[Intervention A] versus Placebo for ADHD

Review information

Authors

[Empty name][1], Birgitte Lind Amdisen[1]

[1][Empty affiliation]

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What's new

Date / Event	Description

History

Date / Event	Description

Characteristics of studies

Characteristics of included studies

Adler 2009

Methods	This was a randomized, placebo-controlled, double-blind, parallel-group, dose-escalation study conducted in the United States at 27 investigative sites (CR011560). The study consisted of 8 visits. Eligible subjects were randomly assigned in a 1:1 ratio to receive either OROS methylphenidate or placebo. Subjects were randomized using a computer-generated randomization schedule stratified by investigator site with a block size of 4. To randomize subjects, a qualified study staff used an interactive voice recognition system and entered the subject's date of birth, sex, and responses to selected eligibility questions. The system first verified that each subject randomized was unique and then, following the randomization schedule, identified the unique kit number of the dosing

	package that the study staff was to dispense to the subject at the baseline visit. Each investigator received an allotment of double-blind medication before the study started, and each subject received overencapsulated tablets that appeared identical to the treatment of all other subjects at the beginning of the study. The subjects returned any remaining study medication and received a new supply at each of the 5 dose-titration visits regardless of their randomized treatment group.
Participants	The subjects were adults between 18 to 65 years of age (inclusive) with ADHD and weighed a minimum of 100 lb (45.4 kg). At subject screening, the diagnosis of ADHD inattentive, hyperactive/impulsive, or combined type as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria was established through clinical evaluation by the investigator. The subject must have described a chronic course of ADHD symptoms from childhood to adulthood, have had an AISRS score of 24 or greater, and have had a global assessment of functioning score of between 41 and 60 (inclusive), indicating moderate or serious symptoms (according to DSM-IV criteria). Previous formal diagnosis of and/or treatment of ADHD were not required. The Hamilton Anxiety Rating Scale (HAM-A) and the Hamilton Depression Rating Scale (HAM-D) were administered to assess possible symptoms of anxiety and depression, and subjects with symptoms of marked anxiety, tension, agitation, or a HAM-A score of 21 or greater or with symptoms of moderate severity of depression ratings using a HAM-D score of 17 or higher were excluded. The patients who met the DSMIV criteria for depressive or anxiety disorders were excluded from the study, even if their HAM scores did not reach these cutoffs. Known nonresponders to methylphenidate were also excluded, as were subjects with a history of allergy to methylphenidate; any coexisting medical condition or taking any medication that was likely to interfere with the safe administration of methylphenidate; known or suspected structural cardiac abnormality as assessed by history, physical examination, or electrocardiogram (ECG); diagnosis or family history of Tourette syndrome or motor or verbal tics; or history of seizure disorder, uncontrolled hyperthyroidism, or hypothyroidism. Patients with comorbid psychiatric diagnosis per DSM-IV criteria of bipolar disorder, cyclothymic disorder, schizophrenia, pervasive developmental disorder, severe obsessive-compulsive disorders, or any other diagnosis that in the judgment of the investigator could have deemed the subject to be inappropriate for the study were excluded. Subjects with a history of drug or alcohol abuse within the past 6 months or with suicidal ideation or behavior during the past year were also excluded, as were subjects with a current or history of an eating disorder for the last 3 years. Patients taking antipsychotic medication, bupropion, modafinil, clonidine or other alpha-2 adrenergic receptor agonists, tricyclic antidepressants, theophylline, coumarin anticoagulants, anticonvulsants, monoamine oxidase inhibitors, guanethidine, or a serotonin norepinephrine reuptake inhibitor (eg, venlafaxine and duloxetine) were excluded from the study. Because serotonin reuptake inhibitors, downward adjustments to these drugs were permitted, but patients taking a selective serotonin reuptake inhibitor (eg, fluoxetine, paroxetine, sertraline, citalopram, or escitalopram) who were not stable on their medication for at least 30 days before the screening visit were excluded. Subjects were to continue their usual necessary medical therapies, within the inclusion and exclusion criteria, with no medically unnecessary changes in their diet, pattern of physical activity, or lifestyle; such changes were monitored through clinical interview. All medications taken within 30 days before the screening visit were

	recorded as a concomitant medication. During the study, all new concomitant medications were listed. Subjects being treated for ADHD at screening were washed out from all ADHD medication for 7 to 14 days before beginning the study. At the baseline visit, the diagnosis of ADHD was confirmed by the Adult ADHD Clinical Diagnostic Scale, and the eligible subject and the investigator completed the rating scales assessing the subject's behavior while taking no medication for ADHD.
Interventions	All subjects initiated treatment with 36 mg of study medication and continued with incremental increases of 18 mg every 7 days (+2 days) until an individualized dose was achieved (36 mg, 54 mg, 72 mg, 90 mg, or 108 mg). An individualized dose (or minimal effective dose) was achieved when AISRS decreased by 30% from baseline and a CGI-I rating of 1 (verymuch improved) or 2 (much improved) was achieved or titration to the maximum dose of 108 mg was reached. Subjects could have their dose reduced by 18 mg once during the study if a limiting adverse event occurred, but once reduced, the dose could not be changed again for the duration of the study. Downward dose titration was also required for resting a heart rate greater than 100 beats per minute (bpm), a systolic blood pressure greater than 140 mm Hg, or a diastolic blood pressure greater than 90 mm Hg. Subjects unable to tolerate the initial dose of 36 mg were discontinued from the study. Once an individualized dose was achieved, subjects remained on that dose for the remaining duration of the 5-week titration period and for the 2 weeks before the final visit/2-week efficacy assessment visit. Drug holidays and additional methylphenidate beyond that provided by the investigator were not permitted. Subjects who completed the study were expected to receive study medication for 49 + 2 days.
Outcomes	ADHD symptoms, functioning, adverse events
Notes	Ref ID 1621

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Used date of birth and sex to randomise
Allocation concealment (selection bias)	Low risk	Computer 'identified the unique kit number of the dosing package that the study staff was to dispense to the subject at the baseline visit'.
Blinding of participants and personnel (performance bias)	Low risk	Each investigator received an allotment of double-blind medication before the study started, and each subject received overencapsulated tablets that appeared identical to the treatment of all other subjects at the beginning of the study.'
Blinding of outcome assessment (detection bias)	Low risk	Clinican assessors not described.
Incomplete outcome data (attrition bias)	High risk	158/226 patients accounted for

Selective reporting (reporting bias)	Low risk	Outcomes reported as in protocol http://clinicaltrials.gov/show/NCT00326391
Other bias	High risk	LOCF reporting used for side effects and cardiovascular results, None responders to MPH excluded

Biederman 2006

Methods	This was a double-blind, randomized, 6-week, placebo-controlled, parallel-design study of OROS MPH. Patients were randomized to OROS MPH or placebo at a ratio of 1:1.
Participants	Subjects were outpatient adults with ADHD aged 19–60 years. To be included, subjects had to satisfy full diagnostic criteria for DSM-IV ADHD on the basis of clinical assessment andfor anxiety disorders and depression who were receiving a stable medication regimen for at least 3 months and who had a disorder-specific Clinical Global Impression Scale (CGI)-Severity score of 3 or less (mildly ill) were not excluded. Thus, subjects receiving stable doses of non–monoamine oxidase inhibitor antidepressants or benzodiazepines for more than 3 months were eligible for this study. We excluded potential subjects if they had clinically significant chronic medical conditions, abnormal baseline laboratory values, intelligence quotient less than 80, delirium, dementia, or amnesic disorders, other clinically unstable psychiatric conditions (i.e., bipolar disorder, psychosis, suicidality), drug or alcohol abuse or dependence within the 6 months preceding the study, or a previous adequate trial of MPH. We also excluded pregnant or nursing women. confirmation by structured diagnostic interview. Subjects treated
Interventions	Medication was titrated to optimal response (a maximum daily dose of 1.3 mg/kg; initial dose of 36 mg). During titration to optimal response, dose was increased by 36 mg/day but only for subjects who failed to attain an a priori definition of improvement (CGI-Improvement of 1 or 2 or a reduction in the Adult ADHD Investigator System Report Scale [AISRS] score greater than 30%) and who did not experience adverse effects. All doses of OROS MPH and placebo were delivered in identical-appearing tablets.
Outcomes	ADHD symptoms, depression, anxiety, functionin?, adverse events
Notes	Ref ID 1622

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described 'Patients were ran- domized to OROS MPH or placebo at a ratio of 1:1'
Allocation concealment (selection bias)	Unclear risk	Not described 'Patients were ran- domized to OROS MPH or placebo at a ratio of 1:1'
Blinding of participants and personnel (performance bias)	Low risk	Not described 'Patients were ran- domized to OROS MPH or placebo at a ratio of 1:1'
Blinding of outcome assessment (detection bias)	Low risk	not described

Incomplete outcome data (attrition bias)	Low risk	120/149 patients were accounted for
Selective reporting (reporting bias)	High risk	DSM IV ADHD-compulsive, CGI-S & GAF scores not reported
Other bias	Low risk	No other bias detected

