing >30kg).. Duration 6 weeks. Concurrent medication/care: Not stated 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 |

| Study | Kahbazi 2009[371] |
|---|---|
| | 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<br><br>Low risk of bias<br>Weight loss 2;23; 1/23 | |
| 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 | Kaplan 2004[374] (Biederman 2002[93]) |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 2 (n=98) |
| Countries and setting | Conducted in USA; Setting: Multicentre trial in the US; Study 1: 7 sites, Study 2: 10 sites |
| 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 | Patients met diagnostic criteria as defined by DSM-IV and assessed by clinical interview and the Kiddie Schedule for Affective Disorders and Schizophrenia. Patients also met criteria for ODD as characterised by the computerised Diagnostic Interview for Children and Adolescents-IV completed by the parent and confirmed by clinical assessment according to DSM-IV criteria. As a participation requirement, patients scored as least 1.5 standard deviations above the age and gender norms for their ADHD diagnostic subtype on the ADHD-RS-IV-Parent: Inv. All children had an IQ in the normal range, as measured by four subjects of the Wechsler Intelligence Scale for Children - 3rd edition. |

| Study | Kaplan 2004[374] (Biederman 2002[93]) |
|---|---|
| Exclusion criteria | Patients were excluded from the studies if they had significant prior or current medical conditions, psychosis, seizure disorder, history of alcohol or drug abuse within the past 3 months or positive screening for abuse of drugs or were identified as poor metabolisers of the cytochrome P4502D6 |
| Recruitment/selection of patients | Not stated |
| Age, gender and ethnicity | Age - Range: 7-13. Gender (M:F): 78/20. Ethnicity: Not stated |
| Further population details | 1. ADHD subtype: Not applicable / Not stated / Unclear 2. Age: Children (6-12 years) (7-13 years). 3. At risk population: General population 4. Comorbidities: ODD (All patients also had ODD). 5. Diagnostic method: DSM (DSM-IV). 6. Line of treatment: Not applicable / Not stated / Unclear 7. Severity: Not applicable / Not stated / Unclear (ADHD-RS-IV score of at least 1.5 standard deviations above age and gender norms). |
| Extra comments | This population was a subset of patients from two identical multicentre trials that took place in the US. |
| Indirectness of population | No indirectness |
| Interventions | (n=53) Intervention 1: CNS stimulants - Atomoxetine. Atomoxetine was titrated based on clinical response and tolerability. The maximum total daily dose was 2mg/kg or 90mg, whichever was lower based on a flexible dose-titration schedule. Mean dose at conclusion of the studies was 1.6mg/kg/day (SD 0.6) and the mean total daily dose was 55.3mg (SD 19). Duration 9 week. Concurrent medication/care: Not stated<br>Further details: 1. Dose:  2. Method of titration: Titrated to optimum dose (Titrated based on clinical response and tolerability).<br><br>(n=45) Intervention 2: No treatment - Placebo. Drug materials for all treatment groups in the study were identical in appearance. Duration 9 weeks. Concurrent medication/care: Not stated<br>Further details: 1. Dose:  2. Method of titration: |
| Funding | Funding not stated |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE versus PLACEBO<br>Decreased appetite 10;7<br>Nervousness 8;3<br>Emotional lability 6;0<br>Somnolence 6;3<br>Low risk of bias | |
| 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 |

| Study | Kaplan 2004[374] (Biederman 2002[93]) |
|---|---|
| | numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months |

| Study | Kelsey 2004[377] |
|---|---|
| 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) on-going 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 0.8mg/kg per day for 3 days, followed by 1.2mg/kg per day for the reminder 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 |

| Study | Kelsey 2004[377] |
|---|---|
| | (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>Decreased appetite 23;4<br>Somnolence 19;1<br>Supine systolic blood pressure change(mmHg): +1.4(8.3); +1(7.9)<br><br>Low risk of bias | |
| 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[387] |
|---|---|
| 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 |

| Study | Kollins 2011[387] |
|---|---|
| | 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: |
| Funding | Study funded by industry (Shire Development Inc.) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GXR GROUP versus PLACEBO GROUP<br><br>Somnolence 41.3%; 22.8%<br>High risk of bias | |
| 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 | Kooij 2004[394] |
|---|---|

| Study | Kooij 2004[394] |
|---|---|
| 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 |
| 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 adverse 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 |

| Study | Kooij 2004[394] |
|---|---|
| | 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<br>- 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 | Kuperman 2001[399] |
|---|---|
| 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 |

| Study | Kuperman 2001[399] |
|---|---|
| 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). 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 |

| Study | Kuperman 2001[399] |
|---|---|
| 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

Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months
- Actual outcome for Adult: Discontinued due to adverse events at 7 weeks; Group 1: 0/11, Group 2: 1/11; Risk of bias: High; Indirectness of outcome: No indirectness

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 Adult: Treatment response at 7 weeks; Group 1: 4/8, Group 2: 3/11; Risk of bias: High; Indirectness of outcome: No indirectness

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

| Study | Kuperman 2001[399] |
|---|---|
| - 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[406] |
|---|---|
| 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 |
| 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 |

| Study | Lee 2014[406] |
|---|---|
| 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

Protocol outcome 2: ADHD symptoms at <3- or >6-months
- Actual outcome for Adult: Treatment response (CGI-ADHD-S) at 10 weeks; Group 1: 18/36, Group 2: 10/37; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adult: CAARS Total score at 10 weeks; Group 1: mean -18.9 (SD 11.1); n=36, Group 2: mean -9 (SD 8.8); n=37; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adult: CAARS Inattention subscale at 10 weeks; Group 1: mean -10 (SD 5.5); n=36, Group 2: mean -4.2 (SD 4); n=37; CAARS 0-27 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adult: CAARS Hyperactivity subscale at 10 weeks; Group 1: mean -8.9 (SD 6.4); n=36, Group 2: mean -4.9 (SD 5.5); n=37; CAARS 0-27 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness

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

| Study | Lee 2014[406] |
|---|---|
| - 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[435] |
|---|---|
| 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 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 |

| Study | Martenyi 2010[435] |
|---|---|
| | 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 | No indirectness |
| 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) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE versus PLACEBO<br><br>Somnolence 11;3<br>Weight loss 6;0<br>Deaths 0<br>Suicidal ideation 0<br>Total adverse events: 44/72; 11/33<br>Height changes (cm): 0.5(0.8); 0.7(1.1)<br>Systolic BP (mmHg): -1.4(10.4); 2.2(8.8)<br>Low risk of bias | |
| 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 |

| Study | Martenyi 2010[435] |
|---|---|
| | numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months |

| Study | NCT00246220;CR002479 trial: Medori 2008[452] |
|---|---|
| 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 |
| 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 Statisticak 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 |

| Study | NCT00246220;CR002479 trial: Medori 2008[452] |
|---|---|
| | 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 recieved 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<br>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 recieved 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 recieved 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 |

| Study | NCT00246220;CR002479 trial: Medori 2008[452] |
|---|---|
| | 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: |
| 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<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- Actual outcome: CAARS Self Form Total Scores (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 co-morbidities 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: 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);<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 co-morbidities 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 co-morbidities 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>missing:<br><br>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months | |

| Study | NCT00246220;CR002479 trial: Medori 2008[452] |
|---|---|
| - Actual outcome: Drop out due to adverse events at 5 weeks; Group 1: 2/101, Group 2: 0/96<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 co-morbidities 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: METHYLPHENIDATE 36MG (INCLUDING MODIFIED-RELEASE PREPARATIONS) versus METHYLPHENIDATE 72MG (INCLUDING MODIFIED-RELEASE PREPARATIONS)<br><br>Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- Actual outcome: CAARS Self Form Total Scores (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 co-morbidities 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 co-morbidities 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 co-morbidities 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 co-morbidities 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 | |

| Study | NCT00246220;CR002479 trial: Medori 2008[452] |
|---|---|
| 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 co-morbidities 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 | Michelson 2002[457] |
|---|---|
| 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 |

| Study | Michelson 2002[457] |
|---|---|
| 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<br>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[456] |
|---|---|

| Study | Michelson 2003[456] |
|---|---|
| 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 |
| 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

| Study | Michelson 2003[456] |
|---|---|
| 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, 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<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 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 2012[463] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=46) |
| Countries and setting | Conducted in Iran; Setting: |

| Study | Mohammadi 2012[463] |
|---|---|
| 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 |
| 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 (2) |
| 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 Roozveh 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 naive) (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 20-30mg doses depending on weight (20 mg/day for patients<30kg, and 30mg/day for patients over 30kg. . 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 20-30mg doses depending on weight (20 mg/day for patients less than 30kg, and 30mg/day for patients over 30kg. . 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) |

| Study | Mohammadi 2012[463] |
|---|---|
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MPH GROUP versus BUSPIRONE<br><br>High risk of bias due to attrition bias<br>Insomnia: 9/23; 1/23<br>Tics 4/23; 3/23<br>Decreased appetite 9/23; 2/23 | |
| 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 | Montoya 2009[466] |
|---|---|
| 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-naive, 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 |

| Study | Montoya 2009[466] |
|---|---|
| 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 disorder; 3.4% affective disorder; 12.8% anxiety disorder)). 5. Diagnostic method: DSM (DSM-IV-TR). 6. Line of treatment: 1st line (drug naive) (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<br><br>Low risk of bias<br>Total adverse events: 65/100; 19/51<br>Decreased appetite: 27/100; 4/51 | |
| 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 | Newcorn 2008[481] |
|---|---|
| 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, symptom severity was required to be at least 1.5 SD above the 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 |

| Study | Newcorn 2008[481] |
|---|---|
| | (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 versus PLACEBO<br><br>Change in weight (kg)<br>ATX 221 -0.6(1.4)<br>MPH 219 -0.9(1.3)<br>PLC 74 1.1(1.3)<br><br>Total adverse events: 149/221; 146/219; 40/74<br>Changes in systolic BP(mmHg): -0.6(1.4); -0.9(1.3); 1.1(1.3) | |
| 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 | Merged with Newcorn 2005 trial: Michelson 2001[459] |
|---|---|
| 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 |

| Study | Merged with Newcorn 2005 trial: Michelson 2001[459] |
|---|---|
| Stratum | Overall: Children |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Diagnosis confirmed by KSADS-PL, ADHD-RS score 1.5 standard deviations above age and gender norms |
| Exclusion criteria | Patients who met diagnostic criteria for current major depression or anxiety disorder or for current or past bipolar or psychotic disorders were exclude, IQ below 80, history of seizure disorder |
| Recruitment/selection of patients | Recruitment was 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% unspecified |
| 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 given for each treatment group in both studies) |
| Indirectness of population | No indirectness |
| Interventions | (n=84) 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 0.5mg/kg per day, and this was titrated up to 0.8mg/kg and then 1.2mg/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:<br><br>(n=44) Intervention 3: 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 0.5mg/kg per day.. Duration 8 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=85) Intervention 4: CNS stimulants - Atomoxetine. dose/quantity, brand name, extra details. Duration 8 weeks. Concurrent medication/care: 12 to 18 day evaluation and medication washout period was followed by randomisation to dosage, for approximately 8 weeks. All patients began on 0.5mg/kg per day, and this was titrated up to 0.8mg/kg and then 1.2mg/kg at weekly intervals. |

| Study | Merged with Newcorn 2005 trial: Michelson 2001[459] |
|---|---|
| | Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose |
| Funding | Study funded by industry (research funded by Eli Lilly and Company) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE 1.2MG versus PLACEBO<br>High risk of bias due to attrition<br>ATX 1,2kg 84 Placebo 83<br>Anorexia 10;4<br>Insomnia 5;5<br>Depression 0;5<br>Weight (kg) -0.4(1.4); 1.7(1.6)<br><br>Systolic BP change: +3.4(9.84); +2.1(9.5) | |
| 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 | Nagaraj 2006[476] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=39) |
| Countries and setting | Conducted in India; Setting: Pediatric Neurodevelopment Clinic of the department of Paediatrics at the Advanced Pediatric 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. |

| Study | Nagaraj 2006[476] |
|---|---|
| Exclusion criteria | Severe mental retardation, any significant co-existing disease or illness (neurologic, cardiovascular, respiratory, genetic) or 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, aggression, stereotypies and language difficulties |
| Age, gender and ethnicity | Age - Other: Up to 12 years old. Gender (M:F): 34/5. Ethnicity: |
| 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. Sizodon, Sun pharmaceuticals, Mumbai. Duration 6 months. Concurrent medication/care: Psychoactive medication was stopped at least one month prior to entering the trial, no medication was administered concurrently<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>Low risk of bias<br>Mean weight change(kg): 2.81kg(2.04); 1.71kg(1.3) | |
| 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 (subsidiary papers) | Newcorn 2013[483] (Stein 2015[601]; Young 2014[707] |
|---|---|

| Study (subsidiary papers) | Newcorn 2013[483] (Stein 2015[601]; Young 2014[707] |
|---|---|
| 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 | Any controlled or uncontrolled psychiatric diagnosis (except oppositional defiant disorder). Risk of suicidality, history or presence of cardiac abnormalities or a primary sleep disorder, body weight of less than 55lbs or a body mass index over the 95th percentile. Use of another investigational product within 30 days of baseline |
| 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 America (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 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. |

| Study (subsidiary papers) | Newcorn 2013[483] (Stein 2015[601]; Young 2014[707] |
|---|---|
| | 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: |
| 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
Total AEs 190/221; 64/112
Suicidal ideation 1;0
Increased app 2;6 decreased 9; 3
Insomnia 9;4

| Study (subsidiary papers) | Newcorn 2013[483] (Stein 2015[601]; Young 2014[707] |
|---|---|
| Irritability 16;3 | |
| 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 |

| Study | Paterson 1999[498] |
|---|---|
| Study type | RCT ( randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=45) |
| Countries and setting | Conducted in Australia; Setting: Not reported |
| Line of therapy | Unclear |
| Duration of study | Intervention time: 6 weeks |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis: DSM-IV ADHD symptom checklist questionnaire |
| Stratum | Adult |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Subjects were eligible for inclusion if they reported the presence of at least four inattentive and/or five hyperactive symptoms during the previous 6 months. |
| Exclusion criteria | Subjects were excluded from the study on the grounds of either having an insufficient ADHD score, or comorbidity for other major psychiatric disorders including a history of current substance abuse. Patients were screened for organic disorders that would contraindicate the use of dexamphetamine. All patients had a sample of urine tested to screen for illicit substance abuse. |
| Recruitment/selection of patients | Two psychiatrists working in private practice, screened consecutive patients for a research trial into adult ADHD using a questionnaire based on the DSM-IV symptoms. |
| Age, gender and ethnicity | Age - Range: 19-57. Gender (M:F): 27:18. Ethnicity: Not reported |
| Further population details | 1. ADHD subtype: All/mixed subtypes 2. Age: Adults 18-65 years) (19-57). 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: DSM (DSM-IV ADHD symptom checklist questionnaire). 6. Line of treatment: Not applicable / Not stated / Unclear 7. |

| Study | Paterson 1999[498] |
|---|---|
| | Severity: Not applicable / Not stated / Unclear |
| Indirectness of population | Serious indirectness: Unclear line of therapy |
| Interventions | (n=24) Intervention 1: CNS stimulants - Dexamphetamine. Subjects began at a low dose and the dose was gradually increased, patients were told to take the dose before early afternoon to avoid insomnia. For the first week patients took one tablet each morning after breakfast. For the second week, they took one tablet after breakfast and one tablet after lunch. For the third week, they took two tablets after breakfast and one after lunch. For the remaining three weeks, patients were instructed that they could take up to six tablets per day but incremental increases were not to be more than one tablet per day, with two days between increases. Duration 6 weeks. Concurrent medication/care: Not reported<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 with identical instructions to dexamphetamine 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: DEXAMPHETAMINE 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) | Palumbo 2008[495] (Daviss 2008[206], Cannon 2009[141]) |
|---|---|
| Study type | RCT |
| Number of studies (number of participants) | 2 (n=122) |
| Countries and setting | Conducted in USA; Setting: University of Rochester Clinical Trials Co-ordination Center (CTCC).Four sites |

| Study (subsidiary papers) | Palumbo 2008[495] (Daviss 2008[206], Cannon 2009[141]) |
|---|---|
| | 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 |
| 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 Iowa 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 |

| Study (subsidiary papers) | Palumbo 2008[495] (Daviss 2008[206], Cannon 2009[141]) |
|---|---|
| | 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 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 adverse 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. Not sure-check. 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 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. |

| Study (subsidiary papers) | Palumbo 2008[495] (Daviss 2008[206], Cannon 2009[141]) |
|---|---|
| | Further details: 1. Dose: 2. Method of titration:<br><br>(n=92) Intervention 5: Clonidine. Three treatments groups combined (MPH, Clonidine and combination of MPH and Clonidine). 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: |
| Funding | Academic or government funding (Project supported by NINDS grant 5R01 NS039087. Additional NIG support came from K23 MH065375 and K24 AA000301) |
| 16 weeks; high risk of bias due to attrition<br>Psychotic symptoms<br>Depression: Placebo (30) 20%; MPH (29) 17.2%; CLON (31) 22.6% COMB (32) 12.5%<br>Insomnia: Placebo (30) 16.7%; MPH (29) 3.4%; CLON (31) 16.1% COMB (32) 12.5%<br>Hallucinations: all 0 but COMB 3.1%<br>Loss of appetite 10%; 13.8%; 29%; 9.4%<br>Palpitations: all 0 but MPH 3.4%<br>Weight change 1.4(1.6) 0.3(2.3) 2.0(2.9) 0.6(2.3)<br>Supine SBP: Placebo (30) -2(7.1); MPH (29) -1.1(7.6); CLON (31) 0.9(10); COMB (32) 2.8(11.6) | |
| 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; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months |

| Study (subsidiary papers) | PATS trial: Greenhill 2006[297] (Kollins 2006[384]) |
|---|---|
| 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 |

| Study (subsidiary papers) | PATS trial: Greenhill 2006[297] (Kollins 2006[384]) |
|---|---|
| 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 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 |

| Study (subsidiary papers) | PATS trial: Greenhill 2006[297] (Kollins 2006[384]) |
|---|---|
| | 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 (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 |

| Study (subsidiary papers) | PATS trial: Greenhill 2006[297] (Kollins 2006[384]) |
|---|---|
| | 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<br>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 All INTERVENTION GROUPS versus PLACEBO GROUP<br><br>Tachycardia: 0 events 10 weeks | |
| 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) | Reimherr 2007[527] (Robison 2010[535]) |
|---|---|
| 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 | Adequate method of assessment/diagnosis: DSM-IV |

| Study (subsidiary papers) | Reimherr 2007[527] (Robison 2010[535]) |
|---|---|
| condition | |
| 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 / 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

| Study (subsidiary papers) | Reimherr 2007[527] (Robison 2010[535]) |
|---|---|
| Top=High is poor outcome<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: 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<br>- 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<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: 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<br>- 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<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: 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<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[529] |
|---|---|
| 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 |

| Study | Retz 2012[529] |
|---|---|
| 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 n 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. 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 | |

| Study | Retz 2012[529] |
|---|---|
| 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 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 | Low risk of bias |

| Study | Riahi 2010[532] |
|---|---|
| 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 |

| Study | Riahi 2010[532] |
|---|---|
| | 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 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

Protocol outcome 1: ADHD symptoms at <3- or >6-months
- Actual outcome for Adult: Conners Adult ADHD Rating Scale inattentiveness subscore at 6 weeks; Group 1: mean 11.31 (SD 5.17); n=22, Group 2: mean 16.05 (SD 4.65); n=17; CAARS ? Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Adult: Conners Adult ADHD Rating Scale hyperactivity subscore at 6 weeks; Group 1: mean 10.54 (SD 4.89); n=22, Group 2: mean 11.47 (SD 5.14); n=17; CAARS ? Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Adult: Conners Adult ADHD Rating Scale ADHD index subscore at 6 weeks; Group 1: mean 15.77 (SD 6.36); n=22, Group 2: mean 21.05 (SD 5.6); n=17; CAARS ? Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Adult: Conners Adult ADHD Rating Scale total score at 6 weeks; Group 1: mean 21.86 (SD 9.63); n=22, Group 2: mean 27.47 (SD 8.18); n=17; CAARS ? Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness

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

Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months
- Actual outcome for Adult: Drop out due to adverse events at 6 weeks; Group 1: 2/23, Group 2: 1/17; Risk of bias: Low; Indirectness of outcome: No indirectness

| Study | Riahi 2010[532] |
|---|---|
| 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[538] (Rosler 2010[540]) |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=359) |
| 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 |

| Study (subsidiary papers) | Rosler 2009[538] (Rosler 2010[540]) |
|---|---|
| | 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: |
| 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 | Scahill 2015[557] |
|---|---|
| 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 |
| 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 |

| Study | Scahill 2015[557] |
|---|---|
| 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, 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 |
| Funding | Academic or government funding (Funded by NIMH grants) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GUANFACINE EXTENDED RELEASE versus PLACEBO | |

| Study | Scahill 2015[557] |
|---|---|
| psychotic symptoms (1;0)<br>Mid sleep awakening 9;2 | |
| 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 |

| Study | ISRCTN 68384912 trial: Simonoff 2013[579] |
|---|---|
| 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 |
| 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. |

| Study | ISRCTN 68384912 trial: Simonoff 2013[579] |
|---|---|
| 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<br><br>(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>High risk of bias due to attrition<br>Trouble sleeping 13;2<br>Poor appetite 9;1<br>Weight change kg -2.7 (-3.72, -1.67) mean difference<br>Systolic BP at endpoint 104.2(11.5); 102.1(12.1) | |
| 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- |

| Study | ISRCTN 68384912 trial: Simonoff 2013[579] |
|---|---|
| | 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 | Sallee 2009[549] |
|---|---|
| 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 pulse 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 |

| Study | Sallee 2009[549] |
|---|---|
| | Further details: 1. Dose: Mixed 2. Method of titration: Fixed dose<br><br>(n=66) Intervention 2: No treatment - Placebo. Placebo. Duration 6 weeks (plus 3 weeks discontinuation). 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>High risk of bias due to attrition<br>Total adverse events: 189/256; 50/66;<br>CV events 0 | |
| 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[556] |
|---|---|
| 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 condition | Adequate method of assessment/diagnosis: clinical evaluation by an interdisciplinary team consisting of a 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 |

| Study | Scahill 2001[556] |
|---|---|
| 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 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 | |

| Study | Scahill 2001[556] |
|---|---|
| Low risk of bias<br>Systolic blood pressure at end point(mmHg): 110.8(11); 110.6(17)<br>Yale Global Tic Severity total score endpoint: 10.7(7); 15.4(5.5) (range 0-25; high is poor outcome)17 | |
| 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 |

| Study | Shin 2016[571] |
|---|---|
| Study type | NRS (case series) |
| Number of studies (number of participants) | (n=114,647) |
| Countries and setting | South Korea; Setting: South Korea national health insurance claims database. This program was initiated in Korea in 1977 and achieved coverage of the entire population by 1989. |
| Line of therapy | 1st line |
| Duration of study | Intervention time: 6 months (median) |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis: ICD-10 |
| Stratum | Children; low/normal risk |
| Subgroup analysis within study | |
| Inclusion criteria | (1)ICD-10 diagnosis of ADHD (2) had started taking methylphenidate (3) had an incident cardiovascular adverse event during the study period (defined as arrhythmia, hypertension, myocardial infarction, ischemic stroke or heart failure) |
| Exclusion criteria | None specified |
| Recruitment/selection of patients | Claims data for children and young people with a diagnosis of ADHD that was submitted by healthcare providers from 1 January 2007 to 31 December 2011 |
| Age, gender and ethnicity | Age - Range: 17 or less years.<br>Gender only reported in those with events: 75-80%<br>Ethnicity: Not specified |
| Further population details | 1. ADHD subtype: Not applicable / Not stated / Unclear (Not specified). |

| Study | Shin 2016[571] |
|---|---|
| | 2. Age: Children 17 years old or younger<br>3. At risk population: Not applicable / Not stated / Unclear<br>4. Comorbidities: Only reported in those with events: 29.4% had previous depressive episodes, 10.3% tic disorder, 10.3% emotional disorders, 10% conduct disorder, 7.3% congenital heart disease<br>5. Diagnostic method: ICD-10<br>6. Line of treatment: 1st line (all participants were newly diagnosed)<br>7. Severity: Not applicable / Not stated / Unclear |
| Extra comments | |
| Indirectness of population | No indirectness |
| Interventions | (n=114,647) Intervention: Methylphenidate. Exposure was defined by submitted prescriptions, mean duration of 0.5 months for each period of drug use; Concomitant therapy: only described for those with events: 4-13% antipsychotics, 1-2% atomoxetine, 15-20% heart failure, 7-25% antiepileptic drugs |
| Funding | No funding received; supported by NHMRC fellowship. |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE<br><br>Cardiovascular events<br>Actual outcome for Children: First cardiovascular event at 6 months; Risk of bias: ; Indirectness of outcome: No indirectness<br>Intervention: 350/114,647 (234 arrhythmias, 92 hypertension, 10 myocardial infarction, 10 ischaemic stroke, 4 heart failure)<br>Comparison:1073/114,647 (630 arrhythmias, 304 hypertension, 42 myocardial infarction, 57 ischaemic stroke, 40 heart failure) | |
| Risk of bias details | Very high risk of bias due to (1) outcome reporting bias (2) possibility of inaccurate ADHD diagnosis due to reliance on medical records) |

| Study | Singer 1995[580] |
|---|---|
| Study type | RCT (Patient randomised; Crossover: 1 week) |
| 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 |

| Study | Singer 1995[580] |
|---|---|
| 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. A paediatric neurologist using Diagnostic and Statistical Manual IIIR criteria, with independent confirmation by a child psychologist, made the diagnosis of TS and ASDHD. |
| 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  - Desipramine. 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 adverse 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 adverse 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 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 adverse 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 |

| Study | Singer 1995[580] |
|---|---|
| | (Each patient was maintained at the highest dose that did not produce adverse 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 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 CLONIDINE<br><br>High risk of bias<br>Total adverse effects: 26/34; 28/34 | |
| 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 | Spencer 2002[594] |
|---|---|
| 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 |

| Study | Spencer 2002[594] |
|---|---|
| | abuse or dependence, or current use of other psychotropic drugs. Pregnant or nursing females were also excluded. Patients with a personal history of nongeriatric 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 months 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: 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 months of the baseline assessment, and no additional psychoactive medication was allowed in the trial. Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear |
| Funding | Academic or government funding (Funded by the Tourette's Society Association and the National Institute of Mental Health) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DESIPRAMINE versus PLACEBO<br><br>Low risk of bias<br>Decreased appetite: 5/21; 0/20<br>Difficulty sleeping: 4/21; 1/20<br>Improvement to tics: 11/21; 1/20 | |
| 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 | Spencer 2002[594] |
|---|---|
| | months; Emotional dysregulation at <3- or >6-months |

| Study | Spencer 2005[595](Biederman 2006)[97] |
|---|---|
| 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 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). |

| Study | Spencer 2005[595](Biederman 2006)[97] |
|---|---|
| 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 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 |

| Study | Spencer 2005[595](Biederman 2006)[97] |
|---|---|
| Risk of bias details | High risk of attrition bias |

| Study | Spencer 2007[596] |
|---|---|
| Study type | RCT |
| Number of studies (number of participants) | 1 (n=221) |
| Countries and setting | Conducted in USA; Setting: multicentre 18 sites |
| Line of therapy | Mixed line |
| Duration of study | Intervention time: 5 weeks |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis: Adults 18-60 years diagnosed with ADHD according to DSM-IV criteria with childhood onset<br><br>ADHD-RS score > 24 |
| 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 score > 24, 2 Age 18-60 years |
| Exclusion criteria | Known mental health conditions, substance misuse, known poor response to stimulants, |
| Recruitment/selection of patients | unclear |
| Age, gender and ethnicity | Age - Range: 18-60., mean age 38.7 years Gender: Male 127 female 94 . Ethnicity: Not reported |
| Further population details | 1. ADHD subtype: All/mixed subtypes (Inattentive (59), Combined (155), Hyperactive (7)). 2. Age: Adults 18-65 years) 3. At risk population: General population 5. Diagnostic method: DSM-IV. Line of treatment: Mixed line (including drug naive) 7. Severity: Unclear |
| Indirectness of population | No indirectness |
| Interventions | Intervention 1:<br>Dexamphetamine ER<br>20mg/d ( n=58)<br><br>Intervention 2:<br>Dexamphetamine ER |

| Study | Spencer 2007[596] |
|---|---|
| | 30mg/d ( n=55)<br><br>Intervention 3:<br>Dexamphetamine ER<br>40mg/d( n=55)<br><br>Comparison :Placebo (n=53) |
| Funding | Funding industry ( Novartis pharmaceuticals Corporation) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DEXAMPHETAMINE versus PLACEBO<br>Insomnia<br>20mg 10/58,30mg 7/55,40mg 10/55,placebo 6/53 | |
| Protocol outcomes not reported by the study | Total numbers of participants with adverse events, All-cause mortality, Suicide or suicidal ideation ,Cardiac mortality, Cardiac events including tachycardia/palpitations (defined by >/120bpm), and systolic and diastolic blood pressure changes, Substance abuse, Abnormal growth ( height and weight),Appetite changes, Increase in seizures in people with epilepsy, Liver damage (defined by deranged LFTs),Increased tics , Tremors, Congenital defects amongst patients who are pregnant, Sexual dysfunction, Psychotic symptoms |
| Risk of bias details | |

| Study | Spencer 2008[600] |
|---|---|
| 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[600] |
|---|---|
| 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<br><br>Tics continuous outcome<br>Yale global tic severity scale -5.1(7.1); -2(8.4) 0-100<br>Tic symptom self-report: -4.7(6.9); -2.4(5.5)<br>Decreased appetite 11;1<br>Decreased weight (-1kg(2.1);+1.3kg(2.2) | |
| 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 | Spencer 2008[600] |
|---|---|
| study | outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months |

| Study | Sutherland 2012[612] |
|---|---|
| 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. |
| 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 |

| Study | Sutherland 2012[612] |
|---|---|
| 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) |

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: Adult ADHD Investigator Rating Scale total scores (LS mean difference, adj for baseline scores, study week, treatment group, week-by treatment interaction) at 8 weeks;  Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adult: Adult ADHD Investigator Rating Scale inattentive subscale change scores (LS mean difference, adj for baseline scores, study week, treatment group, week-by treatment interaction) at 8 weeks;  Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adult: Adult ADHD Investigator Rating Scale hyperactive/impulsive subscale change scores (LS mean difference, adj for baseline scores, study week, treatment group, week-by treatment interaction) at 8 weeks;  Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adult: Brown Attention Deficit Disorder scale total change scores at 8 weeks; Group 1: mean -32.3  (SD 25.6); n=97, Group 2: mean -

| Study | Sutherland 2012[612] |
|---|---|
| 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 (subsidiary papers) | Svanborg 2009[614] (Svanborg 2009[613]) |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | (n=99) |
| Countries and setting | Conducted in Sweden; Setting: Multi-centre (9 outpatient investigative sites) |
| Line of therapy | 1st line |
| Duration of study | Intervention time: 10 weeks |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis: DSM-IV |
| Stratum | Overall: Children |

| Study (subsidiary papers) | Svanborg 2009[614] (Svanborg 2009[613]) |
|---|---|
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | (1) Severity of 1.5 SDs above the US age and gender norms on the ADHD-RS- Parent Version (2) Stimulant naive (3) not in need of immediate symptom relief. |
| Exclusion criteria | (1) Intelligence impairment (2) serious medical illnesses (3) a history of psychosis or bipolar disorder (4) alcohol or drug abuse within the previous 3 months (5) on-going use of psychoactive medication other than the study drug (6) requirement of immediate pharmacotherapy |
| Recruitment/selection of patients | Consecutive recruitment from clinic waiting lists |
| Age, gender and ethnicity | Age - Range: 6 to 15 years. Gender (M:F): 80:19. Ethnicity: 93.9% Caucasian, 3% Asian, 1% African, 2% Other |
| Further population details | 1. ADHD subtype: All/mixed subtypes (77.8% combined, 4% hyperactive, 18.2% inattentive). 2. Age: Mixed (Children and young people aged 6-15years). 3. At risk population: Not applicable / Not stated / Unclear (Not stated). 4. Comorbidities: Mixed (Some comorbidities excluded; ODD 20.2%; tic disorder 14.1%; MDD 5.1%; conduct disorder 0%). 5. Diagnostic method: DSM (DSM-IV). 6. Line of treatment: 1st line (drug naive) (Stimulant naive). 7. Severity: Not applicable / Not stated / Unclear (Mean total ADHD-RS-IV = 39). |
| Extra comments | ADHD |
| Indirectness of population | No indirectness |
| Interventions | (n=49) Intervention 1: CNS stimulants - Atomoxetine. 2 capsules every morning. In week 1 patients weighing 70kg or less received a dose of 0.5mg/kg per day, and patients weighing more than 70kg received 40mg/day. This was titrated to 1.2mg/kg after 1 week, or 80mg/day respectively. . Duration 10 weeks. Concurrent medication/care: 4 session psych educational training offered, aimed at improving caregivers' understanding of ADHD. Attendance was not monitored so numbers receiving this training is unknown. Further details: 1. Dose:  2. Method of titration:<br><br>(n=50) Intervention 2: No treatment - Placebo. placebo. Duration 10 weeks. Concurrent medication/care: 4 session psych educational training offered, aimed at improving caregivers' understanding of ADHD. Attendance was not monitored so numbers receiving this training is unknown.<br>Further details: 1. Dose:  2. Method of titration: |
| Funding | Study funded by industry (Eli Lilly Sweden) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE versus PLACEBO<br><br>Anorexia 17;0 | |

| Study (subsidiary papers) | Svanborg 2009[614] (Svanborg 2009[613]) |
|---|---|
| Depressive symptoms 5;2 | |
| Protocol outcomes not reported by the study | 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 | Swanson 2006[615] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=246) |
| Countries and setting | Conducted in USA; Setting: 17 sites in the USA |
| 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 | Patients were 6 to 17 years of age and had a diagnosis of ADHD on the basis of criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) for ADHD at screening, Clinical Global Impression Severity of Illness (CGI-S) rating of 4 or higher (“moderately ill” or worse).22 In addition, patients were attending full-time school (i.e., they were not being home-schooled); had a teacher-/investigator-rated Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) School Version total and/or subscale score at least 1.5 SDs above normal values for age and gender, were between the 5th and 95th percentile for weight and height on the basis of National Center for Health Statistics guidelines, had an IQ of at least 80 as estimated by the Wechsler Intelligence Scale for Children–Third Edition, and had a score of at least 80 on the Wechsler Individual Achievement Test–Second Edition–Abbreviated |
| Exclusion criteria | Patients were excluded when they had a history or current diagnosis of pervasive developmental disorder, schizophrenia, or other psychotic disorders (DSM-IV Axis I); evidence of suicide risk; current psychiatric comorbidity that required pharmacotherapy; or other active clinically significant disease. To avoid potential ethical concerns, patients whose ADHD was well controlled and who were satisfied with current ADHD therapy (with low levels of adverse effects) were also excluded, as were those who had failed to respond to 2 or more adequate courses (dose and duration) of stimulant therapy for ADHD. Other exclusion criteria included a clinically significant drug sensitivity to stimulants, a history of alcohol or substance abuse as defined by DSM-IV criteria,21 consumption of >250 mg/day caffeine, absolute neutrophil count <1 × 109/L, |

| Study | Swanson 2006[615] |
|---|---|
| | hypertension (systolic blood pressure [SBP] of ≥122 mm Hg or diastolic blood pressure [DBP] of ≥78 mm Hg for patients aged 6–9 years; SBP of ≥126 mm Hg or DBP of ≥82 mm Hg for patients aged 10–12 years; SBP of ≥136 mm Hg or DBP of ≥86 mm Hg for patients aged 13–17 years), hypotension (sitting SBP <50 mm Hg for patients younger than 12 years or <80 mm Hg for patients 12 years and older), and resting pulse rate outside the range of 60 to 115 beats per minute. Concomitant use of prescription or non-prescription agents with psychotropic properties, including ADHD treatments and dietary supplements, was prohibited within 1 week of the baseline visit (within 2 weeks for monoamine oxidase inhibitors and selective serotonin reuptake inhibitors) and during the study. |
| Recruitment/selection of patients | Multicentre trial conducted between November 2003 and June 2004. A screening visit was conducted within 28 days of baseline testing to determine eligibility. Patients who satisfied all entry criteria and discontinued previous medication for ADHD |
| Age, gender and ethnicity | Age - Range: 6-17 years. Gender (M:F): 135/55. Ethnicity: 9 weeks |
| Further population details | 1. ADHD subtype: All/mixed subtypes (38.2% of the population were of Inattentive subtype of ADHD, 2.84% were hyperactive/impulsive subtype and 58.9% were of the combined subtype). 2. Age:  3. At risk population:  4. Comorbidities:  5. Diagnostic method:  6. Line of treatment:  7. Severity: |
| Extra comments | 38.2% of the population were of Inattentive subtype of ADHD, 2.84% were hyperactive/impulsive subtype and 58.9% were of the combined subtype |
| Indirectness of population | No indirectness |
| Interventions | (n=126) Intervention 1: CNS stimulants - Modafanil. Modafinil film–coated tablets (340 or 425 mg/day depending on weight) once daily in the morning. Patients weighing <30 kg received modafinil 340 mg and those weighing >30 kg received modafinil 425 mg. The dose of modafinil was individually titrated on the basis of tolerability and efficacy using the following schedule: 85 mg (1 tablet) on days 1 and 2, 170 mg (2 tablets) on days 3 to 7, 255 mg (3 tablets) on days 8 to 14, 340 mg (4 tablets) on days 15 to 21, and 425 mg (5 tablets) on day 22. Titration was stopped when any of the following conditions was met: poor tolerability, no additional expected incremental improvement in efficacy, patient's request, or achievement of a Clinical Global Impression of Improvement (CGI-I) rating of 1. The minimum and maximum daily dosages allowed during the study were 170 mg and 425 mg, respectively. . Duration 7 weeks. Concurrent medication/care: No concomitant medication allowed and washout period for previous medication for ADHD over a 1- to 4-week period implemented<br>Further details: 1. Dose:  2. Method of titration:<br><br>(n=64) Intervention 2: No treatment - Placebo. Matching placebo to active treatment. Duration 7 weeks. Concurrent medication/care: No concomitant medication allowed and  washout period for previous medication for ADHD over a 1- to 4-week period implemented<br>Further details: 1. Dose:  2. Method of titration: |

| Study | Swanson 2006[615] |
|---|---|
| | |
| Funding | Study funded by industry (Study was funded by Cephalon) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MODAFANIL GROUP versus PLACEBO GROUP<br><br>High risk of bias due to attrition<br>Weight change<br>Insomnia<br>Decreased appetite<br>Blood pressure endpoint 102.7(10.4); 103.1(8.8) | |
| 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 | Takahashi 2009[618] |
|---|---|
| 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. |

| Study | Takahashi 2009[618] |
|---|---|
| | 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:<br><br>(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 (all doses) versus PLACEBO
High risk of bias
Total adverse events 144/183; 43/62
Decreased weight(kg) -0.656(0.44); +0.91(0.5)

| Study | Takahashi 2009[618] |
|---|---|
| | |
| 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 | Taylor 2000[623] |
|---|---|
| Study type | RCT (Patient randomised; Crossover: 4 days) |
| Number of studies (number of participants) | 1 (n=22) |
| Countries and setting | Conducted in USA; Setting: Not reported |
| Line of therapy | Mixed line |
| Duration of study | Intervention time: 7 weeks |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis: A neurological exam; clinical, developmental and childhood histories; and a semi-structured interview |
| Stratum | Adult |
| 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 |

| Study | Taylor 2000[623] |
|---|---|
| | 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 - Dexamphetamine. Patients were given 5mg of dexamphetamine; each drug phase began with one capsule twice daily and was increased by an addition capsule twice daily every 1 to 2 days as tolerated up to four capsules per dose (a maximum of 8 capsules daily). Duration 2 weeks. Concurrent medication/care: No details given<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 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: DEXAMPHETAMINE 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 DEXAMPHETAMINE

| Study | Taylor 2000[623] |
|---|---|
| Protocol outcome 1: ADHD symptoms at <3- or >6-months<br>- 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, Group 2: mean 12.2 (SD 6.8); n=21; Risk of bias: Low; Indirectness of outcome: No indirectness<br><br>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 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 | Trzepacz 2011[636] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | (n=394) |
| Countries and setting | Conducted in Germany; Setting: 16 study sites across Germany |
| Line of therapy | Unclear |
| Duration of study | Intervention time: 15 months |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis: DSM-IV |
| Stratum | Children (up to 18 years) |