Biederman 2010

Methods	Phase 1 was a double-blind, randomized, 6 week, placebo controlled, parallel design study of OROS-MPH. Patients were randomized to OROS-MPH or placebo at a ratio of 1:1.
Participants	Subjects were outpatient adults with ADHD between 19 and 60 years of age. To be included, subjects had to satisfy full diagnostic criteria of ADHD based on DSM-IV with childhoodonset and persistent symptoms based on clinical assessment and confirmed by structured diagnostic interview and an Adult ADHD Investigator Symptom Report Scale (AISRS) score of 24 or higher. Subjects treated for anxiety disorders and depression who were on a stable medication regimen for at least 3 months and who had a disorder-specific Clinical Global Impression (CGI)-Severity score of 3 or lower (mildly ill) were included. We excluded potential subjects if they had clinically significant chronic medical conditions, abnormal baseline laboratory values, IQ of less than 80, delirium, dementia, or amnestic disorders, other clinically unstable psychiatric conditions (ie, bipolar disorder, psychosis, suicidality), drug or alcohol abuse or dependence within the 6 months preceding the study, or a previous adequate trial of MPH. We also excluded pregnant or breast-feeding females.
Interventions	Medication was titrated to optimal response (a maximum daily dosage of 1.3 mg/kg; initial dose of 36 mg). During titration to optimal response, dosage was increased by 36 mg/d but only for subjects who failed to attain an a priori definition of improvement (CGI-I of 1 or 2 or a reduction in the AISRS score of larger than 30%) and who did not experience adverse effects.
Outcomes	ADHD symptoms, Anxiety, Depression, Adverse events
Notes	Ref ID 1652

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	randomizid 1:1 not futher described
Allocation concealment (selection bias)	Low risk	Medications were administrered by the reseach phamacy at the Massachusetts general Hospital in identical tablets
Blinding of participants and personnel (performance bias)	Low risk	Double blind
Blinding of outcome assessment (detection bias)	Low risk	Double blind

Incomplete outcome data (attrition bias)	High risk	Drop out rate described Only 4 dropout out of 227
Selective reporting (reporting bias)	Low risk	All outcome reported
Other bias	High risk	Only responders to MPH in earlier 6 week phase

Bouffard 2003

Methods	The trial was designed as a double-blind crossover comparison of 2 dosages of methylphenidate (10 mg 3 times daily and 15 mg 3 times daily) to each other and to equivalent dosages of placebo. The placebo was a commercially available sugar pill. Each dosage was given for 2 weeks. Subjects were randomly assigned to start either methylphenidate or placebo. We gave the hospital pharmacy a numbered list indicating a randomly chosen (from a hat) order of medication to start first (either methylphenidate or placebo) and assigned each subject a number. Subjects gave their number to the pharmacist when picking up their prescriptions.
Participants	Subjects had to meet the following inclusion-exclusion criteria to participate in the study: 1. DSM-IV criteria for ADHD 2. 1.5 or more on at least 1ADHDself-report questionnaire (either Conners'Adult ADHD Rating Scale [12] or the Adult ADHD Problem Behaviours [13] scale) 3. Estimated IQ of 80 or above on abbreviated WAIS-R 4. No psychiatric conditions that better accounted for their current symptoms or required other treatment 5. No substance abuse in the preceding 6 months 6. No medical condition contraindicating stimulants (that is, hypertension or cardiac disease)
Interventions	Medication was started with a 3-day lead-in of increasing dosages, as follows: day 1, 5 mg 3 times daily; day 2, 10 mg 3 times daily; day 3, 15 mg 3 times daily. All subjects were asked to call in or fax a side effect scale for each day of the lead-in. If no prohibitive side effects were found, the subjects resumed the lower dosage (10 mg 3 times daily) and returned to the clinic after 2 weeks for a profile, focused physical exam, self-reported ADHD symptom profile, and objective testing on computers). We requested subjects to take their medication 1 hour before testing to ensure a satisfactory level of medication during testing. The dosage was increased to 15 mg 3 times daily for 2 subsequent weeks, after which we asked subjects to return for a reevaluation similar to that undertaken after the first 2 weeks. At the end of this 4-week period, each subject had a minimum 5-day washout. The sequence starting with the lead-in was then repeated with the second "medication" (either methylphenidate or placebo).
Outcomes	ADHD symptoms, depression, anxiety, heat rate, blood pressure, weigth, AE
Notes	Ref ID 1623

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Numbers chosen from a hat
Allocation concealment (selection bias)	Low risk	Centrally allocated by pharmacist
Blinding of participants and personnel (performance bias)	Unclear risk	Unclear if commercially available sugar pill was identical in appearance, taste, etc
Blinding of outcome assessment (detection bias)	Low risk	Not stated
Incomplete outcome data (attrition bias)	Low risk	30/38 patients completed the trial
Selective reporting (reporting bias)	High risk	Some Medication & Placebo 1 results are not reported
Other bias	Unclear risk	Unclear if half of each crossover intervention's results can be meaningfully merged like the study has done.

Carpentier 2005

Methods	A small-scale pilot study, double-blind, placebo-controlled, multiple crossover design was used that lasted 8 weeks (four treatment phases of 2 weeks each). Each patient completed two phases of placebo (A) and two phases of active medication (B). They were randomised independently by a clinical pharmacologist to follow the A-B-A-B or B-A-B-A schedule. Owing to study limitations, there was no chance to titrate the medication dosage for each participant. All the patients were put on a fixed dosage schedule of three doses a day.To our knowledge, this is the first European study that compared methylphenidate to placebo in a sample of adult substance abusers diagnosed with ADHD.
Participants	Twenty-five participants were recruited from a group of in-patients at an open addiction treatment facility; they remained on clinical rehabilitation treatment throughout the study. A positive diagnosis of ADHD was the primary inclusion criterion; newly diagnosed patients, as well as patients with a negative therapeutic response to alternative medication were eligible for participation. As the study aimed to reflect clinical practice, psychiatric comorbidity was not a reason for exclusion, unless its severity prevented compliance with the requirements of the trial or necessitated urgent treatment. Participants had to remain abstinent for the total duration of the study: if detoxification was necessary, the study was started 3 weeks at the earliest after achieving abstinence. Participants had to stop all psychotropic medication before entering the trial.
Interventions	All the patients were put on a fixed dosage schedule of three doses a day (see Table 1). The maximum daily dose for all the participants was 45 mg MPH. This design enabled us not only to compare the group results of MPH and placebo, but also to obtain a clear result regarding the effectiveness of the trial medication

	in each individual. As an indication of robust effectiveness, a positive response was defined as improvement of at least 30% on all three treatment scales. The nursing staff monitored medication compliance. To check for abstinence (e.g. during weekend leave), urine samples were tested weekly for all the major drugs of abuse.
Outcomes	ADHD symptoms, functioning (CGI)
Notes	Ref ID 1624

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Randomized indepently by a clinical pharmacologist to follow the A-B-AB or B-A-B-A and medication was carried out by the clinical psarmacologist
Blinding of participants and personnel (performance bias)	Low risk	Double blinded patients
Blinding of outcome assessment (detection bias)	Unclear risk	Not descibed
Incomplete outcome data (attrition bias)	Low risk	No differential attrition
Selective reporting (reporting bias)	High risk	Harms not specified though significantly more occured in intervention arm
Other bias	Low risk	None detected

Casas 2013

Methods	LAMDA-II (EudraCT #: 2007-002111-82) was a double-blind, randomized, placebo-controlled, fixeddose study conducted at 42 European sites between February 2008 and April 2009. After up to 2 weeks ' screening to enable safe tapering and discontinuation of disallowed medications (4 weeks for monoamine oxidase inhibitors), eligible subjects were randomly allocated (1:1:1) to OROS MPH 54 or 72 mg/day, or matching placebo. Randomization was based on a computer-generated scheme prepared by the sponsor, balanced by using permuted blocks of treatments and stratifi ed by study centre. Based on this scheme, study drug was packaged for each subject. Medication kit numbers were pre-printed on drug labels and assigned as subjects were randomly assigned to treatment. Treatment codes were obtained from a central interactive voice response system giving a medication kit number for the drug to which the subject had been assigned.
Participants	Eligible subjects were adults (18 – 65 years) with ADHD according to the criteria described in the Diagnostic and Statistical Manual for Mental Disorders 4th Edition Text Revision (DSM-IV-TR) (Ameri can Psychiatric Association 2000), confirmed using Conners ' Adult ADHD Diagnostic Interview Part II for DSM - IV (Conners et al. 1999). To be eligible, subjects had to score 24 on the 18 DSM-IV

	items measured by the investigator-rated Conners Adult ADHD Rating Scale – Screening Version (CAARS-O:SV) (Conners et al. 1999). The Structured Clinical Interview for DSM-IV Axis I Disorders was used to evaluate the presence of comorbidities and exclude other disorders (First et al. 1994); ADHD was not diagnosed if the symptoms were better accounted for by another psychiatric (e.g., mood, anxiety, psychotic or personality) disorder. Women of child-bearing potential had to use appropriate contraception during the study. Key exclusion criteria included known nonresponse to MPH; any clinically unstable psychiatric condition; family history of schizophrenia or affective psychosis; autism, Asperger ' s syndrome, eating disorder, motor tics or history (including family history) of Tourette ' s syndrome; substance use disorder (not including caffeine or nicotine dependence), hyperthyroidism, myocardial infarction or stroke 6 months before screening; history of seizures, glaucoma or uncontrolled hypertension; and angina pectoris or cardiac arrhythmias. Women who were pregnant or breastfeeding were also excluded.
Interventions	MPH started at 36mg and from day 8 randomly assigned dose for 12 weeks 54 or 72mg fixed doses. Subjects randomly assigned to placebo received placebo for 13 weeks. A post-study visit was conducted 1 week after the last dose of study medication. At baseline, efficacy and safety measures were evaluated on the day of randomization (1 day before the fi rst study dose). Medication adherence was evaluated by subjects returning all used and unused blister containers to the study centre
Outcomes	ADHD symptoms, QoL, Functioning, Adeverse events
Notes	Ref ID 1658

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated scheme prepared by the sponser
Allocation concealment (selection bias)	Low risk	Study drug was packaged for each subject. Codes from a central interactive voice response system giving amedication kit number
Blinding of participants and personnel (performance bias)	Low risk	Double blinding
Blinding of outcome assessment (detection bias)	Unclear risk	Double blinding
Incomplete outcome data (attrition bias)	High risk	Drop out rate different i PBO and higher in MPH due to AE
Selective reporting (reporting bias)	Low risk	all data reported
Other bias	High risk	exclusion criteria was nown non-responders to MPH

Ginsberg 2012

Methods	Randomized controlled trial. The OROS methylphenidate was delivered at a daily dose of 72 mg compared with placebo over a 5-week period, followed by an open-label extension with OROS methylphenidate delivered at a flexible dosage of up to 1.3 mg/kg daily over a 47-week period. The aim was to recruit 30 eligible participants with established ADHD to the randomised clinical trial (RCT): participants were initially selected on the basis of the ADHD questionnaires, with diagnosis subsequently confirmed in comprehensive assessments by experienced board-certified psychiatrists and clinical psychologists. Participants were randomly assigned in equal numbers to either the placebo or the OROS methylphenidate group according to a parallel-group design. The pharmacy laboratory assigned participants to the two study groups using a random number table prior to preparing and dispensing the study drug according to the study protocol. The random number table was stored in the pharmacy department and was concealed from study staff and participants until completion of the study. The placebo and methylphenidate capsules and packaging were identical in appearance and were coded with a unique randomisation number.
Participants	Eligible participants were adult male prison inmates, aged 21–61 years, with ADHD according to DSM-IV criteria.2 All inmates were hosted at Norrta¨lje Prison, a high-security prison outside Stockholm, Sweden, for long-term, adult male inmates, typically convicted of violent or drug-related crimes. The initial screening survey and diagnostic assessments have been previously reported. Briefly, inmates hosted at Norrta¨lje Prison between December 2006 and April 2009 were approached for screening for both childhood and adulthood ADHD by self-reported questionnaires. All inmates were approached except those deemed too mentally unstable and those to be deported from Sweden after serving their sentence. To enter the trial, participants had to have confirmed ADHD in accordance with DSM-IV and to agree not to behave violently during the study. Participants with comorbid disorders such as autism-spectrum disorder, anxiety and depression could take part if they were considered to be stable at baseline. Previous drugelicited episodes of psychosis were not a cause for exclusion, other than chronic psychoses. Concurrent medication not interfering with methylphenidate was permitted for treating comorbid disorders, as long as doses were stable for at least 1 month at baseline. Medications interfering with methylphenidate had to be tapered off before the baseline visit took place. Participants were excluded if they were known to be non- responsive or intolerant to methylphenidate, or intolerant to lactose. In addition, participants were excluded if they showed evidence of substance misuse up to 3 months before baseline, assessed in urine samples. Intellectual disability, epilepsy, glaucoma, uncontrolled hypertension, angina pectoris, cardiac arrhythmias, cardiac abnormality or a family history of serious cardiac illnesses were exclusion criteria, but hepatitis C without liver insufficiency did not preclude inclusion.
Interventions	The study drug was titrated from 36 mg/day for 4 days to 54 mg/day for 3 days and then to 72 mg/day for the remaining 4 weeks. All participants completing the 5-week RCT were eligible to enter the 47-week open-label extension, starting the day after completion of the 5-week RCT. During the open-label extension, methylphenidate was titrated from 36 mg/day to determine the optimal response and tolerability, but not exceeding 1.3 mg/kg daily. In case of adverse events,

	downward titration was allowed, followed by upward titration once the participant had recovered. In addition to medication, all participants received personal psychosocial treatment as part of prison routine, including school activities according to the Swedish curriculum and cognitive programmes addressing addiction, criminality, aggression and social skills. The psychosocial treatment did not specifically address ADHD.
Outcomes	ADHD symptoms
Notes	Ref ID 1673

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	”The pharmacy laboratory assigned participants to the two study groups using a random number table prior to preparing and dispensing the study drug according to the study protocol.”
Allocation concealment (selection bias)	Low risk	”The random number table was stored in the pharmacy department and was concealed from study staff and participants until completion of the study.”
Blinding of participants and personnel (performance bias)	Low risk	” The placebo and methylphenidate capsules and packaging were identical in appearance and were coded with a unique randomisation number.”
Blinding of outcome assessment (detection bias)	Low risk	”Both study staff and participants were masked to assignment during the RCT.”
Incomplete outcome data (attrition bias)	Low risk	All completed 5 weeks
Selective reporting (reporting bias)	Low risk	None detected
Other bias	High risk	Known non-responders excluded

Ginsberg 2012 A

Methods	This study (ClinicalTrials.gov:NCT00482313) was a randomized, double-blind, placebo-controlled parallel-group 5-week trial, followed by a 47-week open-label extension. Participants were randomly assigned to placebo or OROS-methylphenidate at a ratio of 1:1.
Participants	Adult male prison inmates confirmed with ADHD took part in the present study. All participants were hosted at Norrta¨lje Prison, located outside Stockholm, Sweden. This high-security prison hosts primarily long-term, adult male inmates convicted of drug-related or violent crimes. Participants randomized to the clinical trial had to be established with ADHD in consistence with DSM-IV and to agree not to behave violently during the trial. Coexisting disorders, such as anxiety, depression and autism-spectrum disorder, were allowed. Previous drug-elicited episodes of psychosis or psychopathy as defined by Hare (total sumscore >30) were not a cause for exclusion. Concurrent medication not interfering with methylphenidate was allowed for treating coexisting disorders, as

	long as doses were kept stable for at least 4 weeks at baseline. Pharmacological treatment interfering with methylphenidate had to be tapered off in advance to the baseline visit. Also, participants had to be confirmed without substance abuse during the preceding 3 months and should not fulfil the diagnostic criteria for mental retardation or for any serious medical illness. However, participants with hepatitis C without liver insufficiency could take part in the trial.
Interventions	The study drug was titrated from 36 mg daily for 4 days to 54 mg daily for 3 days and then to 72 mg daily for the remaining 4 weeks. All participants that completed the 5-week trial were eligible to enter the 47-week open-label extension, starting the day after completion of the 5-week phase. During the open-label extension, OROS-methylphenidate was individually titrated from 36 mg daily to an optimal dose, on the basis of response and tolerability, with a maximum daily dose of 1.3 mg/kg body weight. In case of intolerable adverse events, lower doses were administered, the adverse event. In addition to studymedication, participants were, as part of regular prison routines, provided educational activities and accredited treatment programmes. However, these psychosocial interventions did not specifically address symptoms and associated impairments of ADHD.
Outcomes	QoL
Notes	Ref ID 1672

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	participants were randomly assigned to placebo or MPG at a ratio of 1:1
Allocation concealment (selection bias)	High risk	not described
Blinding of participants and personnel (performance bias)	High risk	open label follow up, med individuel titrering i follow up delen
Blinding of outcome assessment (detection bias)	High risk	not described
Incomplete outcome data (attrition bias)	Low risk	? rater har intet skrevet
Selective reporting (reporting bias)	Low risk	None detected
Other bias	High risk	Known non-responders excluded

Gualtieri 1985

Methods	Randomized double-blind controlled cross-over study
Participants	Patients had Attention deficit disorder with hyperactivity residual type DSM-III. Met childhood and adult criteria aged 18-38.
Interventions	MPH (0.3 mg/kg)
Outcomes	ADHD symptoms, anxiety
Notes	Ref ID 1625

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Low risk	Double blinded
Blinding of outcome assessment (detection bias)	High risk	All patients were able to break the randomization code
Incomplete outcome data (attrition bias)	Low risk	None detected
Selective reporting (reporting bias)	Low risk	None detected
Other bias	High risk	Population poorly described (in and exclusion criteria) and very short follow-up period