| Study | Trzepacz 2011[636] |
|---|---|
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Aged 6 to 15 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 15 years. Gender (M:F): 355:39. Ethnicity: Not specified |
| Further population details | 1. ADHD subtype: All/mixed subtypes 2. Age: Children (6-15 years) 3. At risk population: General population 4. Comorbidities: Not specified 5. Diagnostic method: DSM 5. Line of treatment: Not applicable / Not stated / Unclear 7. Severity: Mixed |
| Indirectness of population | No indirectness |
| Interventions | (n=281) 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. After 100 weeks patients meeting response criteria during the last 2 weeks of treatment (defined as CGI-S score of 2 or less and ADHD-RS-IV decrease of 25% or more from baseline, were randomised to atomoxetine or placebo for an additional 9 months. At the end of this, those who were still receiving atomoxetine were randomised again to atomoxetine or placebo. Duration 15 months. Concurrent medication/care: Not specified<br>Further details: 1. Dose:  2. Method of titration:<br><br>(n=113) 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>High risk due to attrition bias<br>Sexual dysfunction: 0 events in both arms | |

| Study | Van der heijden 2007[642] ; Hoebert 2008[337] |
|---|---|
| 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; high risk for sleep problems |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Children aged between 6-12 years, diagnosis of ADHD and chronic sleep-onset insomnia (SOI) as well as written informed consent from parents |
| Exclusion criteria | Total IQ<8-, pervasive developmental disorder, chronic pain, known disturbed hepatic or renal function, epilepsy, earlier use of melatonin and use of stimulants, neuroleptics, clonidine antidepressants, hypnotics or beta blockers within 4 weeks before enrolment |
| Recruitment/selection of patients | Children with possible ADHD were referred for participation to outpatient clinics for sleep-wake disorders of the Gelderse Vallei General Hospital and Kempenhaeghe by seven Dutch community mental health institutions and three paediatric hospital departments. 20 children were also recruited through advertisements in magazines, newspapers or via the Dutch ADHD patient support Centre. |
| 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 |

| Study | Van der heijden 2007[642] ; Hoebert 2008[337] |
|---|---|
| | 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..<br>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 GROUP<br>4 weeks low risk<br><br>64.9 at 4 year follow up<br>2 sleep maintenance insomnia | |
| 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 |

| Study | Wang 2007[649] |
|---|---|
| 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 |

| Study | Wang 2007[649] |
|---|---|
| | well as a CGI-S score of ≥4 |
| Exclusion criteria | Any history of bipolar, psychotic or pervasive developmental disorders; suicidal risk; or on-going use of psychoactive medications other than the study drug. Patients with motor tics, a diagnosis or family history of Tourette's syndrome or those who met DSM-IV criteria for anxiety disorder |
| Recruitment/selection of patients | Not reported |
| Age, gender and ethnicity | Age - Range: 6-16. Gender (M:F): 270:60. Ethnicity: |
| Further population details | 1. ADHD subtype: All/mixed subtypes 2. Age: Mixed (6-16). 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: DSM 6. Line of treatment: Mixed line (including drug naive) 7. Severity: Not applicable / Not stated / Unclear |
| Indirectness of population | No indirectness |
| Interventions | (n=164) Intervention 1: CNS stimulants - Atomoxetine. Therapy began at 0.8mg/kg/day administered once 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)<br>-1.2kg vs. -0.4kg (p<0.001)<br>Anorexia 61;42<br>Irritability 7;10<br>Insomnia 5;9 | |
| 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) | NCT00546910 trial: Wehmeier 2012[658] (Wehmeier 2015[657], Wehmeier 2014[655]) |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 2 (n=125) |
| Countries and setting | Conducted in Germany; Setting: 16 study sites located all over Germany included 3 university departments for child and adolescent psychiatry, 1 non-university hospital for child and adolescent psychiatry, and 12 office-based practices for child and adolescent psychiatry and/or paediatrics. |
| Line of therapy | Mixed line |
| Duration of study | Intervention + follow up: 8 weeks |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis: DSM-IV |
| Stratum | Children (up to 18 years) |
| 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 |

| Study (subsidiary papers) | NCT00546910 trial: Wehmeier 2012[658] (Wehmeier 2015[657], Wehmeier 2014[655]) |
|---|---|
| | 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 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<br><br>High risk of bias due to attrition bias<br>Total adverse events 32/63; 27/62 | |
| 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 | Wehmeier 2011[659] |
|---|---|
| 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 | Adequate method of assessment/diagnosis: DSM-IV |

| Study | Wehmeier 2011[659] |
|---|---|
| condition | |
| 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:<br><br>(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>High risk due to selection bias<br>Overall Adverse events: 32/63;  27/62 | |
| 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) | Weisler 2009 (Mattingly 2013) [660]([440]) |
|---|---|
| Study type | Open label non comparative<br>52 week open label non comparative extension of Adler 2008[10] |
| Number of studies (number of participants) | (n=349) |
| Countries and setting | Conducted in USA; Setting: New York. No further details |
| Line of therapy | Unclear |
| Duration of study | Intervention time: 48 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) 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 pulse 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 | Intervention Lisdexamfetamine, max dose 70mg/day |

| Study (subsidiary papers) | Weisler 2009 (Mattingly 2013) [660]([440]) |
|---|---|
| | |
| Funding | Industry funded (Shire Development) |
| RESULTS (NUMBERS ANALYSED)<br>N=298<br>Total numbers of participants with adverse events 306/349<br>Decreased appetite 50/349<br>Decreased weight 21/349<br>Insomnia 68/349<br>High risk of bias | |
| Protocol outcomes not reported by the study | All-cause mortality Suicide or suicidal ideation ,Cardiac mortality, cardiac events, Substance misuse , Increase in seizures in people with epilepsy, Liver damage (defined by deranged LFTs),Increased tics, Tremors, Congenital defects amongst patients who are pregnant, Sexual dysfunction, Psychotic symptoms |

| Study | Weiss 2005[664] |
|---|---|
| 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 |

| Study | Weiss 2005[664] |
|---|---|
| | module of the Schedule for Affective Disorders and Schizophrenia for School-age Children-Present and Lifetime Version. Symptom severity had to be at least 1 SD above age and sex norms on the ADHD-RS-IV-Teacher version: Investigation administered and scored. Patients were also required to have a mean Conners Parent Rating Scale ADHD Index score at least 1.5 SDs above age and sex norms. |
| Exclusion criteria | Unavailability of a primary teacher willing to keep telephone appointments and to provide ratings and reports as part of the study, evidence of a significant intellectual deficit, serious medical illness, or use of other psychotropic medication. |
| Recruitment/selection of patients | Community advertisements were used to aid in patient recruitment |
| Age, gender and ethnicity | Age - Range: 8-12 years. Gender (M:F): 123/30. Ethnicity: |
| Further population details | 1. ADHD subtype: All/mixed subtypes (Hyperactive/impulsive 0.7%, Inattentive 26.8%, 72.5%). 2. Age: Children (6-12 years) (8-12 years). 3. At risk population: General population 4. Comorbidities: Mixed (ODD 33.3%, Generalised anxiety disorder 2.6%, Learning disorder 29.8%, Motor skills disorder 6.5%, Communications disorder 8.1%). 5. Diagnostic method: DSM (DSM-IV). 6. Line of treatment: Mixed line (including drug naive) 7. Severity: Not applicable / Not stated / Unclear (At least 1.0 SDs above age and sex norms on ADHD-RS-IV-T and CPRS-RS score at least 1.5 SDs above age sex and norms). |
| Indirectness of population | No indirectness |
| 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<br><br>High risk of bias due to attrition bias | |

| Study | Weiss 2005[664] |
|---|---|
| Weight change(kg): -0.67(1.21); 1.21(1.38)<br>Somnolence: 17/101; 2/52 | |
| 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 |

| Study | Wilens 2008[686] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=147) |
| Countries and setting | Conducted in Canada, USA; Setting: Multicentre trial conducted in 14 sites (13 in the US and 1 in Canada) |
| Line of therapy | Unclear |
| Duration of study | Intervention + follow up: 3 months |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis: DSM-IV-TR + AISRS |
| Stratum | Adult: Adults |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | (1) Subjects >18 years of age meeting DSM-IV-TR criteria for ADHD (any subtype) and ADHD symptoms > 20 on the AISRS. (2) subjects also met DSM-IV-TR criteria for alcohol use disorders (abuse or dependence) (3) other substance use did not preclude participation provided that the primary substance the patient abused or had dependence on was alcohol and that subjects were not actively abusing other substances at study entry (4) all subjects included were alcohol free for at least 4 days before randomisation but not longer than 30 days. The minimum four abstinent days had to be consecutive and overlap with the week before randomisation |
| Exclusion criteria | Patients with a diagnosis of current bipolar disorder, major depressive disorder or psychosis were excluded as well as subjects with significant cognitive impairment. |
| Recruitment/selection of patients | Not reported |
| Age, gender and ethnicity | Age - Other: >18 years. Mean (SD)= 34.3 (10.2) in Atomoxetine group and 34.8 (9.9) in Placebo. Gender (M:F): 125/22. Ethnicity: 88% Caucasian, 4% African descent, 0.7% Asian, 6% Hispanic and 1.4% other |

| Study | Wilens 2008[686] |
|---|---|
| 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
- Actual outcome for Adult: ADHD Investigator Symptom Rating Scale (AISRS) at 12 weeks; Group 1: mean -13.6 (SD 11.35); n=32, Group 2: mean -8.31 (SD 11.44); n=48; AISRS 0-54 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Adult: Adult ADHD Self-report Scale (ASRS) at 12 weeks; Group 1: mean -12.9 (SD 12.8); n=32, Group 2: mean -8.3 (SD 12.9); n=48; ASRS 0-54? Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness

| Study | Wilens 2008[686] |
|---|---|
| - 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[691] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 15 weeks, including 7 week dose titration, 6 week maintenance phase and 2 week taper (n=312) |
| Countries and setting | Conducted in USA; Setting: Phase 3 trial, multicentre, 48 sites |
| Line of therapy | 1st line |
| Duration of study | --: |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis: DSM-IV ADHD determined by K-SADS-PL assessment |
| Stratum | Children (up to 18 years) |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Age 13-17 with ADHD and ADHDRS-IV score >=32 and CGI-S >=4 |
| Exclusion criteria | Comorbid psychiatric diagnosis except oppositional defiant disorder, cardiac disorder, or any medications that affected the heart or led to sedation. |

| Study | Wilens 2015[691] |
|---|---|
| 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<br><br>Insomnia 14;6<br>Decreased app 23;21 increased 14;13<br>0;0 deaths<br>Any adverse event: 147/157; 120/155 | |
| 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[698] |
|---|---|
| Study type | RCT (Patient randomised; Parallel |
| Number of studies (number of participants) | (n=282) |
| 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, on-going 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 | 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 |

| Study | Wolraich 2001[698] |
|---|---|
| | interventions allowed as long as they had been initiated before the start of the study<br><br>(n=95) Intervention 2: CNS stimulants - Methylphenidate (including modified-release preparations) . Participants were assigned to either 5mg tid, 10mg tid, 15mg tid based on their titration or previous methylphenidate dosage prior to the study. 29 were on 5mg tid, 41 on 10mg tid and 25 on 15mg tid.. Duration 4 weeks. Concurrent medication/care: Behavioural interventions allowed if started before the study<br><br>(n=89) Intervention 3: No treatment - Placebo. Placebo. Duration 4 weeks. Concurrent medication/care: Behavioural interventions allowed if started before the trial |
| Funding | Study funded by industry (AZLA Corporation) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OROS METHYLPHENIDATE versus IR METHYLPHENIDATE<br>Very high risk of bias due to attrition bias (n=94)<br>Tics 0,1<br>Overall adverse events 40/94; 44/95<br>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OROS METHYLPHENIDATE versus PLACEBO<br>Tics 0,4<br>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OROS METHYLPHENIDATE versus IR METHYLPHENIDATE<br>Tics 0,1 | |
| 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[708] (Wietecha 2012[669]) |
|---|---|
| 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 |

| Study (subsidiary papers) | Young 2011[708] (Wietecha 2012[669]) |
|---|---|
| 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)).<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 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.<br>Serious indirectness: 16% have had previous treatment |
| Indirectness of population | No indirectness |
| 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<br>Further details: 1. Dose:  2. Method of titration: |

| Study (subsidiary papers) | Young 2011[708] (Wietecha 2012[669]) |
|---|---|
| | (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>• Decreased appetite at 8 and 24 weeks<br>• Sleep (insomnia) at 8 and 24 weeks<br>• Sexual dysfunction at 8 and 24 weeks | |
| Protocol outcomes not reported by the study | Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months |
| Risk of bias details | All outcomes: very high risk of bias, downgraded twice for attrition bias due to (1) over 10% of the data missing overall and (2) a difference of over 10% in missing rates between groups, with an attrition rate of over 50% in the experimental group. |

| Study | Zarinara 2010[710] |
|---|---|
| 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 |

| Study | Zarinara 2010[710] |
|---|---|
| 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 mental retardation. 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 an exclusion criteria). 5. Diagnostic method: DSM (DSM-IV-TR). 6. Line of treatment: Not applicable / Not stated / Unclear (Unclear line. Response not an exclusion criteria). 7. Severity: Not applicable / Not stated / Unclear (Baseline ADHD-RS-IV scores were ~ 30 (teacher)). |
| Indirectness of population | No indirectness |
| Interventions | (n=19) Intervention 1: Other antidepressants - Venlafaxine . Patients were randomised to receive 50-75 mg/day depending on weight.50mg 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). |

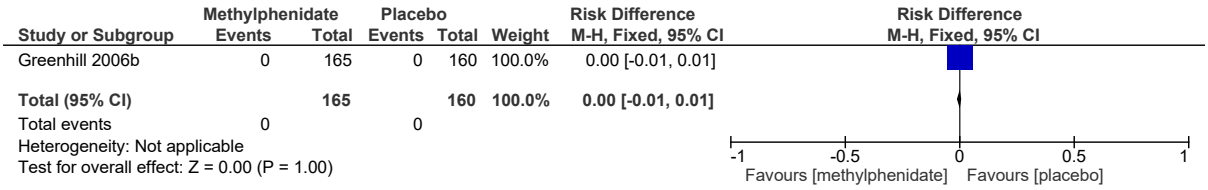
| Study | Zarinara 2010[710] |
|---|---|
| | |
| Funding | Academic or government funding (Grant from Tehran University of Medical Sciences ) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VENLAFAXINE versus METHYLPHENIDATE<br><br>Low risk of bias<br>Insomnia 10/18; 2/19<br>Decreased appetite 7/18; 2/19 | |
| 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 |

# Appendix E: Forest plots

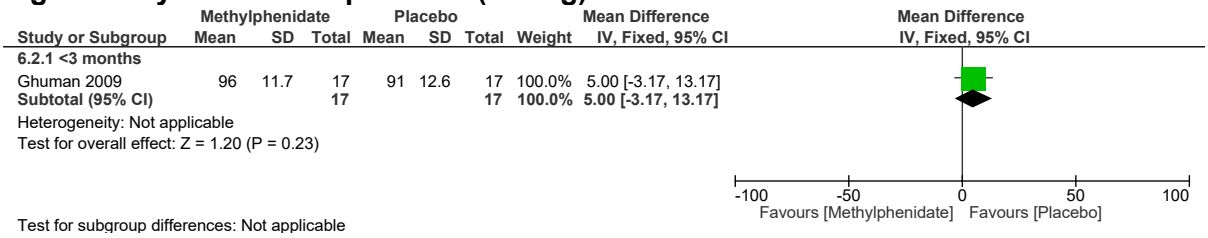
## E.1 Pre-school children (under the age of 5)

### E.1.1 Methylphenidate versus placebo

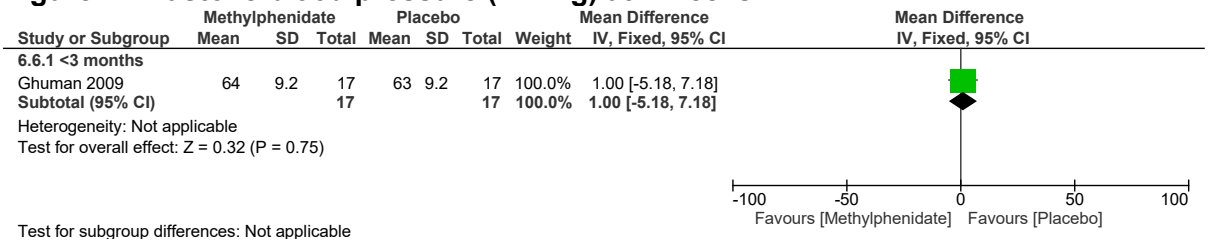
#### Figure 2: Tachycardia at 1 week




#### Figure 3: Systolic blood pressure (mmHg) at 4 weeks




#### Figure 4: Diastolic blood pressure (mmHg) at 4 weeks




#### Figure 5: Weight(kg) at 4 weeks

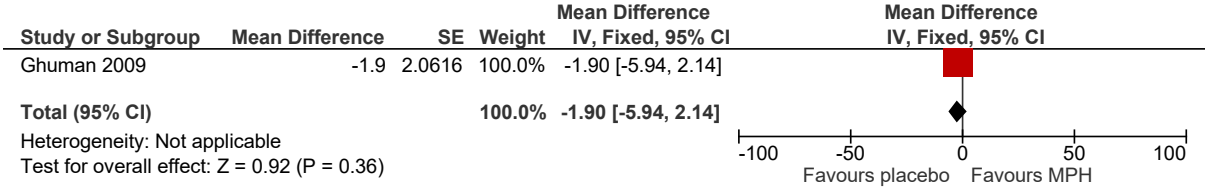
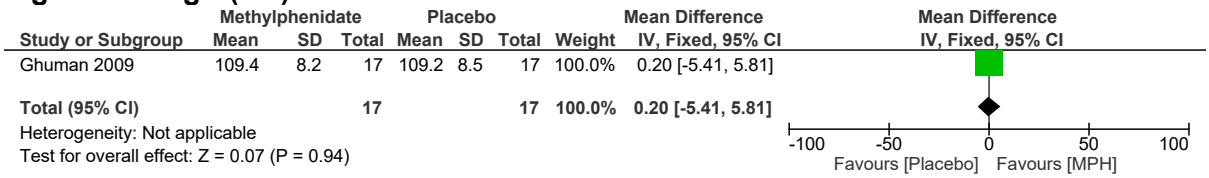


**Figure 6: Height(cm) at 4 weeks**




## E.1.2 Methylphenidate versus risperidone

**Figure 7: Decreased appetite at 6 weeks**

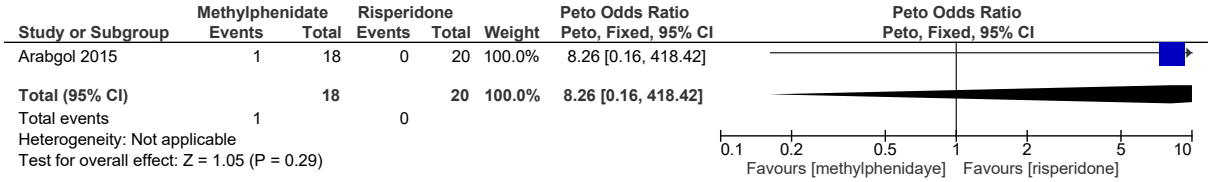
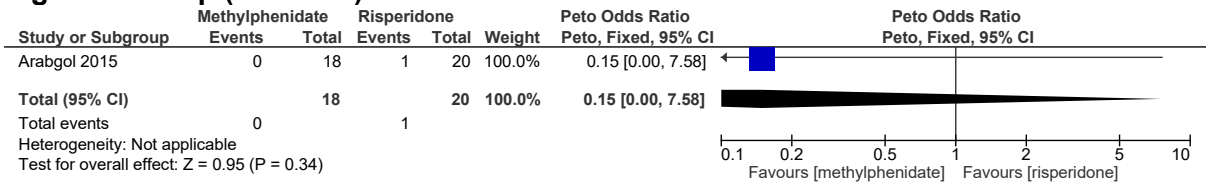



**Figure 8: Sleep (sedation) at 6 weeks**




# E.2 Children and young people (aged 5 to 18)

## E.2.1 Immediate release methylphenidate versus placebo

**Figure 9: Total participants with adverse events at 3 to 16 weeks**

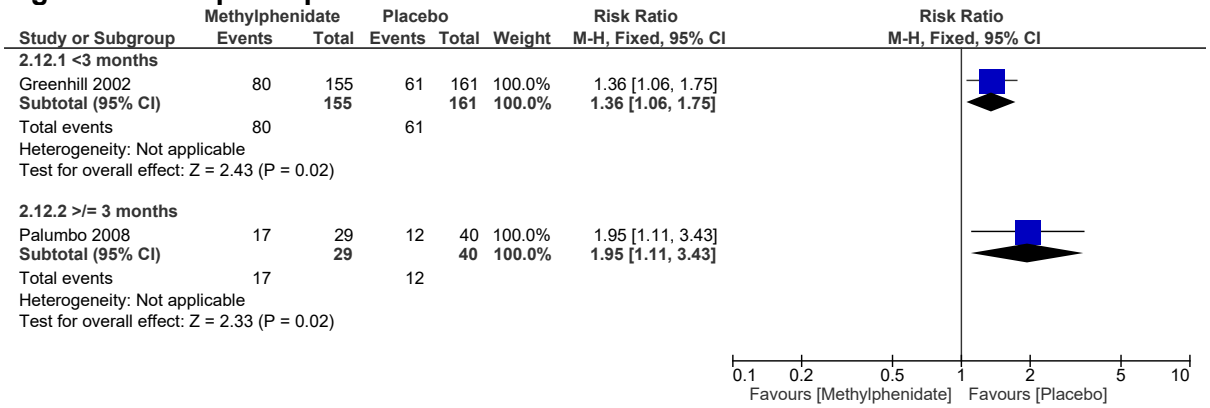
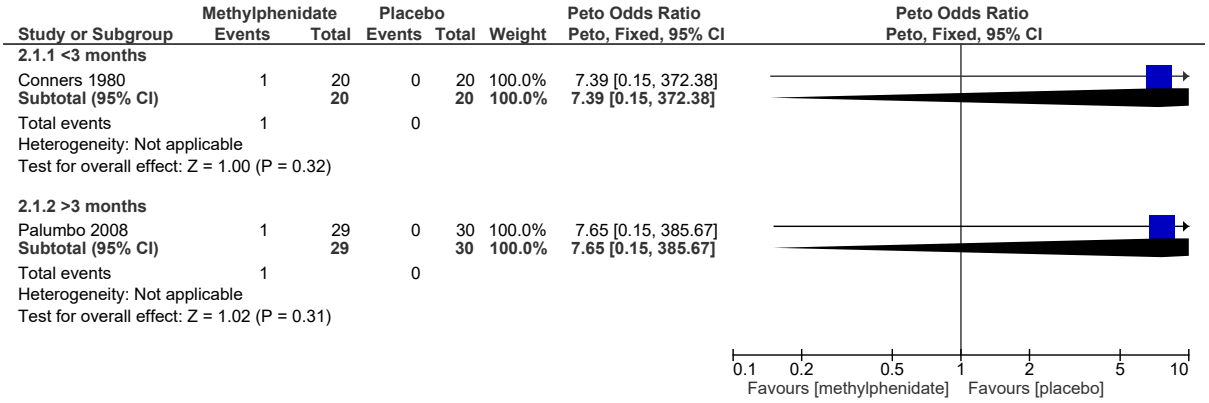
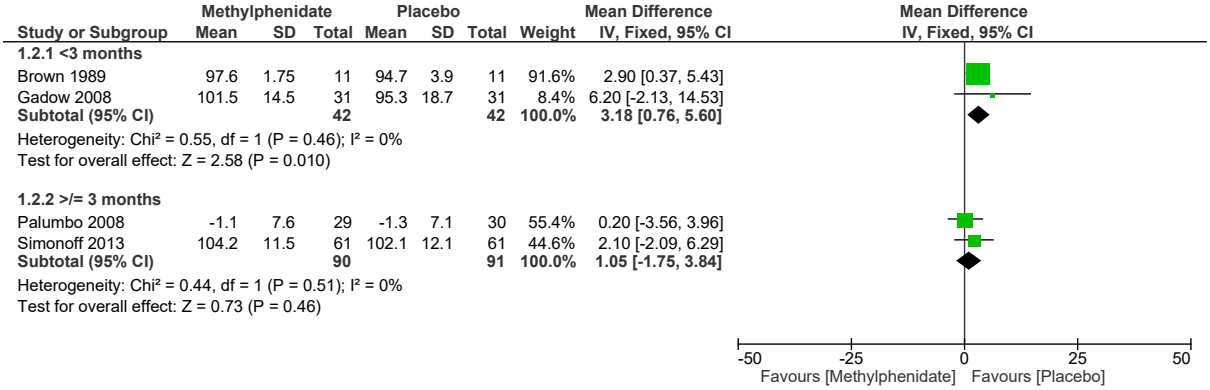


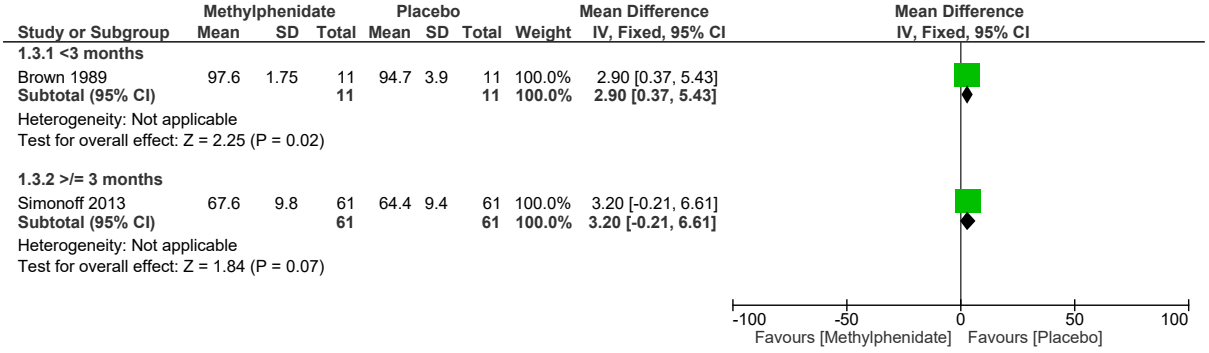

**Figure 10: Tachycardia events at 8 weeks - 16 weeks**



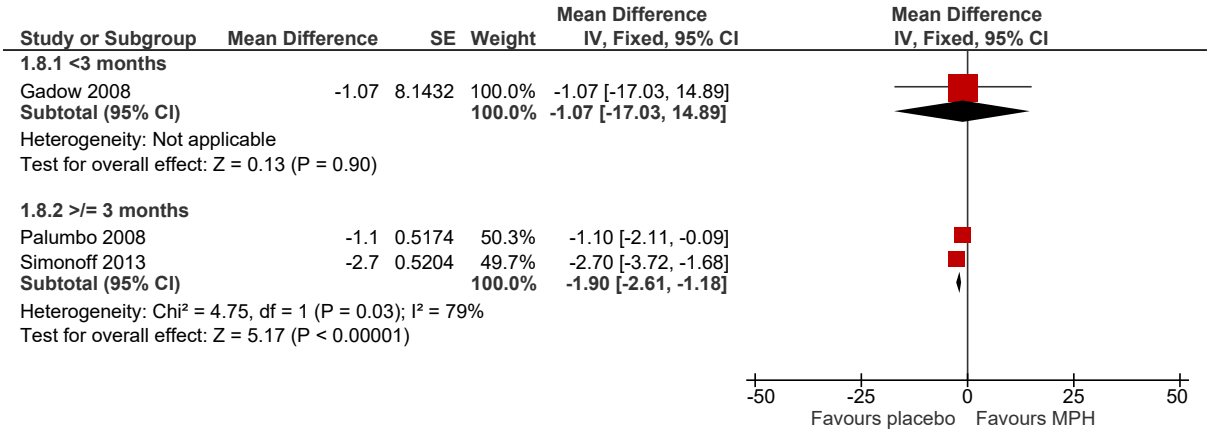

## Figure 11: Systolic blood pressure (mmHg) 2-16 weeks



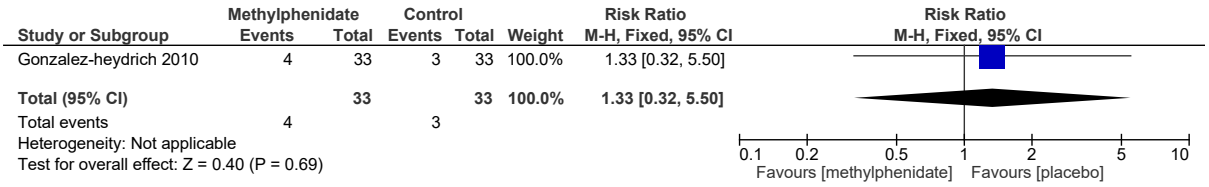

## Figure 12: Diastolic blood pressure (mmHg) at 2-16 weeks



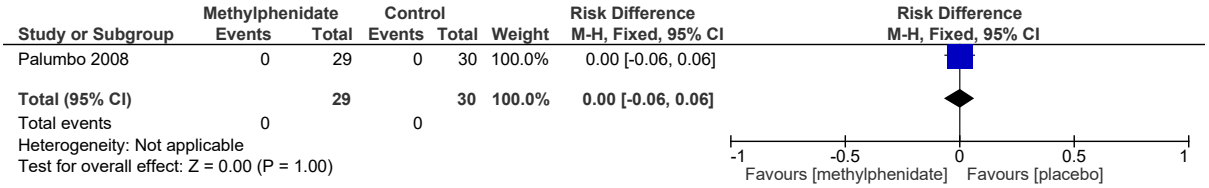

## Figure 13: Decreased weight at 2-16 weeks




## Figure 14: Seizures at 3 weeks




## Figure 15: Psychotic symptoms at 16 weeks




## Figure 16: Sleep (insomnia) at 3-8 weeks

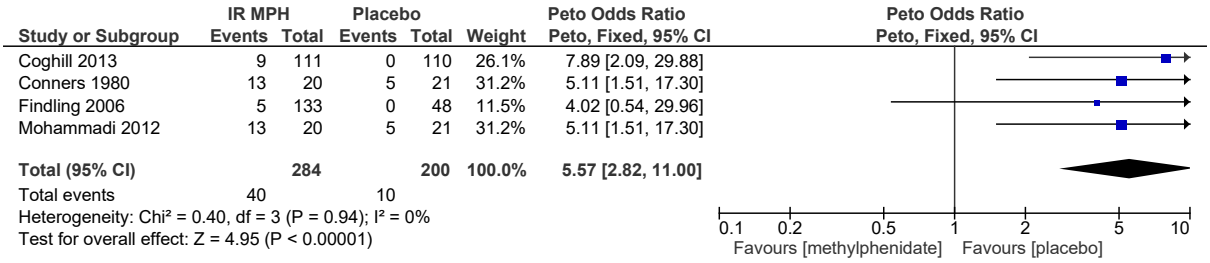


**Figure 17: Sleep (insomnia) at 16 weeks**

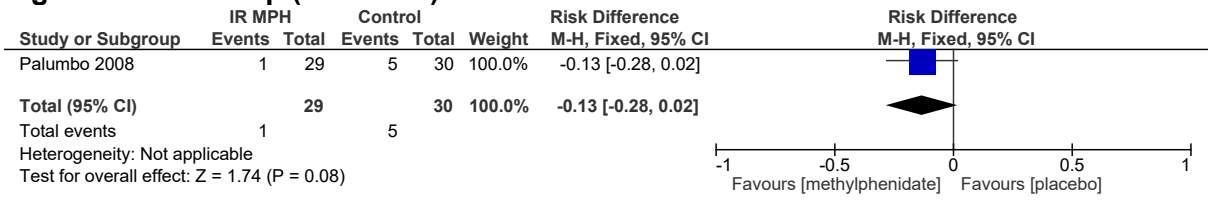



**Figure 18: Tics at 4 weeks and 16 weeks**

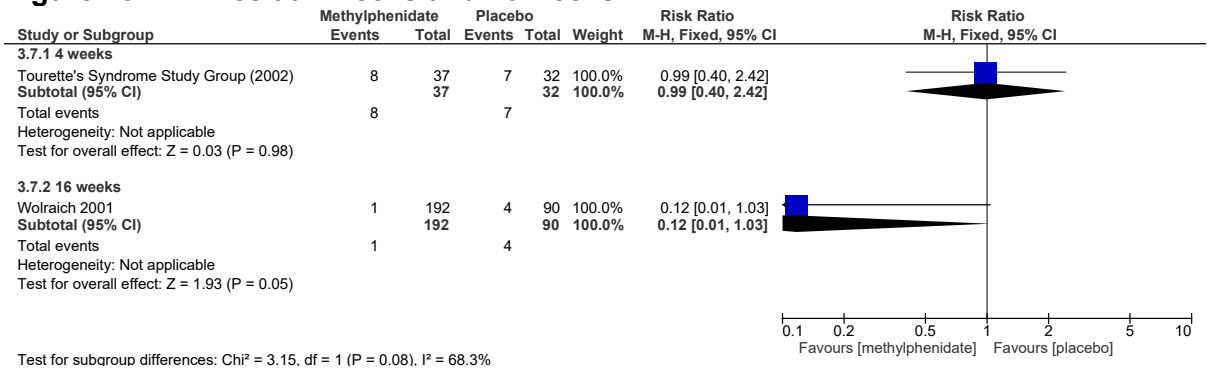
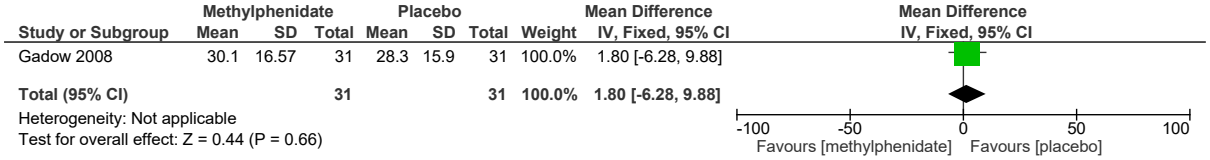



**Figure 19: YGTSS Rating Scale at 9 weeks (Tics global severity; 0-100; lower scores are beneficial)**




## E.2.2 OROS methylphenidate versus placebo

**Figure 20: Total participants with adverse events at 6 weeks**

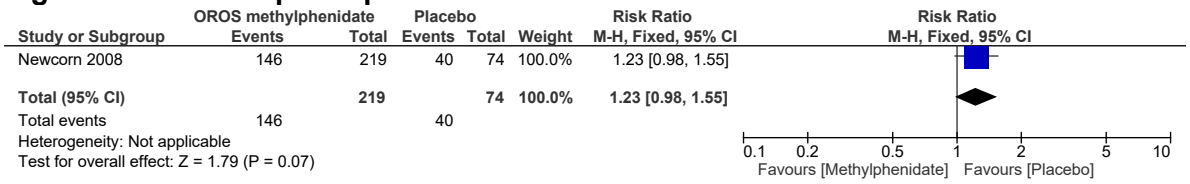



**Figure 21: Systolic blood pressure (mmHg) at 6-7 weeks**

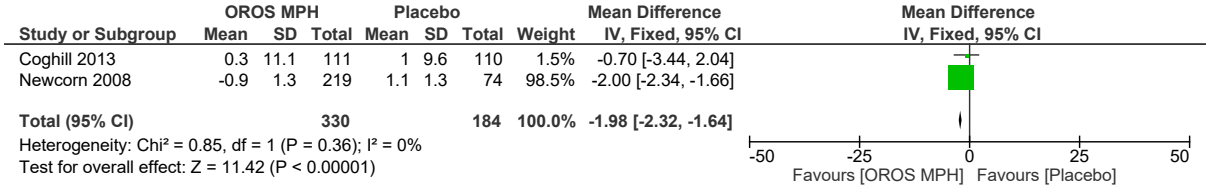


**Figure 22: Diastolic blood pressure (mmHg) at 6-7 weeks**

| Study or Subgroup | OROS MPH Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Coghill 2013 | 1.7 | 9.9 | 111 | 1.2 | 8.7 | 110 | 45.2% | 0.50 [-1.96, 2.96] |
| Newcorn 2008 | 2.4 | 9.7 | 219 | 1.3 | 8 | 74 | 54.8% | 1.10 [-1.13, 3.33] |
| **Total (95% CI)** | | | **330** | | | **184** | **100.0%** | **0.83 [-0.82, 2.48]** |

Heterogeneity: Chi² = 0.13, df = 1 (P = 0.72); I² = 0%
Test for overall effect: Z = 0.98 (P = 0.33)

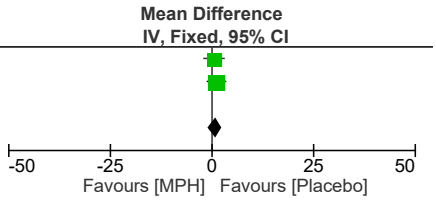



**Figure 23: Decreased weight (kg) at 6-7 weeks**

| Study or Subgroup | OROS MPH Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **4.4.1 <3 months** | | | | | | | | |
| Coghill 2013 | -1.3 | 1.4 | 111 | 0.7 | 1 | 110 | 53.3% | -2.00 [-2.32, -1.68] |
| Newcorn 2008 | -0.9 | 1.3 | 219 | 1.1 | 1.3 | 74 | 46.7% | -2.00 [-2.34, -1.66] |
| **Subtotal (95% CI)** | | | **330** | | | **184** | **100.0%** | **-2.00 [-2.23, -1.77]** |

Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 16.75 (P < 0.00001)

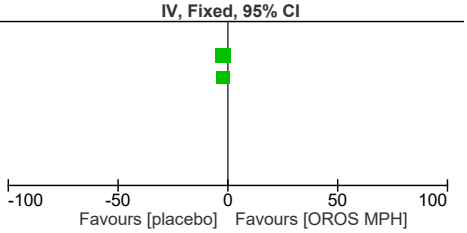
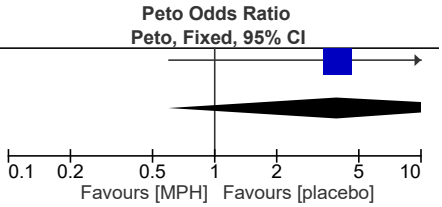



**Figure 24: Sleep (insomnia) at 7 weeks**

| Study or Subgroup | MPH Events | Total | Placebo Events | Total | Weight | Peto Odds Ratio Peto, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Findling 2006 | 6 | 139 | 0 | 46 | 100.0% | 3.93 [0.60, 25.66] |
| **Total (95% CI)** | | **139** | | **46** | **100.0%** | **3.93 [0.60, 25.66]** |
| Total events | 6 | | 0 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.43 (P = 0.15)




## E.2.3 IR methylphenidate versus OROS methylphenidate

**Figure 25: Total participants with adverse events at 3 weeks**

| Study or Subgroup | Methylphenidate IR Events | Total | OROS methylphenidate Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Wolraich 2001 | 44 | 95 | 40 | 94 | 100.0% | 1.09 [0.79, 1.50] |
| **Total (95% CI)** | | **95** | | **94** | **100.0%** | **1.09 [0.79, 1.50]** |
| Total events | 44 | | 40 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.52 (P = 0.60)

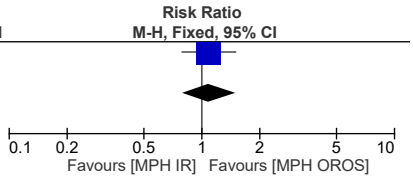



**Figure 26: Decreased appetite at 3 weeks**

| Study or Subgroup | Methylphenidate IR Events | Total | OROS methylphenidate Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Findling 2006 | 4 | 133 | 9 | 139 | 100.0% | 0.46 [0.15, 1.47] |
| **Total (95% CI)** | | **133** | | **139** | **100.0%** | **0.46 [0.15, 1.47]** |
| Total events | 4 | | 9 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.30 (P = 0.19)

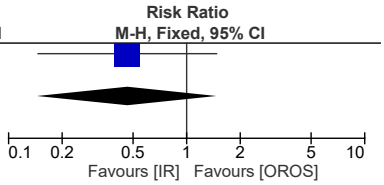
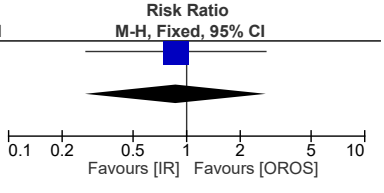


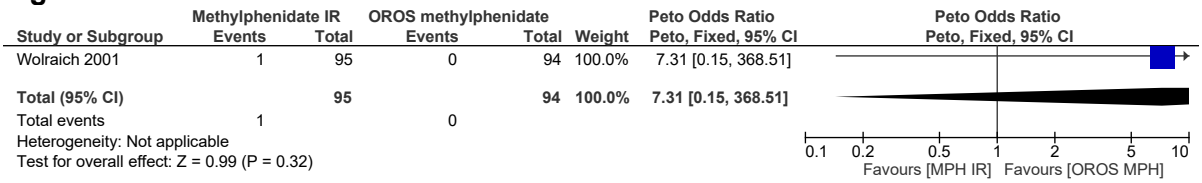

**Figure 27: Insomnia at 3 weeks**

| Study or Subgroup | Methylphenidate IR Events | Total | OROS methylphenidate Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Findling 2006 | 5 | 133 | 6 | 139 | 100.0% | 0.87 [0.27, 2.79] |
| **Total (95% CI)** | | **133** | | **139** | **100.0%** | **0.87 [0.27, 2.79]** |
| Total events | 5 | | 6 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.23 (P = 0.82)

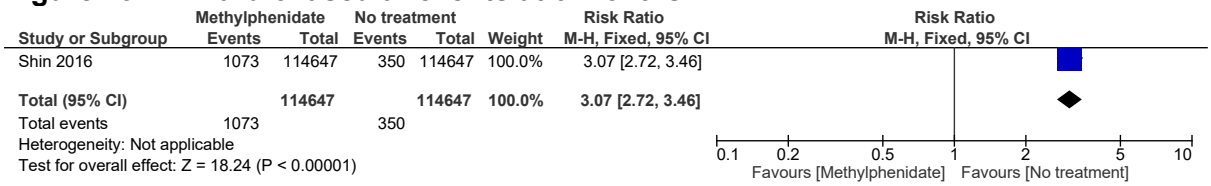


### Figure 28: Tics at 3 weeks

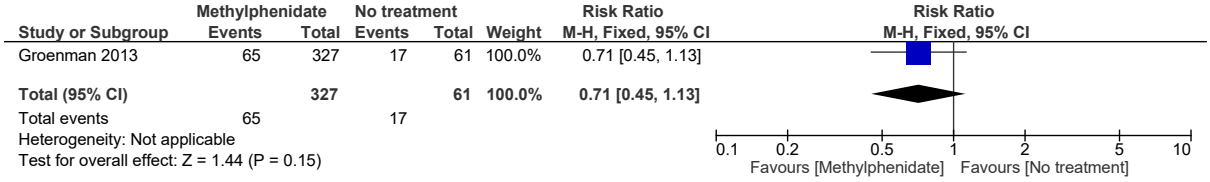



## E.2.4 Methylphenidate versus no treatment (non-randomised)

### Figure 29: Cardiovascular events at 6 months

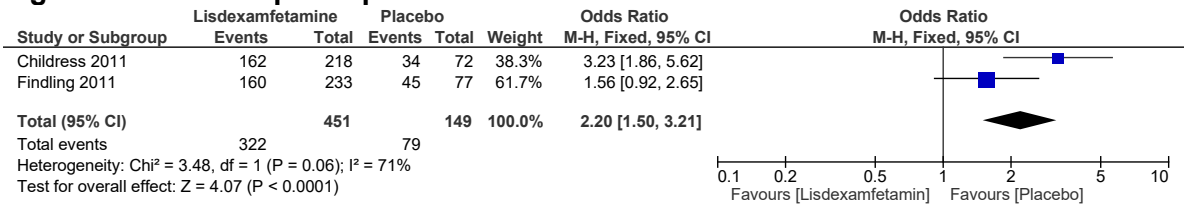



### Figure 30: Substance use at 4.4 years




## E.2.5 Lisdexamfetamine dimesylate versus placebo

### Figure 31: Total participants with adverse events at 4 to 7 weeks




### Figure 32: All-cause mortality at 4 weeks

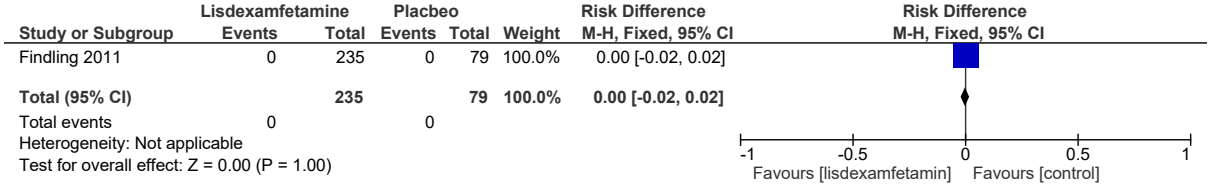


**Figure 33: Systolic blood pressure change (mmHg) at 4 to 7 weeks**

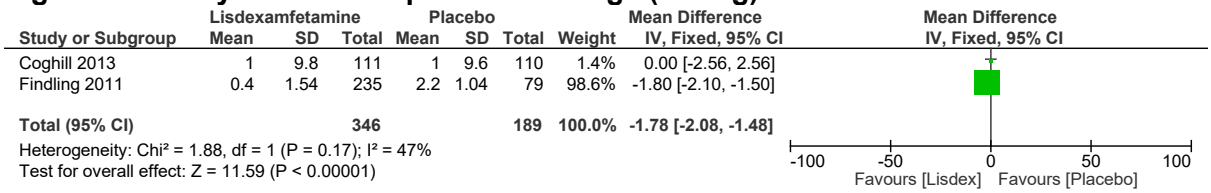



**Figure 34: Diastolic blood pressure (mmHg) at 4 to 7 weeks**

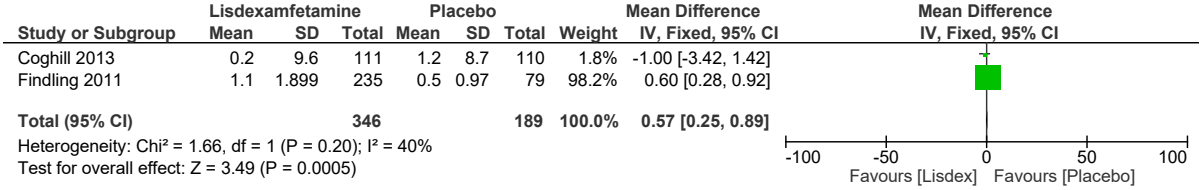



**Figure 35: Weight change (kg) at 7 weeks**

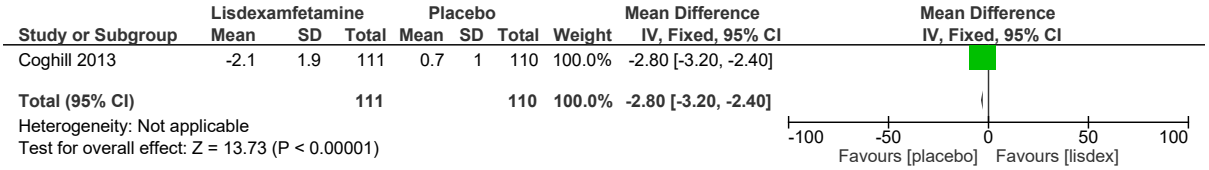



**Figure 36: Decreased weight at 4 weeks**

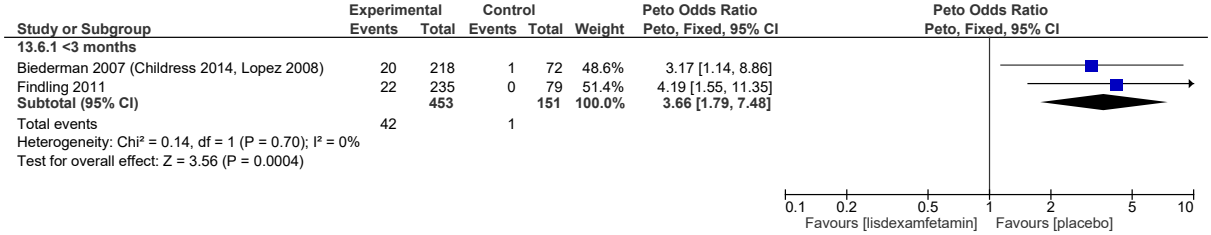
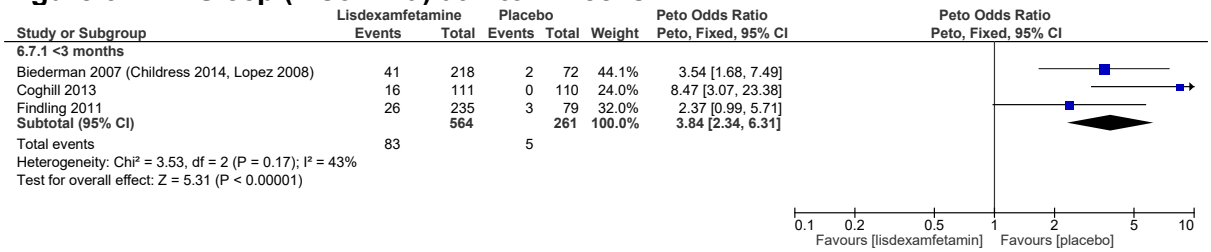



**Figure 37: Sleep (insomnia) at 4 to 7 weeks**




## E.2.6 Lisdexamfetamine versus methylphenidate

**Figure 38: Systolic blood pressure (mmHg) change at 7 weeks**

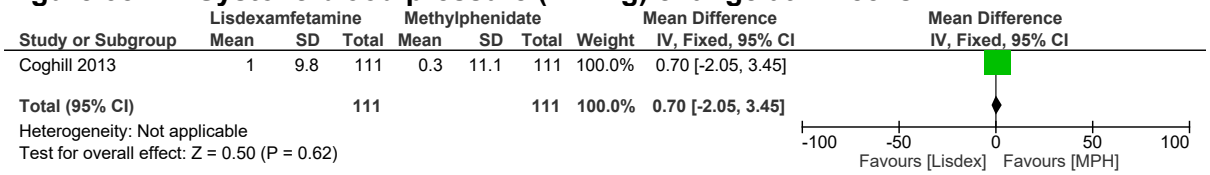
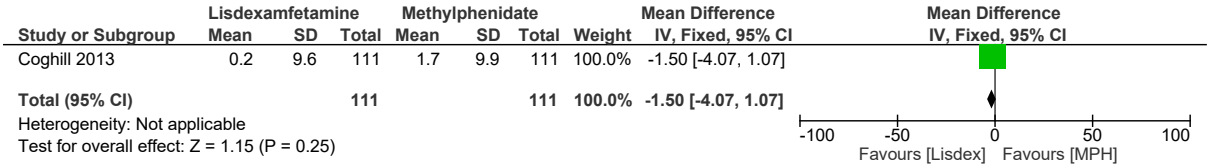
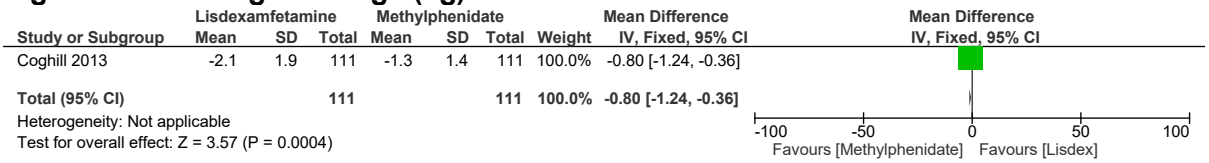


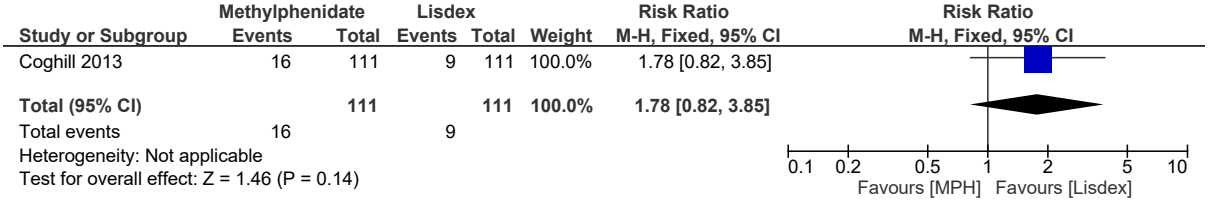

**Figure 39: Diastolic blood pressure (mmHg) change at 7 weeks**




## Figure 40: Weight change (kg) at 7 weeks

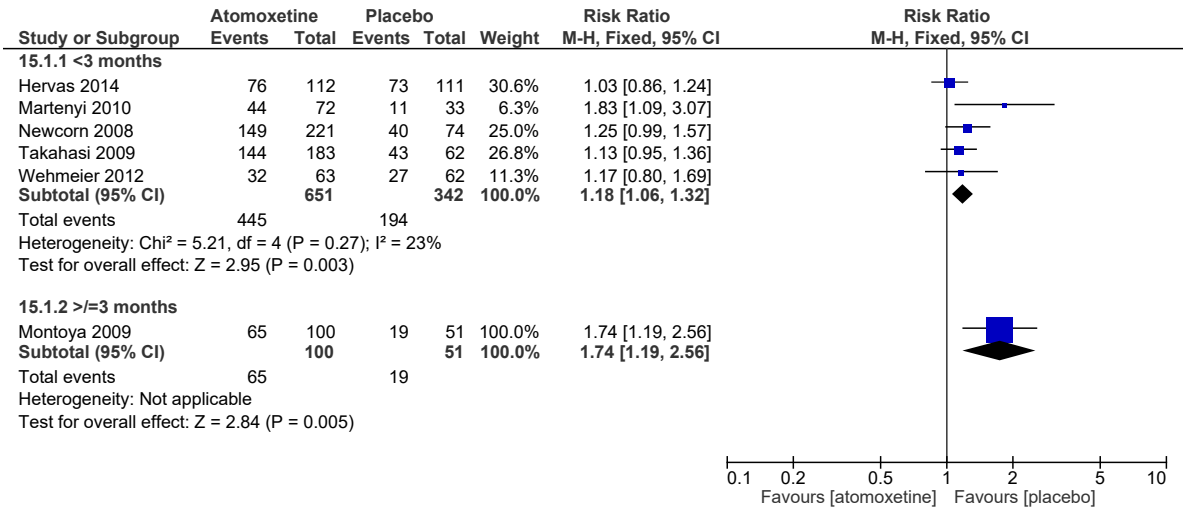



## Figure 41: Sleep (insomnia) at 7 weeks

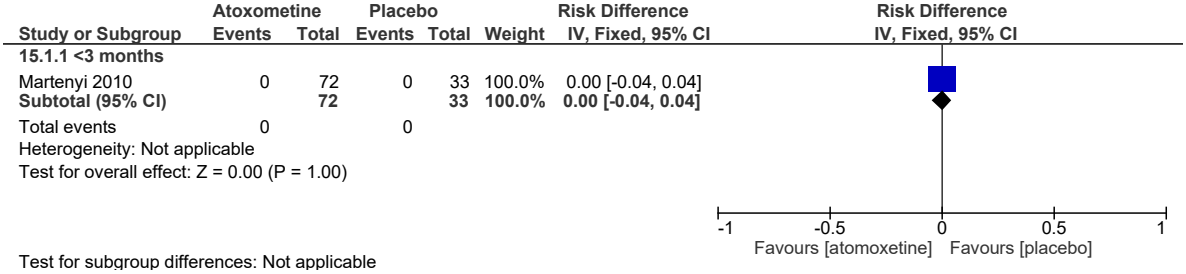



# E.2.7 Atomoxetine versus placebo

## Figure 42: Total participants with adverse events at 6-10 weeks



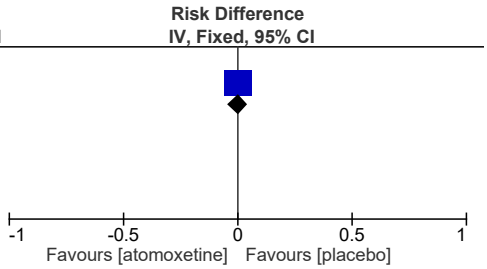

## Figure 43: All-cause mortality at 6 weeks



## Figure 44: Suicidal ideation at 6 weeks

| Study or Subgroup | Atoxometine Events | Total | Placebo Events | Total | Weight | Risk Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **15.2.1 <3 months** | | | | | | |
| Martenyi 2010 | 0 | 72 | 0 | 33 | 100.0% | 0.00 [-0.04, 0.04] |
| **Subtotal (95% CI)** | | **72** | | **33** | **100.0%** | **0.00 [-0.04, 0.04]** |
| Total events | 0 | | 0 | | | |

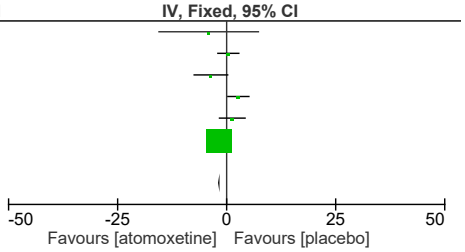
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)




## Figure 45: Systolic blood pressure change (mmHg) at 6 to 13 weeks

| Study or Subgroup | Atomoxetine Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Dell'agnello 2009 | 1 | 28.8 | 105 | 5.1 | 28.8 | 32 | 0.0% | -4.10 [-15.50, 7.30] |
| Kelsey 2004 | 1.4 | 8.3 | 133 | 1 | 7.9 | 64 | 1.1% | 0.40 [-1.99, 2.79] |
| Martenyi 2010 | -1.4 | 10.4 | 72 | 2.2 | 8.8 | 33 | 0.4% | -3.60 [-7.45, 0.25] |
| Michelson 2001 | 2 | 8.7 | 85 | -0.7 | 7.3 | 85 | 1.1% | 2.70 [0.29, 5.11] |
| Michelson 2002 | 3.4 | 9.84 | 84 | 2.1 | 9.5 | 83 | 0.7% | 1.30 [-1.63, 4.23] |
| Newcorn 2008 | -0.6 | 1.4 | 221 | 1.1 | 1.3 | 219 | 96.7% | -1.70 [-1.95, -1.45] |
| **Total (95% CI)** | | **700** | | | | **516** | **100.0%** | **-1.62 [-1.87, -1.37]** |

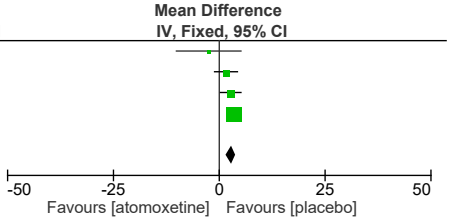
Heterogeneity: Chi² = 20.42, df = 5 (P = 0.001); I² = 76%
Test for overall effect: Z = 12.78 (P < 0.00001)




## Figure 46: Diastolic blood pressure change (mmHg) at 6 to 13 weeks

| Study or Subgroup | Atomoxetine Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Dell'agnello 2009 | -0.2 | 3.4782 | 105 | 2.3 | 21.9136 | 32 | 2.2% | -2.50 [-10.12, 5.12] |
| Kelsey 2004 | 2.6 | 10.1 | 133 | 1 | 8.5 | 64 | 17.5% | 1.60 [-1.10, 4.30] |
| Michelson 2001 | 2 | 8.7 | 85 | -0.7 | 7.3 | 85 | 21.9% | 2.70 [0.29, 5.11] |
| Newcorn 2008 | 3.8 | 8 | 221 | 0.4 | 7.8 | 219 | 58.5% | 3.40 [1.92, 4.88] |
| **Total (95% CI)** | | **544** | | | | **400** | **100.0%** | **2.80 [1.67, 3.93]** |

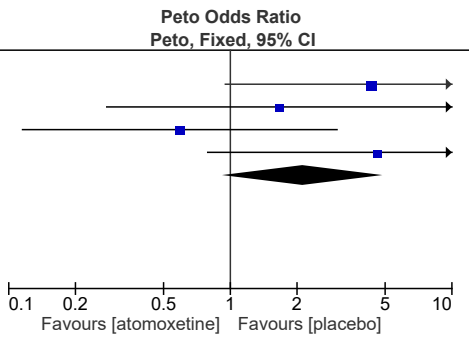
Heterogeneity: Chi² = 3.26, df = 3 (P = 0.35); I² = 8%
Test for overall effect: Z = 4.87 (P < 0.00001)



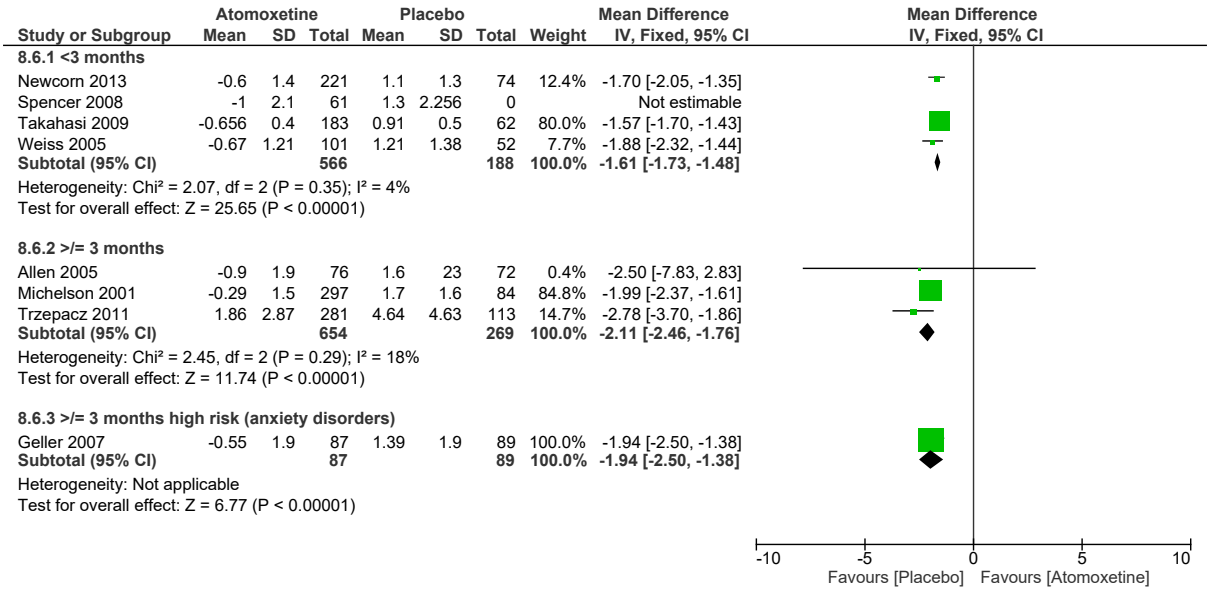

## Figure 47: Change in weight (kg) at 6 to 9 weeks

| Study or Subgroup | Atoxometine Events | Total | Placebo Events | Total | Weight | Peto Odds Ratio Peto, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **8.7.1 <3 months** | | | | | | |
| Bangs 2007 | 6 | 72 | 1 | 70 | 30.3% | 4.32 [0.95, 19.63] |
| Dell'agnello 2009 | 6 | 107 | 1 | 32 | 21.5% | 1.67 [0.28, 10.12] |
| Gau 2007 | 4 | 72 | 3 | 34 | 26.0% | 0.59 [0.12, 3.03] |
| Martenyi 2010 | 6 | 72 | 0 | 33 | 22.3% | 4.63 [0.79, 27.07] |
| **Subtotal (95% CI)** | | **323** | | **169** | **100.0%** | **2.13 [0.93, 4.91]** |
| Total events | 22 | | 5 | | | |

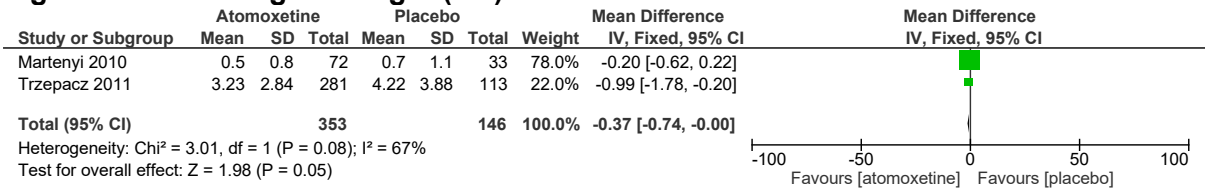
Heterogeneity: Chi² = 4.01, df = 3 (P = 0.26); I² = 25%
Test for overall effect: Z = 1.78 (P = 0.07)



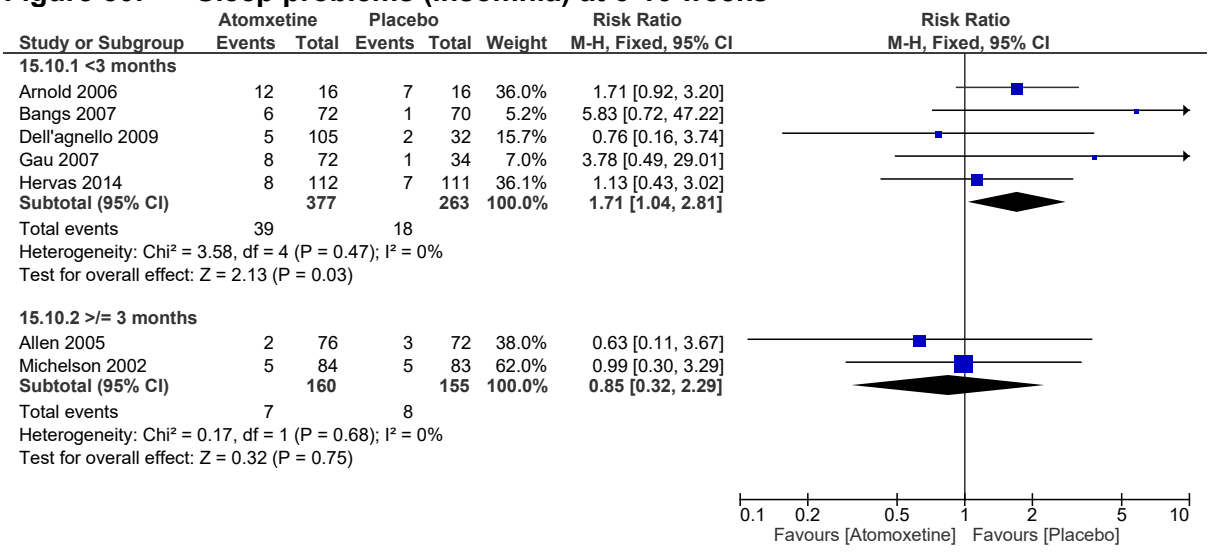
## Figure 48: Weight change (kg) at 6-18 weeks



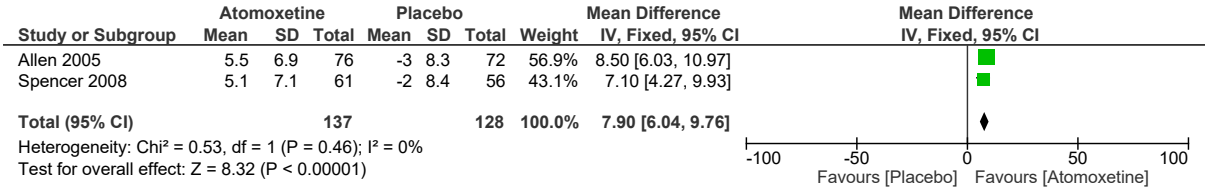

## Figure 49: Change in height (cm) at 6 to 8 weeks



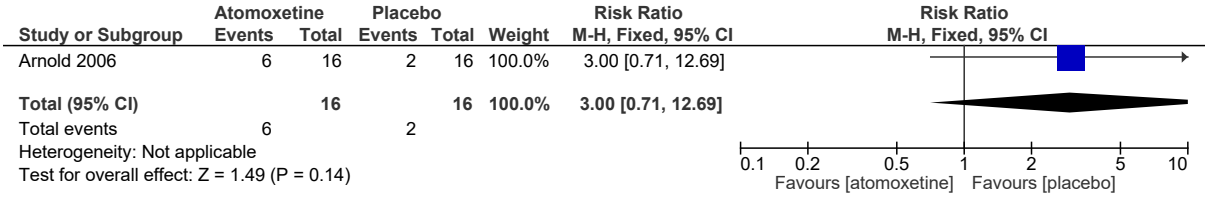

## Figure 50: Sleep problems (insomnia) at 6-16 weeks



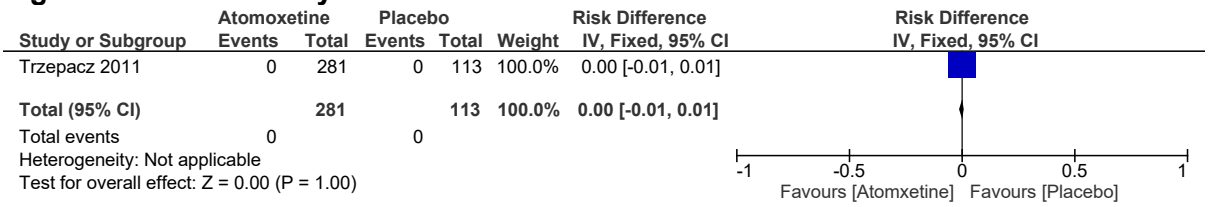

## Figure 51: Yale Global Tics Severity scale scores at 7 to 18 weeks (high is good outcome; range 0-10)



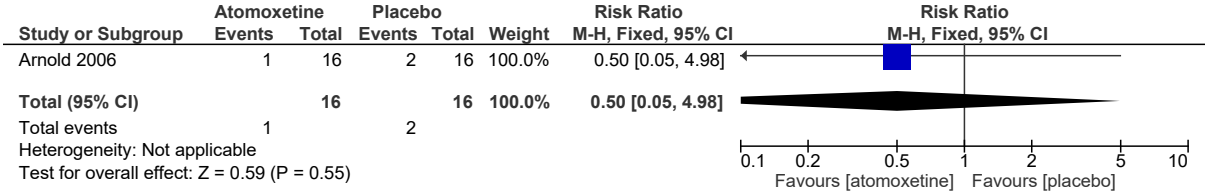

## Figure 52: Tics at 6 weeks




## Figure 53: Sexual dysfunction at 8 weeks

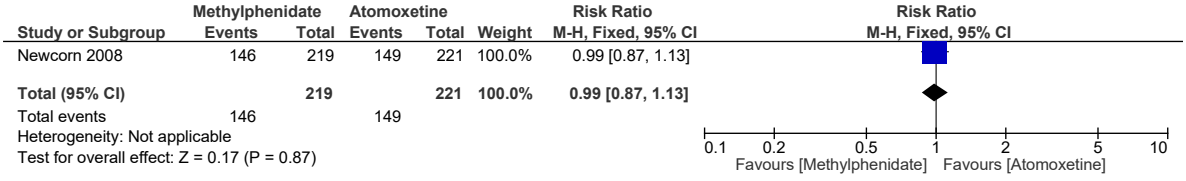



## Figure 54: Tremor at 6 weeks




# E.2.8 Methylphenidate versus atomoxetine

## Figure 55: Total participants with adverse events at 6 weeks




## Figure 56: Systolic blood pressure at 6 weeks

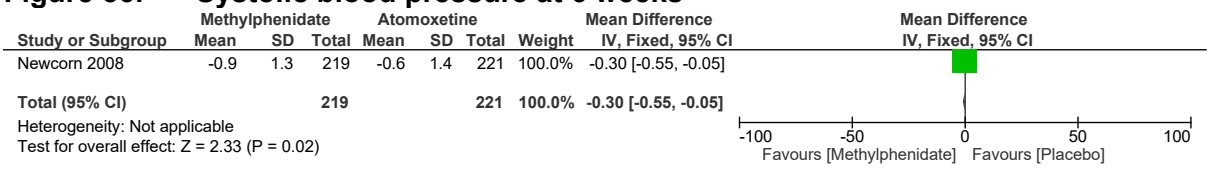


**Figure 57: Diastolic blood pressure at 6 weeks**

| Study or Subgroup | Methylphenidate Mean | SD | Total | Atomoxetine Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Newcorn 2008 | 3.1 | 8.4 | 219 | 3.8 | 8 | 74 | 100.0% | -0.70 [-2.84, 1.44] |
| **Total (95% CI)** | | | **219** | | | **74** | **100.0%** | **-0.70 [-2.84, 1.44]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.64 (P = 0.52)

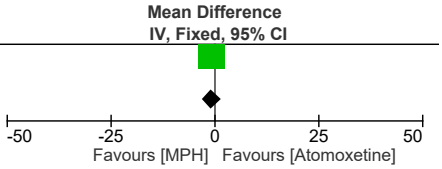



**Figure 58: Decreased weight(kg) at 6 to 8 weeks**

| Study or Subgroup | Methylphenidate Mean | SD | Total | Atomoxetine Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Newcorn 2008 | -0.9 | 1.3 | 219 | -0.6 | 1.4 | 221 | 85.8% | -0.30 [-0.55, -0.05] |
| Wang 2007 | -1.2 | 3.8524 | 164 | -0.4 | 1.2923 | 166 | 14.2% | -0.80 [-1.42, -0.18] |
| **Total (95% CI)** | | | **383** | | | **387** | **100.0%** | **-0.37 [-0.60, -0.14]** |

Heterogeneity: Chi² = 2.13, df = 1 (P = 0.14); I² = 53%
Test for overall effect: Z = 3.11 (P = 0.002)

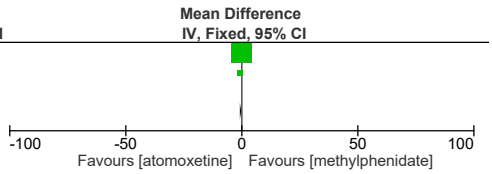
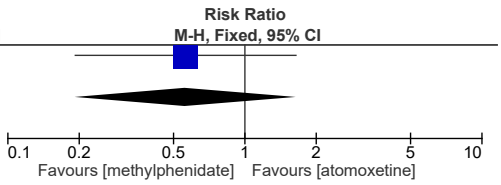



**Figure 59: Sleep (insomnia) at 8 weeks**

| Study or Subgroup | Methylphenidate Events | Total | Atomoxetine Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Wang 2007 | 5 | 164 | 9 | 166 | 100.0% | 0.56 [0.19, 1.64] |
| **Total (95% CI)** | | **164** | | **166** | **100.0%** | **0.56 [0.19, 1.64]** |
| Total events | 5 | | 9 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.05 (P = 0.29)




## E.2.9 Methylphenidate versus atomoxetine (non-randomised)

Figure 60:Weight at 24 months

| Study or Subgroup | Methylphenidate Mean | SD | Total | Atomoxetine Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Germanario 2013 | 46.8 | 13.41 | 55 | 49.11 | 18.33 | 28 | 100.0% | -2.31 [-9.97, 5.35] |
| **Total (95% CI)** | | | **55** | | | **28** | **100.0%** | **-2.31 [-9.97, 5.35]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.59 (P = 0.55)

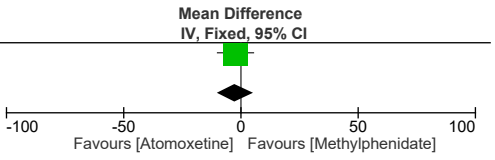
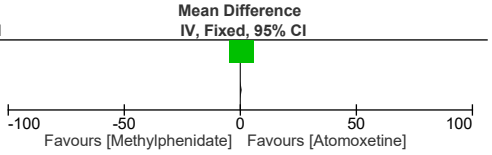



**Figure 61: Height at 24 months**

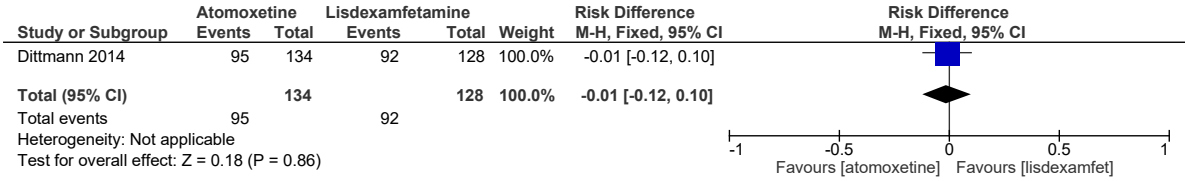
| Study or Subgroup | Methylphenidate Mean | SD | Total | Atomoxetine Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Germanario 2013 | -0.037 | 0.075 | 55 | -0.441 | 0.734 | 35 | 100.0% | 0.40 [0.16, 0.65] |
| **Total (95% CI)** | | | **55** | | | **35** | **100.0%** | **0.40 [0.16, 0.65]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 3.25 (P = 0.001)

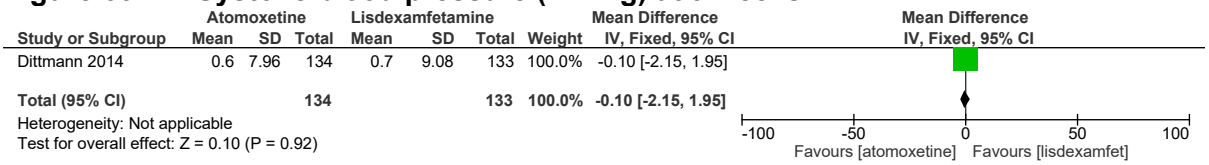


## E.2.10 Atomoxetine versus lisdexamfetamine dimesylate

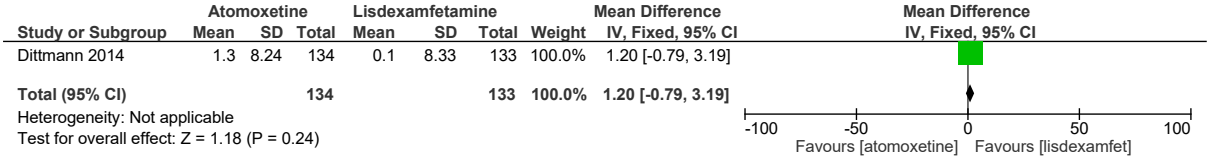
### Figure 62: Total participants with adverse events at 9 weeks




### Figure 63: Systolic blood pressure (mmHg) at 9 weeks

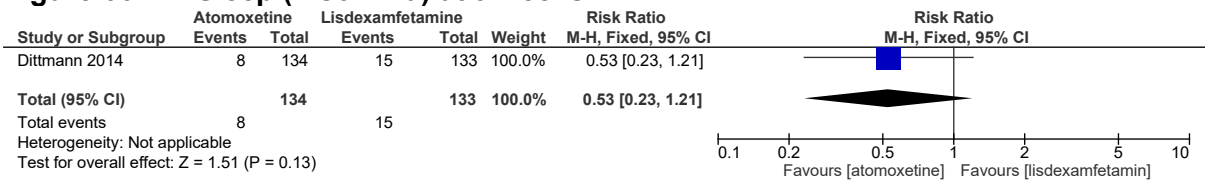



### Figure 64: Diastolic blood pressure (mmHg) at 9 weeks




### Figure 65: Decreased weight at 9 weeks


### Figure 66: Sleep (insomnia) at 9 weeks

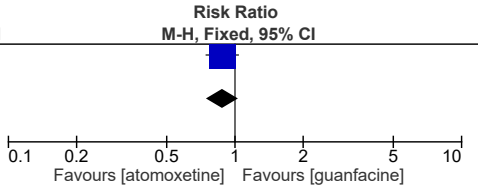


## E.2.11 Atomoxetine versus guanfacine

### Figure 67: Total participants with adverse events at 10 to 13 weeks

| Study or Subgroup | Atomoxetine Events | Atomoxetine Total | Guanfacine Events | Guanfacine Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Hervas 2014 | 76 | 112 | 88 | 114 | 100.0% | 0.88 [0.75, 1.03] |
| **Total (95% CI)** | | **112** | | **114** | **100.0%** | **0.88 [0.75, 1.03]** |
| Total events | 76 | | 88 | | | |

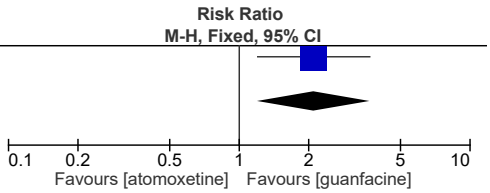
Heterogeneity: Not applicable
Test for overall effect: Z = 1.56 (P = 0.12)




### Figure 68: Decreased appetite at 10 to 13 weeks

| Study or Subgroup | Atomoxetine Events | Atomoxetine Total | Guanfacine Events | Guanfacine Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Hervas 2014 | 31 | 112 | 15 | 114 | 100.0% | 2.10 [1.20, 3.68] |
| **Total (95% CI)** | | **112** | | **114** | **100.0%** | **2.10 [1.20, 3.68]** |
| Total events | 31 | | 15 | | | |

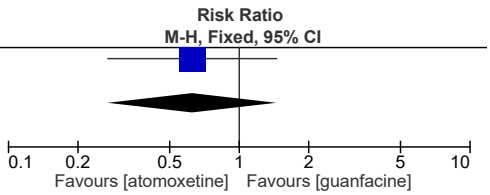
Heterogeneity: Not applicable
Test for overall effect: Z = 2.61 (P = 0.009)




### Figure 69: Sleep (insomnia) at 10 to 13 weeks

| Study or Subgroup | Atomoxetine Events | Atomoxetine Total | Guanfacine Events | Guanfacine Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Hervas 2014 | 8 | 112 | 13 | 114 | 100.0% | 0.63 [0.27, 1.45] |
| **Total (95% CI)** | | **112** | | **114** | **100.0%** | **0.63 [0.27, 1.45]** |
| Total events | 8 | | 13 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.09 (P = 0.28)