Huss 2014

Methods	This was a 40-week, double-blind, randomized, placebo-controlled, international multicenter efficacy and safety study of MPH-LA in the treatment of adult patients with ADHD conducted between November 24, 2010 and August 7, 2012 in 67 centers including nine countries. The study consisted of the following three treatment phases (Fig. 1): (1) The doubleblind dose-confirmation phase was a 9-week, double-blind, randomized, placebo-controlled, parallel-group period consisting of a 3-week titration stage and a 6-week fixed-dose stage to confirm the effective dose range of MPH-LA. Randomization was performed at the beginning of the double-blind dose-confirmation phase and the double-blind maintenance of effect phase upon fulfillment of the inclusion/exclusion criteria mentioned above. Patients were randomized to one of the treatment arms using a validated Interactive Voice/Web Response System (IVRS/ IWRS). A unique, confidential randomization number was assigned to each patient and IVRS/ IWRS allocated medication accordingly, as assigned, throughout the respective treatment periods. An unbiased, confidential patient randomization list was produced by the IVRS/ IWRS provider using a validated system that automated the random assignment of patient numbers to randomization numbers. A separate medication randomization list was produced under the responsibility of Novartis Drug Supply Management using a validated system that automated the random assignment of medication numbers to medication packs containing each of the study drugs. The randomization scheme was reviewed and approved by a member of the Biostatistics Quality Assurance Group. All sites and personnel for clinical, medical, statistical, data management and monitoring were blinded, and randomization data were kept strictly confidential until the time of un-blinding after the conclusion of the study. The identity of the treatments has been concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, taste, and odor, in line with Consort

	guidelines.
Participants	Adult patients (18–60 years) with diagnosis of ADHD, all types, with a confirmed childhood onset according to DSM-IV diagnostic criteria and a DSM-IV ADHD RS total score of C30 at screening and baseline were included in the study. Exclusion criteria were: pre-existing cardiovascular or cerebrovascular diseases, or any other co-morbid psychiatric disorder requiring medical intervention/therapy or that might interfere with the study conduct at the time of enrollment; patients demonstrating a C30% improvement in DSM-IV ADHD RS total score at baseline relative to that at screening were also excluded from this study. Any psychological or behavioral therapies for the treatment of ADHD were discontinued at least 1 month prior to the screening visit. Patients who initiated these therapies within 3 months prior to screening visit for reasons other than ADHD were excluded from the trial. Additionally, patients with either hypersensitivity or history of poor response or intolerance to stimulants as per the investigator's judgment were excluded from this study. Patients with use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment (whichever was longer), were excluded from the study. In patients receiving any psychotropic medications the minimum discontinuation period varied according to drug class as follows: 1 week prior to the screening visit for stimulants including MPH, antidepressants other than fluoxetine, antipsychotics, anticonvulsants for nonepilepsy uses, mood stabilizing medications such as lithium, and herbal preparations with psychotropic potential; 2 weeks prior to the screening visit for benzodiazepines, barbiturates, all other sedatives or hypnotics, and monoamine oxidase inhibitors and 4 weeks prior to the screening visit for fluoxetine. Other exclusion criteria included pregnancy, seizures, recent alcohol or drug abuse and patients with body mass index\18.5 kg/m2 or[35 kg/m2.
Interventions	Eligible patients meeting all inclusion criteria at the baseline visit (day 1) and none of the exclusion criteria received either MPH-LA 40, 60, or 80 mg/day or matching placebo in a 1:1:1:1 ratio [study drug (in the formulation of 20 mg or 30 mg) and matching placebo was dispensed as three bottles to eligible patients before start of treatment]. Therapy was started at a dose of 20 mg/day that was increased at weekly intervals in increments of 20 mg/day until the assigned dose of 40, 60, or 80 mg was reached. Following the 3-week titration stage, patients received their allocated dose for a period of 6 weeks. (2) The real-life doseoptimization phase was a 5-week period during which all patients, including those treated with placebo in the double-blind dose-confirmation phase, were started on a dose of 20 mg/day and titrated each week, in increments of 20 mg/day, to their optimal dose (considered by the investigator to achieve optimum symptom control with good tolerability profile) of MPHLA (40, 60 or 80 mg/day) within 3 weeks. The optimal dose was maintained for at least 1 week. At the last visit of the real-life dose-optimization phase, responders [defined as patients with >30% improvement compared to baseline score on the Diagnostic and Statistical Manual of Mental Disorders-IV ADHD Rating Scale (DSM-IV ADHD RS)] who continued to meet inclusion criteria were re-randomized to enter the double-blind maintenance of effect phase in a 3:1 ratio to their optimal dose or placebo. (3) The double-blind maintenance of effect phase was a 6-month, double-blind, randomized, placebo controlled, withdrawal phase to evaluate the maintenance of effect of MPH-LA in adults with ADHD. Patients with >30% worsening from baseline during this 6-month maintenance of effect phase and <30% remaining improvementfrom

	phase 1 baseline on the DSM-IV ADHD RS were required to discontinue the study due to a lack of therapeutic effect.
Outcomes	ADHD symptoms, functioning, adverse events
Notes	Ref ID 1748

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomized to one of the treatment arms using a validated Interactive Voice/Web Response System (IVRS/IWRS)
Allocation concealment (selection bias)	Low risk	Interactive Voice/Web Response System . All sites and personnel for clinical, medical, statistical, data management and monitoring were blinded, and randomization data were kept strictly confidential until the time of un-blinding after the conclusion of the study. The identity of the treatments has been concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, taste, and odor, in line with Consort guidelines.
Blinding of participants and personnel (performance bias)	Low risk	All sites and personnel for clinical, medical, statistical, data management and monitoring were blinded, and randomization data were kept strictly confidential until the time of un-blinding after the conclusion of the study. The identity of the treatments has been concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, taste, and odor
Blinding of outcome assessment (detection bias)	Low risk	All sites and personnel for clinical, medical, statistical, data management and monitoring were blinded, and randomization data were kept strictly confidential until the time of un-blinding after the conclusion of the study.
Incomplete outcome data (attrition bias)	Low risk	722/725 patients accounted for
Selective reporting (reporting bias)	Low risk	Reporting matched protocol http://www.clinicaltrials.gov/ct2/show/NCT01259492
Other bias	High risk	Particpants judged to be low or non responders by the investigator were excluded from the study

Jain 2007

Methods	This randomized, multicenter, double-blind, placebocontrolled, crossover study was designed to evaluate both the efficacy and the side effect profile of MLR methylphenidate over a period of 5 to 11 weeks in adults with ADHD in outpatient settings. Data were collected between October 2003 and April 2004. The study consisted of a screening visit, a randomization visit, 3 phase 1 dose-titration visits separated by intervals of 1 week, a crossover visit separated by an interval of 2 weeks from the last dose-titration visit, 3 phase 2 dose-titration visits, and a final termination visit at the end of the second treatment phase separated by an interval of 2 weeks from the last dose-titration visit.
Participants	Fifty-four adults 18 to 60 years of age with a childhood history consistent with ADHD and meeting the DSM-IV diagnosis of ADHD were screened for study entry. Subjects were diagnosed with ADHD using the DSM-IV criteria for ADHD, inattentive or combined, adapted for adults as the Wender Utah Criteria for ADHD, by displaying either motor hyperactivity persisting from childhood or attentional deficits persisting from childhood, plus 2 of the following: (1) affective lability, (2) inability to complete tasks, (3) hot or explosive temper, (4) impaired interpersonal relationships or inability to sustain relationships over time, (5) impulsivity, or (6) stress intolerance. Patients were eligible to participate in the study if they had a T score greater than or equal to 65 on the ADHD Index of 1 of the 2 Conners'Adult ADHD Rating Scales–Self-rated (CAARS-S) forms completed during the baseline week and 1 of the 2 Conners' Adult ADHD Rating Scales– Observer-rated (CAARS-O) forms completed during the baseline week; if they weighed between 50 and 90 kg at baseline assessment; if they had an IQ greater than or equal to 80 as assessed using the Wechsler Adult Intelligence Scale-III (WAIS-III) at visit 1 or during the prior 5 years; and if they were otherwise able to comply with the study protocol. Patients were excluded from the study if they had a true allergy to methylphenidate or amphetamines; a his- tory of serious adverse reactions to methylphenidate or were known to be methylphenidate nonresponders; serious or unstable medical illness; serious hypertension, defined as any values above 100 mm Hg diastolic and 170 mm Hg systolic; anxiety of sufficient severity to warrant treatment, based upon the Hamilton Rating Scale for Anxiety (HAM-A); depression of sufficient severity to warrant treatment, based upon the Hamilton Rating Scale for Depression (HAM-D); a history of drug or alcohol abuse;
Interventions	Patients who met the entry criteria were entered into a 1-week washout/baseline period. Following the washout/ baseline period, patients were randomly assigned, in a blinded fashion, to either MLR methylphenidate given once daily (10-, 15-, 20-, 30-, 40-, 50-, 60- or 80-mg capsules, administered orally) or matching placebo given once daily. Patients received 1 of the 2 study medications and were titrated to optimal effect during a period of 1 to 3 weeks. At the end of the dose titration period, patients were crossed over to the alternate treatment group, and were titrated to optimal effect during a period of 1 to 3 weeks. Medication compliance was monitored by capsule count of returns in the pharmacy and by direct questioning of the patient. Patients who were less than 80%, or more than 120%, compliant were to be withdrawn from the study.
Outcomes	ADHD symptoms, functioning, angst, depression, QoL

Notes	Ref ID 1641

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not sufficient described
Allocation concealment (selection bias)	Unclear risk	Not sufficient described
Blinding of participants and personnel (performance bias)	Low risk	Blinded PBO group
Blinding of outcome assessment (detection bias)	Unclear risk	Not sufficient described
Incomplete outcome data (attrition bias)	High risk	No data for the crossover phase. No data for 11/50
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	High risk	No medication baseline week makes separation between withdrawal symptoms and beneficial effects difficult.

Konstenius 2010

Methods	Patients were recruited on a referral basis from outpatient addiction units in the Stockholm metropolitan region (pop. 2m). Amphetamine dependent patients newly diagnosed with ADHD were referred to the project manager and their eligibility was ascertained via phone interviews. Thirty-four treatment seeking patients (both male and female) were finally screened in person for the study. The participants were required to fulfill the Diagnostic and Statistical Manual of Mental Disorders (DSM IV; APA, 1994) criteria for amphetamine dependence during the last 12-month period. Exclusion criteria included: (1) current or past DSM IV diagnosis of any other substance dependence except nicotine, (2) history of any major psychiatric disorder (e.g., schizophrenia and major depression) or any current psychiatric condition requiring medication, (3) use of any opioid medication or illicit opiates in the last
Participants	Patients were 18-65 years of age and were recruited on a referral basis from outpatient addiction units in the Stockholm metropolitan region (pop. 2m). Amphetamine dependent patients newly diagnosed with ADHD were referred to the project manager and their eligibility was ascertained via phone interviews. Thirty-four treatment seeking patients (both male and female) were finally screened in person for the study. The participants were required to fulfill the Diagnostic and Statistical Manual of Mental Disorders (DSM IV; APA, 1994) criteria for amphetamine dependence during the last 12-month period. Exclusion criteria included: (1) current or past DSM IV diagnosis of any other substance dependence except nicotine, (2) history of any major psychiatric disorder (e.g., schizophrenia and major depression) or any current psychiatric condition requiring medication, (3) use of any opioid medication or illicit opiates in

	the last.
Interventions	18mg titrated over 10 days to max 72mg
Outcomes	ADHD symptoms, Depression, Anxiety, Craving, Drug abuse (4 different messures)
Notes	Ref ID 1684

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized via Trombul software
Allocation concealment (selection bias)	Low risk	Randomized via Trombul software
Blinding of participants and personnel (performance bias)	Low risk	Double blinding
Blinding of outcome assessment (detection bias)	Low risk	Double blinding
Incomplete outcome data (attrition bias)	High risk	7 out 24 participant swas accounted for
Selective reporting (reporting bias)	High risk	Addiction serverity index scale and "psychiatric symptoms" was not reported
Other bias	High risk	They use LOCF when reporting their final outcomes

Konstenius 2013

Methods	This study was a double-blind, placebo-controlled, randomized trial. The randomization list was generated by an independent pharmacist using the computer-based program design by Trombult Programing. Between March 2007 and February 2011, 54 subject numbers were randomized into two parallel groups (MPH or identical placebo) with the block size 2. Block randomization was used because of the length of the trial and the nature of the medication effect, and was unknown to the principle investigator and the study staff. The randomization code was retained by the Karolinska Pharmacy and disclosed after the end of the trial. No interim analysis was performed.
Participants	The study included men aged between 18 and 65 years, recruited from three medium-security prisons in Stockholm County, Sweden. The study included participants who met the diagnostic criteria for ADHD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [21] and the DSM-IV diagnostic criteria for amphetamine dependence during the last 12 months prior to the current incarceration, and had used amphetamines on a minimum of 12 occasions during the last 12 weeks preceding the incarceration. Potential participants met with the study physician and the study psychologist and underwent an extensive clinical assessment, including the Adult ADHD Self-Rating Scale [22], theWender Utah Rating Scale [23], the Structured Clinical Interview for DSM-IV I and II (SCID I and II) [24], the Addiction Severity Index (ASI) [25], Conners' continuous performance test [26] and a short form of the Wechsler Adult Intelligence Scale–III [27]. Collateral information from significant

	others was collected by telephone interviews. The study exclusion criteria were: (i) DSM-IV diagnosis of any other substance dependence except nicotine, currently or during the 12 months prior to incarceration, (ii) a major psychiatric disorder (e.g. schizophrenia, severe depression), (iii) current antipsychotic medication, (iv) current use of benzodiazepine, (v) traces of any of the following substances in urine: amphetamine, benzodiazepine, cannabis, cocaine, dextropropoxyphene and opiates, (vi) serious somatic disease (e.g. moderate to severe hypertension >150/95 mm Hg, hyperthyroidism) and (vii) known hypersensitivity to methylphenidate
Interventions	Patients were required to abstain from any illicit substances during the 2 weeks preceding the inclusion, verified by patient self-reports and supervised urine toxicology. The medication started 14 days before release from prison (two participants started 3 days and one 5 days before release) and continued for 24 weeks. Like the majority of prisoners in Sweden, all participants were released on supervised probation involving mandatory meetings with a probation officer. The start dose was 18 mg MPH/placebo titrated over a period of 19 days (with 36 mg increments every 3 days), to a maximum dose of 180 mg/day. For participants who did not requireor tolerate a dose increase, the dosage was adjusted and continued at that level. To enhance compliance, the subjectswere picked up by a prepaid taxi at the prison gate on the day of their release and taken to the out-patient clinic, where they received study medication for 2–4 days and were asked to provide a supervised urine specimen. During the 22-week out-patient treatment phase, the participants visited the clinic twice weekly to meet the research nurse who dispensed the study medication and supervised the urine sampling. A trial completer was defined as a participant who received at least 75% of the study medication. For the MPH group, compliance was verified by analysing MPH in the urines at the end of the trial. Once weekly, for the first 12 weeks, the participants attended individual manual-based cognitive–behavioural therapy sessions targeting relapse [30]. In the case of relapse lasting longer than 3 weeks (defined as six consecutive positive or missing urines), the participant was excluded from the trial.
Outcomes	ADHD symptoms, functioning, substance use, adverse events
Notes	Ref ID 1855

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	”The randomization list was generated by an independent pharmacist using the computer-based program DESIGN by Trombult Programing.”
Allocation concealment (selection bias)	Low risk	”The randomization code was retained by the Karolinska Pharmacy and disclosed after the end of the trial. No interim analysis was performed”
Blinding of participants and personnel (performance bias)	Low risk	MPH or identical placebo
Blinding of outcome assessment (detection bias)	Low risk	”MPH or identical placebo”

Incomplete outcome data (attrition bias)	High risk	High rate of dropout – 10/55 completed (2 placebo, 8MPH)
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	High risk	Very selected sample e.g. only ptts. addicted to amphetamines

Kooij 2004

Methods	A randomized, placebo-controlled, doubleblind cross-over trial comparing methylphenidate with placebo was performed. There were two 3-week treatment periods with 1 week of washout in between. The order of treatment (methylphenidate–placebo or placebo–methylphenidate) was randomized by the pharmacist using a computer generated list. Weekly supplies of methylphenidate or placebo were dispensed by the pharmacy in identically appearing tablets of 10 mg. Medication was prescribed under double-blind conditions in four or five times a day dosing. Subjects used a device (Memos) containing compartments for the tablets and a timer in order to dose four or five times a day on time. Dosing was adjusted to five times a day when rebound occurred. Compliance was monitored by electronic registration of the opening of the device, at each visit to the pharmacy. Compliance was defined as >80% of time opening the device within 15 min after the timer's signal.
Participants	Subjects were 45 out-patient adults with ADHD. They were self-referred or referred by other clinicians for assessment of ADHD to the out-patient clinic of GGZ Delfland in Delft, The Netherlands. The DSM-IV diagnosis of childhood-onset and current ADHD was determined by a psychiatrist's clinical evaluation supplemented by the Dutch version of the DSM-IV ADHD rating scale for current symptoms (DuPaul et al. 1998).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. We prospectively excluded 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, as well as pregnant or nursing women.
Interventions	Study medication was titrated up from low to high doses to avoid exposure to high initial doses of active medication and to minimize side effects. Study treatment started Study treatment started with 0.5 mg/kg per day by week 1, followed by 0.75 mg/kg per day by week 2, and up to 1.0 mg/ kg per day by week 3, unless adverse effects emerged.
Outcomes	ADHD symptoms, functioning, adverse events
Notes	Ref ID 1639

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	" The order of treatment (methylphenidate–placebo or placebo–methyl- phenidate) was randomized by the pharmacist using a computer generated list."
Allocation concealment (selection bias)	Low risk	"Weekly supplies of methylphenidate or placebo were dispensed by the pharmacy in identically appearing tablets of 10 mg."
Blinding of participants and personnel (performance bias)	Low risk	"Weekly supplies of methylphenidate or placebo were dispensed by the pharmacy in identically appearing tablets of 10 mg."
Blinding of outcome assessment (detection bias)	Low risk	Placebo ctrl
Incomplete outcome data (attrition bias)	Low risk	45/45 accounted for
Selective reporting (reporting bias)	Low risk	Outcomes reported.
Other bias	Low risk	None detected

Kuperman 2001

Methods	Following a single-blind 7-day placebo leadin, patients were randomized to either bupropion, methylphenidate, or placebo treatment for the next 7 weeks.
Participants	To be given a diagnosis of ADHD, the patient met the following conditions: 1) the presence of full DSMIV 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. Patients were excluded if they had a clinically significant chronic medical condition(s), another current Axis 1 diagnosis, a history of tic disorders, mental retardation (IQ < 80), organic brain disorders, clinically unstable psychiatric symptoms (suicidal behaviors, psychosis, violence, criminality), or substance abuse within 6 months. Since bupropion SR is contraindicated in individuals with seizure disorders, any patient with a recent seizure history was excluded (14). Patients with eating disorders were excluded since they are predisposed to bupropioninduced seizures (15). Patients were excluded if they were taking other psychotropic medications. Female participants of child-bearing potential were entered into the study only if they were using a medically approved form of contraception. All patients provided written informed consent prior to conducting any study procedures.