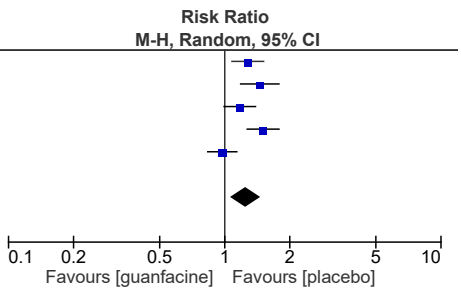



## E.2.12 Guanfacine versus placebo

### Figure 70: Total participants with adverse events at 5 to 12 weeks

| Study or Subgroup | Guanfacine Events | Guanfacine Total | Control Events | Control Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Biederman 2008 | 211 | 258 | 55 | 86 | 20.2% | 1.28 [1.08, 1.51] |
| Connor 2010 | 114 | 136 | 45 | 78 | 18.3% | 1.45 [1.18, 1.78] |
| Hervas 2014 | 88 | 114 | 73 | 111 | 20.3% | 1.17 [0.99, 1.39] |
| Newcorn 2013 | 190 | 221 | 64 | 112 | 20.2% | 1.50 [1.27, 1.78] |
| Salee 2009 | 189 | 256 | 50 | 66 | 20.9% | 0.97 [0.83, 1.14] |
| **Total (95% CI)** | | **985** | | **453** | **100.0%** | **1.26 [1.07, 1.48]** |
| Total events | 792 | | 287 | | | |

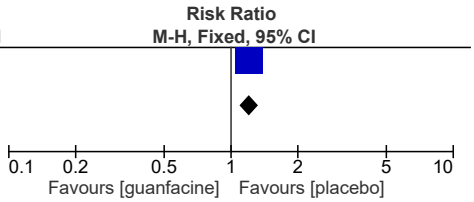
Heterogeneity: Tau² = 0.03; Chi² = 17.68, df = 4 (P = 0.001); I² = 77%
Test for overall effect: Z = 2.77 (P = 0.006)



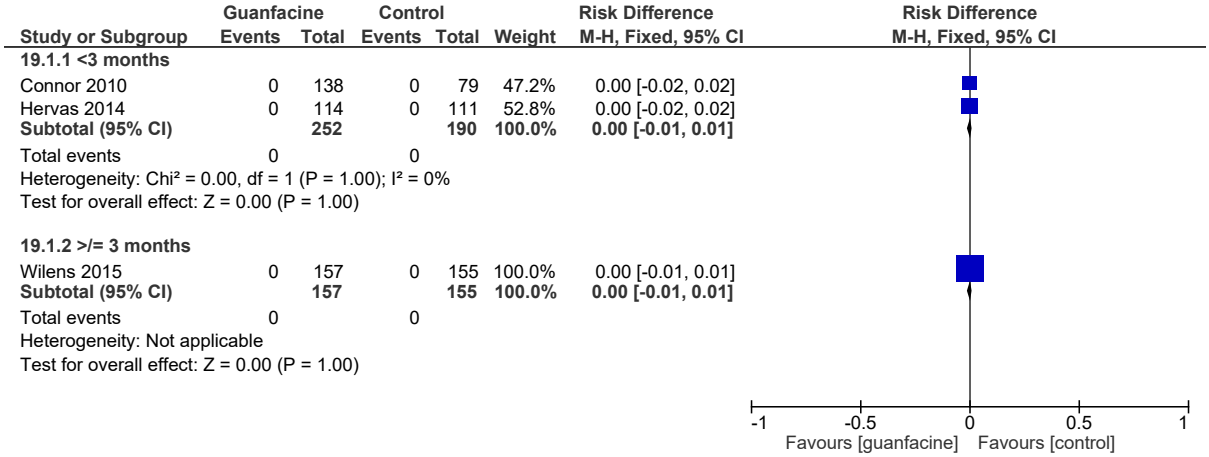

### Figure 71: Total adverse events at 15 weeks

| Study or Subgroup | Guanfacine Events | Guanfacine Total | Control Events | Control Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Wilens 2015 | 147 | 157 | 120 | 155 | 100.0% | 1.21 [1.10, 1.33] |
| **Total (95% CI)** | | **157** | | **155** | **100.0%** | **1.21 [1.10, 1.33]** |
| Total events | 147 | | 120 | | | |

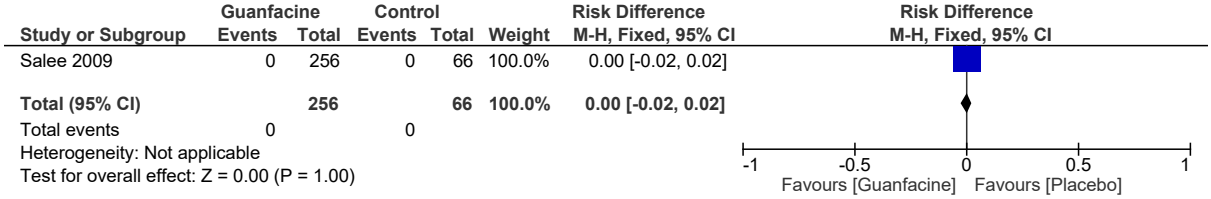
Heterogeneity: Not applicable
Test for overall effect: Z = 3.95 (P < 0.0001)



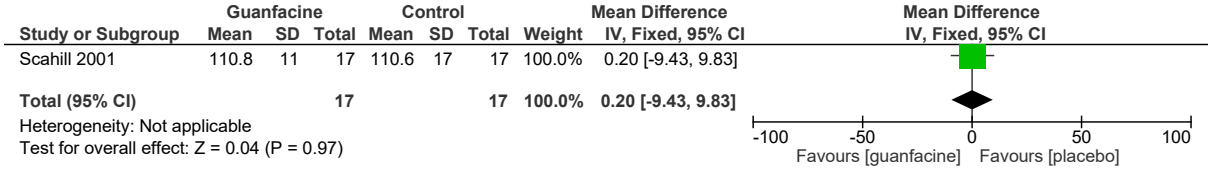
## Figure 72: All-cause mortality at 8 to 15 weeks



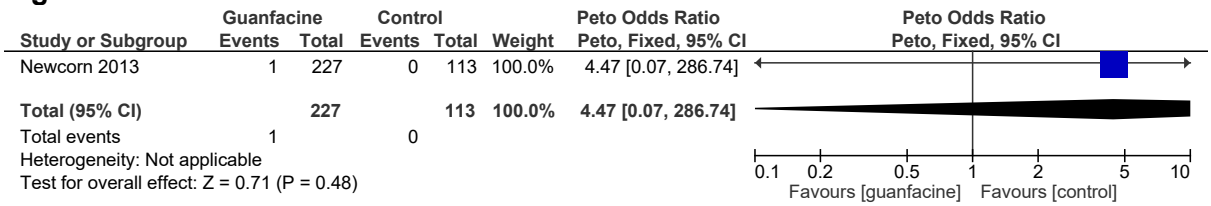

## Figure 73: Cardiovascular events at 9 weeks




## Figure 74: Systolic blood pressure (mmHg) at 8 weeks



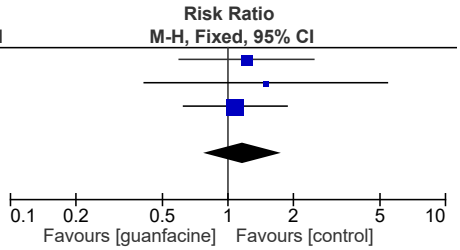

## Figure 75: Suicidal ideation at 8 weeks



## Figure 76: Decreased appetite at 8 to 13 weeks

| Study or Subgroup | Guanfacine Events | Guanfacine Total | Control Events | Control Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Hervas 2014 | 15 | 114 | 12 | 111 | 32.6% | 1.22 [0.60, 2.48] |
| Newcorn 2013 | 9 | 227 | 3 | 113 | 10.7% | 1.49 [0.41, 5.41] |
| Wilens 2015 | 23 | 157 | 21 | 155 | 56.7% | 1.08 [0.62, 1.87] |
| **Total (95% CI)** | | **498** | | **379** | **100.0%** | **1.17 [0.77, 1.77]** |
| Total events | 47 | | 36 | | | |

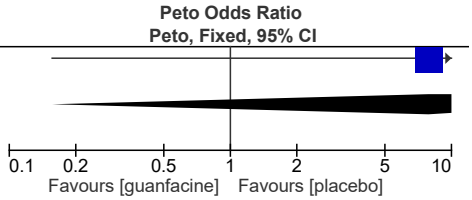
Heterogeneity: Chi² = 0.23, df = 2 (P = 0.89); I² = 0%
Test for overall effect: Z = 0.75 (P = 0.46)




## Figure 77: Psychotic symptoms 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 | | | |

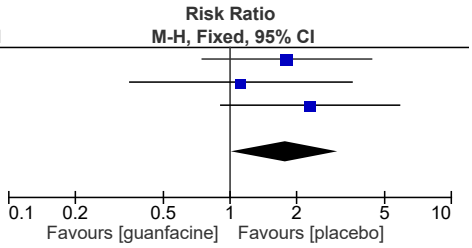
Heterogeneity: Not applicable
Test for overall effect: Z = 1.03 (P = 0.30)




## Figure 78: Sleep (insomnia) at 8 to 13 weeks

| Study or Subgroup | Guanfacine Events | Guanfacine Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Hervas 2014 | 13 | 114 | 7 | 111 | 38.4% | 1.81 [0.75, 4.36] |
| Newcorn 2013 | 9 | 227 | 4 | 113 | 28.9% | 1.12 [0.35, 3.56] |
| Wilens 2015 | 14 | 157 | 6 | 155 | 32.7% | 2.30 [0.91, 5.84] |
| **Total (95% CI)** | | **498** | | **379** | **100.0%** | **1.77 [1.02, 3.08]** |
| Total events | 36 | | 17 | | | |

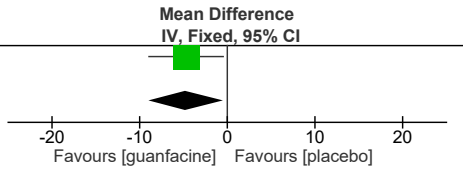
Heterogeneity: Chi² = 0.91, df = 2 (P = 0.63); I² = 0%
Test for overall effect: Z = 2.02 (P = 0.04)




## Figure 79: Yale tic severity scale at 8 weeks; 0-50; lower scores are beneficial

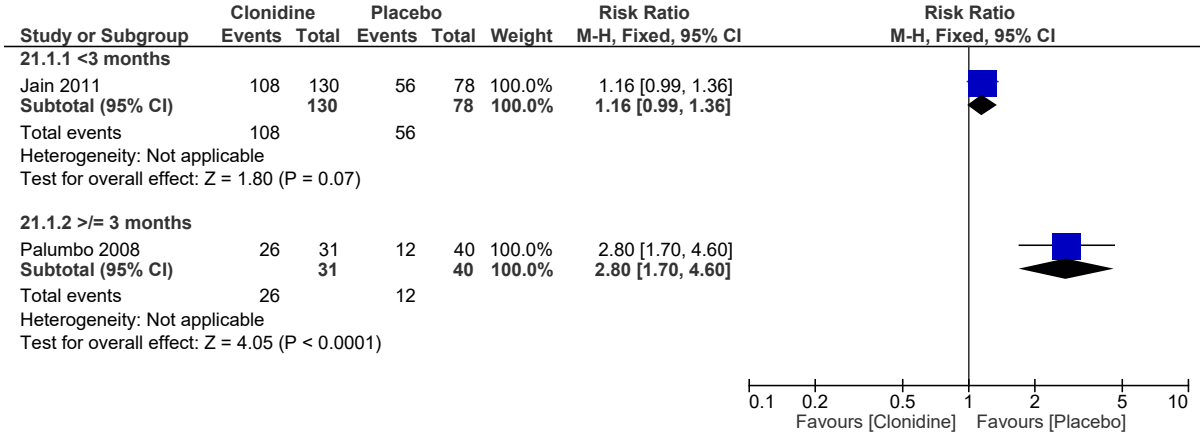
| Study or Subgroup | Guanfacine Mean | Guanfacine SD | Guanfacine Total | Control Mean | Control SD | Control Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Scahill 2001 | 10.7 | 7 | 17 | 15.4 | 5.5 | 17 | 100.0% | -4.70 [-8.93, -0.47] |
| **Total (95% CI)** | | | **17** | | | **17** | **100.0%** | **-4.70 [-8.93, -0.47]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 2.18 (P = 0.03)

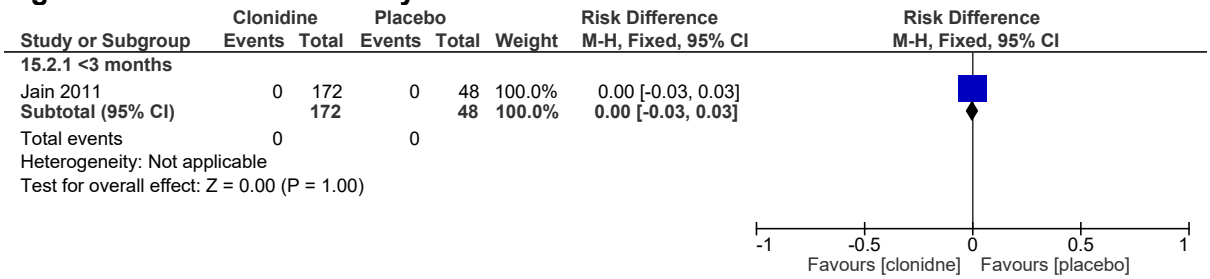


## E.2.13 Clonidine versus placebo

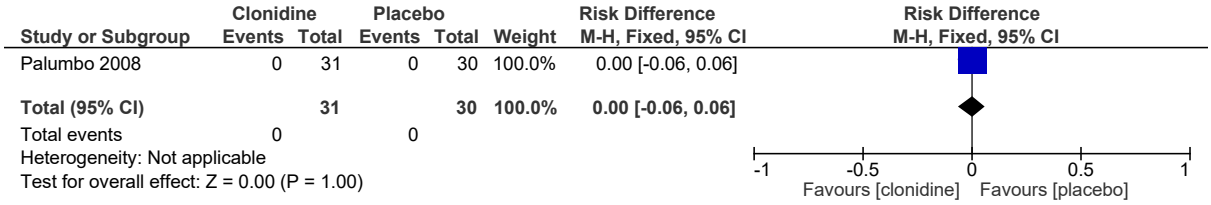
### Figure 80: Total participants with adverse events at 8 to 16 weeks



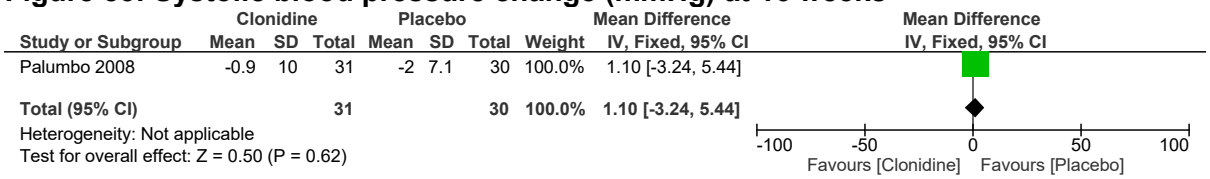

### Figure 81: All-cause mortality at 8 weeks



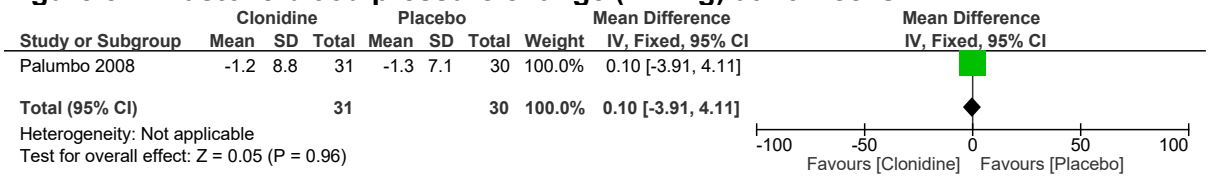

### Figure 82: Tachycardia at 16 weeks



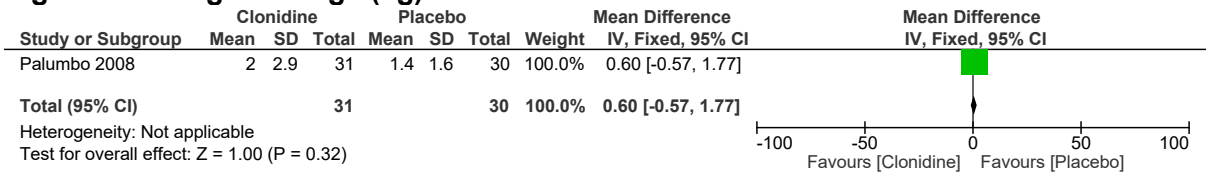

### Figure 83: Systolic blood pressure change (mmHg) at 16 weeks



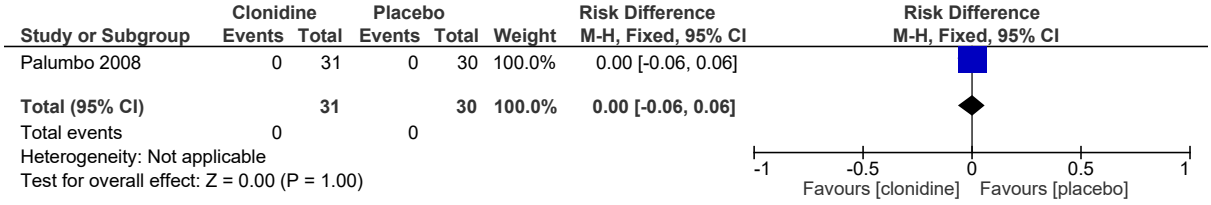

### Figure 84: Diastolic blood pressure change (mmHg) at 16 weeks



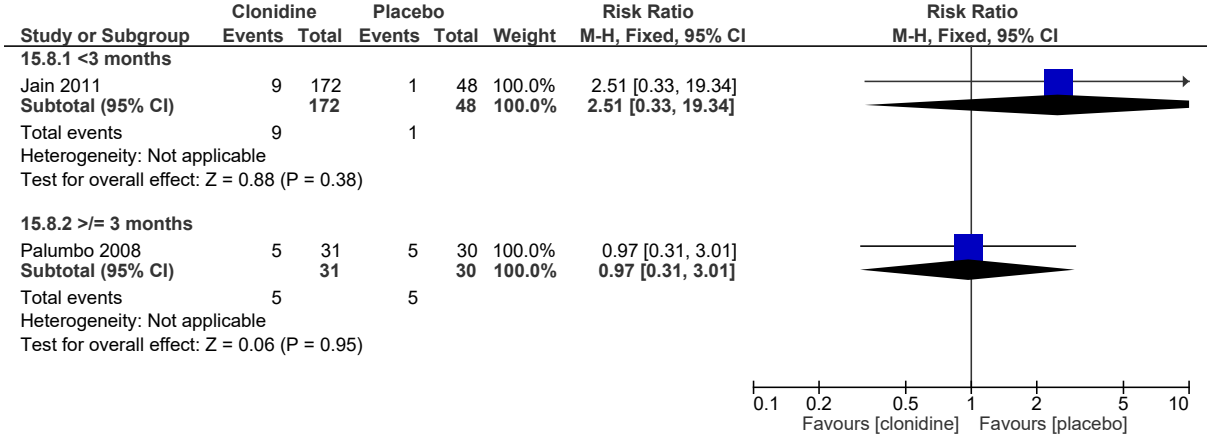
## Figure 85: Weight change (kg) at 16 weeks



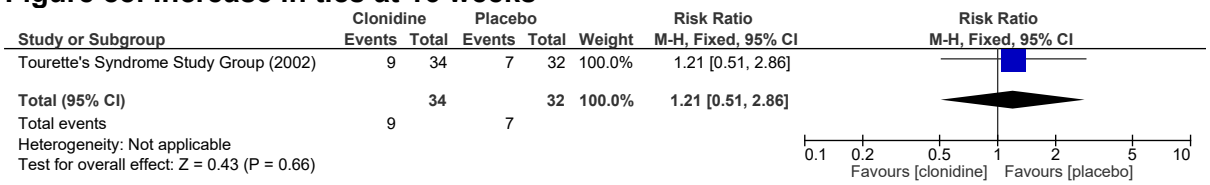

## Figure 86: Psychotic symptoms at 16 weeks




## Figure 87: Sleep (insomnia) at 8 to 16 weeks




## Figure 88: Increase in tics at 16 weeks

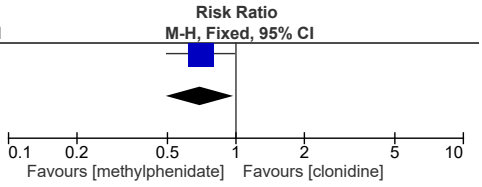


## E.2.14 Methylphenidate versus clonidine

### Figure 89: Total participants with adverse events at 16 weeks

| Study or Subgroup | Methylphenidate Events | Total | Clonidine Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Palumbo 2008 | 17 | 29 | 26 | 31 | 100.0% | 0.70 [0.50, 0.98] |
| **Total (95% CI)** | | **29** | | **31** | **100.0%** | **0.70 [0.50, 0.98]** |
| Total events | 17 | | 26 | | | |

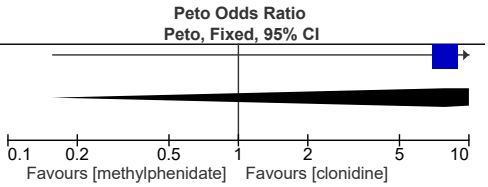
Heterogeneity: Not applicable
Test for overall effect: Z = 2.05 (P = 0.04)




### Figure 90: Tachycardia at 16 weeks

| Study or Subgroup | Methylphenidate Events | Total | Clonidine Events | Total | Weight | Peto Odds Ratio Peto, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Palumbo 2008 | 1 | 29 | 0 | 31 | 100.0% | 7.92 [0.16, 399.84] |
| **Total (95% CI)** | | **29** | | **31** | **100.0%** | **7.92 [0.16, 399.84]** |
| Total events | 1 | | 0 | | | |

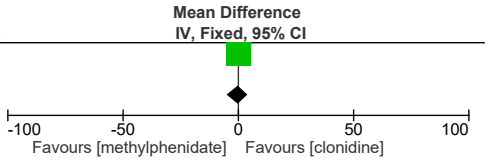
Heterogeneity: Not applicable
Test for overall effect: Z = 1.03 (P = 0.30)




### Figure 91: Systolic blood pressure at 16 weeks

| Study or Subgroup | Methylphenidate Mean | SD | Total | Clonidine Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Palumbo 2008 | -1 | 7.6 | 29 | -0.9 | 10 | 31 | 100.0% | -0.10 [-4.58, 4.38] |
| **Total (95% CI)** | | | **29** | | | **31** | **100.0%** | **-0.10 [-4.58, 4.38]** |

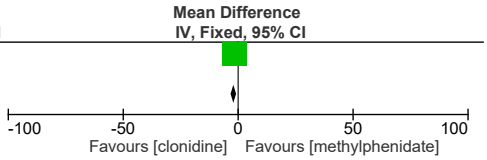
Heterogeneity: Not applicable
Test for overall effect: Z = 0.04 (P = 0.97)




### Figure 92: Weight changes(kg) at 16 weeks

| Study or Subgroup | Methylphenidate Mean | SD | Total | Clonidine Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Palumbo 2008 | 0.3 | 2.3 | 29 | 2 | 2.9 | 31 | 100.0% | -1.70 [-3.02, -0.38] |
| **Total (95% CI)** | | | **29** | | | **31** | **100.0%** | **-1.70 [-3.02, -0.38]** |

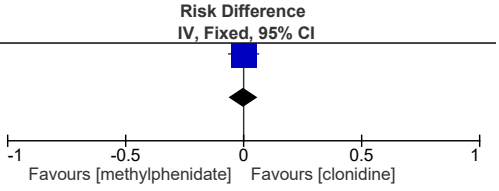
Heterogeneity: Not applicable
Test for overall effect: Z = 2.52 (P = 0.01)




### Figure 93: Psychotic symptoms (hallucinations) at 16 weeks

| Study or Subgroup | Methylphenidate Events | Total | Clonidine Events | Total | Weight | Risk Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Palumbo 2008 | 0 | 29 | 0 | 31 | 100.0% | 0.00 [-0.06, 0.06] |
| **Total (95% CI)** | | **29** | | **31** | **100.0%** | **0.00 [-0.06, 0.06]** |
| Total events | 0 | | 0 | | | |

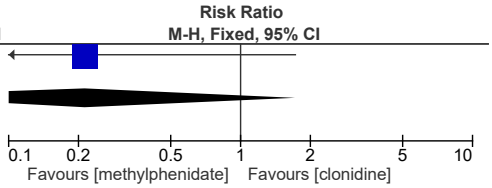
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



### Figure 94: Sleep (insomnia) at 16 weeks

| Study or Subgroup | Methylphenidate Events | Total | Clonidine Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Palumbo 2008 | 1 | 29 | 5 | 31 | 100.0% | 0.21 [0.03, 1.72] |
| **Total (95% CI)** | | **29** | | **31** | **100.0%** | **0.21 [0.03, 1.72]** |
| Total events | 1 | | 5 | | | |

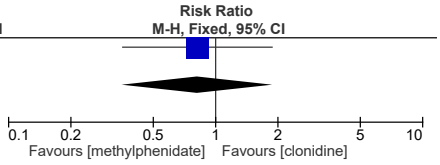
Heterogeneity: Not applicable
Test for overall effect: Z = 1.45 (P = 0.15)




### Figure 95: Increase in tics at 16 weeks

| Study or Subgroup | Methylphenidate Events | Total | Clonidine Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Tourette's Syndrome Study Group (2002) | 8 | 37 | 9 | 34 | 100.0% | 0.82 [0.36, 1.87] |
| **Total (95% CI)** | | **37** | | **34** | **100.0%** | **0.82 [0.36, 1.87]** |
| Total events | 8 | | 9 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.48 (P = 0.63)

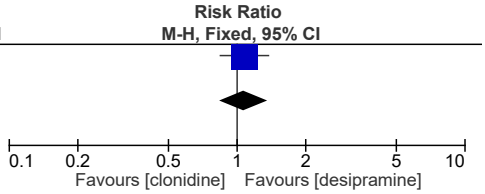



## E.2.15 Clonidine versus desipramine

### Figure 96: Total participants with adverse events at 6 weeks

| Study or Subgroup | Clonidine Events | Total | Desipramine Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Singer 1995 | 28 | 34 | 26 | 34 | 100.0% | 1.08 [0.84, 1.37] |
| **Total (95% CI)** | | **34** | | **34** | **100.0%** | **1.08 [0.84, 1.37]** |
| Total events | 28 | | 26 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.60 (P = 0.55)

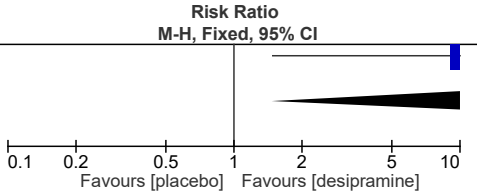



## E.2.16 Desipramine versus placebo

### Figure 97: Improvement of tics at 6 weeks

| Study or Subgroup | Desipramine Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Spencer 2002 | 11 | 21 | 1 | 20 | 100.0% | 10.48 [1.49, 73.88] |
| **Total (95% CI)** | | **21** | | **20** | **100.0%** | **10.48 [1.49, 73.88]** |
| Total events | 11 | | 1 | | | |

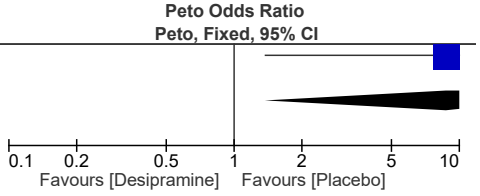
Heterogeneity: Not applicable
Test for overall effect: Z = 2.36 (P = 0.02)




### Figure 98: Decreased appetite at 6 weeks

| Study or Subgroup | Desipramine Events | Total | Placebo Events | Total | Weight | Peto Odds Ratio Peto, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Spencer 2002 | 5 | 21 | 0 | 20 | 100.0% | 8.75 [1.38, 55.58] |
| **Total (95% CI)** | | **21** | | **20** | **100.0%** | **8.75 [1.38, 55.58]** |
| Total events | 5 | | 0 | | | |

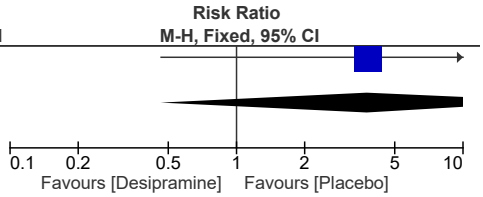
Heterogeneity: Not applicable
Test for overall effect: Z = 2.30 (P = 0.02)



### Figure 99: Sleep (difficulty sleeping) at 6 weeks

| Study or Subgroup | Desipramine Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Spencer 2002 | 4 | 21 | 1 | 20 | 100.0% | 3.81 [0.46, 31.23] |
| **Total (95% CI)** | | **21** | | **20** | **100.0%** | **3.81 [0.46, 31.23]** |
| Total events | 4 | | 1 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.25 (P = 0.21)

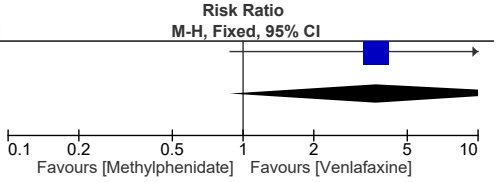



## E.2.17 Methylphenidate versus venlafaxine

### Figure 100: Decreased appetite at 6 weeks

| Study or Subgroup | Methylphenidate Events | Total | Venlafaxine Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Zarinara 2010 | 7 | 18 | 2 | 19 | 100.0% | 3.69 [0.88, 15.49] |
| **Total (95% CI)** | | **18** | | **19** | **100.0%** | **3.69 [0.88, 15.49]** |
| Total events | 7 | | 2 | | | |

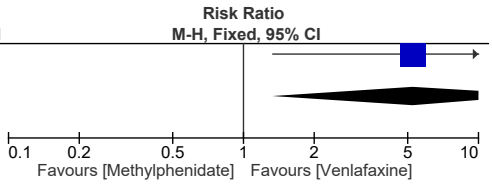
Heterogeneity: Not applicable
Test for overall effect: Z = 1.79 (P = 0.07)




### Figure 101: Sleep (insomnia) at 6 weeks

| Study or Subgroup | Methylphenidate Events | Total | Venlafaxine Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Zarinara 2010 | 10 | 18 | 2 | 19 | 100.0% | 5.28 [1.34, 20.86] |
| **Total (95% CI)** | | **18** | | **19** | **100.0%** | **5.28 [1.34, 20.86]** |
| Total events | 10 | | 2 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 2.37 (P = 0.02)

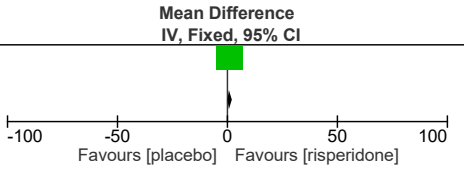



## E.2.18 Risperidone versus placebo

### Figure 102: Weight change (kg) at 24 weeks

| Study or Subgroup | risperidone Mean | SD | Total | placebo Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Nagaraj 2006 | 2.81 | 2.04 | 20 | 1.71 | 1.3 | 20 | 100.0% | 1.10 [0.04, 2.16] |
| **Total (95% CI)** | | | **20** | | | **20** | **100.0%** | **1.10 [0.04, 2.16]** |

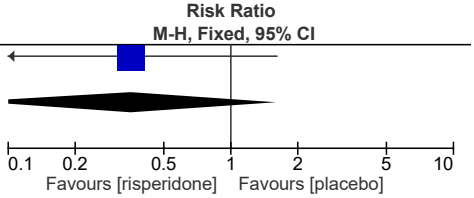
Heterogeneity: Not applicable
Test for overall effect: Z = 2.03 (P = 0.04)



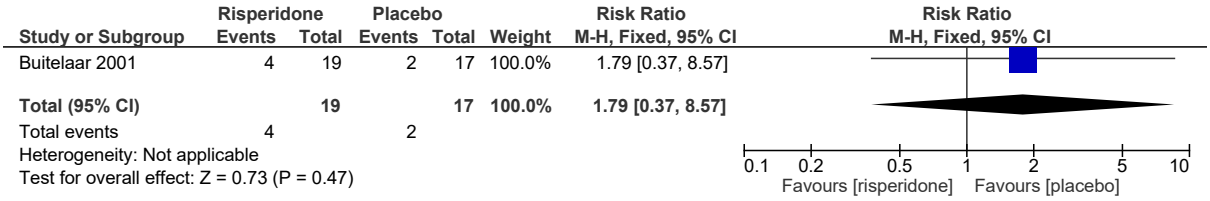

### Figure 103: Sleeping problems at 10 weeks

| Study or Subgroup | Risperidone Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Buitelaar 2001 | 2 | 19 | 5 | 17 | 100.0% | 0.36 [0.08, 1.61] |
| **Total (95% CI)** | | **19** | | **17** | **100.0%** | **0.36 [0.08, 1.61]** |
| Total events | 2 | | 5 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.34 (P = 0.18)

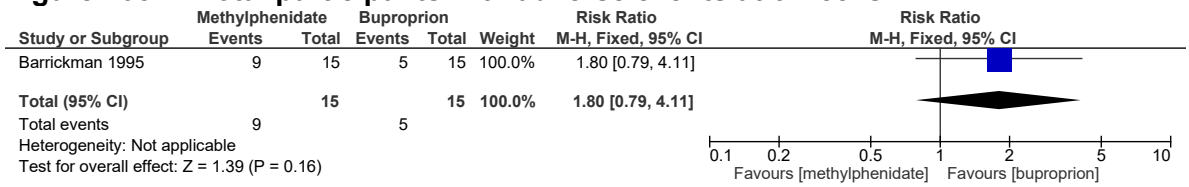


### Figure 104: Tremor at 10 weeks

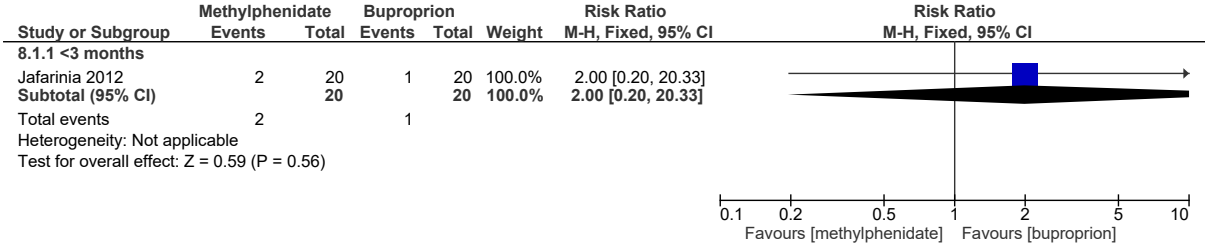



## E.2.19 Methylphenidate versus buproprion

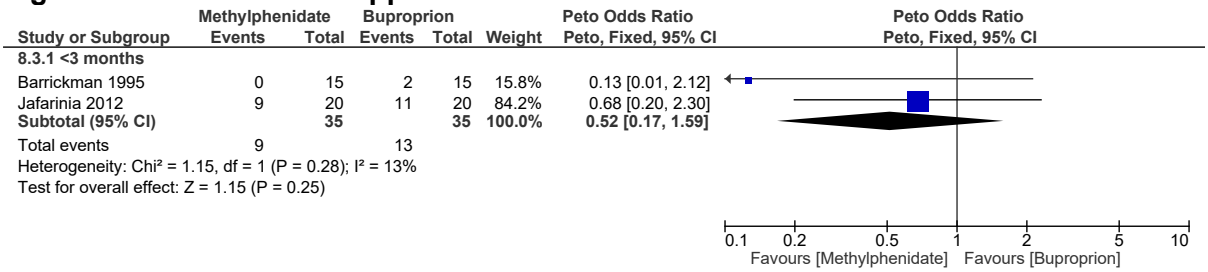
### Figure 105: Total participants with adverse events at 6 weeks



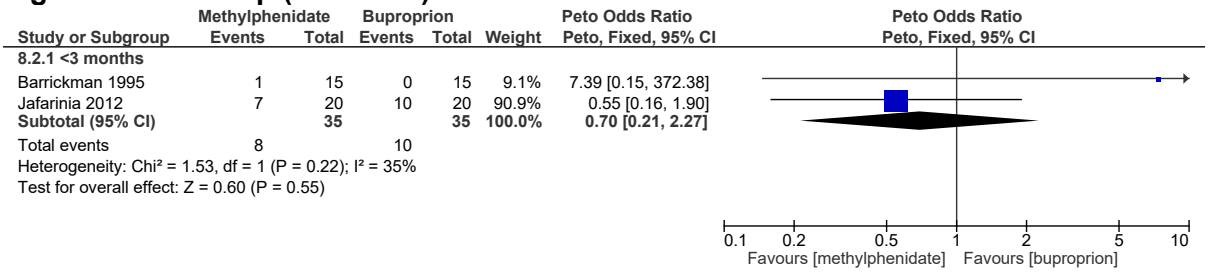

### Figure 106: Tachycardia at 6 weeks




### Figure 107: Decreased appetite at 6 weeks



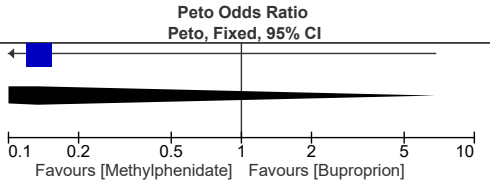

### Figure 108: Sleep (insomnia) at 6 weeks



### Figure 109: Tremor at 6 weeks

| Study or Subgroup | Methylphenidate Events | Methylphenidate Total | Buproprion Events | Buproprion Total | Weight | Peto Odds Ratio Peto, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Barrickman 1995 | 0 | 15 | 1 | 15 | 100.0% | 0.14 [0.00, 6.82] |
| **Total (95% CI)** | | **15** | | **15** | **100.0%** | **0.14 [0.00, 6.82]** |
| Total events | 0 | | 1 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.00 (P = 0.32)

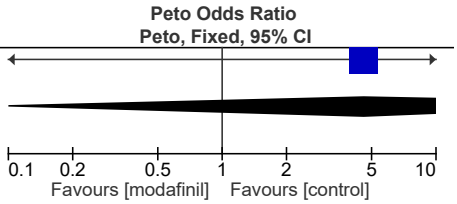



## E.2.20 Modafinil versus placebo

### Figure 110: Tachycardia at 9 weeks

| Study or Subgroup | Modafinil Events | Modafinil Total | Control Events | Control Total | Weight | Peto Odds Ratio Peto, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Swanson 2001 | 1 | 120 | 0 | 63 | 100.0% | 4.60 [0.07, 284.33] |
| **Total (95% CI)** | | **120** | | **63** | **100.0%** | **4.60 [0.07, 284.33]** |
| Total events | 1 | | 0 | | | |

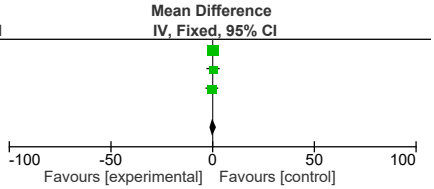
Heterogeneity: Not applicable
Test for overall effect: Z = 0.72 (P = 0.47)




### Figure 111: Systolic blood pressure (mmHg) at 9 weeks

| Study or Subgroup | Experimental Mean | Experimental SD | Experimental Total | Control Mean | Control SD | Control Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Biederman 2005 (Biederman 2006) | -0.18 | 8.67 | 164 | -0.5 | 9.6 | 82 | 40.5% | 0.32 [-2.15, 2.79] |
| Greenhill 2006 | 104.7 | 9.8 | 133 | 104.5 | 10.1 | 67 | 28.5% | 0.20 [-2.74, 3.14] |
| Swanson 2001 | 102.7 | 10.4 | 126 | 103.1 | 8.8 | 64 | 31.0% | -0.40 [-3.22, 2.42] |
| **Total (95% CI)** | | | **423** | | | **213** | **100.0%** | **0.06 [-1.51, 1.63]** |

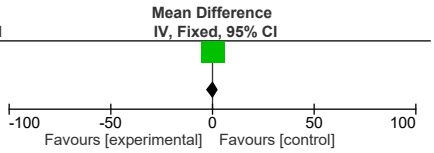
Heterogeneity: Chi² = 0.15, df = 2 (P = 0.93); I² = 0%
Test for overall effect: Z = 0.08 (P = 0.94)




### Figure 112: Diastolic blood pressure (mmHg) at 9 weeks

| Study or Subgroup | Experimental Mean | Experimental SD | Experimental Total | Control Mean | Control SD | Control Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Biederman 2005 (Biederman 2006) | -0.466 | 8.935 | 197 | -0.5 | 9.6 | 51 | 100.0% | 0.03 [-2.88, 2.95] |
| **Total (95% CI)** | | | **197** | | | **51** | **100.0%** | **0.03 [-2.88, 2.95]** |