Interventions	Following a single-blind 7-day placebo leadin, patients were randomized to either bupropion, methylphenidate, or placebo treatment for the next 7 weeks. In those patients receiving bupropion, the sustained release form (Wellbutrin SR) was used and given at 8 A.M. and 4 P.M. while a placebo tablet was given at noon. Bupropion SR was titrated over 2 weeks to a maximum daily dose of 300 mg/d, administered as 200 mg at 8 A.M. and 100 mg at 4 P.M. Methylphenidate was titrated over 1 week to a maximum dose of 0.9 mg/kg/d divided into 3 doses, administered at 8 A.M., noon, and 4 P.M. Placebo patients received placebo doses at 8 A.M., noon, and 4 P.M. Compliance with medication was assessed by two different methods. Medication logs and pill counts were obtained at each visit, and blood samples for measurement of medication blood levels were obtained at the endpoint of the study.
Outcomes	ADHD symptoms, anxiety, depression, adverse events
Notes	Ref ID 1627

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Low risk	Placebo dosed to match medication
Blinding of outcome assessment (detection bias)	Low risk	Placebo dosed to match medication
Incomplete outcome data (attrition bias)	Low risk	30/30 reported
Selective reporting (reporting bias)	High risk	Lack of specific reporting of adverse events for MPH.
Other bias	Low risk	None detected

Levin 2006

Methods	A double-blind, placebo-controlled, randomized, three-arm trial comparing sustained-release MPH, sustained-release BPR and placebo. The trial length was 12 weeks and included a 2-week placebo lead-in phase, a 2-week dose titration period followed by 8 weeks at a stable dose.
Participants	Study inclusion required participants to meet DSM-IV (American Psychiatric Association, 1994) criteria for opiate dependence and adult ADHD, to be between the age of 18 and 60, and on the same dose of methadone for at least 3 weeks. Participants were excluded if they (1) met DSM-IV criteria for current psychiatric disorders (other than ADHD or substance abuse) which required psychiatric intervention or had a history of an eating disorder; (2) were hysiologically dependent on either sedatives or alcohol, such that medical attention was required during periods of abstinence or significant reduction in amount of use; (3) exhibited suicidal or homicidal behavior within the past 2 years; (4) were taking any prescription psychotropic medications other than

	methadone; (5) had an unstable medical condition that would make participation hazardous (i.e., uncontrolled diabetes); (6) had a known sensitivity to MPH or BPR; (7) were nursing and/or pregnant; and (8) could not read or understand the self-report assessment forms unaided and/or were so severely impaired they could not comply with the requirements of the study, and were therefore unable to give full and informed consent.
Interventions	MPH twice a day starting with 10mg an the dose was increased by 10mg. Pr. day up to 40mg. Then a sustaned release formulation was used and adminstreret as two 20mg doses morning and afternoon. Increased to max 80mg. Depending on tolerance.
Outcomes	Drug abuse cocaine and any drugs, ADHD symptoms, AE
Notes	Ref ID 1628

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Only described "randomizing was stratified by site and by amount of recent cocaine use"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Low risk	Double blind
Blinding of outcome assessment (detection bias)	Low risk	Double blind
Incomplete outcome data (attrition bias)	Low risk	Equal drop out and desribed
Selective reporting (reporting bias)	High risk	Insuffieciente data
Other bias	Low risk	None detected

Levin 2007

Methods	This study was a double-blind, placebo-controlled, randomized trial comparing sustained-release MPH and PBO. The trialwas 14 weeks long and included a 1-week PBO lead-in phase, a 2-week dose titration phase followed by 11 weeks at a stable dose. All patients received two capsules twice a day, even when maintained on PBO. Following the PBO lead-in phase, participants were randomized into either the MPH or PBO group.
Participants	All participants were seeking outpatient treatment for problems related to cocaine use and were recruited by local advertising or by referrals in the New York City metropolitan area. Two types of advertisements were placed: those that recruited individuals who were seeking treatment for cocaine dependence and those that recruited individuals who were seeking treatment for cocaine dependence and might have problems with inattention and or hyperactivity. The study was initiated in January 1998 and the last participantwas entered in March 2004. Potential participants underwent a detailed medical and psychiatric assessment. The

	medical screening included a complete history and physical exam, an electrocardiogram and laboratory tests (including hematology, blood chemistry [including liver function tests], thyroid stimulating hormone [TSH], and blood pregnancy test for females). The psychiatric evaluation included the structured clinical interview (SCID) (First et al., 1995) for Diagnostic and Statistical Manual of Mental Disorders (4th ed. [DSM-IV]); (APA, 1994)—Axis I disorders. Study inclusion required participants between the ages of 18–60 to meet DSM-IV criteria for cocaine dependence and persistent adult attention deficit hyperactivity disorder (ADHD). Participants were excluded if they (1) met DSMIV criteria for current psychiatric disorders (other than ADHD or substance abuse) which required psychiatric intervention, (2) were physiologically dependent on opioids, sedatives or alcohol such that medical attention was required during periods of abstinence or significant reductions in use, (3) exhibited suicidal or homicidal behavior within the past 2 years, (4) were prescribed any psychotropic medication, (5) had an unstable medical condition thatwould make participation hazardous (i.e. uncontrolled diabetes), (6) had a known sensitivity to MPH, (7) were nursing and/or pregnant and (8) were unable to give full and informed consent.
Interventions	The dosing was initiated at 10 mg/day of standard formulation methylphenidate and increased up to 20 mg two times a day (40 mg/day). If tolerated, the sustained-release formulation replaced the standard formulation and was administered as two 20mg doses (one in the morning, one in the afternoon). The dose was then increased to the maximal dose of 60 mg/day (40 mg in the morning and 20 mg in the afternoon), depending on patient tolerance of MPH. Patients who could not tolerate a dose of at least 40 mg/day of MPH were discontinued off the medication but were continued in the trial. Folic acid in the form of a 1 mg tablet was added to all placebo capsules in an attempt to improve the double-blind. Also, 25 mg of riboflavin was added to each of the four prescribed capsules (approximately 100 mg/day) in an effort to track compliance. All participant attended weekly individual CBT.
Outcomes	ADHD symptoms, Cocaine abuse, Cocaine craving, Hash abuse, adverse events
Notes	Ref ID 1629

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Low risk	Double blind
Blinding of outcome assessment (detection bias)	Low risk	Double blind
Incomplete outcome data (attrition bias)	High risk	Stort dropout. Randomizered 106 personer dropout på 47 personer
Selective reporting (reporting bias)	Low risk	All outcome reported

Other bias	High risk	Exclusion criteria: Known sensitivity to MPH

Medori 2008

Methods	This double-blind, randomized, placebo-controlled, parallelgroup, fixed-dose trial was conducted at 51 investigator sites in 13 European countries from April 2005 to June 2006. Randomization was based on a computer-generated randomization and stratification scheme prepared before the study. Randomization was balanced by using permuted blocks of treatments, stratified by study center, and implemented via an interactive voice response system.
Participants	The trial included adult men and women with a diagnosis of ADHD according to the criteria of the Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition (DSM-IV) (25) and confirmed by the Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID) (26). Other requirements for inclusion were age 18 to 65 years; chronic course of ADHD symptomatology from childhood to adulthood with some symptoms present before age 7 years, as determined by investigators following the CAADID interview; and CAARS total score of 24 at screening (26). The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/P) was used to evaluate the presence of other comorbidities and exclude other symptoms (27). Attentiondeficit/ hyperactivity disorder was not diagnosed if symptoms were better accounted for by another psychiatric disorder (e.g., mood, anxiety, psychotic, personality disorder). 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., acute mood disorder, bipolar disorder, acute obsessive-compulsive disorder), as determined by the investigator; or they had been diagnosed with substance use disorder (abuse/dependence) according to DSM-IV criteria within the last 6 months. Other exclusion criteria included family history of schizophrenia or affective psychosis; serious illnesses (e.g., hepatic or renal insufficiency or significant cardiac, gastrointestinal, psychiatric, or metabolic disturbances); hyperthyroidism, myocardial infarction, or stroke within 6 months of screening; and history of seizures, glaucoma, or uncontrolled hypertension.
Interventions	Eligible patients were randomized into one of four treatment groups to receive oral dosages of 18 mg, 36 mg, or 72 mg methylphenidate or placebo once daily. Patients receiving 18 mg or 36 mg/day methylphenidate or placebo received the treatment dose for 5 weeks. Patients in the 72-mg methylphenidate group 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 administered for 4 weeks.
Outcomes	Adverse events
Notes	Ref ID 1630

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	”Randomization was based on a computer-generated randomization and stratification scheme prepared before the study. Randomization was balanced by using permuted blocks of treatments, stratified by study center, and implemented via an interactive voice response system.”
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Low risk	Placebo blinded
Blinding of outcome assessment (detection bias)	Low risk	Placebo blinded
Incomplete outcome data (attrition bias)	Low risk	394/402 analysed for efficacy, 401 in safety group
Selective reporting (reporting bias)	Low risk	outcomes reported.
Other bias	High risk	Non-responders not included