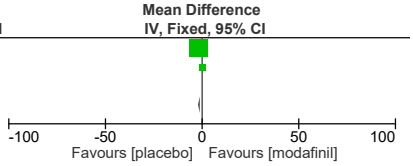
Heterogeneity: Not applicable
Test for overall effect: Z = 0.02 (P = 0.98)




### Figure 113: Weight change(kg) at 9 weeks

| Study or Subgroup | Modafinil Mean | Modafinil SD | Modafinil Total | Control Mean | Control SD | Control Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Biederman 2005 (Biederman 2006) | -1 | 1.1 | 164 | 0.7 | 1.1 | 82 | 78.8% | -1.70 [-1.99, -1.41] |
| Swanson 2001 | 1 | 2.7206 | 120 | 0.6 | 1.1451 | 63 | 21.2% | 0.40 [-0.16, 0.96] |
| **Total (95% CI)** | | | **284** | | | **145** | **100.0%** | **-1.26 [-1.51, -1.00]** |

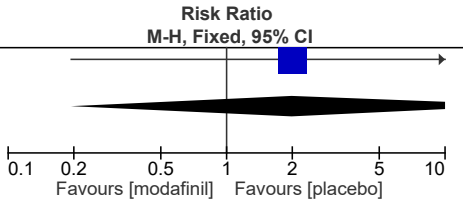
Heterogeneity: Chi² = 42.15, df = 1 (P < 0.00001); I² = 98%
Test for overall effect: Z = 9.51 (P < 0.00001)



## Figure 114: Decreased weight at 5 weeks

| Study or Subgroup | Modafinil Events | Modafinil Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Kahbazi 2009 | 2 | 23 | 1 | 23 | 100.0% | 2.00 [0.19, 20.55] |
| **Total (95% CI)** | | **23** | | **23** | **100.0%** | **2.00 [0.19, 20.55]** |
| Total events | 2 | | 1 | | | |

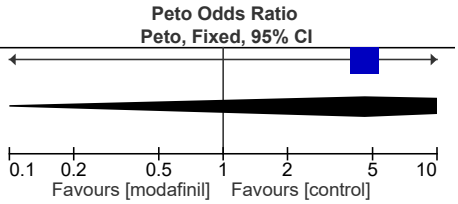
Heterogeneity: Not applicable
Test for overall effect: Z = 0.58 (P = 0.56)




## Figure 115: Psychotic symptoms at 9 weeks

| Study or Subgroup | Modafinil Events | Modafinil Total | Control Events | Control Total | Weight | Peto Odds Ratio Peto, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Swanson 2001 | 1 | 120 | 0 | 63 | 100.0% | 4.60 [0.07, 284.33] |
| **Total (95% CI)** | | **120** | | **63** | **100.0%** | **4.60 [0.07, 284.33]** |
| Total events | 1 | | 0 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.72 (P = 0.47)



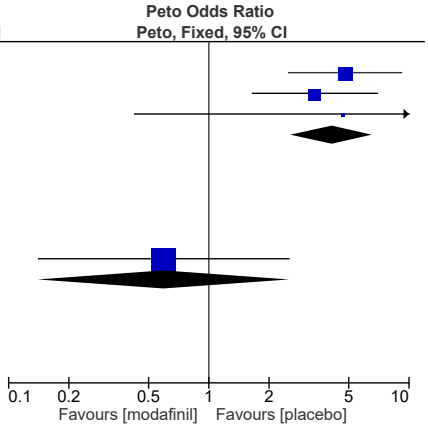

## Figure 116: Sleep (insomnia) at 5 to 9 weeks

| Study or Subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight | Peto Odds Ratio Peto, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **20.2.1 < 3 months** | | | | | | |
| Biederman 2005 (Biederman 2006) | 48 | 164 | 3 | 84 | 52.9% | 4.79 [2.50, 9.17] |
| Greenhill 2006 | 37 | 133 | 5 | 67 | 43.2% | 3.39 [1.65, 6.96] |
| Swanson 2001 | 3 | 120 | 0 | 63 | 3.9% | 4.67 [0.43, 51.25] |
| **Subtotal (95% CI)** | | **417** | | **214** | **100.0%** | **4.12 [2.57, 6.61]** |
| Total events | 88 | | 8 | | | |

Heterogeneity: Chi² = 0.50, df = 2 (P = 0.78); I² = 0%
Test for overall effect: Z = 5.88 (P < 0.00001)

| | | | | | | |
|---|---|---|---|---|---|---|
| **20.2.3 <3 months high risk (autism)** | | | | | | |
| Harfterkamp 2012 | 3 | 48 | 5 | 49 | 100.0% | 0.60 [0.14, 2.52] |
| **Subtotal (95% CI)** | | **48** | | **49** | **100.0%** | **0.60 [0.14, 2.52]** |
| Total events | 3 | | 5 | | | |

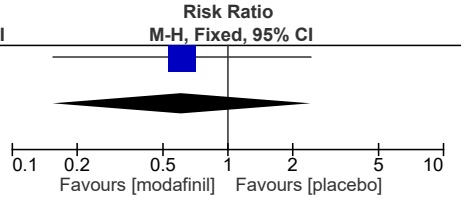
Heterogeneity: Not applicable
Test for overall effect: Z = 0.70 (P = 0.48)




## Figure 117: Sleep (insomnia) at 8 weeks (autism population)

| Study or Subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Harfterkamp 2012 | 3 | 48 | 5 | 49 | 100.0% | 0.61 [0.15, 2.42] |
| **Total (95% CI)** | | **48** | | **49** | **100.0%** | **0.61 [0.15, 2.42]** |
| Total events | 3 | | 5 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.70 (P = 0.48)

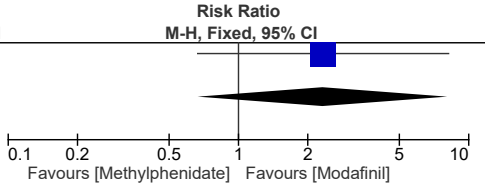


### E.2.21 Methylphenidate versus modafinil

**Figure 118: Participants with decreased weight at 6 weeks**

| Study or Subgroup | Methylphenidate Events | Total | Modafinil Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Amiri 2008 | 7 | 30 | 3 | 30 | 100.0% | 2.33 [0.67, 8.18] |
| **Total (95% CI)** | | **30** | | **30** | **100.0%** | **2.33 [0.67, 8.18]** |
| Total events | 7 | | 3 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.32 (P = 0.19)




## E.3 Forest plots (Adults)

### E.3.1 Methylphenidate versus placebo

**Figure 119: Total participants with adverse events at 5-8 weeks**

| Study or Subgroup | MPH Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **1.1.1 Immediate release** | | | | | | |
| Kuperman 2001 | 9 | 12 | 8 | 12 | 2.4% | 1.13 [0.67, 1.89] |
| **Subtotal (95% CI)** | | **12** | | **12** | **2.4%** | **1.13 [0.67, 1.89]** |
| Total events | 9 | | 8 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.45 (P = 0.65) | | | | | | |
| **1.1.2 OROS** | | | | | | |
| Adler 2009#8 | 93 | 113 | 74 | 116 | 22.3% | 1.29 [1.10, 1.52] |
| Goodman 2017 | 126 | 178 | 87 | 179 | 26.5% | 1.46 [1.22, 1.74] |
| Medori 2008 | 237 | 305 | 63 | 96 | 29.3% | 1.18 [1.01, 1.39] |
| Reimherr 2007 | 26 | 47 | 18 | 47 | 5.5% | 1.44 [0.93, 2.25] |
| Retz 2012 | 62 | 84 | 44 | 78 | 13.9% | 1.31 [1.04, 1.65] |
| **Subtotal (95% CI)** | | **727** | | **516** | **97.6%** | **1.31 [1.20, 1.44]** |
| Total events | 544 | | 286 | | | |
| Heterogeneity: Chi² = 3.21, df = 4 (P = 0.52); I² = 0% | | | | | | |
| Test for overall effect: Z = 6.11 (P < 0.00001) | | | | | | |
| **Total (95% CI)** | | **739** | | **528** | **100.0%** | **1.31 [1.20, 1.43]** |
| Total events | 553 | | 294 | | | |
| Heterogeneity: Chi² = 3.52, df = 5 (P = 0.62); I² = 0% | | | | | | |
| Test for overall effect: Z = 6.11 (P < 0.00001) | | | | | | |
| Test for subgroup differences: Chi² = 0.34, df = 1 (P = 0.56), I² = 0% | | | | | | |

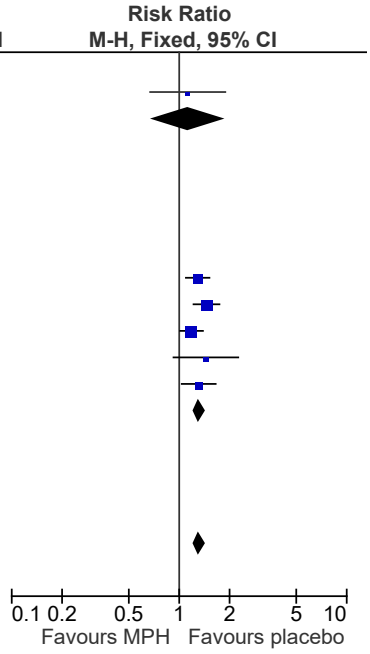
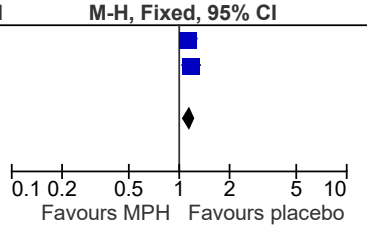



**Figure 120: Total participants with adverse events at over 13 – 24 weeks**

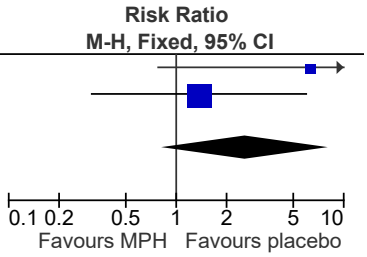
| Study or Subgroup | MPH Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Casas 2013 | 161 | 181 | 76 | 97 | 51.1% | 1.14 [1.01, 1.28] |
| Winhusen 2010 | 111 | 127 | 95 | 128 | 48.9% | 1.18 [1.04, 1.33] |
| **Total (95% CI)** | | **308** | | **225** | **100.0%** | **1.16 [1.06, 1.26]** |
| Total events | 272 | | 171 | | | |
| Heterogeneity: Chi² = 0.18, df = 1 (P = 0.67); I² = 0% | | | | | | |
| Test for overall effect: Z = 3.38 (P = 0.0007) | | | | | | |



## Figure 121: Cardiac events at 6 weeks

| Study or Subgroup | MPH Events | MPH Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Biederman 2006 | 6 | 72 | 1 | 76 | 24.7% | 6.33 [0.78, 51.32] |
| Biederman 2010 | 4 | 112 | 3 | 115 | 75.3% | 1.37 [0.31, 5.98] |
| **Total (95% CI)** | | **184** | | **191** | **100.0%** | **2.60 [0.83, 8.13]** |
| Total events | 10 | | 4 | | | |

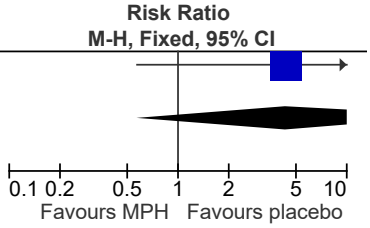
Heterogeneity: Chi² = 1.42, df = 1 (P = 0.23); I² = 30%
Test for overall effect: Z = 1.64 (P = 0.10)




## Figure 122: Cardiac events at 24 weeks

| Study or Subgroup | MPH Events | MPH Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Biederman 2010 | 8 | 62 | 1 | 34 | 100.0% | 4.39 [0.57, 33.62] |
| **Total (95% CI)** | | **62** | | **34** | **100.0%** | **4.39 [0.57, 33.62]** |
| Total events | 8 | | 1 | | | |

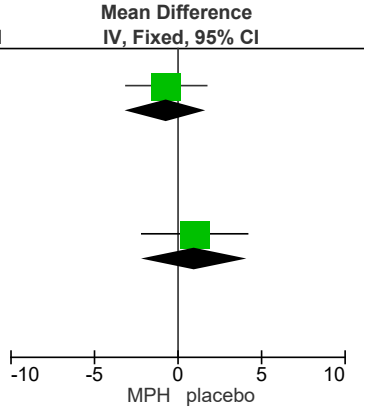
Heterogeneity: Not applicable
Test for overall effect: Z = 1.42 (P = 0.15)




## Figure 123: Systolic blood pressure

| Study or Subgroup | MPH Mean | MPH SD | MPH Total | Placebo Mean | Placebo SD | Placebo Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.5.1 systolic blood pressure 7 weeks** | | | | | | | | |
| Adler 2009#8 | -1.2 | 8.92 | 113 | -0.5 | 9.72 | 116 | 100.0% | -0.70 [-3.12, 1.72] |
| **Subtotal (95% CI)** | | | **113** | | | **116** | **100.0%** | **-0.70 [-3.12, 1.72]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 0.57 (P = 0.57) | | | | | | | | |
| **1.5.2 Systolic blood pressure 24 weeks** | | | | | | | | |
| Rosler 2009 | 124 | 13 | 241 | 123 | 15 | 118 | 100.0% | 1.00 [-2.17, 4.17] |
| **Subtotal (95% CI)** | | | **241** | | | **118** | **100.0%** | **1.00 [-2.17, 4.17]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 0.62 (P = 0.54) | | | | | | | | |

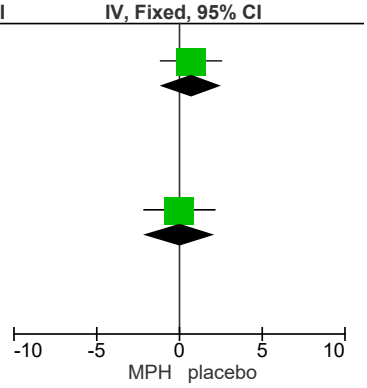
Test for subgroup differences: Chi² = 0.70, df = 1 (P = 0.40), I² = 0%



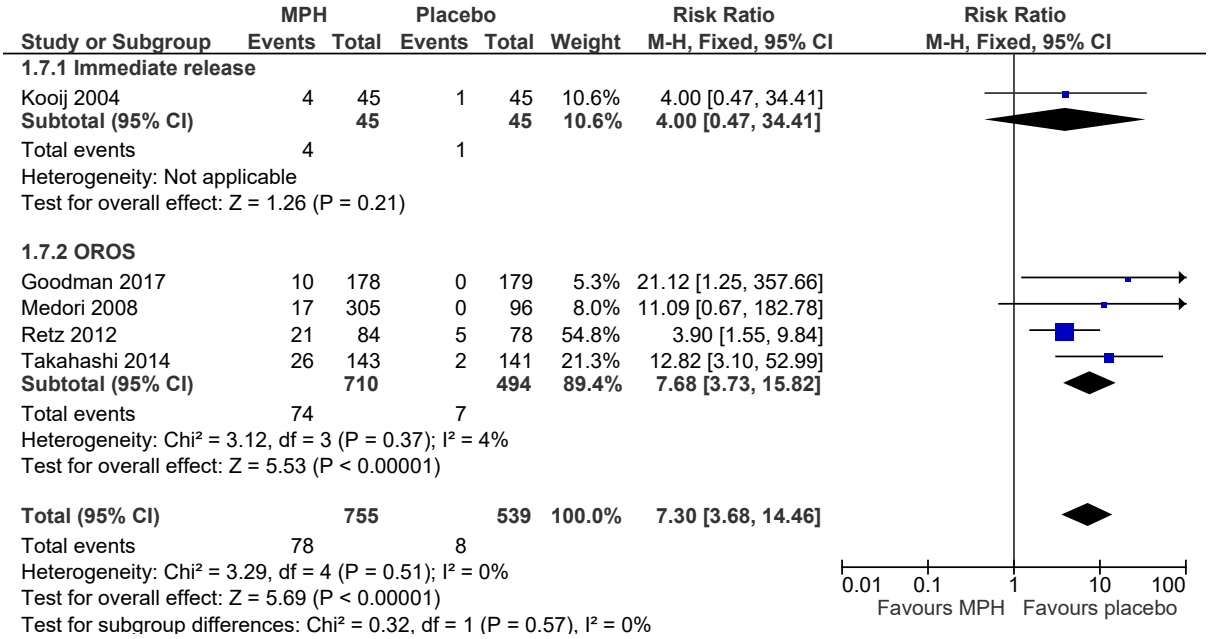

## Figure 124: Diastolic blood pressure

| Study or Subgroup | MPH Mean | MPH SD | MPH Total | Placebo Mean | Placebo SD | Placebo Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.6.1 diastolic blood pressure 7 weeks** | | | | | | | | |
| Adler 2009#8 | 1.1 | 6.72 | 113 | 0.4 | 7.43 | 116 | 100.0% | 0.70 [-1.13, 2.53] |
| **Subtotal (95% CI)** | | | **113** | | | **116** | **100.0%** | **0.70 [-1.13, 2.53]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 0.75 (P = 0.45) | | | | | | | | |
| **1.6.2 diastolic blood pressure 24 weeks** | | | | | | | | |
| Rosler 2009 | 78 | 9 | 241 | 78 | 10 | 118 | 100.0% | 0.00 [-2.13, 2.13] |
| **Subtotal (95% CI)** | | | **241** | | | **118** | **100.0%** | **0.00 [-2.13, 2.13]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 0.00 (P = 1.00) | | | | | | | | |

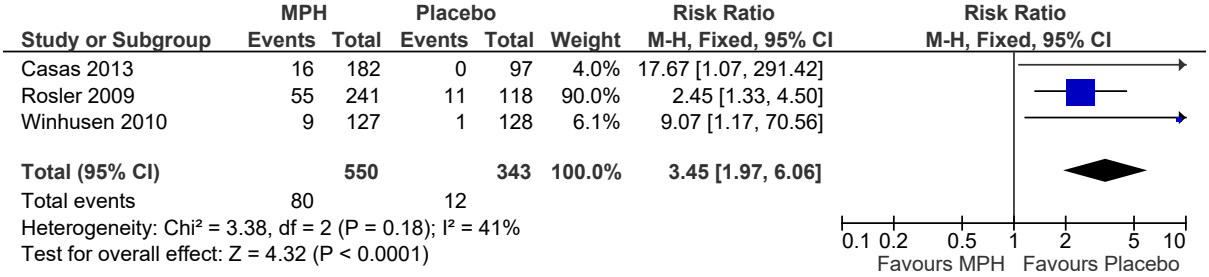
Test for subgroup differences: Chi² = 0.24, df = 1 (P = 0.63), I² = 0%



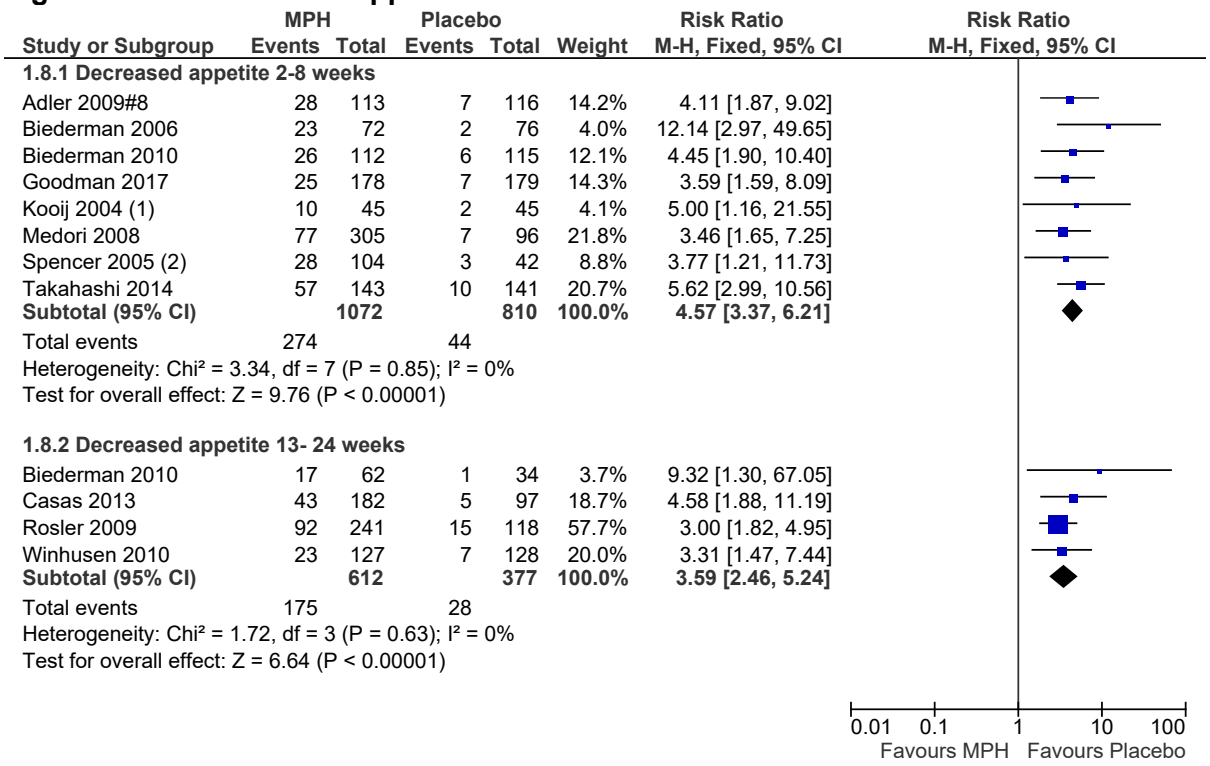
## Figure 125: Palpitations 3-9 weeks




## Figure 126: Palpitations 13 – 24 weeks

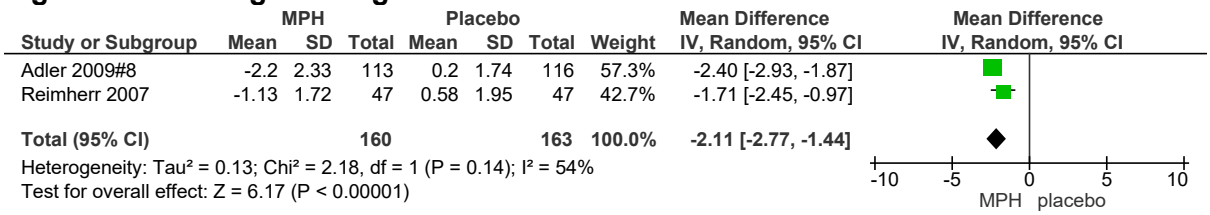


## Figure 127: Decreased appetite

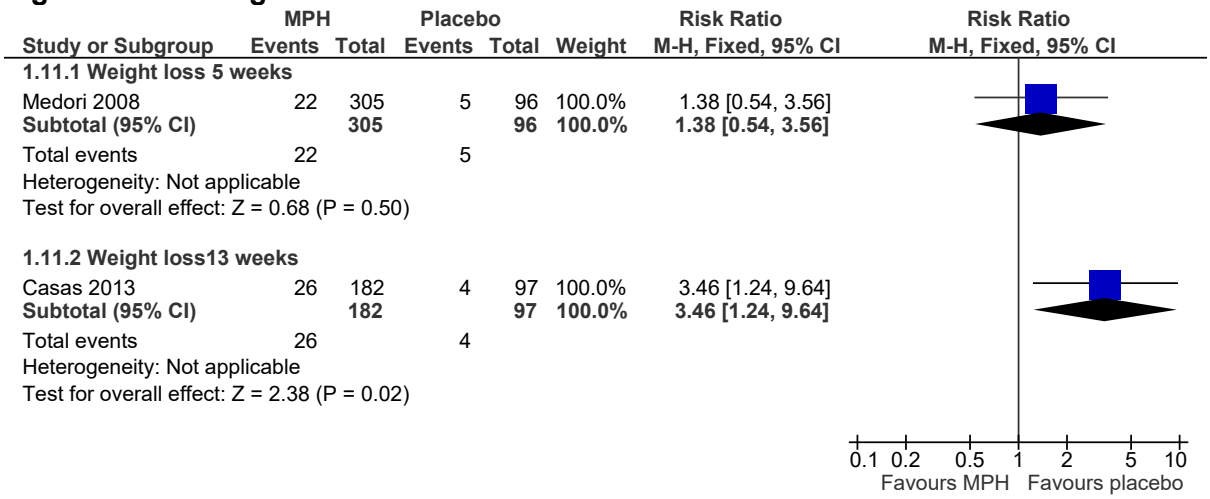



(1) Immediate release
(2) Immediate release

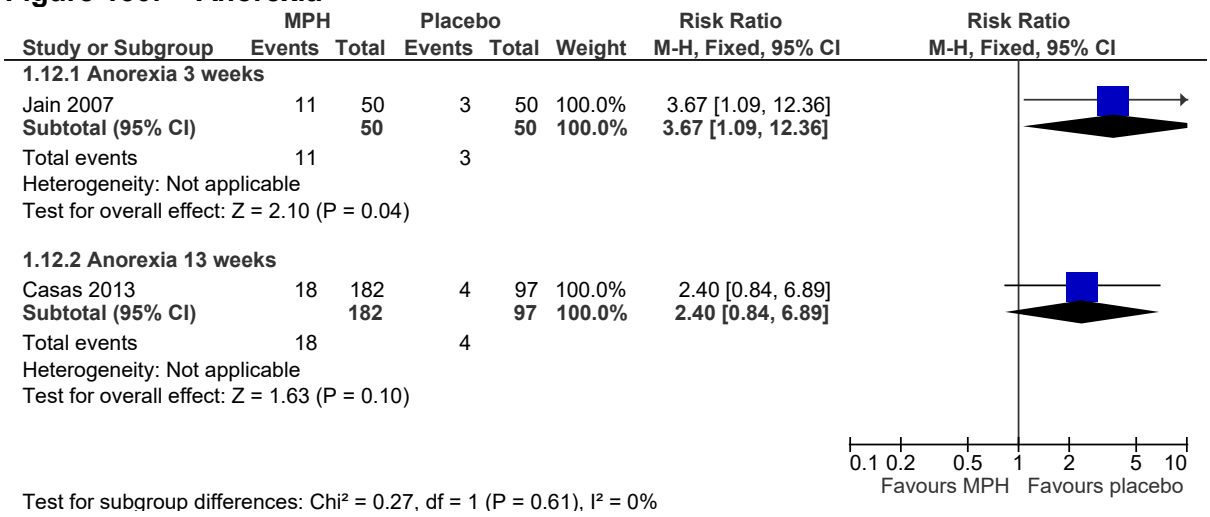
## Figure 128: Weight change 4-7 weeks




## Figure 129: Weight loss

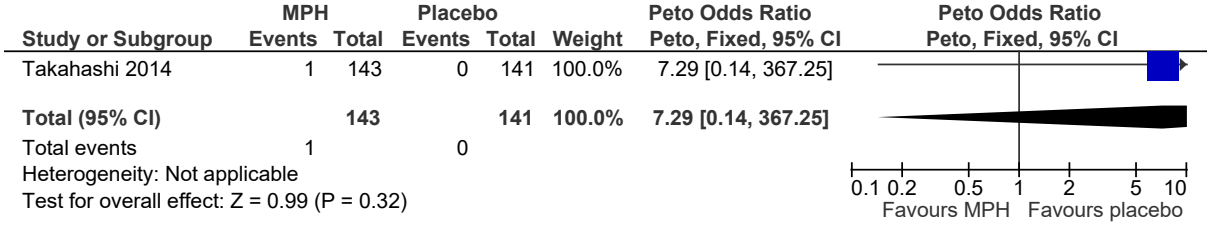


## Figure 130: Anorexia

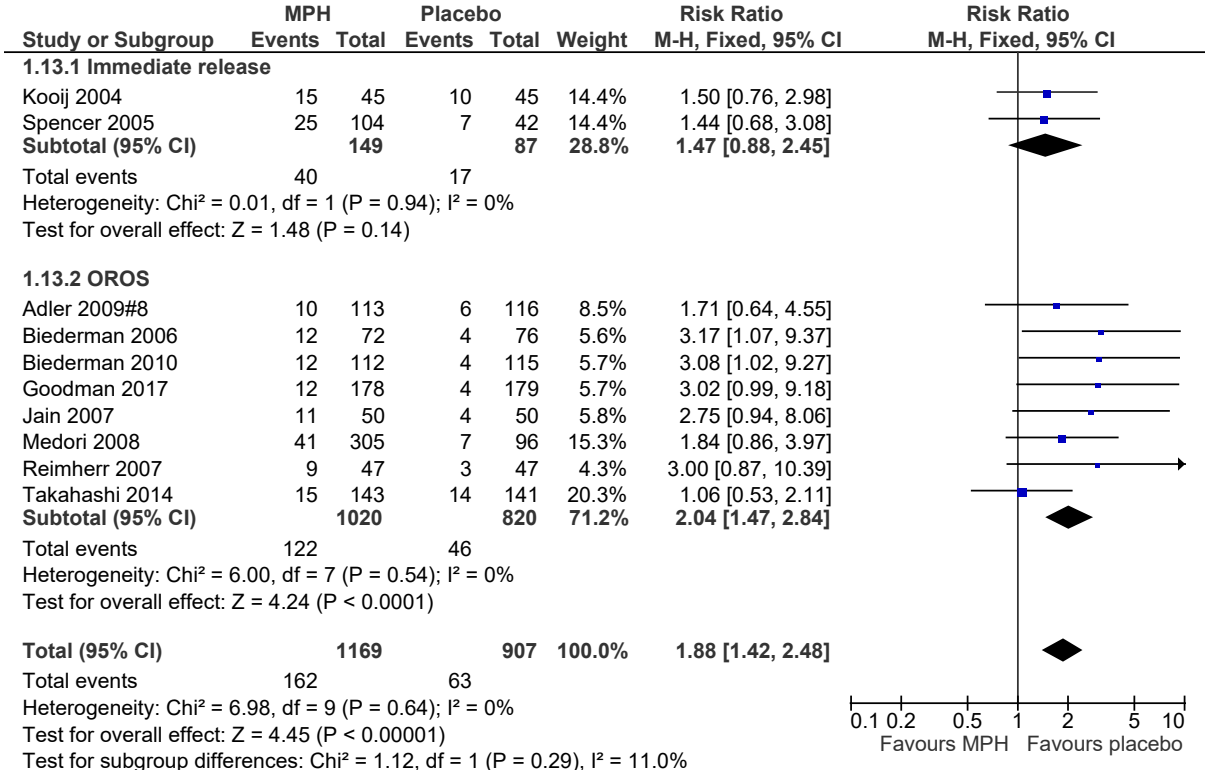



Test for subgroup differences: Chi² = 0.27, df = 1 (P = 0.61), I² = 0%

## Figure 131: Psychotic symptoms 4 weeks




## Figure 132: Insomnia 2-9 weeks

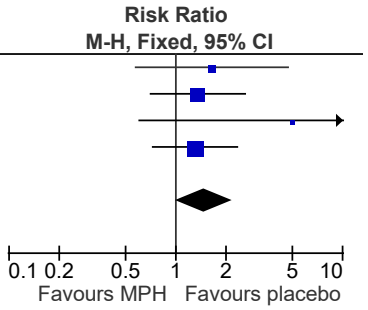



Test for subgroup differences: Chi² = 1.12, df = 1 (P = 0.29), I² = 11.0%

## Figure 133: Insomnia 13-24 weeks

| Study or Subgroup | MPH Events | MPH Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Biederman 2010 | 12 | 62 | 4 | 34 | 13.8% | 1.65 [0.57, 4.71] |
| Casas 2013 | 28 | 182 | 11 | 97 | 38.3% | 1.36 [0.71, 2.61] |
| Levin 2007 | 5 | 53 | 1 | 53 | 2.7% | 5.00 [0.60, 41.37] |
| Winhusen 2010 | 22 | 127 | 17 | 128 | 45.2% | 1.30 [0.73, 2.34] |
| **Total (95% CI)** | | **424** | | **312** | **100.0%** | **1.47 [0.99, 2.18]** |
| Total events | 67 | | 33 | | | |

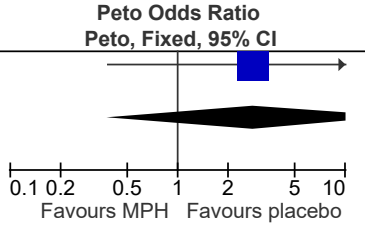
Heterogeneity: Chi² = 1.55, df = 3 (P = 0.67); I² = 0%
Test for overall effect: Z = 1.93 (P = 0.05)




## Figure 134: Tics 3 weeks

| Study or Subgroup | MPH Events | MPH Total | Placebo Events | Placebo Total | Weight | Peto Odds Ratio Peto, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Kooij 2004 | 3 | 45 | 1 | 45 | 100.0% | 2.81 [0.38, 20.67] |
| **Total (95% CI)** | | **45** | | **45** | **100.0%** | **2.81 [0.38, 20.67]** |
| Total events | 3 | | 1 | | | |

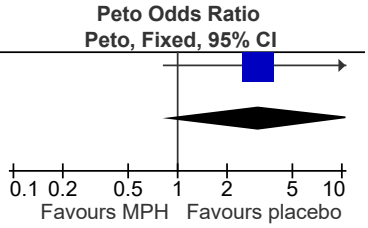
Heterogeneity: Not applicable
Test for overall effect: Z = 1.02 (P = 0.31)




## Figure 135: Tremor

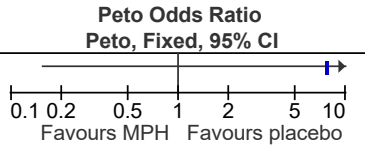
| Study or Subgroup | MPH Events | MPH Total | Placebo Events | Placebo Total | Weight | Peto Odds Ratio Peto, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Casas 2013 | 9 | 182 | 1 | 97 | 100.0% | 3.09 [0.82, 11.61] |
| **Total (95% CI)** | | **182** | | **97** | **100.0%** | **3.09 [0.82, 11.61]** |
| Total events | 9 | | 1 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.67 (P = 0.09)




## Figure 136: Sexual dysfunction 6 weeks

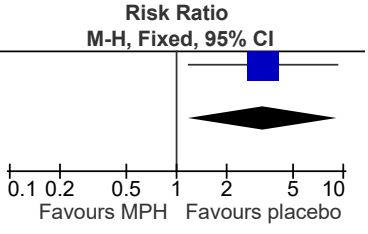
| Study or Subgroup | MPH Events | MPH Total | Placebo Events | Placebo Total | Weight | Peto Odds Ratio Peto, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Biederman 2006 | 1 | 72 | 0 | 76 | | 7.81 [0.15, 394.22] |




## Figure 137: Sexual dysfunction 24 weeks

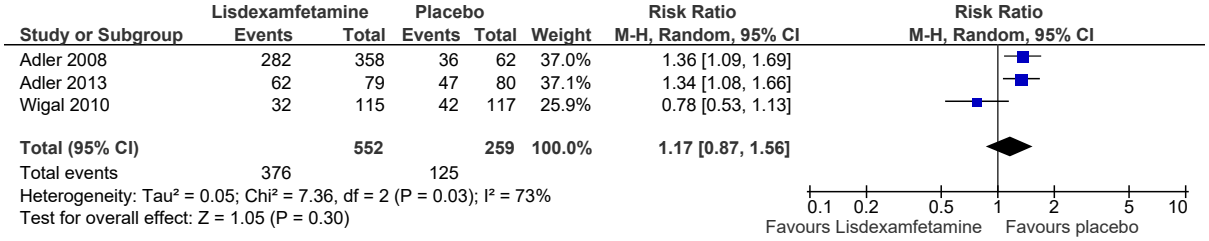
| Study or Subgroup | MPH Events | MPH Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Rosler 2009 | 27 | 241 | 4 | 118 | 100.0% | 3.30 [1.18, 9.23] |
| **Total (95% CI)** | | **241** | | **118** | **100.0%** | **3.30 [1.18, 9.23]** |
| Total events | 27 | | 4 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 2.28 (P = 0.02)

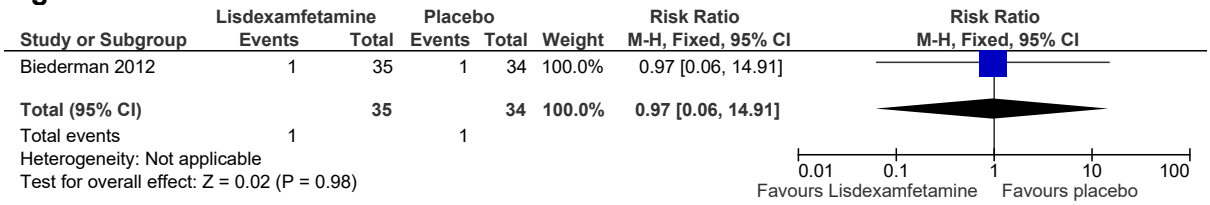


## E.3.2 Lisdexamphetamine versus placebo

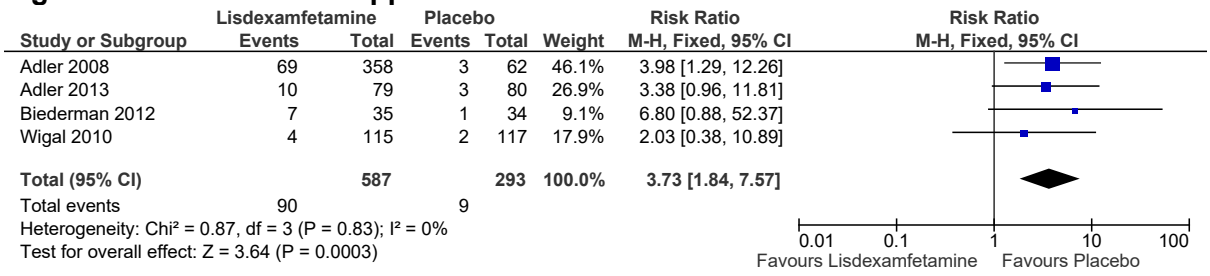
### Figure 138: Total number of participants with adverse events 2-10 weeks