Reimherr 2007

Methods	This was a placebocontrolled trial of OROS methylphenidate containing a screening/baseline phase followed by a double-blind, crossover phase with two 4-week arms. Data were collected from August 2004 through December 2005. During the double-blind, crossover phase, subjects were randomly assigned to 1 of 2 groups in a double-blind manner: placebo or OROS methylphenidate. At the end of 4 weeks, subjects were crossed to the other treatment arm for an additional 4 weeks. Subjects were seen weekly.
Participants	We planned to enroll sufficient subjects to have 40 complete both phases. The subjects were required to have a current diagnosis of adult ADHD using DSM-IV-TR criteria for current ADHD based on the Conners Adult ADHD Diagnostic Interview for FOR DSM-IV with at least moderate ADHD symptoms and the Utah Criteria for ADHD in adults. Subjects were between 18 and 65 years of age. Female subjects were eligible to enter and participate in this study if they were of non–childbearing potential or agreed to use an approved form of contraception. The following DSM-IV Axis I diagnoses were exclusionary: current diagnosis of major depressive disorder, generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, posttraumatic stress disorder, bipolar disorder, schizophrenia, or other psychotic disorder. Subjects with a seizure disorder were also excluded. Subjects with hyperthyroidism or hypothyroidism were excluded. Finally, subjects with significant medical conditions likely to become unstable during the trial or likely to be destabilized by treatment with methylphenidate (e.g., cardiovascular disease) were excluded.
Interventions	Subjects were given 2 bottles of study medication (labeled bottle A or B). Bottle A contained 18 mg of OROS methylphenidate or placebo. Bottle B contained 27 mg of OROS methylphenidate or placebo. The use of these bottles allowed subjects to be started at 18 mg per day and to have the dose increased every 2

	to 3 days by 9 mg on the basis of response and tolerance up to a maximum dose of 90 mg per day. Once a patient was rated as much improved or better on the CGI-I or improved 50% on the WRAADDS, the dose remained constant for the remainder of that treatment arm. Generally, a stable dose was obtained in 2 weeks and held constant the last 2 weeks.
Outcomes	ADHD symptoms, adverse events, cardiovascular safety
Notes	Ref ID 1640

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization not descibed
Allocation concealment (selection bias)	Unclear risk	Only descibed they get bottle A and B
Blinding of participants and personnel (performance bias)	Low risk	Double blinded
Blinding of outcome assessment (detection bias)	Unclear risk	Not sufficent described
Incomplete outcome data (attrition bias)	Low risk	alomost eaual dropout only 1 in each group during trial period
Selective reporting (reporting bias)	Low risk	None deteted
Other bias	High risk	Cross-over design with no data presented before the cross over makes differentiation between beneficial and withdrawal symptoms difficult

Retz 2012

Methods	A double-blind, randomized, placebo-controlled study with parallel-group design was conducted at 10 sites. The treatment period was 8 weeks with a 2-week titration and a 6-week maintenance phase. Randomisation was performed by Medice's Galenic Department which included the generation of the randomisation list and the preparation of emergency envelopes. We used block randomisation with a block size of 4. The block size was not mentioned in the investigational plan or the consent given to patients.
Participants	Subjects were outpatients with ADHD aged 18 years and older. For study inclusion the subject had to fulfil the DSM-IV criteria for ADHD (314.00 and 314.01). The diagnosis was established by clinical assessment and by use of a German standardized diagnostic instrument for psychiatric experts (ADHD-DC, R ö sler et al. 2004). A retrospective assessment of DSM-IV ADHD symptoms was made in the presence of an informant whenever possible. In addition, the German short version of the Wender Utah Rating scale (WURS, Wender 1995) was administered to all subjects in order to make surethat childhood ADHD symptoms were present by a retrospective self report of the patient. Individuals with low intelligence (IQ 85), dementia, schizophrenia, bipolar disorder, current

	major depression, acute anxiety disorders and other unstable psychiatric conditions were excluded, as were subjects with any serious medical illness. Also subjects with drug or alcohol dependence during the 6 months before screening, pregnant or nursing women, persons with a Body Mass Index 20 or body weight 130 kg, and individuals treated with any psychopharmacological drug in addition to study medication were not included. Urine screenings for drugs of abuse were performed at screening visit and at week 8 and could be repeated at any time of the study at the investigator ' s discretion. A wash-out period of at least 2 weeks was necessary for any psychopharmacological drug before study inclusion.
Interventions	Medication was individually titrated b.i.d. after breakfast and lunch during the fi rst 2 weeks to an optimal dose on the basis of tolerability and according to the body weight with a maximum daily dose of approximately 1 mg/kg body weight, starting with 10 – 30 mg/day. Patients were assigned to one of four weight classes (less than 55 kg, 55 – 69 kg, 70 – 104 kg and 105 – 130 kg) with doses of 40, 60, 80 and 120 mg daily, respectively. The interval between the two doses was 6 – 8 h.
Outcomes	ADHD symptoms, functioning, adverse events
Notes	Ref ID 1695

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation was performed by Medice's Galenic Department which included the generation of the randomisation list and the preparation of emergency envelopes."
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding of participants and personnel (performance bias)	Low risk	Incl-excl- criterial were carefully re eksamined to avoid protocol violations
Blinding of outcome assessment (detection bias)	Unclear risk	not described
Incomplete outcome data (attrition bias)	Low risk	good describtion of discontinuation
Selective reporting (reporting bias)	Low risk	not detected
Other bias	Unclear risk	Raters har ikke beskrevet det i deres konsensus?

Rösler 2009

Methods	A multi-center, double-blind, randomized, placebo-controlled, 24- week study with parallel-group design was conducted. Clinicians and research staff from 28 study centres across Germany were well experienced in diagnosing and treating adult ADHD patients and were trained to the instruments used in the trial. The participants (mean number 13 participants/study centre) were randomized to MPH ER or placebo at a ratio of 2:1. MPH ER is a MPH preparation manufactured by Medice Company (Germany) with a proportion of 50% immediate release MPH and 50% of extended release MPH. The effective time of action is at least 7 h.
Participants	Subjects were outpatients with ADHD aged >18 years. For study inclusion the subject had to fulfil the DSM-IV criteria for ADHD.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. Also subjects with evidence of drug or alcohol dependence during the preceding 6 months, pregnant or nursing women, persons who had participated in a previous drug trial in the last 30 days and individuals treated with any psychopharmacological drug in addition to study medication were not included. A washout period of at least 2 weeks was necessary for any psychopharmacological drug before study inclusion. Urine screening for drugs of abuse was performed at the screening visit, at weeks 8 and 24, and could be repeated at any time of the study at the investigator's discretion.
Interventions	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. Lower daily doses were administered in the case of intolerable adverse events and if higher daily doses did not lead to increased improvement. The interval between the two doses should be 6–8 h. The minimum maintenance dose after week 5 was 20 mg/ day. A standardised disease management programme consisting of 7 sessions was administered to all participants of the study. The programme was designed especially for the study to avoid ethical objections to keeping subjects on placebo therapy for at least 24 weeks. Disease management sessions were performed at baseline, weeks 1, 3, 5, 8, 12 and 18. During these sessions patients received information about ADHD aetiology and symptoms, support in perception of symptoms and specific problems, help with the management of self-regulation and emotional problems, time management and performing daily routines.
Outcomes	Adhd symptoms, adverse events
Notes	Ref ID 1632

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described

Blinding of participants and personnel (performance bias)	Low risk	Patient and physician blinded
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessor blinded
Incomplete outcome data (attrition bias)	High risk	High drop out rate, 110 of 363. lower 24% in intervention thatn control group (43%)
Selective reporting (reporting bias)	Low risk	None detected
Other bias	High risk	Wash-out period of two weeks for any psychotropic drug prior to inclusion was necessary

Rösler 2010

Methods	A multi-center, double-blind, randomized, placebocontrolled, 24-week study with parallel-group design was conducted. The participants were randomized to MPH-ER or placebo at a ratio of 2:1.
Participants	Subjects were outpatients with ADHD aged 18 years. For study inclusion the subject had to fulfi l the DSM-IV criteria for ADHD. The diagnosis was established by psychiatric expert assessment including a German version of the ADHD Rating Scale – IV (ADHD RS-IV, DuPaul et al. 1998; ADHD-DC, Rösler et al. 2004).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. Also subjects with evidence of drug or alcohol dependenceduring the preceding 6 months, pregnant or nursing women, persons who had participated in a previous drug trial in the last 30 days and individuals treated with any psychopharmacological drug in addition to study medication were not included.
Interventions	Medication was titrated b.i.d. after breakfast and lunch during the first 5 weeks by use of a flexible dose schedule to a maximum dose of 60 mg/day, starting with 10 mg/day. Lower daily doses were administered in the case of intolerable adverse events and if higher daily doses did not lead to an increased improvement. The interval between the two doses was 6–8 h. The minimum maintenance dose afterweek 5 was 20 mg/day MPH-ER is a MPH preparation manufactured by Medice (Germany) with a proportion of 50% immediate release MPH and 50% of extended release MPH. The effective time of action is about 8 h.A wash-out period of at least 2 weeks was necessary for any psychopharmacological drug before study inclusion. Urine screening for drugs of abuse was performed at the screening visit, at weeks 8 and 24, and could be repeated at any time of the study at the investigator's discretion.
Outcomes	Anxiety, Depression
Notes	Ref ID 1698

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Low risk	Doubleblind
Blinding of outcome assessment (detection bias)	Low risk	Doubleblind
Incomplete outcome data (attrition bias)	High risk	249/353 Particpants acounted for
Selective reporting (reporting bias)	Low risk	All outcomes reported as described in protocol, http://clinicaltrials.gov/show/NCT00619840
Other bias	High risk	Use LOCF for missing data. Persons who had participated in a previous drug trial in the last 30 days and individuals treated with any psychopharmacological drug in addition to study medication were not included.