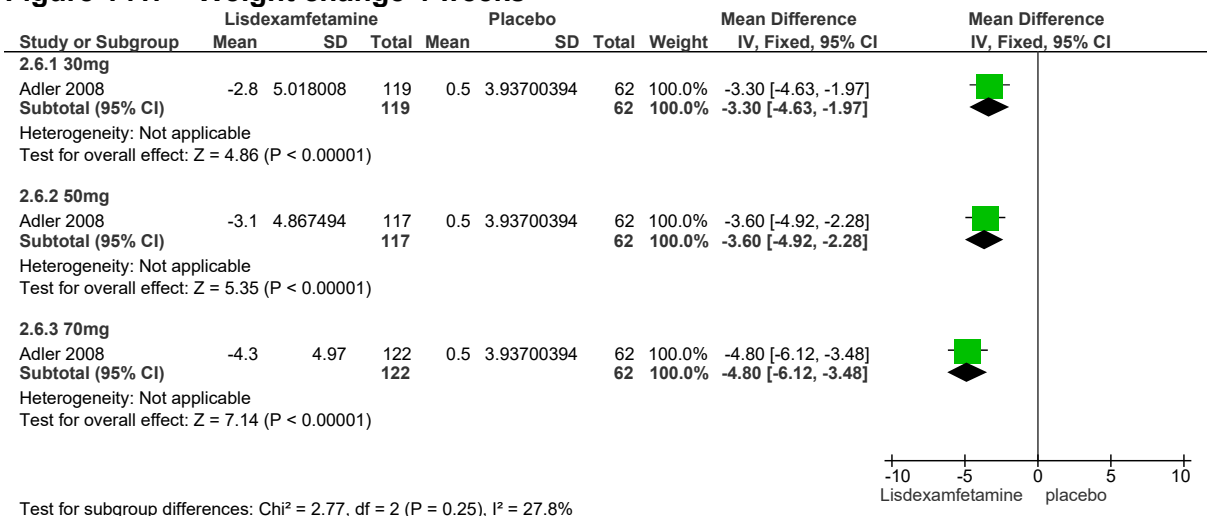

### Figure 139: Cardiac events 6 weeks



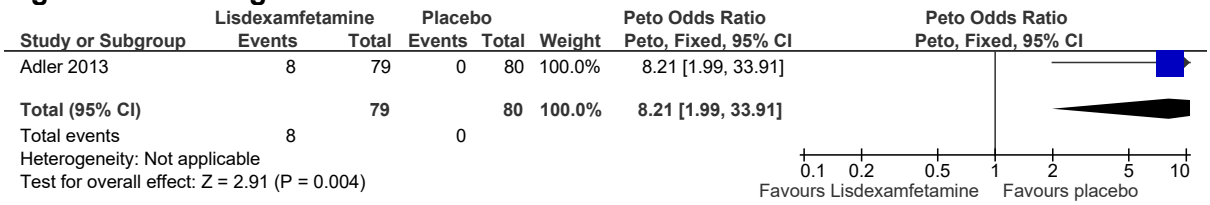

### Figure 140: Decreased appetite 2-10 weeks



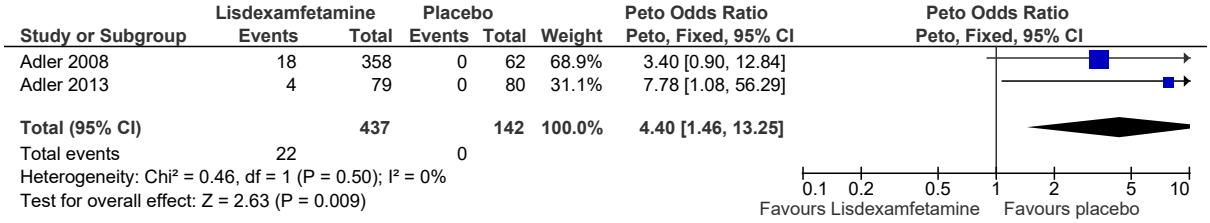

### Figure 141: Weight change 4 weeks



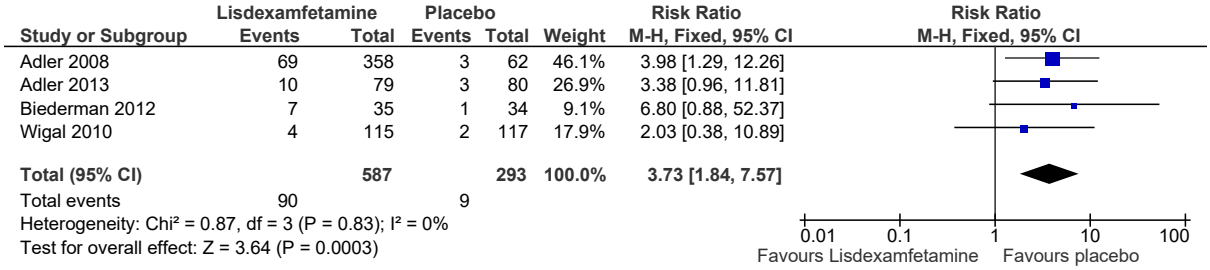
### Figure 142: Weight loss 10 weeks



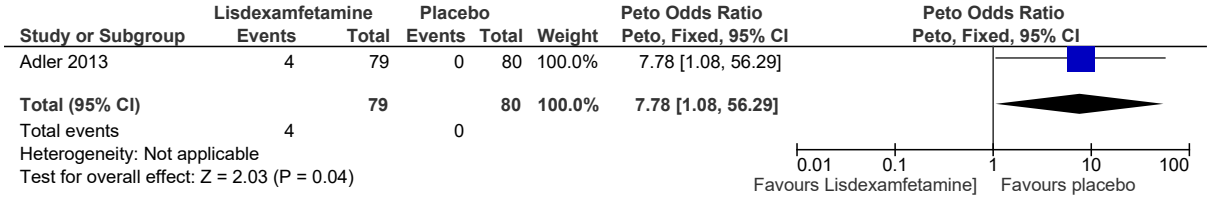

### Figure 143: Anorexia 4 – 10 weeks




### Figure 144: Insomnia at 2- 10 weeks

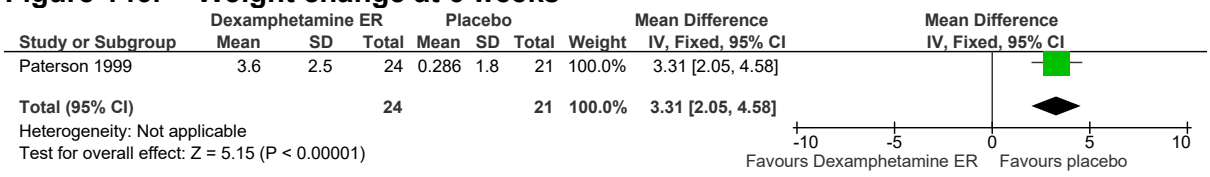



### Figure 145: Sexual dysfunction 10 weeks




## E.3.3 Dexamphetamine versus placebo

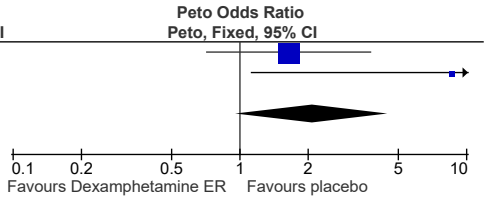
### Figure 146: Weight change at 6 weeks



### Figure 147: Decreased appetite 2-5 weeks

| Study or Subgroup | Dexamphetamine ER Events | Total | Placebo Events | Total | Weight | Peto Odds Ratio Peto, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Spencer 2007 | 30 | 165 | 6 | 53 | 85.7% | 1.64 [0.71, 3.77] |
| Taylor 2000 | 4 | 22 | 0 | 22 | 14.3% | 8.58 [1.13, 65.51] |
| **Total (95% CI)** | | **187** | | **75** | **100.0%** | **2.08 [0.96, 4.49]** |
| Total events | 34 | | 6 | | | |

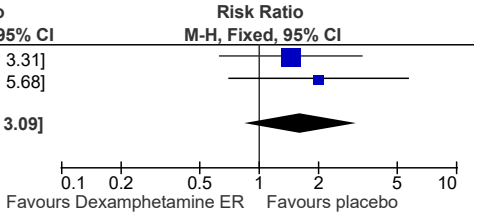
Heterogeneity: Chi² = 2.18, df = 1 (P = 0.14); I² = 54%
Test for overall effect: Z = 1.87 (P = 0.06)




### Figure 148: Insomnia at 2-5 weeks

| Study or Subgroup | Dexamphetamine ER Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Spencer 2007 | 27 | 165 | 6 | 53 | 69.4% | 1.45 [0.63, 3.31] |
| Taylor 2000 | 8 | 22 | 4 | 22 | 30.6% | 2.00 [0.70, 5.68] |
| **Total (95% CI)** | | **187** | | **75** | **100.0%** | **1.62 [0.84, 3.09]** |
| Total events | 35 | | 10 | | | |

Heterogeneity: Chi² = 0.23, df = 1 (P = 0.63); I² = 0%
Test for overall effect: Z = 1.45 (P = 0.15)

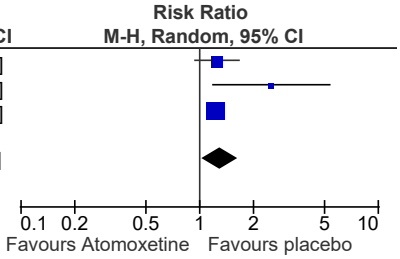



## E.3.4 Atomoxetine versus placebo

### Figure 149: Total participants with adverse events at 8-10 weeks

| Study or Subgroup | Atomoxetine Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Lee 2014 | 30 | 37 | 24 | 37 | 32.9% | 1.25 [0.94, 1.66] |
| Michelson 2003 | 23 | 270 | 9 | 266 | 8.4% | 2.52 [1.19, 5.34] |
| Young 2011 8 weeks | 240 | 268 | 174 | 237 | 58.6% | 1.22 [1.12, 1.33] |
| **Total (95% CI)** | | **575** | | **540** | **100.0%** | **1.31 [1.03, 1.65]** |
| Total events | 293 | | 207 | | | |

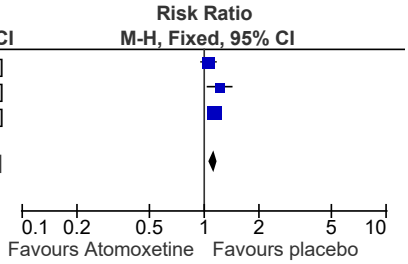
Heterogeneity: Tau² = 0.02; Chi² = 4.23, df = 2 (P = 0.12); I² = 53%
Test for overall effect: Z = 2.24 (P = 0.03)




### Figure 150: Total participants with adverse events at 12-25 weeks

| Study or Subgroup | Atomoxetine Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Adler 2009#6 | 183 | 224 | 167 | 216 | 34.4% | 1.06 [0.96, 1.16] |
| Durrell 2013 | 145 | 220 | 122 | 225 | 24.4% | 1.22 [1.04, 1.42] |
| Young 2011 24 weeks | 248 | 268 | 191 | 234 | 41.2% | 1.13 [1.06, 1.22] |
| **Total (95% CI)** | | **712** | | **675** | **100.0%** | **1.13 [1.06, 1.19]** |
| Total events | 576 | | 480 | | | |

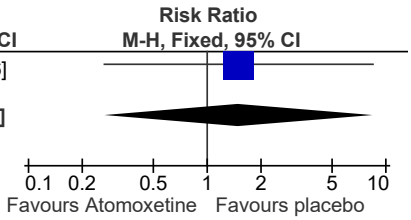
Heterogeneity: Chi² = 2.73, df = 2 (P = 0.26); I² = 27%
Test for overall effect: Z = 4.06 (P < 0.0001)



## Figure 151: Palpitations

| Study or Subgroup | Atomoxetine Events | Atomoxetine Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Lee 2014 | 3 | 37 | 2 | 37 | 100.0% | 1.50 [0.27, 8.46] |
| **Total (95% CI)** | | **37** | | **37** | **100.0%** | **1.50 [0.27, 8.46]** |
| Total events | 3 | | 2 | | | |

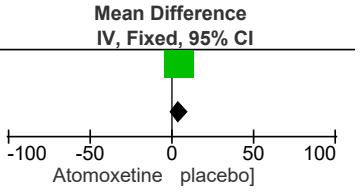
Heterogeneity: Not applicable
Test for overall effect: Z = 0.46 (P = 0.65)




## Figure 152: Systolic blood pressure 10 weeks

| Study or Subgroup | Atomoxetine Mean | Atomoxetine SD | Atomoxetine Total | Placebo Mean | Placebo SD | Placebo Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Lee 2014 | 3.3 | 11.5 | 34 | -1.2 | 11.1 | 37 | 100.0% | 4.50 [-0.77, 9.77] |
| **Total (95% CI)** | | | **34** | | | **37** | **100.0%** | **4.50 [-0.77, 9.77]** |

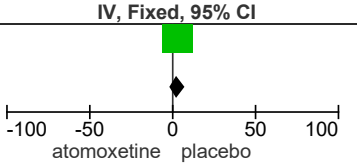
Heterogeneity: Not applicable
Test for overall effect: Z = 1.67 (P = 0.09)




## Figure 153: Diastolic blood pressure 10 weeks

| Study or Subgroup | Atomoxetine Mean | Atomoxetine SD | Atomoxetine Total | Placebo Mean | Placebo SD | Placebo Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Lee 2014 | 1.3 | 10 | 34 | -1.4 | 9 | 37 | 100.0% | 2.70 [-1.74, 7.14] |
| **Total (95% CI)** | | | **34** | | | **37** | **100.0%** | **2.70 [-1.74, 7.14]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.19 (P = 0.23)




## Figure 154: Weight change

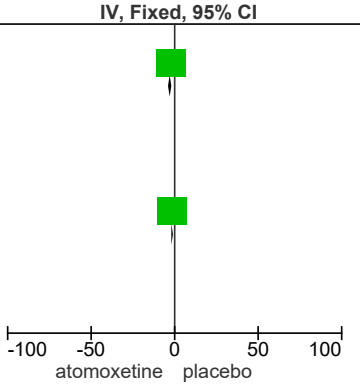
| Study or Subgroup | Atomoxetine Mean | Atomoxetine SD | Atomoxetine Total | Placebo Mean | Placebo SD | Placebo Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **4.14.1 Weight change at 10 weeks** | | | | | | | | |
| Lee 2014 | -2.1 | 3.2 | 34 | 0.3 | 2 | 37 | 100.0% | -2.40 [-3.65, -1.15] |
| **Subtotal (95% CI)** | | | **34** | | | **37** | **100.0%** | **-2.40 [-3.65, -1.15]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 3.75 (P = 0.0002)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **4.14.2 Weight change 13 weeks** | | | | | | | | |
| Wilens 2008 | -0.91 | 2.1 | 72 | 0.42 | 1.9 | 75 | 100.0% | -1.33 [-1.98, -0.68] |
| **Subtotal (95% CI)** | | | **72** | | | **75** | **100.0%** | **-1.33 [-1.98, -0.68]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 4.02 (P < 0.0001)

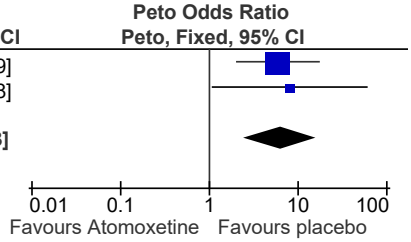
Test for subgroup differences: Chi² = 2.21, df = 1 (P = 0.14), I² = 54.7%




## Figure 155: Weight loss 10 weeks

| Study or Subgroup | Atomoxetine Events | Atomoxetine Total | Placebo Events | Placebo Total | Weight | Peto Odds Ratio Peto, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Goto 2012 | 13 | 195 | 1 | 196 | 77.9% | 5.92 [2.04, 17.19] |
| Lee 2014 | 4 | 37 | 0 | 37 | 22.1% | 8.05 [1.09, 59.58] |
| **Total (95% CI)** | | **232** | | **233** | **100.0%** | **6.34 [2.47, 16.23]** |
| Total events | 17 | | 1 | | | |

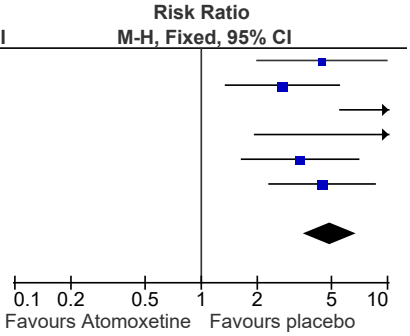
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0%
Test for overall effect: Z = 3.85 (P = 0.0001)



## Figure 156: Decreased appetite 8-10 weeks

| Study or Subgroup | Atomoxetine Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Adler 2009 10 weeks | 31 | 250 | 7 | 251 | 17.5% | 4.45 [2.00, 9.91] |
| Durell 2010 | 28 | 270 | 10 | 263 | 25.4% | 2.73 [1.35, 5.50] |
| Goto 2012 | 45 | 195 | 2 | 196 | 5.0% | 22.62 [5.56, 91.93] |
| Lee 2014 | 14 | 37 | 1 | 37 | 2.5% | 14.00 [1.94, 101.09] |
| Michelson 2002 | 31 | 270 | 9 | 266 | 22.7% | 3.39 [1.65, 6.99] |
| Young 2011 8 weeks | 51 | 268 | 10 | 234 | 26.8% | 4.45 [2.31, 8.57] |
| **Total (95% CI)** | | **1290** | | **1247** | **100.0%** | **4.92 [3.52, 6.87]** |
| Total events | 200 | | 39 | | | |

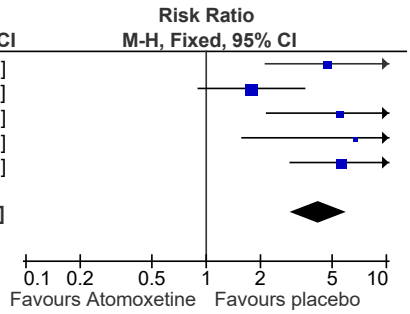
Heterogeneity: Chi² = 9.50, df = 5 (P = 0.09); I² = 47%
Test for overall effect: Z = 9.35 (P < 0.00001)




## Figure 157: Decreased appetite 12-25 weeks

| Study or Subgroup | Atomoxetine Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Adler 2009 24 weeks | 33 | 250 | 7 | 251 | 19.5% | 4.73 [2.13, 10.50] |
| Adler 2009#6 | 22 | 224 | 12 | 218 | 34.0% | 1.78 [0.91, 3.52] |
| Durrell 2013 | 27 | 220 | 5 | 225 | 13.8% | 5.52 [2.17, 14.08] |
| Wilens 2008 | 13 | 72 | 2 | 75 | 5.5% | 6.77 [1.58, 28.96] |
| Young 2011 24 weeks | 53 | 234 | 10 | 248 | 27.2% | 5.62 [2.93, 10.78] |
| **Total (95% CI)** | | **1000** | | **1017** | **100.0%** | **4.19 [2.95, 5.96]** |
| Total events | 148 | | 36 | | | |

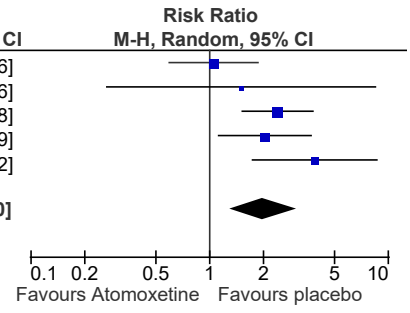
Heterogeneity: Chi² = 7.71, df = 4 (P = 0.10); I² = 48%
Test for overall effect: Z = 7.97 (P < 0.00001)




## Figure 158: Insomnia 8-10 weeks

| Study or Subgroup | Atomoxetine Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Adler 2009 10 weeks | 22 | 250 | 21 | 251 | 24.5% | 1.05 [0.59, 1.86] |
| Lee 2014 | 3 | 37 | 2 | 37 | 5.6% | 1.50 [0.27, 8.46] |
| Michelson 2003 | 56 | 270 | 23 | 266 | 28.9% | 2.40 [1.52, 3.78] |
| Sutherland 2012 | 42 | 97 | 10 | 47 | 23.6% | 2.04 [1.12, 3.69] |
| Young 2011 8 weeks | 31 | 268 | 7 | 234 | 17.5% | 3.87 [1.74, 8.62] |
| **Total (95% CI)** | | **922** | | **835** | **100.0%** | **2.00 [1.29, 3.10]** |
| Total events | 154 | | 63 | | | |

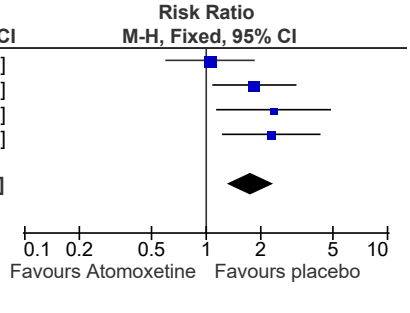
Heterogeneity: Tau² = 0.12; Chi² = 8.21, df = 4 (P = 0.08); I² = 51%
Test for overall effect: Z = 3.09 (P = 0.002)




## Figure 159: Insomnia 12-25 weeks

| Study or Subgroup | Atomoxetine Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Adler 2009 24 weeks | 23 | 250 | 22 | 251 | 33.8% | 1.05 [0.60, 1.83] |
| Adler 2009#6 | 36 | 224 | 19 | 218 | 29.6% | 1.84 [1.09, 3.11] |
| Durrell 2013 | 23 | 220 | 10 | 225 | 15.2% | 2.35 [1.15, 4.83] |
| Young 2011 24 weeks | 34 | 268 | 13 | 234 | 21.4% | 2.28 [1.24, 4.22] |
| **Total (95% CI)** | | **962** | | **928** | **100.0%** | **1.75 [1.30, 2.34]** |
| Total events | 116 | | 64 | | | |

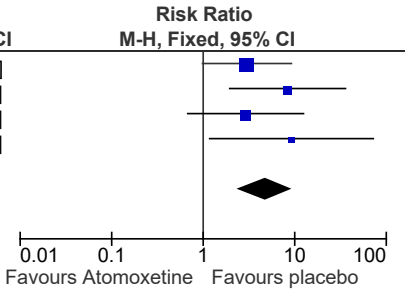
Heterogeneity: Chi² = 4.63, df = 3 (P = 0.20); I² = 35%
Test for overall effect: Z = 3.74 (P = 0.0002)



### Figure 160: Sexual dysfunction 8-10 weeks

| Study or Subgroup | Atomoxetine Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Adler 2009 10 weeks | 12 | 250 | 4 | 251 | 41.2% | 3.01 [0.98, 9.21] |
| Michelson 2003 | 17 | 270 | 2 | 266 | 20.8% | 8.37 [1.95, 35.89] |
| Sutherland 2012 | 12 | 97 | 2 | 47 | 27.8% | 2.91 [0.68, 12.47] |
| Young 2011 8 weeks | 9 | 234 | 1 | 240 | 10.2% | 9.23 [1.18, 72.29] |
| **Total (95% CI)** | | **851** | | **804** | **100.0%** | **4.73 [2.36, 9.49]** |
| Total events | 50 | | 9 | | | |

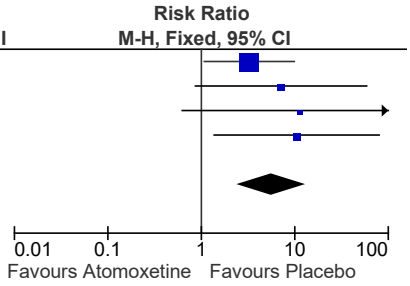
Heterogeneity: Chi² = 2.05, df = 3 (P = 0.56); I² = 0%
Test for overall effect: Z = 4.38 (P < 0.0001)




### Figure 161: Sexual dysfunction 12-24 weeks

| Study or Subgroup | Atomoxetine Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Adler 2009 24 weeks | 13 | 250 | 4 | 251 | 61.7% | 3.26 [1.08, 9.87] |
| Adler 2009#6 | 6 | 224 | 1 | 266 | 14.1% | 7.13 [0.86, 58.74] |
| Durrell 2013 | 5 | 220 | 0 | 225 | 7.6% | 11.25 [0.63, 202.23] |
| Young 2011 24 weeks | 12 | 268 | 1 | 234 | 16.5% | 10.48 [1.37, 79.97] |
| **Total (95% CI)** | | **962** | | **976** | **100.0%** | **5.61 [2.44, 12.89]** |
| Total events | 36 | | 6 | | | |

Heterogeneity: Chi² = 1.56, df = 3 (P = 0.67); I² = 0%
Test for overall effect: Z = 4.06 (P < 0.0001)

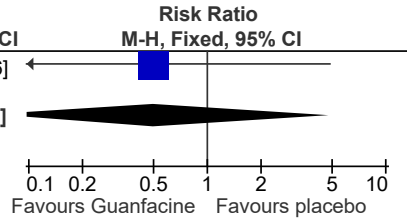



## E.3.5 Guanfacine versus placebo

### Figure 162: Increased appetite 9 weeks

| Study or Subgroup | Guanfacine Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Butterfield 2016 | 1 | 13 | 2 | 13 | 100.0% | 0.50 [0.05, 4.86] |
| **Total (95% CI)** | | **13** | | **13** | **100.0%** | **0.50 [0.05, 4.86]** |
| Total events | 1 | | 2 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.60 (P = 0.55)

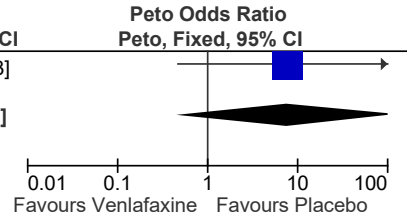



## E.3.6 Venlafaxine versus placebo

### Figure 163: Sexual dysfunction at 6 weeks

| Study or Subgroup | Venlafaxine Events | Total | Placebo Events | Total | Weight | Peto Odds Ratio Peto, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Amiri 2012 | 2 | 22 | 0 | 22 | 100.0% | 7.75 [0.47, 128.03] |
| **Total (95% CI)** | | **22** | | **22** | **100.0%** | **7.75 [0.47, 128.03]** |
| Total events | 2 | | 0 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.43 (P = 0.15)

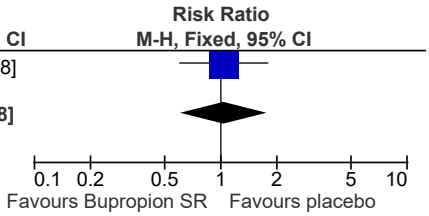



## E.3.7 Bupropion SR versus placebo

**Figure 164 Total participants with adverse events 7 weeks**

| Study or Subgroup | Buproprin SR Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Kuperman 2001 | 9 | 13 | 8 | 12 | 100.0% | 1.04 [0.61, 1.78] |
| **Total (95% CI)** | | **13** | | **12** | **100.0%** | **1.04 [0.61, 1.78]** |
| Total events | 9 | | 8 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.14 (P = 0.89)

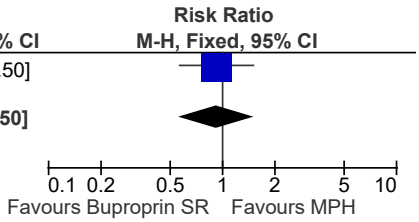



## E.3.8 Bupropion SR versus methylphenidate

**Figure 165: Total participants with adverse events**

| Study or Subgroup | Buproprin SR Events | Total | MPH Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Kuperman 2001 | 9 | 13 | 9 | 12 | 100.0% | 0.92 [0.57, 1.50] |
| **Total (95% CI)** | | **13** | | **12** | **100.0%** | **0.92 [0.57, 1.50]** |
| Total events | 9 | | 9 | | | |

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




## E.3.9 Modafinil versus placebo

**Figure 166: Total number of participants with adverse events 9 weeks**

| Study or Subgroup | Modafinil Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Arnold 2014 | 227 | 264 | 63 | 74 | 100.0% | 1.01 [0.91, 1.12] |
| **Total (95% CI)** | | **264** | | **74** | **100.0%** | **1.01 [0.91, 1.12]** |
| Total events | 227 | | 63 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.18 (P = 0.86)

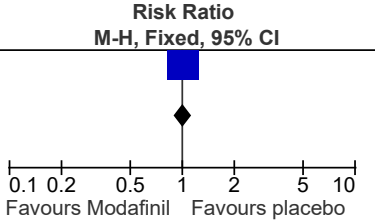



**Figure 167: Suicidal ideation 9 weeks**

| Study or Subgroup | Modafinil Events | Total | Placebo Events | Total | Weight | Peto Odds Ratio Peto, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Arnold 2014 | 1 | 264 | 0 | 74 | 100.0% | 3.60 [0.03, 411.56] |
| **Total (95% CI)** | | **264** | | **74** | **100.0%** | **3.60 [0.03, 411.56]** |
| Total events | 1 | | 0 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.53 (P = 0.60)

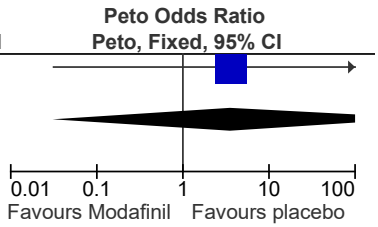



**Figure 168: Tachycardia 9 weeks**

| Study or Subgroup | Modafinil Events | Total | Placebo Events | Total | Weight | Peto Odds Ratio Peto, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Arnold 2014 | 1 | 264 | 0 | 74 | 100.0% | 3.60 [0.03, 411.56] |
| **Total (95% CI)** | | **264** | | **74** | **100.0%** | **3.60 [0.03, 411.56]** |
| Total events | 1 | | 0 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.53 (P = 0.60)

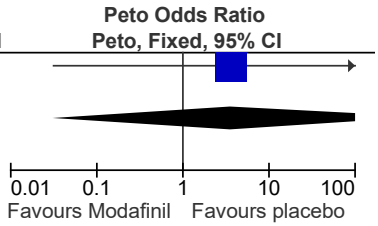


**Figure 169: Decreased appetite 2 weeks**

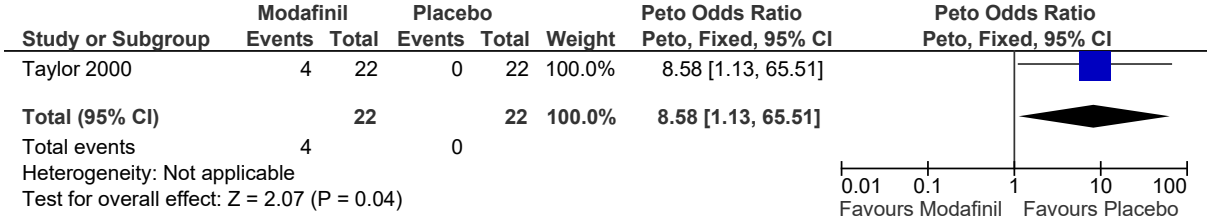



**Figure 170: Anorexia at 9 weeks**

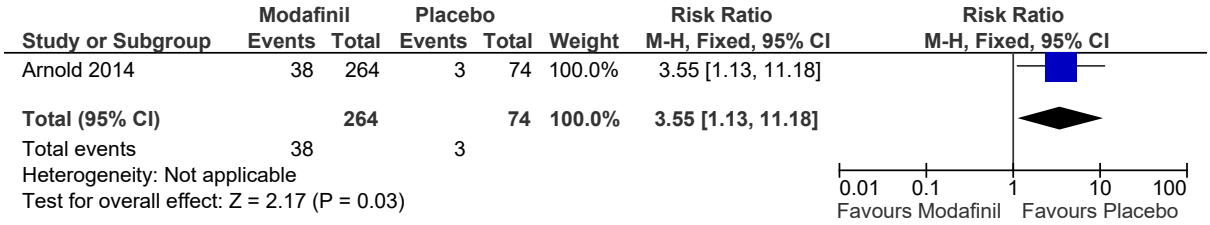



**Figure 171: Psychotic symptoms 9 weeks**

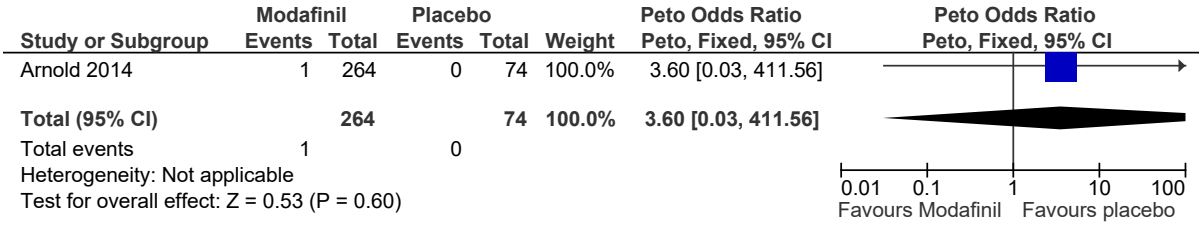
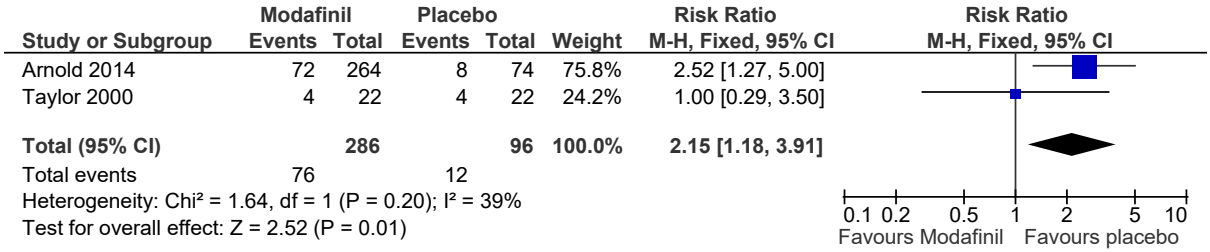
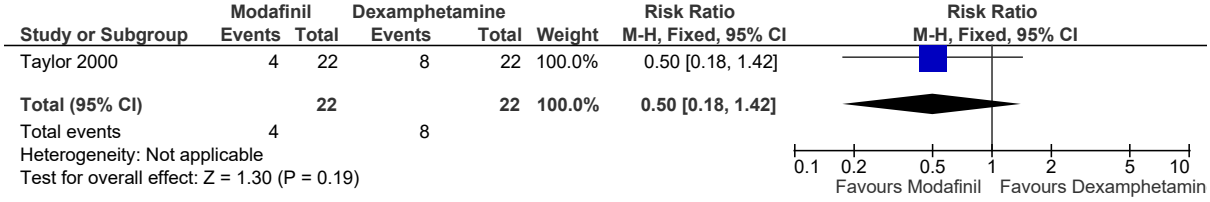



**Figure 172: Insomnia 2-9 weeks**



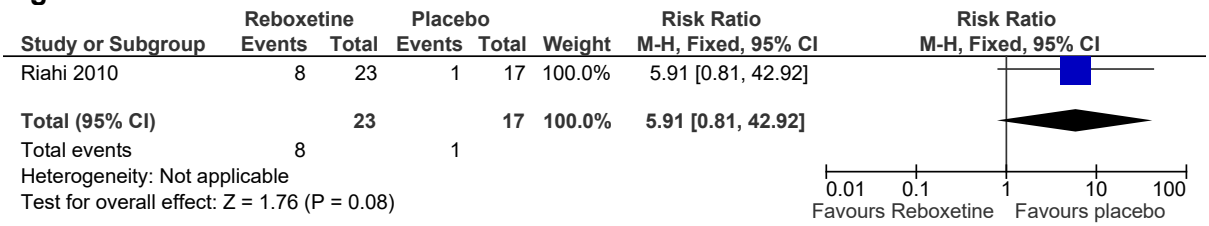

## E.3.10 Modafinil versus dexamphetamine

**Figure 173: Insomnia 2 weeks**




## E.3.11 Reboxetine versus placebo

## Figure 174: Insomnia 4 weeks



# Appendix F: GRADE tables

## F.1 Pre-school children (under the age of 5)

**Table 45 Clinical evidence profile: Methyphenidate 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-schoolers) | Control | Relative (95% CI) | Absolute | | |
| **Tachycardia (follow-up 1 week)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 0/165 (0%) | 0/160 (0%) | RD 0 (-0.01 to 0.01) | 0 events in both arms | LOW | CRITICAL |
| **Systolic blood pressure (follow-up 4 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[2] | no serious inconsistency | no serious indirectness | serious[3] | none | 17 | 17 | - | MD 5 higher (3.17 lower to 13.17 higher) | VERY LOW | CRITICAL |
| **Diastolic blood pressure (follow-up 4 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | serious[3] | none | 17 | 17 | - | MD 1 higher (5.18 lower to 7.18 higher) | VERY LOW | CRITICAL |
| **Decreased weight (Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 17 | 17 | - | MD 1.9 lower (5.94 lower to 2.14 higher) | LOW | CRITICAL |
| **Height changes (follow-up 4 weeks; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | randomised | very | no serious | no serious | serious[3] | none | 17 | 17 | - | MD 0.2 higher | VERY | CRITICAL |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | trials | serious[1] | inconsistency | indirectness | | | | | | (5.41 lower to 5.81 higher) | LOW | |

[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] No explanation was provided
[3] 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 profile: Methyphenidate versus risperidone**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Methylphenidate versus risperidone | Control | Relative (95% CI) | Absolute | | |
| **Sleep (sedation) (follow-up 6 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[1] | none | 0/18 (0%) | 1/20 (5%) | OR 0.15 (0 to 7.58) | 42 fewer per 1000 (from 50 fewer to 235 more) | VERY LOW | CRITICAL |
| **Decreased appetite (follow-up 6 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[2] | no serious inconsistency | serious[3] | very serious[1] | none | 1/18 (5.6%) | 0/20 (0%) | OR 8.26 (0.16 to 418.42) | 60 more 1000 (from 80 fewer to 190 more) | 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

[3]Downgraded by 1 or 2 increments if the majority of the evidence had indirect outcomes

# F.2 Children and young people (aged 5 to 18)

**Table 47 Clinical evidence profile: IR Methyphenidate 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 | Control | Relative (95% CI) | Absolute | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Total participants with adverse events (follow-up 3 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 80/155 (51.6%) | 61/161 (37.9%) | RR 1.36 (1.06 to 1.75) | 136 more per 1000 (from 23 more to 284 more) | VERY LOW | CRITICAL |
| **Total participants with adverse events (follow-up 16 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 17/29 (58.6%) | 12/40 (30%) | RR 1.95 (1.11 to 3.43) | 285 more per 1000 (from 33 more to 729 more) | LOW | CRITICAL |
| **Tachycardia (follow-up 8 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | Very serious[2] | none | 1/20 (5%) | 0/20 (0%) | OR 7.39 (0.15 to 372.38) | 50 more per 1000 (from 80 less to 100 more) | LOW | CRITICAL |
| **Tachycardia - (follow-up 16 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | Very serious[2] | none | 1/29 (3.4%) | 0/30 (0%) | OR 7.65 (0.15 to 385.67) | 30 more per 1000 (from 60 less to 120 more) | LOW | CRITICAL |
| **Systolic blood pressure - (follow-up 2 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 42 | 42 | - | MD 3.18 higher (0.76 to 5.6 higher) | MODERATE | CRITICAL |
| **Systolic blood pressure - (follow-up 16 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 90 | 91 | - | MD 1.05 higher (1.75 lower to 3.84 higher) | MODERATE | CRITICAL |
| **Diastolic blood pressure - (follow-up 2 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 11 | 11 | - | MD 2.9 higher (0.37 to 5.43 higher) | LOW | CRITICAL |
| **Diastolic blood pressure - (follow-up 16 weeks; Better indicated by lower values)** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 61 | 61 | - | MD 3.2 higher (0.21 lower to 6.61 higher) | LOW | CRITICAL |
| **Decreased weight - (follow-up 2 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 122 | - | - | MD 1.07 lower (17.03 lower to 14.89 higher) | LOW | CRITICAL |
| **Decreased weight - (follow-up 16 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 181 | - | - | MD 1.9 lower (2.61 to 1.18 lower) | LOW | CRITICAL |
| **Seizures (follow-up 3 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 4/33 (12.1%) | 3/33 (9.1%) | RR 1.33 (0.32 to 5.5) | 30 more per 1000 (from 62 fewer to 409 more) | LOW | CRITICAL |
| **Psychotic symptoms (follow-up 16 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 0/29 (0%) | 0/30 (0%) | RD 0 (-0.06 TO 0.06) | 0 events in both arms | MODERATE | CRITICAL |
| **Sleep (insomnia) - (follow-up 3 weeks)** | | | | | | | | | | | | |
| 4 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 40/284 (14.1%) | 10/200 (5%) | OR 5.57 (2.82 to 11) | 177 more per 1000 (from 79 more to 317 more) | MODERATE | CRITICAL |
| **Sleep (insomnia) - (follow-up 16 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 1/29 (3.4%) | 5/30 (16.7%) | RR 0.21 (0.03 to 1.67) | 131 fewer per 1000 (from 290 fewer to 20 more) | VERY LOW | CRITICAL |
| **Increase in tics - Participants with tic disorder (follow-up 16 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 1/192 (0.52%) | 4/90 (4.4%) | RR 0.12 (0.01 to 1.03) | 39 fewer per 1000 (from 44 fewer to 1 more) | VERY LOW | CRITICAL |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Increase in tics - Participants without tic disorder** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 8/37 (21.6%) | 7/32 (21.9%) | RR 0.99 (0.4 to 2.42) | 2 fewer per 1000 (from 131 fewer to 311 more) | VERY LOW | CRITICAL |
| **YGTSS tics global severity (follow-up 16 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 31 | 31 | - | MD 1.8 higher (6.28 lower to 9.88 higher) | 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 48 Clinical evidence profile: OROS Methyphenidate 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** | | |
| **Total participants with adverse events (follow-up 6 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 146/219 (66.7%) | 40/74 (54.1%) | RR 1.23 (0.98 to 1.55) | 124 more per 1000 (from 11 fewer to 297 more) | LOW | CRITICAL |
| **Systolic blood pressure (follow-up 6-7 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 330 | 184 | - | MD 1.98 lower (2.32 to 1.64 lower) | MODERATE | CRITICAL |
| **Diastolic blood pressure (follow-up 6-7 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 330 | 184 | - | MD 0.83 higher (0.82 lower to 2.48 | MODERATE | CRITICAL |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | higher) | | |
| **Decreased weight (follow-up 6-7 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 330 | 184 | - | MD 2 lower (2.23 to 1.77 lower) | MODERATE | CRITICAL |
| **Sleep (insomnia) (follow-up 7 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 6/139 (4.3%) | 0/46 (0%) | OR 3.93 (0.6 to 25.66) | 40 more per 1000 (from 0 to 90 more) | 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 49 Clinical evidence profile: IR Methyphenidate versus OROS Methylphenidate

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Methylphenidate IR versus OROS methylphenidate** | **Control** | **Relative (95% CI)** | **Absolute** | | |
| **Total participants with adverse events (follow-up 4 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 44/95 (46.3%) | 40/94 (42.6%) | RR 1.09 (0.79 to 1.5) | 38 more per 1000 (from 89 fewer to 213 more) | LOW | CRITICAL |
| **Decreased appetite (follow-up 3 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | serious[3] | serious[2] | none | 4/133 (3%) | 9/139 (6.5%) | RR 0.46 (0.15 to 1.47) | 35 fewer per 1000 (from 55 fewer to 30 more) | VERY LOW | CRITICAL |
| **Insomnia (follow-up 3 weeks)** | | | | | | | | | | | | |
| 1 | randomised | serious[1] | no serious | no serious | very | none | 5/133 | 6/139 | RR 0.87 | 6 fewer per 1000 | VERY | CRITICAL |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | trials | | inconsistency | indirectness | serious[2] | | (3.8%) | (4.3%) | (0.27 to 2.79) | (from 32 fewer to 77 more) | LOW | |
| **Increase in tics (follow-up 4 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 1/95 (1.1%) | 0/94 (0%) | OR 7.31 (0.15 to 368.51) | 10 more per 1000 (from 20 fewer to 40 more) | VERY LOW | CRITICAL |

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Downgraded by 1 increment if the majority of evidence had indirect outcomes

## Table 50 Clinical evidence profile: Methyphenidate versus no treatment (non-randomised)

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Methylphenidate versus no treatment** | **Control** | **Relative (95% CI)** | **Absolute** | | |
| **Cardiovascular events (follow-up mean 6 months)** | | | | | | | | | | | | |
| 1 | observational studies | serious[1] | no serious inconsistency | serious[2] | no serious imprecision | none | 1073/114647 (0.94%) | 350/114647 (0.31%) | RR 3.07 (2.72 to 3.46) | 6 more per 1000 (from 5 more to 8 more) | VERY LOW | CRITICAL |
| **Substance use (follow-up mean 4.4 years)** | | | | | | | | | | | | |
| 1 | observational studies | Serious[1] | no serious inconsistency | no serious indirectness | Serious[3] | none | 65/327 (19.9%) | 17/61 (27.9%) | RR 0.71 (0.45 to 1.13) | 81 fewer per 1000 (from 153 fewer to 36 more) | VERY LOW | CRITICAL |

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the majority of evidence had indirect outcomes
[3] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

**Table 51 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 dimesylate versus placebo | Control | Relative (95% CI) | Absolute | | |
| **Total any adverse event (follow-up 4-7 weeks)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 322/451 (71.4%) | 79/149 (53%) | OR 2.2 (1.5 to 3.21) | 183 more per 1000 (from 98 more to 253 more) | MODERATE | CRITICAL |
| **All-cause mortality (follow-up 4 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 0/235 (0%) | 0/79 (0%) | RD 0 (-0.02 to 0.02) | 0 events in both arms | MODERATE | CRITICAL |
| **Systolic blood pressure (follow-up 4-7 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 346 | 189 | - | MD 1.78 lower (2.08 to 1.48 lower) | MODERATE | CRITICAL |
| **Diastolic blood pressure (follow-up 4-7 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 346 | 189 | - | MD 0.57 higher (0.25 to 0.89 higher) | MODERATE | CRITICAL |
| **Weight change (follow-up 7 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 111 | 110 | - | MD 2.8 lower (3.2 to 2.4 lower) | MODERATE | CRITICAL |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Decreased weight - (follow-up 4-7 weeks)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 42/453 (9.3%) | 1/151 (0.66%) | OR 3.66 (1.79 to 7.48) | 17 more per 1000 (from 5 more to 41 more) | MODERATE | CRITICAL |
| **Sleep (insomnia) (follow-up 4-7 weeks)** | | | | | | | | | | | | |
| 3 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 83/564 (14.7%) | 5/261 (1.9%) | OR 3.84 (2.34 to 6.31) | 51 more per 1000 (from 25 more to 91 more) | 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

## Table 52 Clinical evidence profile: Lisdexamfetamine versus methylphenidate

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Lisdexamfetamine versus methylphenidate** | **Control** | **Relative (95% CI)** | **Absolute** | | |
| **Diastolic blood pressure change (follow-up 7 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 111 | 111 | - | MD 1.5 lower (4.07 lower to 1.07 higher) | MODERATE | CRITICAL |
| **Systolic blood pressure change (follow-up 7 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 111 | 111 | - | MD 0.7 higher (2.05 lower to 3.45 higher) | MODERATE | CRITICAL |
| **Weight change (follow-up 7 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 111 | 111 | - | MD 0.8 lower (1.24 to 0.36 lower) | MODERATE | CRITICAL |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Insomnia (follow-up 7 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 16/111 (14.4%) | 9/111 (8.1%) | RR 1.78 (0.82 to 3.85) | 63 more per 1000 (from 15 fewer to 231 more) | 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 53 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 guanfacine** | **Control** | **Relative (95% CI)** | **Absolute** | | |
| **Overall participants with adverse events (follow-up 6-13 weeks)** | | | | | | | | | | | | |
| 5 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious | none | 445/651 | 194/342 | RR 1.18 (1.06 to 1.32) | 102 fewer per 1000 (from 34 fewer to 173 more) | LOW | CRITICAL |
| **Overall participants with adverse events (follow-up 12 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious | none | 65/100 | 19/51 | RR 1.75 (1.19, 2.56) | 276 more per 1000 (from 71 more to 581 more) | LOW | CRITICAL |
| **All-cause mortality (follow up 6 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | No serious risk of bias | no serious inconsistency | no serious indirectness | No serious imprecision | none | 0/72 | 0/33 | RD 0 (-0.04 to 0.04 | 0 events in both arms | HIGH | CRITICAL |
| **Suicidal ideation (follow-up 6 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | No serious imprecision | none | 0/72 | 0/33 | RD 0 (-0.04 to 0.04) | 0 events in both arms | HIGH | CRITICAL |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Systolic blood pressure (follow-up 6-13 weeks)** | | | | | | | | | | | | |
| 6 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | No serious | none | 601 | 432 | - | 1.62mmHg lower (1.87 to 1.37 lower) | MODERATE | CRITICAL |
| **Diastolic blood pressure (follow-up 6-13 weeks)** | | | | | | | | | | | | |
| 5 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious | none | 544 | 400 | - | 2.8mmHg higher (1.67 to 3.93 higher) | LOW | CRITICAL |
| **Change in height (follow-up 6-8 weeks)** | | | | | | | | | | | | |
| 4 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | No serious imprecision | none | 353 | 146 | - | 0.99cm lower (1.78 to 0.2 lower) | MODERATE | CRITICAL |
| **Change in weight (follow-up 6-12 weeks)** | | | | | | | | | | | | |
| 4 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | No serious imprecision | none | 566 | 188 | - | 1.61kg lower in the intervention group (1.73 to 1.48 lower) | MODERATE | CRITICAL |
| **Change in weight (follow-up 12-18 weeks)** | | | | | | | | | | | | |
| 3 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | No serious imprecision | none | 654 | 269 | - | 2.11kg lower in the intervention group (2.46 to 1.76 lower) | MODERATE | CRITICAL |
| **Change in weight; high risk group; anxiety disorders (follow-up 12 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | No serious imprecision | none | 87 | 89 | - | 1.94kg lower (2.5 lower to 1.38 lower) | MODERATE | CRITICAL |
| **Decreased weight (follow-up 6-9 weeks)** | | | | | | | | | | | | |
| 4 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious | none | 22/323 | 5/169 | OR 2.13 (0.93 to 4.91) | 31 more per 1000 (from 2 to 101 more) | LOW | CRITICAL |
| **Sleep (follow-up 6-12 weeks)** | | | | | | | | | | | | |
| 5 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious | none | 39/377 | 18/263 | RR 1.71 (1.04 to 2.81 | 49 more per 1000 (from 3 more to 124 more) | LOW | CRITICAL |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Sleep (follow-up 13-16 weeks)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | Very serious | none | 7/160 | 2/16 | RR 0.85 (0.32 to 2.29) | 8 fewer per 1000 (from 35 fewer to 67 more) | VERY LOW | CRITICAL |
| **Tic severity (YGTSS); 0-100; lower scores are beneficial (follow-up 8-16 weeks)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | No serious imprecision | none | 61 | 56 | - | 7.9 lower in the intervention group (9.35 to 4.85 lower) | MODERATE | CRITICAL |
| **Tics (follow-up 6 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | Very serious | none | 8/112 (7.1%) | 13/114 (11.4%) | RR 3 (0.71 to 12.69) | 250 more per 1000 (36 more to 1000 more | VERY LOW | CRITICAL |
| **Tremor (follow-up 6 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | Very serious | none | 1/16 | 2/16 | RR 0.5 (0.05 to 4.98) | 62 more pre 1000 (6 more to 623 more) | VERY LOW | CRITICAL |
| **Sexual dysfunction (follow-up 70 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | No serious imprecision | none | 0/281 | 0/113 | RD 0 (-0.01 to 0.01) | 0 events in both arms | 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.
[3] Downgraded by 1 increment if the majority of evidence had indirect outcomes

**Table 54 Clinical evidence profile: Methylphenidate versus atomoxetine**

| Quality assessment | No of patients | Effect | Quality | Importance |
|---|---|---|---|---|

| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Methylphenidate versus atomoxetine | Control | Relative (95% CI) | Absolute | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Total participants with adverse events (follow-up 9 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[1] | none | 146/219 (66.7%) | 149/221 (67.4%) | RR 0.99 (0.87 to 1.13) | 7 fewer per 1000 (from 88 fewer to 88 more) | MODERATE | CRITICAL |
| **Systolic blood pressure (follow-up 9 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 219 | 221 | - | MD 0.3 lower (0.55 to 0.05 lower) | HIGH | CRITICAL |
| **Diastolic blood pressure (follow-up 9 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 219 | 74 | - | MD 0.7 lower (2.84 lower to 1.44 higher) | HIGH | CRITICAL |
| **Decreased weight (follow-up 9 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 2 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 383 | 387 | - | MD 0.37 lower (0.6 to 0.14 lower) | HIGH | CRITICAL |
| **Sleep (insomnia) (follow-up 9 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | Very serious[1] | none | 5/164 (3%) | 9/166 (5.4%) | RR 0.56 (0.19 to 1.64) | 24 fewer per 1000 (from 44 fewer to 35 more) | 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.

**Table 55 Clinical evidence profile: Methyphenidate versus atomoxetine (non-randomised)**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of | Design | Risk of | Inconsistency | Indirectness | Imprecision | Other | Atomoxetine versus | Control | Relative | Absolute | | |

| studies | | bias | | | | considerations | methylphenidate | | (95% CI) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Weight (follow-up mean 24 months; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | observational studies | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 55 | 28 | - | MD 2.31 lower (9.97 lower to 5.35 higher) | VERY LOW | CRITICAL |
| **Height (follow-up mean 24 months; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | observational studies | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 55 | 35 | - | MD 0.4 higher (0.16 to 0.65 higher) | 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 56 Clinical evidence profile: Atomoxetine versus lisdexamfetamine**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Atomoxetine versus lisdexamfetamine | Control | Relative (95% CI) | Absolute | | |
| **Total adverse events at 6 weeks** | | | | | | | | | | | | |
| 1 | randomised trials | no serious imprecision | no serious inconsistency | no serious indirectness | Serious[2] | none | 95/134 (70.9%) | 92/128 (71.9%) | RR 0.99 (0.85 to 1.15) | 7 fewer per 1000 (from 108 fewer to 108 more) | MODERATE | CRITICAL |
| **Systolic blood pressure (Better indicated by lower values) at 6 weeks** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | Serious[2] | none | 134 | 133 | - | MD 0.1 lower (2.15 lower to 1.95 higher) | MODERATE | CRITICAL |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Diastolic blood pressure (Better indicated by lower values) at 6 weeks** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | Serious[2] | none | 134 | 133 | - | MD 1.2 higher (0.79 lower to 3.19 higher) | MODERATE | CRITICAL |
| **Decreased weight at 6 weeks** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | Serious[2] | none | 9/134 (6.7%) | 28/133 (21.1%) | RR 0.32 (0.16 to 0.65) | 143 fewer per 1000 (from 74 fewer to 177 fewer) | MODERATE | CRITICAL |
| **Insomnia at 8 weeks** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | Serious[2] | none | 8/134 (6%) | 15/133 (11.3%) | RR 0.53 (0.23 to 1.21) | 53 fewer per 1000 (from 87 fewer to 24 more) | 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 57 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** | **Control** | **Relative (95% CI)** | **Absolute** | | |
| **Total participants with adverse events (follow-up 10-13 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 76/112 (67.9%) | 88/114 (77.2%) | RR 0.88 (0.75 to 1.03) | 93 fewer per 1000 (from 193 fewer to 23 more) | MODERATE | CRITICAL |
| **Sleep (insomnia) (follow-up 10-13 weeks)** | | | | | | | | | | | | |
| 1 | randomised | serious[1] | no serious | no serious | very serious[2] | none | 8/112 | 13/114 | RR 0.63 | 42 fewer per 1000 | VERY LOW | CRITICAL |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | trials | | inconsistency | indirectness | | | (7.1%) | (11.4%) | (0.27 to 1.45) | (from 83 fewer to 51 more) | | |
| **Decreased appetite (follow-up 10-13 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | serious[3] | serious[2] | none | 31/112 (27.7%) | 15/114 (13.2%) | RR 2.1 (1.2 to 3.68) | 145 more per 1000 (from 26 more to 353 more) | VERY LOW | CRITICAL |

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Downgraded by 1 increment if the majority of evidence had indirect outcomes

## Table 58 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** | | |
| **Total participants with adverse events (follow-up 5-13 weeks)** | | | | | | | | | | | | |
| 5 | randomised trials | serious[1] | serious[2] | no serious indirectness | serious[3] | none | 792/985 (80.4%) | 287/453 (63.4%) | RR 1.26 (1.07 to 1.48) | 171 more per 1000 (from 114 more to 234 more) | VERY LOW | CRITICAL |
| **Total participants with adverse events (follow-up 15 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[3] | none | 147/157 (93.6%) | 120/155 (77.4%) | RR 1.21 (1.1 to 1.33) | 163 more per 1000 (from 77 more to 255 more) | LOW | CRITICAL |
| **All-cause mortality (follow-up 8-15 weeks)** | | | | | | | | | | | | |
| 3 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 0/409 (0%) | 0/263 (0%) | RD 0 (-0.01 to 0.01) | 0 events in both arms | LOW | CRITICAL |
| **Cardiovascular events (follow-up 9 weeks)** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 0/256 (0%) | 0/66 (0%) | RD 0 (-0.02 to 0.02) | 0 events in both arms | MODERATE | CRITICAL |
| **Suicidal ideation (follow-up 8 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[3] | none | 1/227 (0.44%) | 0/113 (0%) | OR 4.47 (0.07 to 286.74) | 0 more per 1000 (from 10 fewer to 20 more) | LOW | CRITICAL |
| **Systolic blood pressure (follow-up 8 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[3] | none | 17 | 17 | - | MD 0.2 higher (9.43 lower to 9.83 higher) | LOW | CRITICAL |
| **Decreased appetite (follow-up 8-15 weeks)** | | | | | | | | | | | | |
| 3 | randomised trials | serious[1] | no serious inconsistency | serious[4] | serious[3] | none | 47/498 (9.4%) | 36/379 (9.5%) | RR 1.17 (0.77 to 1.77) | 16 more per 1000 (from 22 fewer to 73 more) | VERY LOW | CRITICAL |
| **Psychotic symptoms (follow-up 8 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[3] | none | 1/30 (3.3%) | 0/32 (0%) | OR 7.9 (0.16 to 398.87) | 30 more per 1000 (from 50 fewer to 120 more) | LOW | CRITICAL |
| **Sleep (insomnia) (follow-up 8-15 weeks)** | | | | | | | | | | | | |
| 3 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | serious[3] | none | 36/498 (7.2%) | 17/379 (4.5%) | RR 1.77 (1.02 to 3.08) | 35 more per 1000 (from 1 more to 93 more) | VERY LOW | CRITICAL |
| **Tic severity (follow-up 1 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[3] | none | 17 | 17 | - | MD 4.7 lower (8.93 to 0.47 lower) | 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 due to heterogeneity, unexplained by subgroup analysis
[3] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
[4] Downgraded by 1 increment if the majority of evidence had indirect outcomes

**Table 59 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 | | |
| **Total participants with adverse events (follow-up 8 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 108/130 (83.1%) | 56/78 (71.8%) | RR 1.16 (0.99 to 1.36) | 115 more per 1000 (from 7 fewer to 258 more) | LOW | CRITICAL |
| **Total participants with adverse events (follow-up 16 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 26/31 (83.9%) | 12/40 (30%) | RR 2.8 (1.7 to 4.6) | 540 more per 1000 (from 210 more to 1000 more) | MODERATE | CRITICAL |
| **All-cause mortality (follow-up 8 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 0/172 (0%) | 0/48 (0%) | RD 0 (-0.03 TO 0.03) | 0 events in both arms | MODERATE | CRITICAL |
| **Tachycardia (follow-up 16 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 0/31 (0%) | 0/30 (0%) | RD 0 (-0.06 TO 0.06) | 0 events in both arms | MODERATE | CRITICAL |
| **Systolic blood pressure (follow-up 16 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 31 | 30 | - | MD 1.1 higher (3.24 lower to 5.44 higher) | LOW | CRITICAL |
| **Diastolic blood pressure (follow-up 16 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 31 | 30 | - | MD 0.1 higher (3.91 lower to 4.11 higher) | MODERATE | CRITICAL |
| **Weight changes (follow-up 16 weeks; Better indicated by lower values)** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 31 | 30 | - | MD 0.6 higher (0.57 lower to 1.77 higher) | LOW | CRITICAL |
| **Psychotic symptoms (follow-up 16 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | No serious imprecision | none | 0/31 (0%) | 0/30 (0%) | RD 0 (-0.06 to 0.06) | 0 events in both arms | MODERATE | CRITICAL |
| **Sleep (insomnia) (follow-up 8 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 9/172 (5.2%) | 1/48 (2.1%) | RR 2.51 (0.33 to 19.34) | 31 more per 1000 (from 14 fewer to 382 more) | LOW | CRITICAL |
| **Sleep (insomnia) (follow-up 16 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 5/31 (16.1%) | 5/30 (16.7%) | RR 0.97 (0.31 to 3.01) | 5 fewer per 1000 (from 115 fewer to 335 more) | LOW | CRITICAL |
| **Increase in tics (follow-up 16 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 9/34 (26.5%) | 7/32 (21.9%) | RR 1.21 (0.51 to 2.86) | 46 more per 1000 (from 107 fewer to 407 more) | 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 60 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** | | |
| **Total Participants with adverse events (follow-up 6 weeks)** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[1] | none | 28/34 (82.4%) | 26/34 (76.5%) | RR 1.08 (0.84 to 1.37) | 61 more per 1000 (from 122 fewer to 283 more) | 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.

**Table 61 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 | Despiramine versus placebo | Control | Relative (95% CI) | Absolute | | |
| **Decreased appetite (follow-up 6 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | serious[1] | no serious imprecision | none | 5/21 (23.8%) | 0/20 (0%) | OR 8.75 (1.38 to 55.58) | 240 more per 1000 (from 50 more to 430 more) | MODERATE | CRITICAL |
| **Sleep (difficulty sleeping) (follow-up 6 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[2] | none | 4/21 (19%) | 1/20 (5%) | RR 3.81 (0.46 to 31.23) | 140 more per 1000 (from 27 fewer to 1000 more) | LOW | CRITICAL |
| **Improvement of tics (follow-up 6 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 11/21 (52.4%) | 1/20 (5%) | RR 10.48 (1.49 to 73.88) | 474 more per 1000 (from 25 more to 1000 more) | HIGH | CRITICAL |

[1] Downgraded by 1 increment if the majority of evidence had indirect outcomes
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

**Table 62 Clinical evidence profile: Methylphenidate versus clonidine**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Methylphenidate versus Clonidine | Control | Relative (95% CI) | Absolute | | |
| **Total with any adverse events (follow-up 16 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 17/29 (58.6%) | 26/31 (83.9%) | RR 0.7 (0.5 to 0.98) | 252 fewer per 1000 (from 17 fewer to 419 fewer) | LOW | CRITICAL |
| **Tachycardia (follow-up 16 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 1/29 (3.4%) | 0/31 (0%) | OR 7.92 (0.16 to 399.84) | 30 more (from 50 fewer to 120 more) | LOW | CRITICAL |
| **Systolic blood pressure (follow-up 16 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 29 | 31 | - | MD 0.1 lower (4.58 lower to 4.38 higher) | LOW | CRITICAL |
| **Weight changes (follow-up 16 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 29 | 31 | - | MD 1.7 lower (3.02 to 0.38 lower) | LOW | CRITICAL |
| **Psychotic symptoms (hallucinations) (follow-up 16 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 0/29 (0%) | 0/31 (0%) | RD 0 (-0.06 to 0.06) | 0 events in both arms | MODERATE | CRITICAL |
| **Sleep(insomnia) (follow-up 16 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | Very serious[2] | none | 1/29 (3.4%) | 5/31 (16.1%) | RR 0.21 (0.03 to 1.72) | 127 fewer per 1000 (from 156 fewer to 116 more) | VERY LOW | CRITICAL |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Increase in tics (follow-up 16 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 8/37 (21.6%) | 9/34 (26.5%) | RR 0.82 (0.36 to 1.87) | 48 fewer per 1000 (from 169 fewer to 230 more) | VERY LOW | CRITICAL |

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

**Table 63 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** | | |
| **Weight change (follow-up 6 months; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 20 | 20 | - | MD 1.1 higher (0.04 to 2.16 higher) | LOW | CRITICAL |
| **Sleeping problems (follow-up 6 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 2/19 (10.5%) | 5/17 (29.4%) | RR 0.36 (0.08 to 1.61) | 188 fewer per 1000 (from 271 fewer to 179 more) | VERY LOW | CRITICAL |
| **Tremor (follow-up 6 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 4/19 (21.1%) | 2/17 (11.8%) | RR 1.79 (0.37 to 8.57) | 93 more per 1000 (from 74 fewer to 891 more) | 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 64 Clinical evidence profile: Methylphenidate versus venlafaxine**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Methylphenidate versus venlafaxine | Control | Relative (95% CI) | Absolute | | |
| **Decreased appetite (follow-up 6 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | serious[1] | serious[2] | none | 7/18 (38.9%) | 2/19 (10.5%) | RR 3.69 (0.88 to 15.49) | 283 more per 1000 (from 13 fewer to 1000 more) | LOW | CRITICAL |
| **Sleep (insomnia) (follow-up 6 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 10/18 (55.6%) | 2/19 (10.5%) | RR 5.28 (1.34 to 20.86) | 451 more per 1000 (from 36 more to 1000 more) | HIGH | CRITICAL |

[1] Downgraded by 1 increment if the majority of evidence had indirect outcomes
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

**Table 65 Clinical evidence profile: Methylphenidate versus buproprion**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Methylphenidate versus Buproprion | Control | Relative (95% CI) | Absolute | | |
| **Total participants with adverse events (follow-up 6 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 9/15 (60%) | 5/15 (33.3%) | RR 1.8 (0.79 to 4.11) | 267 more per 1000 (from 70 fewer to 1000 more) | LOW | CRITICAL |
| **Tachycardia (follow-up 6 weeks)** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[2] | none | 2/20 (10%) | 1/20 (5%) | RR 2 (0.2 to 20.33) | 50 more per 1000 (from 40 fewer to 966 more) | LOW | CRITICAL |
| **Decreased appetite - <3 months (follow-up 6 weeks)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | serious[3] | serious[2] | none | 9/35 (25.7%) | 13/35 (37.1%) | OR 0.52 (0.17 to 1.59) | 136 fewer per 1000 (from 280 fewer to 113 more) | VERY LOW | CRITICAL |
| **Sleep (insomnia) (follow-up 6 weeks)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 8/35 (22.9%) | 10/35 (28.6%) | OR 0.7 (0.21 to 2.27) | 67 fewer per 1000 (from 208 fewer to 190 more) | VERY LOW | CRITICAL |
| **Tremor (follow-up 6 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 0/15 (0%) | 1/15 (6.7%) | OR 0.14 (0 to 6.82) | 57 fewer per 1000 (from 67 fewer to 261 more) | VERY LOW | CRITICAL |

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Downgraded by 1 increment if the majority of evidence had indirect outcomes

## Table 66 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** | | |
| **Tachycardia (follow-up 7 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 1/120 (0.83%) | 0/63 (0%) | OR 4.6 (0.07 to 284.33) | 10 more per 1000 (from 20 fewer to 40 more) | VERY LOW | |
| **Systolic blood pressure (follow-up 3-9 weeks; Better indicated by lower values)** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 423 | 213 | - | MD 0.07 higher (1.56 lower to 1.71 higher) | VERY LOW | |
| **Diastolic blood pressure (follow-up 9 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 197 | 51 | - | MD 0.03 higher (2.88 lower to 2.95 higher) | MODERATE | |
| **Weight change (follow-up 7-9 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 284 | 145 | - | MD 1.26 lower (1.51 to 1 lower) | VERY LOW | |
| **Decreased weight (follow-up 5 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 2/23 (8.7%) | 1/23 (4.3%) | RR 2 (0.19 to 20.55) | 43 more per 1000 (from 35 fewer to 850 more) | VERY LOW | |
| **Sleep (insomnia) (follow-up 3-9 weeks)** | | | | | | | | | | | | |
| 3 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 88/417 (21.1%) | 8/214 (3.7%) | OR 4.12 (2.57 to 6.61) | 101 more per 1000 (from 53 more to 167 more) | MODERATE | |
| **Sleep (insomnia) - high risk (autism) (follow-up 8 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 3/48 (6.3%) | 5/49 (10.2%) | OR 0.6 (0.14 to 2.52) | 38 fewer per 1000 (from 86 fewer to 121 more) | VERY LOW | |
| **Psychotic symptoms (follow-up 7 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 1/120 (0.83%) | 0/63 (0%) | OR 4.6 (0.07 to 284.33) | 10 more per 1000 (from 20 fewer to 40 more) | VERY LOW | |

**Table 67 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 | Methylphenidate versus modafinil | Control | Relative (95% CI) | Absolute | | |
| **Decreased weight (follow-up 6 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | Very serious[1] | none | 7/30 (23.3%) | 3/30 (10%) | RR 2.33 (0.67 to 8.18) | 133 more per 1000 (from 33 fewer to 718 more) | 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.

# F.3 Adults

**Table 68 Clinical evidence profile: Methyphenidate 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 | Control | Relative (95% CI) | Absolute | | |
| **Total participants with adverse events (follow-up 5-8 weeks)** | | | | | | | | | | | | |
| 6 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 553/739 (74.8%) | 60.1% | RR 1.31 (1.2 to 1.43) | 186 more per 1000 (from 120 more to 258 more) | VERY LOW | CRITICAL |
| **Total participants with adverse events - Immediate release (follow-up 5-8 weeks)** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | serious[3] | no serious inconsistency | no serious indirectness | serious[4] | none | 9/12 (75%) | 66.7% | RR 1.12 (0.67 to 1.89) | 80 more per 1000 (from 220 fewer to 594 more) | LOW | CRITICAL |
| **Total participants with adverse events - OROS (follow-up 5-8 weeks)** | | | | | | | | | | | | |
| 5 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | serious[4] | none | 544/727 (74.8%) | 56.4% | RR 1.31 (1.2 to 1.44) | 175 more per 1000 (from 113 more to 248 more) | VERY LOW | CRITICAL |
| **Total participants with adverse events (follow-up 13-24 weeks)** | | | | | | | | | | | | |
| 2 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | serious[4] | none | 272/308 (88.3%) | 76.3% | RR 1.16 (1.06 to 1.26) | 122 more per 1000 (from 46 more to 198 more) | VERY LOW | CRITICAL |
| **Cardiac events (follow-up 6 weeks)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[3] | no serious inconsistency | no serious indirectness | serious[4] | none | 10/184 (5.4%) | 2% | RR 2.6 (0.83 to 8.13) | 32 more per 1000 (from 3 fewer to 143 more) | LOW | CRITICAL |
| **Cardiac events 24 weeks (follow-up 24 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[3] | no serious inconsistency | no serious indirectness | very serious[2] | none | 8/62 (12.9%) | 2.9% | RR 4.39 (0.57 to 33.62) | 98 more per 1000 (from 12 fewer to 946 more) | VERY LOW | CRITICAL |
| **Systolic blood pressure - systolic blood pressure (follow-up 7 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[3] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 113 | 116 | - | MD 0.7 lower (3.12 lower to 1.72 higher) | MODERATE | CRITICAL |
| **Systolic blood pressure - Systolic blood pressure (follow-up mean 24 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[3] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 241 | 118 | - | MD 1 higher (2.17 lower to 4.17 higher) | MODERATE | CRITICAL |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Diastolic blood pressure - diastolic blood pressure (follow-up 7 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[3] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 113 | 116 | - | MD 0.7 higher (1.13 lower to 2.53 higher) | MODERATE | CRITICAL |
| **Diastolic blood pressure - diastolic blood pressure (follow-up 24 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[3] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 241 | 118 | - | MD 0 higher (2.13 lower to 2.13 higher) | MODERATE | CRITICAL |
| **Palpitations (follow-up 3-9 weeks)** | | | | | | | | | | | | |
| 5 | randomised trials | serious[3] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 78/755 (10.3%) | 1.4% | RR 7.3 (3.68 to 14.46) | 88 more per 1000 (from 38 more to 188 more) | MODERATE | CRITICAL |
| **Palpitations - Immediate release MPH (follow-up 3 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[3] | no serious inconsistency | no serious indirectness | very serious[2] | none | 4/45 (8.9%) | 2.2% | RR 4 (0.47 to 34.41) | 66 more per 1000 (from 12 fewer to 735 more) | VERY LOW | CRITICAL |
| **Palpitations- OROS MPH (follow-up 3-9 weeks)** | | | | | | | | | | | | |
| 4 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 74/710 (10.4%) | 0.7% | RR 7.68 (3.73 to 15.82) | 47 more per 1000 (from 19 more to 104 more) | HIGH | CRITICAL |
| **Palpitations (follow-up 13-24 weeks)** | | | | | | | | | | | | |
| 3 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 80/550 (14.5%) | 0.8% | RR 3.45 (1.97 to 6.06) | 20 more per 1000 (from 8 more to 40 more) | LOW | CRITICAL |
| **Decreased appetite (follow-up 2-9 weeks)** | | | | | | | | | | | | |
| 8 | randomised | very | no serious | Serious[5] | no serious | none | 274/1072 | 5.6% | RR 4.57 (3.37 to | 200 more per 1000 (from 133 more to | VERY LOW | CRITICAL |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | trials | serious[1] | inconsistency | | imprecision | | (25.6%) | | 6.21) | 292 more) | | |
| **Decreased appetite - Decreased appetite 13- 24 weeks (follow-up 13-24 weeks)** | | | | | | | | | | | | |
| 4 | randomised trials | very serious[1] | no serious inconsistency | Serious[5] | no serious imprecision | none | 175/612 (28.6%) | 5.3% | RR 3.59 (2.46 to 5.24) | 137 more per 1000 (from 77 more to 225 more) | VERY LOW | CRITICAL |
| **Weight change (follow-up 4-7 weeks; Better indicated by higher values)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[3] | serious inconsistency[5] | no serious indirectness | serious[4] | none | 160 | 163 | - | MD 2.11 lower (2.77 to 1.44 lower) | VERY LOW | CRITICAL |
| **Weight loss (follow-up 5 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 22/305 (7.2%) | 5.2% | RR 1.38 (0.54 to 3.56) | 20 more per 1000 (from 24 fewer to 133 more) | VERY LOW | CRITICAL |
| **Weight loss (follow-up 13 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | serious[4] | none | 26/182 (14.3%) | 4.1% | RR 3.46 (1.24 to 9.64) | 101 more per 1000 (from 10 more to 354 more) | VERY LOW | CRITICAL |
| **Anorexia (follow-up 3 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | serious[4] | none | 11/50 (22%) | 6% | RR 3.67 (1.09 to 12.36) | 160 more per 1000 (from 5 more to 682 more) | VERY LOW | CRITICAL |
| **Anorexia (follow-up 13 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | serious[4] | none | 18/182 (9.9%) | 4.1% | RR 2.4 (0.84 to 6.89) | 57 more per 1000 (from 7 fewer to 241 more) | VERY LOW | CRITICAL |
| **Psychotic symptoms (follow-up 4 weeks)** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 1/143 (0.7%) | 0% | OR 7.29 (0.14 to 367.25) | 10 more per 1000 (from 10 fewer to 30 more) | VERY LOW | CRITICAL |
| **Insomnia (follow-up 2-9 weeks)** | | | | | | | | | | | | |
| 10 | randomised trials | serious[3] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 162/1169 (13.9%) | 6.8% | RR 1.88 (1.42 to 2.48) | 60 more per 1000 (from 29 more to 101 more) | MODERATE | CRITICAL |
| **Insomnia- Immediate release MPH (follow-up 2-9 weeks)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[3] | no serious inconsistency | no serious indirectness | serious[4] | none | 40/149 (26.8%) | 19.4% | RR 1.47 (0.88 to 2.45) | 91 more per 1000 (from 23 fewer to 281 more) | MODERATE | CRITICAL |
| **Insomnia - OROS MPH (follow-up 2-9 weeks)** | | | | | | | | | | | | |
| 8 | randomised trials | serious[3] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 122/1020 (12%) | 5.8% | RR 2.04 (1.47 to 2.84) | 60 more per 1000 (from 27 more to 107 more) | MODERATE | CRITICAL |
| **Insomnia (follow-up 13-24 weeks)** | | | | | | | | | | | | |
| 4 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | serious[4] | none | 67/424 (15.8%) | 11.6% | RR 1.47 (0.99 to 2.18) | 55 more per 1000 (from 1 fewer to 137 more) | VERY LOW | CRITICAL |
| **Tics (follow-up 3 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[3] | no serious inconsistency | no serious indirectness | very serious[2] | none | 3/45 (6.7%) | 2.2% | OR 2.81 (0.38 to 20.67) | 37 more per 1000 (from 14 fewer to 295 more) | VERY LOW | CRITICAL |
| **Tremor (follow-up 13 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[2] | no serious inconsistency | no serious indirectness | very serious[2] | none | 9/182 (4.9%) | 1% | RR 4.8 (0.62 to 37.31) | 38 more per 1000 (from 4 fewer to 363 more) | VERY LOW | CRITICAL |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Sexual dsyfunction (follow-up 24 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[3] | no serious inconsistency | no serious indirectness | serious[4] | none | 27/241 (11.2%) | 3.4% | RR 3.3 (1.18 to 9.23) | 78 more per 1000 (from 6 more to 280 more) | VERY LOW | CRITICAL |

[1] Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 2 increments if the confidence interval crossed both MIDs.
[3] Downgraded by 1 increment if the majority of the evidence was at high risk of bias.
[4] Downgraded by 1 increment if the confidence interval crossed one MID.
[5] Downgraded due to heterogeneity, unexplained by subgroup analysis
[6] Downgraded by 1 or 2 increments because the majority of evidence had indirect outcomes

**Table 69 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** | | |
| **Total participants with adverse events (follow-up 2-10 weeks)** | | | | | | | | | | | | |
| 3 | randomised trials | very serious[1] | serious[2] | no serious indirectness | serious[3] | none | 376/552 (68.1%) | 58.1% | RR 1.17 (0.87 to 1.56) | 99 more per 1000 (from 76 fewer to 325 more) | VERY LOW | CRITICAL |
| **Cardiac events (follow-up 6 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[4] | no serious inconsistency | no serious indirectness | very serious[5] | none | 1/35 (2.9%) | 2.9% | RR 0.97 (0.06 to 14.91) | 1 fewer per 1000 (from 27 fewer to 403 more) | VERY LOW | CRITICAL |
| **Decreased appetite (follow-up 2-10 weeks)** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 4 | randomised trials | very serious[1] | no serious inconsistency | serious[6] | no serious imprecision | none | 144/587 (24.5%) | 3.8% | RR 7.2 (3.64 to 14.26) | 236 more per 1000 (from 100 more to 504 more) | VERY LOW | CRITICAL |
| **Weight change - 30mg (follow-up 4 weeks; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | randomised trials | Serious[4] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 119 | 62 | - | MD 3.3 lower (4.63 to 1.97 lower) | MODERATE | CRITICAL |
| **Weight change - 50mg (follow-up 4 weeks; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[4] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 117 | 62 | - | MD 3.6 lower (4.92 to 2.28 lower) | MODERATE | CRITICAL |
| **Weight change - 70mg (follow-up 4 weeks; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | randomised trials | Serious[4] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 122 | 62 | - | MD 4.8 lower (6.12 to 3.48 lower) | MODERATE | CRITICAL |
| **Weight loss at 10 weeks** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 8/79 (10.1%) | 0% | OR 8.21 (1.99 to 33.91) | 100 more per 1000 (from 30 more to 170 more) | LOW | CRITICAL |
| **Anorexia 4-10 weeks (follow-up 4-10 weeks)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[4] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 22/437 (5%) | 0% | OR 4.4 (1.46 to 13.25) | 50 more per 1000 (from 20 more to 80 more) | MODERATE | CRITICAL |
| **Insomnia (follow-up 2-10 weeks)** | | | | | | | | | | | | |
| 4 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 90/587 (15.3%) | 3.4% | RR 3.73 (1.84 to 7.57) | 93 more per 1000 (from 29 more to 223 more) | LOW | CRITICAL |
| **Sexual dysfunction at 10 weeks** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | serious[3] | none | 4/79 (5.1%) | 0% | OR 7.78 (1.08 to 56.29) | 50 more per 1000 (from 0 more to 100 more) | VERY LOW | CRITICAL |

[1] Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded due to heterogeneity, unexplained by subgroup analysis. It should be noted that Wigal, 2010 #730 reported five times more cases of respiratory tract infections in the placebo group. This was resulted in a higher number of the placebo group reporting adverse events compared to the other studies.
[3] Downgraded by 1 increment if the confidence interval crossed one MID.
[4] Downgraded by 1 increment if the majority of the evidence was at high risk of bias.
[5] Downgraded by 2 increments if the confidence interval crossed both MIDs.

[6]Downgraded by 1 or 2 increments if the majority of evidence had indirect outcomes

**Table 70 Clinical evidence profile Dexamphetamine versus placebo**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Dexamphetamine ER versus placebo** | **Control** | **Relative (95% CI)** | **Absolute** | | |
| **Weight change (follow-up 6 weeks; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 24 | 21 | - | MD 3.31 higher (2.05 to 4.58 higher) | HIGH | CRITICAL |
| **Decreased appetite (follow-up 2-5 weeks)** | | | | | | | | | | | | |
| 2 | randomised trials | very serious[1] | no serious inconsistency | serious[3] | serious[2] | none | 34/187 (18.2%) | 5.7% | OR 2.08 (0.96 to 4.49) | 56 more per 1000 (from 4 fewer to 188 more) | VERY LOW | CRITICAL |
| **Insomnia (follow-up 2-5 weeks)** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 35/187 (18.7%) | 14.8% | RR 1.62 (0.84 to 3.09) | 92 more per 1000 (from 24 fewer to 309 more) | VERY LOW | CRITICAL |

[1] Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID.
[3]Downgraded by 1 or 2 increments if the majority of evidence had indirect outcomes

**Table 71 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** | | |
| **Total participants with adverse events (follow-up 8-10 weeks)** | | | | | | | | | | | | |
| 3 | randomised trials | serious[1] | serious[2] | no serious indirectness | serious[3] | none | 293/575 (51%) | 64.9% | RR 1.31 (1.03 to 1.65) | 201 more per 1000 (from 19 more to 422 more) | VERY LOW | CRITICAL |
| **Total participants with adverse events (follow-up 12-25 weeks)** | | | | | | | | | | | | |
| 3 | randomised trials | very serious[4] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 576/712 (80.9%) | 77.3% | RR 1.13 (1.06 to 1.19) | 100 more per 1000 (from 46 more to 147 more) | LOW | CRITICAL |
| **Palpitations** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[5] | none | 3/37 (8.1%) | 5.4% | RR 1.5 (0.27 to 8.46) | 27 more per 1000 (from 39 fewer to 403 more) | VERY LOW | CRITICAL |
| **Systolic blood pressure 1 (follow-up 10 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised | serious[1] | no serious | no serious | serious[3] | none | 34 | 37 | - | MD 4.5 higher (0.77 | LOW | CRITICAL |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | trials | | inconsistency | indirectness | | | | | | lower to 9.77 higher) | | |
| **Diastolic blood pressure (follow-up 10 weeks; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[3] | none | 34 | 37 | - | MD 2.7 higher (1.74 lower to 7.14 higher) | LOW | CRITICAL |
| **Weight change (follow-up 10 weeks; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | serious[2] | no serious indirectness | serious[3] | none | 34 | 37 | - | MD 2.4 lower (3.65 to 1.15 lower) | VERY LOW | CRITICAL |
| **Weight change (follow-up 13 weeks; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[5] | none | 72 | 75 | - | MD 1.33 lower (1.98 to 0.68 lower) | VERY LOW | CRITICAL |
| **Weight loss (follow-up 10 weeks)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 17/232 (7.3%) | 0.3% | OR 6.34 (2.47 to 16.23) | 16 more per 1000 (from 4 more to 44 more) | MODERATE | CRITICAL |
| **Decreased appetite (follow-up 8-10 weeks)** | | | | | | | | | | | | |
| 6 | randomised trials | serious[1] | no serious inconsistency | serious[6] | no serious imprecision | none | 200/1290 (15.5%) | 3.1% | RR 4.92 (3.52 to 6.87) | 122 more per 1000 (from 78 more to 182 more) | LOW | CRITICAL |
| **Decreased appetite (follow-up 12-24 weeks)** | | | | | | | | | | | | |
| 5 | randomised trials | very serious[4] | no serious inconsistency | serious[6] | no serious imprecision | none | 148/1000 (14.8%) | 2.8% | RR 4.19 (2.95 to 5.96) | 89 more per 1000 (from 55 more to 139 more) | VERY LOW | CRITICAL |
| **Insomnia (follow-up 8-10 weeks)** | | | | | | | | | | | | |
| 5 | randomised | serious[1] | no serious | no serious | no serious | none | 154/922 | 8.4% | RR 2 (1.29 | 84 more per 1000 (from 24 more to 176 | MODERATE | CRITICAL |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | trials | | inconsistency | indirectness | imprecision | | (16.7%) | | to 3.1) | more) | | |
| **Insomnia (follow-up 12-24 weeks)** | | | | | | | | | | | | |
| 4 | randomised trials | very serious[4] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 116/962 (12.1%) | 7.1% | RR 1.75 (1.3 to 2.34) | 53 more per 1000 (from 21 more to 95 more) | LOW | CRITICAL |
| **Sexual dysfunction (follow-up 8-10 weeks)** | | | | | | | | | | | | |
| 4 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 50/851 (5.9%) | 1.2% | RR 4.73 (2.36 to 9.49) | 45 more per 1000 (from 16 more to 102 more) | MODERATE | CRITICAL |
| **Sexual dsyfunction (follow-up 12-24 weeks)** | | | | | | | | | | | | |
| 4 | randomised trials | very serious[4] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 36/962 (3.7%) | 0.4% | RR 5.43 (2.36 to 12.5) | 18 more per 1000 (from 5 more to 46 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] Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[5] Downgraded by 2 increments if the confidence interval crossed both MIDs.
[6]Downgraded by 1 or 2 increments if the majority of evidence had indirect outcomes

**Table 72 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** | | |
| **Increased appetite (follow-up 9 weeks)** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | Very serious[2] | none | 1/13 (7.7%) | 15.4% | RR 0.5 (0.05 to 4.86) | 77 fewer per 1000 (from 146 fewer to 594 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 increment if the confidence interval crossed both MIDs.

**Table 73 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 | | |
| **Sexual dysfunction (follow-up 6 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | Very serious[1] | none | 2/22 (9.1%) | 0% | OR 7.75 (0.47 to 128.03) | 90 more per 1000 (from 50 fewer to 230 more) | LOW | CRITICAL |

[1] Downgraded by 2 increments if the confidence interval crossed both MIDs.

**Table 74 Clinical evidence profile Bupropion SR versus placebo**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Bupropion SR versus Placebo | Control | Relative (95% CI) | Absolute | | |
| **Total participants with adverse events (follow-up 7 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 9/13 (69.2%) | 66.7% | RR 1.04 (0.61 to 1.78) | 27 more per 1000 (from 260 fewer to 520 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 75 Clinical evidence profile Bupropion SR versus methylphenidate

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Bupropion SR versus methylphenidate | Control | Relative (95% CI) | Absolute | | |
| **Total participants with adverse events 7 weeks (follow-up 7 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 9/13 (69.2%) | 75% | RR 0.92 (0.57 to 1.5) | 60 fewer per 1000 (from 322 fewer to 375 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 76 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 | | |
| **Total participants with adverse events (follow-up 9 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 227/264 (86%) | 85.1% | RR 1.01 (0.91 to 1.12) | 9 more per 1000 (from 77 fewer to 102 more) | LOW | CRITICAL |
| **Suicidal ideation (follow-up 9 weeks)** | | | | | | | | | | | | |
| 1 | randomised | very | no serious | no serious | very serious[2] | none | 1/264 | 0% | OR 3.6 (0.03 | 0 more per 1000 (from | VERY | CRITICAL |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | trials | serious[1] | inconsistency | indirectness | | | (0.38%) | | to 411.56) | 20 less to 20 more) | LOW | |
| **Tachycardia (follow-up 9 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 1/264 (0.38%) | 0% | OR 3.6 (0.03 to 411.56) | 0 more per 1000 (rom 20 less to 20 more) | VERY LOW | CRITICAL |
| **Decreased appetite (follow-up 2 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | serious[4] | serious[3] | none | 4/22 (18.2%) | 0% | OR 8.58 (1.13 to 65.51) | 180 more per 1000 (from 10 more to 350 more) | LOW | CRITICAL |
| **Anorexia (follow-up 9 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | serious[3] | none | 38/264 (14.4%) | 4.1% | RR 3.55 (1.13 to 11.18) | 105 more per 1000 (from 5 more to 417 more) | VERY LOW | CRITICAL |
| **Insomnia (follow-up 2-9 weeks)** | | | | | | | | | | | | |
| 2 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | serious[3] | none | 76/286 (26.6%) | 14.5% | RR 2.15 (1.18 to 3.91) | 167 more per 1000 (from 26 more to 422 more) | VERY LOW | CRITICAL |
| **Psychotic symptoms (follow-up 9 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 1/264 (0.38%) | 0% | OR 3.6 (0.03 to 411.56) | 0 more per 1000 (from 20 fewer to 20 more) | VERY LOW | CRITICAL |

[1] Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 2 increments if the confidence interval crossed both MIDs.
[3] Downgraded by 1 increment if the confidence interval crossed one MID.
[4]Downgraded by 1 or 2 increments if the majority of evidence had indirect outcomes

**Table 77 Clinical evidence profile Modafinil versus dexamphetamine**

| Quality assessment | | | | | | No of patients | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Modafinil versus Dexamphetamine** | **Control** | **Relative (95% CI)** | **Absolute** | | |
| **Insomnia (follow-up 2 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[1] | none | 4/22 (18.2%) | 36.4% | RR 0.5 (0.18 to 1.42) | 182 fewer per 1000 (from 298 fewer to 153 more) | LOW | CRITICAL |

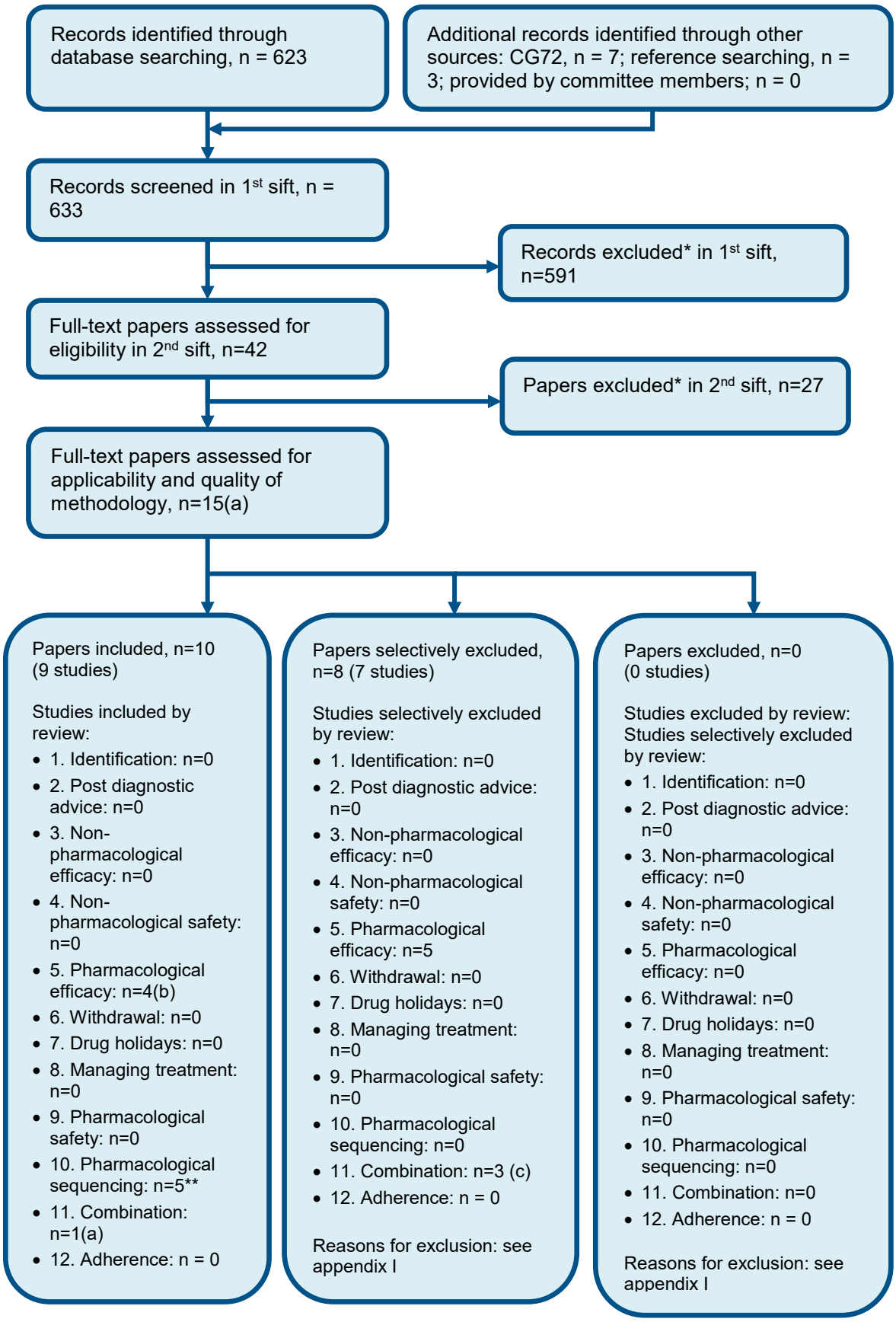
[1] Downgraded by 2 increments if the confidence interval crossed both MIDs.

**Table 78 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** | | |
| **Insomnia (follow-up 4 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 8/23 (34.8%) | 5.9% | RR 5.91 (0.81 to 42.92) | 290 more per 1000 (from 11 fewer to 1000 more) | VERY LOW | CRITICAL |

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

# Appendix G: Health economic evidence selection




* Non-relevant population, intervention, comparison, design or setting; non-English language
(a) note that there were 2 original models from the previous guideline (either included or excluded) which is why the numbers add to more than 15.
(b) Two articles identified were applicable to Q5 and Q10, for the purposes of this diagram it has been included under Q5

only.
(c) One of these is a model from the previous guideline that was exclude. Two articles identified were applicable to both Q5 and Q11 and have only been included here under Q11. One paper here was selectively excluded in Q11 but included in Q5 and so is double counted in this flowchart.

# Appendix H: Health economic evidence tables

None

# Appendix I: Excluded studies

## I.1 Excluded clinical studies

**Table 79: Studies excluded from the clinical review**

| Study | Exclusion reason |
|---|---|
| Abbasi 2011[2] | Incorrect interventions |
| Abikoff 2007[3] | Less than minimum duration |
| Adler 2005[21] | Inappropriate design |
| Adler 2008[17] | No usable outcomes |
| Adler 2011[12] | Incorrect interventions |
| Adler 2011[13] | No relevant outcomes |
| Adler 2014[4] | No relevant outcomes |
| Adler 2014[5] | Incorrect interventions |
| Adler 2016[14] | Incorrect population |
| Agay 2010[22] | Less than minimum duration |
| Agay 2014[23] | Less than minimum duration |
| Altin 2013[25] | No relevant outcomes |
| 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[634] | Incorrect study design |
| Anonymous 2008[39] | Incorrect study design |
| Anonymous 2009[253] | Not article |
| Anonymous 2016[181] | Not in English |
| Apostol 2012[40] | Incorrect intervention |
| Araki 2015[42] | Inappropriate comparison |
| Arango 2014[43] | No relevant outcomes |
| Ardic 2014[44] | Less than minimum duration |
| Arduc 2014[44] | Incorrect diagnosis |
| Armenteros 2007[45] | Incorrect population |
| Armstrong 2012[46] | Incorrect duration |
| Arnold 2007[48] | Incorrect intervention |
| Arnold 2010[49] | No relevant outcomes |
| Arnold 2010[50] | Incorrect population |
| Arnold 2015[51] | Wrong intervention (combination) |

| Study | Exclusion reason |
|---|---|
| Asherson 2015[53] | Systematic review: study designs inappropriate |
| Ashkenasi 2011[54] | Incorrect interventions |
| Babinski 2014[56] | Incorrect interventions |
| Babinski 2014[58] | No relevant outcomes |
| Babinski 2016[57] | Incorrect population |
| Bahcivan saydam 2015[59] | No intervention |
| Bain 2012[60] | Incorrect interventions |
| Bain 2013[61] | Incorrect interventions |
| Bali 2015[62] | Incorrect interventions |
| Banaschewski 2014 [63] | Incorrect population |
| Banerjee 2009[65] | No relevant outcomes |
| Bangs 2008[67] | Abstract |
| Barbaresi 2014[68] | Incorrect study design |
| Barkley 2007[69] | Incorrect interventions |
| Barnard 2002[70] | Review: references checked |
| Barry 2006[72] | Incorrect study design. Commentary |
| Bart 2010[73] | No relevant outcomes |
| Barton 2006[74] | Incorrect study design |
| Bastiaens 2007[75] | No relevant outcomes |
| Becker 2013[77] | Background info |
| Becker 2016[76] | Incorrect study design |
| Bedard 2008[79] | Incorrect duration |
| Bedard 2015[78] | No relevant outcomes |
| Beherec 2011[80] | No relevant outcomes |
| Bejerot 2010[81] | Inappropriate comparison |
| Bendz 2010[82] | Incorrect study design |
| Bental 2008[83] | Incorrect duration |
| Benvenuto 2013[84] | Incorrect study design |
| Berlin 2012[85] | Incorrect interventions |
| Beyer von morgenstern 2014[86] | Incorrect study design |
| Biederman 2005 [104] | Incorrect population |
| Biederman 2007[102] | Meta-analysis: references checked |
| Biederman 2007[99] | No relevant outcomes |
| Biederman 2007[90] | No relevant outcomes |
| Biederman 2008[101] | Meta-analysis of individual studies included in review |
| Biederman 2008[95] | No relevant outcomes |
| Biederman 2008[100] | No relevant outcomes |
| Biederman 2012[91] | No relevant outcomes |
| Bilder 2016[105] | No relevant outcomes |
| Blader 2009[107] | Incorrect interventions |
| Blader 2013[106] | Inappropriate comparison |
| Blum 2011[108] | No relevant outcomes |
| Blumer 2009[109] | Incorrect interventions |
| Boellner 2010[110] | Inappropriate comparison |
| Bögels 2008[111] | Incorrect interventions |

| Study | Exclusion reason |
|---|---|
| Bohnstedt 2005[112] | Insufficient information on full trial |
| Boisjoli 2007[113] | Incorrect interventions |
| Boonstra 2007[114] | No relevant outcomes |
| Borsting 2008[115] | Conference abstract |
| Bottelier 2014[116] | Protocol |
| Brams 2008[119] | Incorrect duration |
| Brams 2010[118] | Review: references checked |
| Brams 2011[117] | No relevant outcomes |
| Brams 2012[120] | Erratum |
| Brams 2012[121] | Incorrect duration |
| Brams 2012[122] | No washout following open label lead in phase |
| Bro 2015[123] | Inappropriate comparison |
| Brown 2010[125] | No relevant outcomes |
| Brown 2010[127] | Meta-analysis of included studies |
| Bubnik 2015[128] | No relevant outcomes |
| Buchmann 2007[129] | Inappropriate comparison |
| Buitelaar 1996[130] | Incorrect study design |
| Buitelaar 1996[130] | No relevant outcomes |
| Buitelaar 1996[135] | No usable outcomes |
| Buitelaar 2007[131] | Incorrect interventions |
| Buitelaar 2009[132] | No relevant outcomes |
| Buitelaar 2012[133] | Less than minimum duration |
| Burton 2015[136] | Incorrect interventions |
| Butter 1983[137] | Less than minimum duration |
| Butter 1984[138] | Less than minimum duration |
| Camporeale 2013 [140] | Incorrect population |
| Cantilena 2012[142] | Incorrect population |
| Cardo 2013[143] | Less than minimum duration |
| Castellanos-ryan 2013[146] | Incorrect interventions |
| Castells 2011[147] | Systematic review: checked for references |
| Cetin 2015[148] | Less than minimum duration |
| Chang 2009[149] | Less than minimum duration |
| Chang 2012[150] | No relevant outcomes |
| Chang 2016[151] | No relevant outcomes |
| Chantiluke 2015[152] | No usable outcomes |
| Chantiluke 2015[153] | Incorrect study design |
| Chavez 2006[154] | Review: references checked |
| Chen 2012[155] | Inappropriate comparison |
| Chen 2014[157] | Incorrect population |
| Chen 2014[156] | Inappropriate comparison |
| Cheng-shannon 2004[158] | Review: references checked |
| Childress 2009 [163] | Inappropriate intervention |
| Childress 2012[159] | Less than minimum duration |
| Childress 2014[162] | Incorrect population |
| Childress 2015[161] | Inappropriate intervention |

| Study | Exclusion reason |
|---|---|
| Ching 2012[164] | Systematic review checked for references |
| Cho 2011[165] | Less than minimum duration |
| Chou 2012[167] | No relevant outcomes |
| Chou 2017[166] | Non randomised study |
| Classen 2013[168] | Systematic review: study designs inappropriate |
| Classen 2013[169] | Incorrect study design |
| Classen 2013[170] | Incorrect study design |
| Classi 2011[171] | Inappropriate comparison |
| Clemow 2015[172] | No relevant outcomes |
| Coghill 2010[173] | Systematic review checked for references |
| Coghill 2014[175] | Systematic review: study designs inappropriate. open label |
| Cohen-yavin 2009[178] | Less than minimum duration |
| Collins 2013[179] | Not article |
| Comer 2013[180] | Incorrect interventions |
| Connolly 2015[184] | Inappropriate comparison |
| Connor 1994[185] | Incorrect study design |
| Connor 2013 [188] | Incorrect study design |
| Connor 2014[186] | References checked |
| Cooper 2011[189] | Inappropriate comparison |
| Corkum 2008[190] | Incorrect duration |
| Cornforth 2010[191] | Review: references checked |
| Correia Filho 2005 [192] | Incorrect method of diagnosis |
| Cortese 2012[193] | No outcomes of interest |
| Costa 2013[194] | Incorrect duration |
| Cottrell 2008[195] | Included in the economic review |
| Covey 2010[198] | Inappropriate comparison |
| Covey 2011[196] | No relevant outcomes |
| Covey 2015[197] | No useable outcomes |
| Cox 2008[200] | No relevant outcomes |
| Cox 2012[199] | No relevant outcomes |
| Cubillo 2014[201] | Incorrect duration |
| Cubillo 2014[202] | Incorrect duration |
| Curtin 2005[203] | Incorrect interventions |
| Cutler 2010[204] | Conference abstract |
| Dalsgaard 2014[205] | Inappropriate comparison |
| Dean 2011[207] | Incorrect population |
| Deputy 2002[209] | Not article |
| Devito 2009[210] | Incorrect study design |
| Dinca 2005[212] | Review: references checked |
| Doig 2008[216] | Incorrect study design |
| Donnelly 1986[217] | Incorrect population (diagnosis) |
| Dopfner 2011[220] | Less than minimum duration |
| Dopfner 2011[219] | Incorrect study design |
| Dopfner 2011[218] | No relevant outcomes |
| Dupaul 2012[221] | Incorrect duration |

| Study | Exclusion reason |
|---|---|
| Durell 2014[223] | Erratum |
| Epstein 2011[225] | Incorrect duration |
| Ercan 2013[226] | Less than minimum duration |
| Erdogan 2010[227] | Not review population |
| Fabiano 2007[228] | Incorrect interventions |
| Fabiano 2010[229, 236] | Incorrect interventions |
| Farah 2009[230] | Incorrect population |
| Farah 2009[231] | No relevant outcomes |
| Faraone 2007[236] | Incorrect intervention |
| Faraone 2009[232] | Review: references checked |
| Faraone 2009[234] | No usable outcomes |
| Faraone 2010[233] | Review: references checked |
| Faraone 2012[235] | Incorrect duration |
| Farmer 2015[237] | Incorrect interventions |
| Farmer 2016[238] | No useable outcomes |
| Fernandez-jaen 2013[239] | Incorrect study design |
| Findling 2007[248] | Incorrect duration |
| Findling 2008[241] | Not article |
| Findling 2009[250] | No relevant outcomes |
| Findling 2010[240] | No relevant outcomes |
| Findling 2010[245] | No relevant outcomes |
| Findling 2010[249] | Incorrect intervention |
| Findling 2013[244] | Incorrect interventions |
| Findling 2014[246] | Incorrect population |
| Fitzpatrick 1990[251] | Incorrect study design |
| Flapper 2008[252] | No relevant outcomes |
| Fortier 2013[254] | Inappropriate comparison |
| Fosi 2013[255] | Incorrect interventions |
| Foster 2007[256] | Incorrect interventions |
| Fox 2014[257] | No relevant outcomes |
| Fredriksen 2014[258] | No relevant outcomes |
| Froehlich 2011[260] | No usable outcomes |
| Froehlich 2014[259] | Incorrect duration |
| Fuentes 2013[261] | No relevant outcomes |
| Fung 2016[262] | Review: references checked |
| Gadow 2011[264] | Incorrect study design |
| Gadow 2012[269] | No relevant outcomes |
| Gadow 2016[263] | Incorrect population |
| Gallucci 2006[268] | Incorrect study design |
| Garfinkel 1983[270] | Incorrect duration |
| Garg 2013[271] | No relevant outcomes |
| Garg 2014[272] | Less than minimum duration |
| Garg 2015[273] | Less than minimum duration |
| Gau 2010[275] | Less than minimum duration |
| Gawrilow 2016[276] | Incorrect interventions |

| Study | Exclusion reason |
|---|---|
| Gehricke 2009[277] | Incorrect study design |
| Gehricke 2011[278] | Incorrect study design |
| Ghanizadeh 2012[281] | Incorrect intervention |
| Ghanizadeh 2013[282] | Incorrect interventions |
| Ghuman 2007[284] | Incorrect duration |
| Giblin 2011[285] | Less than minimum duration |
| Ginsberg 2011[286] | No useable outcomes |
| Ginsberg 2012[288] | No useable outcomes |
| Gittelman-klein 1976[289] | Inappropriate method of diagnosis |
| Goez 2012[290] | Incorrect duration |
| Gonzalez-Carpio Hernandez 2016[291] | Incorrect study design |
| Grant 2015[295] | Conference abstract |
| Green 2011[296] | Incorrect duration |
| Greenhill 2003[301] | Incorrect interventions |
| Greenhill 2006[300] | Wrong population |
| Grizenko 2010[303] | Incorrect duration |
| Grizenko 2012[304] | Incorrect duration |
| Grizenko 2013[302] | Incorrect duration |
| Groom 2013[306] | Incorrect duration |
| Guardiola 1999[307] | Not in English |
| Gunther 2010[308] | No useable outcomes |
| Guo 2013[309] | Conference abstract |
| Gustafsson 2010[310] | Incorrect interventions |
| Haas 2008[311] | No useable outcomes |
| Haghighat 2014[312] | Not article |
| Hammerness 2009 [315] | No relevant outcomes |
| Hammerness 2009[314] | Review: references checked |
| Hammerness 2013[313] | No useable outcomes |
| Handen 2000[316] | Less than mimnum duration |
| Handen 2008[317] | Less than mimnum duration |
| Handen 2011[318] | Incorrect study design |
| Hansen 2015[319] | Incorrect study design |
| Hardan 2005[320] | Incorrect study design |
| Harfterkamp 2013[321] | No useable outcomes |
| Harfterkamp 2015[324] | Post hoc. open label. |
| Hazell 2003[327] | Combination intervention |
| Hazell 2006[326] | Incorrect study design |
| Hazell 2009[325] | Incorrect study design |
| Heffner 2013[328] | No relevant outcomes |
| Hellwig-brida 2011[329] | Incorrect study design |
| Helseth 2015[330] | Incorrect study design |
| Heriot 2008[331] | Incorrect study design |
| Herring 2012[332] | Incorrect interventions |
| Hervas 2014[333] | Inappropriate method of diagnosis |
| Hester 2010[334] | Incorrect population |

| Study | Exclusion reason |
|---|---|
| Hilton 2013[335] | Incorrect population |
| Holden 2013[338] | Not guideline condition |
| Hong 2009[339] | Inappropriate comparison |
| Hong 2014[341] | Incorrect study design |
| Hong 2014[340] | Inappropriate comparison |
| Hosenbocus 2009[342] | Review: references checked |
| Howard 2015[343] | Incorrect interventions |
| Huizink 2009[344] | Incorrect interventions |
| Hurt 2011[345] | Incorrect population |
| Hurwitz 2012[346] | Systematic review: study designs inappropriate |
| Huss 2014[347] | Post hoc analysis |
| Huss 2014[348] | Incorrect population |
| Ialongo 1994[350] | Incorrect study design |
| Inglis 2016[351] | Protocol |
| Ironside 2010[352] | No relevant outcomes |
| Ishii-takahashi 2015[353] | Correction |
| Jacobi-polishook 2009[354] | No relevant outcomes |
| Jahromi 2009[356] | Incorrect duration |
| Jain 2013[358] | Systematic review: study designs inappropriate |
| Jans 2012[361] | Inappropriate intervention |
| Jaselskis 1992[362] | Incorrect population |
| Jasinski 2008[363] | No usable outcomes |
| Jasinski 2009[364] | No usable outcomes |
| Jerrell 2010[365] | No relevant outcomes |
| Jin 2013[366] | Incorrect interventions |
| Johnston 2014[367] | Incorrect interventions |
| Jordan 2012[368] | Incorrect study design |
| Joseph 2016[369] | No relevant outcomes |
| Jucaite 2014[370] | Incorrect interventions |
| Kamble 2015[372] | No relevant outcomes |
| Kandemir 2014[373] | Background information |
| Kay 2009[375] | Incorrect population |
| Keating 2011[376] | Not article |
| Kent 2013[378] | Incorrect population |
| Keulers 2007[379] | Incorrect population |
| Khodadust 2012[380] | Incorrect interventions |
| Kim 2009[381] | No relevant outcomes |
| King 2009[382] | Less than minimum duration |
| Koblan 2015[383] | Incorrect interventions |
| Kollins 2006[384] | Protocol only |
| Kollins 2009[385] | Incorrect duration |
| Kollins 2013[388] | Incorrect duration |
| Kollins 2014[386] | Incorrect comparison |
| Konstenius 2010[390] | Incorrect population |
| Konstenius 2013[391] | No useable outcomes |

| Study | Exclusion reason |
|---|---|
| Konstenius 2013[393] | No useable outcomes |
| Konstenius 2014[392] | Incorrect interventions |
| Krakowski 1965[396] | Inappropriate method of diagnosis |
| Kratochvil 2007[397] | Incorrect population |
| Kubas 2012[398] | No useable outcomes |
| Kupietz 1988[400] | Incorrect population |
| Lamberti 2016[401] | Incorrect population |
| Law 1999[402] | No usable outcomes |
| Leblanc 2005[403] | Incorrect interventions |
| Leddy 2009[404] | No relevant outcomes |
| Lee 2013[405] | Incorrect comparison |
| Lerer 1977[408] | No usable outcomes |
| Lerer 1979[407] | No usable outcomes |
| Leuchter 2014[409] | No relevant outcomes |
| Levin 2015[411] | Incorrect interventions |
| Li 2010[414] | Incorrect interventions |
| Li 2011[412] | Incorrect interventions |
| Li 2013[413] | Incorrect interventions |
| Lin 2014[415] | Incorrect interventions |
| Lin 2016[416] | No useable outcomes |
| Lin 2017[417] | No usable outcomes |
| Linares 2013[418] | No relevant outcomes |
| Lion-francois 2014[419] | Incorrect population |
| Liu 2011[420] | Commentary |
| Logemann 2013[421] | Incorrect duration |
| Loo 2016[422] | No useable outcomes |
| Lufi 2007[424] | No useable outcomes |
| Luman 2015[425] | Incorrect duration |
| Lyon 2010[426] | Incorrect study design |
| Lyon 2011[427] | Incorrect interventions |
| Malone 2009[428] | Incorrect study design |
| Manor 2013[429] | Incorrect interventions |
| Manor 2014[430] | Incorrect interventions |
| Manos 2009[431] | Inappropriate comparison |
| Marchant 2010[432] | No relevant outcomes |
| Marchant 2011[433] | No relevant outcomes |
| Marchant 2011[434] | Incorrect interventions |
| Martin 2007[436] | Incorrect duration |
| Martin 2014[437] | Incorrect duration |
| Martins 2004[438] | Inappropriate comparison |
| Mattes 1984[439] | Incorrect population |
| Mattos 2013[442] | No relevant outcomes |
| Mattos 2014[441] | References checked |
| Matza 2004[444] | Incorrect study design |
| Matza 2007[443] | Incorrect study design |

| Study | Exclusion reason |
|---|---|
| Mccarthy 2009[445] | No relevant outcomes |
| Mccarthy 2012[446] | Inappropriate comparison |
| McCracken 2016[447] | Incorrect study design |
| Mcgough 2006[448] | Incorrect duration |
| Mcgough 2012[449] | Incorrect study design |
| Mcinnes 2007[450] | Less than minimum duration |
| Mcrae-clark 2010[451] | Incorrect interventions |
| Meisel 2013[453] | Incorrect interventions |
| Merrill 2016[454] | No relevant outcomes |
| Michelson 2002[455] | Conference abstract |
| Michelson 2004[458] | Incorrect interventions |
| Mikami 2009[460] | No usable outcomes |
| Mikkelsen 1982[461] | Incorrect study design |
| Miller 2007[462] | Incorrect duration |
| Mohammadi 2012[465] | Incorrect interventions (combination) |
| Mohammadi 2015[464] | Incorrect interventions |
| Monuteaux 2007[467] | Incorrect interventions |
| Moorthy 2015[468] | Incorrect interventions |
| Morash-Conway 2016[469] | Incorrect study design |
| Moriyama 2013[470] | Review: references checked |
| Morrow 2012[471] | Inappropriate comparison |
| Moshe 2012[472] | Less than minimum duration |
| Muir 2010[473] | No primary research |
| Muniz 2008[474] | Incorrect duration |
| Murray 2011[475] | Incorrect population |
| Nandam 2011[478] | Incorrect population |
| Newcorn 2006[482] | Abstract |
| Newcorn 2010[484] | Incorrect study design |
| Newcorn 2016[480] | No useable outcomes |
| Ni 2013[486] | No relevant outcomes |
| Ni 2016[485] | Incorrect study design |
| Niederhofer 2012[487] | Incorrect interventions |
| Nunes 2013[488] | Incorrect interventions |
| Ogrim 2013[489] | Inappropriate comparison |
| Olsen 2012[490] | Incorrect interventions |
| Overtoom 2009[491] | Incorrect duration |
| Owen 2009[492] | Incorrect population (not ADHD) |
| Owens 2016[493] | Incorrect study design |
| Pagano 2008[494] | Incorrect study design |
| Parker 2013[496] | Review: references checked |
| Pataki 1993[497] | Inappropriate washout period |
| Pearson 2013[499] | Incorrect duration |
| Pelham 2011[501] | Less than minimum duration |
| Pelham 2014[500] | Open label dose comparison no washout |
| Perez-alvarez 2009[502] | Incorrect interventions |

| Study | Exclusion reason |
|---|---|
| Perez-alvarez 2009[502] | No relevant outcomes |
| Perrin 2008[503] | Incorrect study design |
| Peterson 2008[504] | Review: references checked |
| Philipsen 2014[505] | Protocol only |
| Philipsen 2015[506] | Incorrect interventions |
| Pierce 2010[507] | Incorrect study design |
| Pollak 2010[508] | Less than minimum duration. |
| Posey 2007[509] | Inappropriate washout period |
| Potter 2008[511] | Incorrect duration |
| Potter 2014[510] | Incorrect intervention |
| Powell 2015[512] | No relevant outcomes |
| Prada 2015[513] | Incorrect study design |
| Prasad 2007[515] | No relevant outcomes |
| Prasad 2009[514] | Incorrect study design |
| Prince 2000[516] | No relevant outcomes |
| Pringsheim 2011[517] | SR checked for references |
| Punja 2012[518] | Protocol |
| Ramtvedt 2013[520] | Incorrect study design |
| Ramtvedt 2014[519] | Incorrect study design |
| Ramtvedt 2014[521] | Incorrect study design |
| Rapoport 1974[522] | Inappropriate method of diagnosis |
| Rapport 2008[523] | Inappropriate washout period |
| Ray 2009[524] | Not guideline condition |
| Redman 2014[525] | Protocol |
| Reichow 2013[526] | SR checked for references |
| Research units on pediatric psychopharmacology autism 2005[528] | Incorrect duration |
| Reyes 2006[530] | Incorrect study design |
| Rezaei 2010[531] | Incorrect population |
| Richardson 1988[533] | Incorrect study design |
| Riggs 2011[534] | Incorrect interventions |
| Roesch 2013[536] | Less than minimum duration |
| Roesch 2013[537] | Incorrect population |
| Rubia 2009[541] | Incorrect study design |
| Rubia 2011[542] | Incorrect duration |
| Rubia 2011[543] | No relevant outcomes |
| Safavi 2016[544] | Incorrect study design |
| Sahin 2014[545] | Incorrect study design |
| Salehi 2010[546] | Incorrect interventions |
| Sallee 2009[548] | Incorrect duration |
| Sallee 2012[547] | Review (not systematic) |
| Sandler 2008[550] | Incorrect study design |
| Sandler 2010[551] | Inappropriate comparison |
| Santisteban 2014[552] | No relevant outcomes |
| Santosh 2006[553] | Incorrect study design |

| Study | Exclusion reason |
|---|---|
| Say 2015[554] | Incorrect study design |
| Sayer 2016[555] | Incorrect study design |
| Schachar 1997[559] | Incorrect interventions |
| Schachar 2008[558] | Less than minimum duration |
| Scheffler 2009[560] | No relevant outcomes |
| Schrantee 2016[561] | Incorrect population |
| Schulz 2010[563] | Less than minimum duration. |
| Schulz 2010[562] | Inappropriate comparison |
| Sciberras 2011[564] | Incorrect interventions |
| Shakibaei 2015[565] | Incorrect interventions |
| Shang 2015[566] | No relevant outcomes |
| Shang 2016[567] | Incorrect study design |
| Sharp 1999[568] | Incorrect study design |
| Shaywitz 2016[569] | Incorrect study design |
| Shea 2004[570] | Incorrect population (not ADHD) |
| Short 2004[572] | Incorrect study design |
| Shytle 2002[573] | Less than minimum duration |
| Sikirica 2013[574] | References checked |
| Sikirica 2013[575] | No relevant outcomes |
| Silva 2008[578] | Less than minimum duration |
| Silva 2008[576] | Less than minimum duration |
| Silva 2013[577] | Inappropriate comparison |
| Sinzig 2007[581] | No useable outcomes |
| Slama 2015[582] | Incorrect duration |
| Snyder 2002[583] | Incorrect interventions |
| So 2008[584] | Incorrect interventions |
| Sobanski 2008[586] | Wrong interventions |
| Sobanski 2012[585] | No relevant outcomes |
| Socanski 2015[587] | No relevant outcomes |
| Solanto 2009[588] | Crossover no washout. Inappropriate washout period |
| Sonuga-barke 2007[590] | Incorrect duration |
| Sonuga-barke 2008[592] | No usable outcomes |
| Sonuga-barke 2009[589] | Crossover with no washout |
| Sonuga-barke 2009[591] | Incorrect duration |
| Spencer 2008[597] | Incorrect interventions |
| Spencer 2008[598] | Incorrect intervention |
| Spencer 2009[593] | Incorrect duration |
| Spencer 2011[599] | Incorrect population |
| Stein 2011[602] | Less than minimum duration |
| Steiner 2014[603] | Incorrect interventions |
| Steinhausen 2014[604] | Wrong comparison |
| Stocks 2012[605] | Incorrect interventions |
| Strand 2012[606] | No relevant outcomes |
| Stray 2009[607] | No relevant outcomes |
| Su 2016[608] | Incorrect study design |

| Study | Exclusion reason |
|---|---|
| Suehs 2015[609] | No relevant outcomes |
| Sung 2010[610] | Review: references checked |
| Surman 2010[611] | Incorrect interventions |
| Swearingen 2007[616] | Incorrect population |
| Szobot 2008[617] | No useable outcomes |
| Tamm 2007[621] | No relevant outcomes |
| Tamm 2012[620] | Inappropriate comparison |
| Taragin 2013[622] | Incorrect study design |
| Taylor 2001[624] | Incorrect study design |
| Tebartz van Elst 2016[625] | Incorrect study design |
| Tehrani-doost 2008[626] | Inappropriate comparison. Less than minimum duration. Open label |
| Tellechea 1991[627] | Incorrect population |
| Ter-stepanian 2010[628] | Incorrect duration |
| The MTA Cooperative Group 1999[1] | Inappropriate interventions |
| Thomson 2009[629] | Systematic review checked for references |
| Thomson 2009[630] | Systematic review is not relevant to review question or unclear PICO |
| Thurstone 2010[631] | Incorrect interventions (combination) |
| Torgersen 2012[632] | No relevant outcomes |
| Torrioli 2008[633] | Incorrect interventions |
| Tucha 2011[637] | No relevant outcomes |
| Upadhyaya 2013[638] | Incorrect population |
| Upadhyaya 2015[639] | No relevant outcomes |
| Valdizan-uson 2013-2[640] | No relevant outcomes |
| Van der donk 2013[641] | Incorrect interventions |
| Van der kolk 2014[643] | Incorrect study design |
| Van der meer 2013[644] | No relevant outcomes |
| Van der oord 2007[646] | Incorrect interventions |
| Van der oord 2008[645] | Review: references checked |
| Verster 2008[647] | No usable outcomes |
| Verster 2010[648] | Incorrect population |
| Warden 2012[650] | Combination. No relevant outcomes |
| Waxmonsky 2008[651] | Incorrect duration |
| Waxmonsky 2011[652] | Dose comparison |
| Waxmonsky 2014[653] | Incorrect population |
| Weber 2008[654] | Incorrect interventions |
| Wehmeier 2007[656] | No relevant outcomes |
| Weisler 2009[660] | No usable outcomes |
| Weisler 2012[661] | Incorrect interventions |
| Weiss 2004[665] | Incorrect interventions |
| Weiss 2006[662] | Incorrect interventions |
| Weiss 2012[663] | Incorrect interventions |
| Wender 2011[666] | No useable outcomes |
| Werry 1980[667] | Inappropriate method of diagnosis |

| Study | Exclusion reason |
|---|---|
| Westover 2013[668] | No relevant outcomes |
| Wigal 2004[670] | Inappropriate intervention |
| Wigal 2005[677] | Inappropriate intervention |
| Wigal 2006[684] | No results reported |
| Wigal 2010[671] | Conference abstract |
| Wigal 2010[675] | No relevant outcomes |
| Wigal 2010[676] | No usable outcomes |
| Wigal 2011[680] | Less than minimum duration |
| Wigal 2011[674] | Less than minimum duration |
| Wigal 2012[681] | Less than minimum duration. Inappropriate comparison |
| Wigal 2013[672] | Less than minimum duration |
| Wigal 2014[673] | Incorrect population |
| Wigal 2015[678] | Less than minimum duration |
| Wigal 2016[679] | Less than minimum duration |
| Wilens 2006[690] | Incorrect population |
| Wilens 2008[687] | Incorrect intervention (wrong drugs) |
| Wilens 2008[689] | Inappropriate intervention |
| Wilens 2010[688] | Incorrect interventions |
| Wilens 2011[685] | No relevant outcomes |
| Williams 2010[692] | Incorrect study design |
| Williamson 2014[693] | Incorrect study design |
| Winhusen 2010[695] | Inappropriate comparison |
| Winhusen 2011[694] | No outcomes of interest reported |
| Witt 2008[697] | No relevant outcomes |
| Wong 2012[699] | No usable outcomes |
| Yang 2012[700] | Incorrect study design |
| Yang 2015[701] | Incorrect interventions |
| Yellin am 1978[702] | Inappropriate method of diagnosis |
| Yepes 1977[703] | Inappropriate method of diagnosis |
| Yildiz 2011[704] | No relevant outcomes |
| Yildiz oc 2007[705] | No relevant outcomes |
| Yilmaz 2013[706] | No relevant outcomes |
| Young 2014[707] | No useable outcomes |
| Yucel 2014 [709] | No relevant outcomes |
| Zeni 2009[711] | Incorrect design |
| Zheng 2015[712] | Incorrect design |
| Zoega 2012[713] | No relevant outcomes |
| Zuvekas 2012[714] | No relevant outcomes |

## I.2 Excluded health economic studies

None.