Rösler 2013

Methods	LAMDA (ClinicalTrials.gov: NCT00246220) was a European, multicenter, double-blind, randomized, placebo-controlled, parallel-group, dose – response study conducted between April 2005 and June 2006.
Participants	Subjects eligible for the study were men and women aged 18 65 years with a diagnosis of ADHD according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV), with symptom onset and chronicity of symptoms before the age of 7 years confirmed by the Conners ' Adult ADHD Diagnostic Interview for DSM-IV (CAADID). A Conners' Adult ADHD Rating Scale (CAARS) score of 24 at screening was required for participation in the study. Full details of the study design and inclusion and exclusion criteria have been published previously (Medori et al. 2008).
Interventions	After a screening period of up to 4 weeks, during which prohibited medications were discontinued, subjects were randomly allocated to treatment with one of three doses of OROS MPH 18, 36 or 72 mg/ day, or matching placebo for 5 weeks.
Outcomes	ADHD symptoms, functioning
Notes	Ref ID 1697

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was based on a computer-generated randomization and stratification scheme prepared before the study. Randomization was balanced by using permuted blocks of treatments, stratified by study center, and implemented via an interactive voice response system.
Allocation concealment (selection bias)	Low risk	Interactive voice response system
Blinding of participants and personnel (performance bias)	Low risk	Placebo and medication once daily
Blinding of outcome assessment (detection bias)	Low risk	Placebo and medication once daily
Incomplete outcome data (attrition bias)	Low risk	365/394 completed
Selective reporting (reporting bias)	Low risk	Measures reported
Other bias	High risk	Non-responders not included

Schubiner 2002

Methods	This study was a double-blind, placebo-controlled, randomized trial comparing MTP with placebo. It was initially structured to have three arms, including one with pemoline. However, the pemoline arm was dropped after the first year because of recruitment difficulties. In addition, preliminary analysis showed no differences between the effects of pemoline and MTP. The duration of the trial was 13 weeks, including 1 week of baseline testing and 12 weeks of treatment. On provision of informed consent to enter the trial, each participant was randomly assigned to receive either MTP or placebo. The sample was stratified by gender so that each arm (MTP vs. placebo) would have equal numbers of women and men. Men were further stratified on the basis of antisocial personality disorder and women on the basis of borderline personality disorder to ensure balance of these potentially important prognostic factors.
Participants	Participants were required to be between the ages of 18 and 55 years, meet Diagnostic and Statistical Manual of Mental Disorders (4th ed. [DSM–IV]; American Psychiatric Association, 1994) criteria for current cocaine dependence, provide a urine specimen with a positive urine toxicology result for cocaine metabolite, meet criteria for the diagnosis of ADHD as a child and as an adult (described later), and be willing to enter an intensive outpatient treatment program. Candidates who scored less than an estimated IQ of 75 on the Shipley Institute of Living scale (Shipley, 1967) were excluded because of concerns that they may not be capable of providing informed consent, complying with the study requirements, and providing reliable and valid data.
Interventions	To maintain anonymous conditions, an independent pharmacist compounded study medications. The doses of MTP were titrated from an initial dosage for the first 2 or 3 days (10 mg of MTP three times a day) to a second-level dosage (20 mg three times a day) for the next 4 to 5 days and finally to the target dosage of

	30 mg three times a day by Day 8. Participants were seen weekly by a physician or nurse practitioner to assess response to medications and the development of any adverse effects. Although double-blind conditions were not broken during the course of the study, the treating physician (Howard Schubiner) was able to request a lower dose of medication if warranted by the emergence of perceived side effects. All participants received twice-weekly cognitive–behavioral group therapy (CBT) for cocaine dependence.
Outcomes	ADHD symptoms, cocaine abuse, adverse events
Notes	Ref ID 1633

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not descibed, only "randomly assigned"
Allocation concealment (selection bias)	Low risk	Independent pharmacist
Blinding of participants and personnel (performance bias)	Low risk	Double blinded
Blinding of outcome assessment (detection bias)	Low risk	Double blinded
Incomplete outcome data (attrition bias)	High risk	Large dropout in MPH 29% and only 8% in PBO
Selective reporting (reporting bias)	High risk	Not reported ASI and substance use outcome, BSI- depression
Other bias	Low risk	none detected

Spencer 1995

Methods	A doubleblind, placebo-controlled, randomized, crossover trial comparing methylphenidate with placebo. There were two 3-week treatment periods with 1 week of washout between to avoid a carryover effect of medication. The order of treatment (methylphenidate followed by placebo or placebo followed by methylphenidate) was randomized.
Participants	Subjects were 25 outpatient adults ofboth sexes with ADHD, between 18 and 60 years of age. We excluded prospective subjects if they had any clinically significant chronic medical conditions or abnor mal baseline laboratory values or a history of tic disorders, mental retardation (IQ, <75), organic brain disorders, clinically unstable psychiatric conditions (ie, suicidal behaviors, psychosis, delinquency, criminality, or violence), or substance or alcohol abuse or dependence within the 6 months preceding the study or currently used psychotropics. We also excluded pregnant or nursing women.
Interventions	Weekly supplies of methylphenidate or placebo were dispensed by the pharmacy in identically appearing 5- and 10-mg capsules. Two of us (T.S and T.W.) prescribed medication under double-blind conditions in three times a day dosing. Compliance was monitored by pill counts at each. Study medication was titrated up to 0.5 mg/kg per day by week 1, 0.75 mg/kg per day by week 2, and

	up to 1.0 mg/kg per day by week 3, unless adverse effects emerged.
Outcomes	ADHD symptomer?
Notes	Ref ID 1634

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Low risk	”Weekly supplies of methylphenidate or placebo were dis¬ pensed by the pharmacy in identically appearing 5- and 10-mg capsules.”
Blinding of outcome assessment (detection bias)	Low risk	”Two of us (T.S and T.W.) prescribed medication under double-blind conditions in three times a day dosing.”
Incomplete outcome data (attrition bias)	Low risk	23/25 completed
Selective reporting (reporting bias)	Low risk	HAM A and Ham D not reported, AEs weakly reported
Other bias	High risk	COI and funding not reported, nogle af deltagere er selvhenvendere - kan have særlige præferencer for behandlingen

Spencer 2005

Methods	This was a double-blind, randomized, 6-week, placebo-controlled, parallel design study of MPH in the treatment of adult ADHD. Patients were randomized to MPH or placebo at a ratio of 2.5:1.
Participants	Subjects were 146 outpatient adults with ADHD aged between 19 and 60 years recruited from clinical referrals and advertisements in the local media. Subjects had to satisfy full diagnostic criteria for DSM-IV ADHD based on clinical assessment and confirmed by structured diagnostic interview (Biederman et al 1993). We excluded potential subjects if they had clinically significant chronic medical conditions; abnormal baseline laboratory values; IQ 80; delirium, dementia, or amnestic disorders; other clinically unstable psychiatric conditions (i.e., bipolar disorder, psychosis, suicidality); drug or alcohol abuse or dependence within the 6 months preceding the study; previous adequate trial of stimulant (.5 mg/kg/day of MPH or equivalent); or current use of other psychotropics. We also excluded pregnant or nursing women.
Interventions	Weekly supplies of MPH or placebo were dispensed by the pharmacy in identically appearing 5- and10-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 .5 mg/kg/day by week 1, .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 weeks 5 and 6 if efficacy was partial and treatment was well tolerated. Other psychoactive medications were not permitted during the protocol.
Outcomes	ADHD symptomer?
Notes	Ref ID 1635

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Low risk	”Weekly supplies of MPH or placebo were dispensed by the pharmacy in identically appearing 5- and10-mg capsules.”
Blinding of outcome assessment (detection bias)	Low risk	”Study physicians prescribed medication under double-blind conditions in TID dosing (7:30 AM, noon, and 5 PM).”
Incomplete outcome data (attrition bias)	Low risk	110/146 completed, equal dropout rate in groups, well described.
Selective reporting (reporting bias)	High risk	Much data underreported GAF, HAMA, HAMD
Other bias	Unclear risk	”We excluded potential subjects with....previous adequate trial of stimulants....” p. 457. Have non-responders been excluded?

Spencer 2007

Methods	This randomized, double-blind, parallel-group, placebo-controlled, fixed-dose study
Participants	Participants eligible for inclusion were aged 18 to 60 years, diagnosed with DSM-IV ADHD (any subtype) with childhood onset of symptoms. They had to have a DSM-IV ADHD Rating Scale (ADHD-RS) total score of at least 24 at screening and baseline. This cutoff was selected to be consistent with previous studies of ADHD in adults and to ensure that the study would be able to detect an effect of treatment (Spencer et al. 1995, 1998). In addition, they were required to display functional impairment, defined as a Global Assessment of Functioning (GAF) score of 60 or less. Patients with a history of alcohol or substance abuse within the last 6 months were excluded, as were patients with any psychiatric or medical comorbidity that may have interfered with study participation or assessments or for which MPH treatment may have posed a risk. Patients were also excluded if the investigator judged that they had a history of poor response or intolerance to stimulants (e.g., MPH, d-MPH, amphetamine salts, or dextroamphetamine salts). No patient had previously used d-MPH-ER. Women were excluded if they were pregnant, nursing, or not using acceptable methods of contraception.

Interventions	After screening and baseline visits, patients were equally randomized to one of four treatments (d-MPH-ER 20 mg, 30 mg, or 40 mg, or placebo), administered once daily for 5 weeks, with weekly visits scheduled during this ouble-blind phase To minimize adverse events (AEs), all patients were started on 10 mg/d, titrated in increments of 10 mg/wk to randomly assigned fixed dosages, and then maintained at that dosage for at least 2 weeks. Compliance was assessed based on patient reports and counting of unused capsules.
Outcomes	ADHD symptomer, functioning (GAF), adverse events
Notes	Ref ID 1636

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“After screening and baseline visits, patients were equally randomized to one of four treatments..., administered once daily for 5 weeks...”
Allocation concealment (selection bias)	Unclear risk	“After screening and baseline visits, patients were equally randomized to one of four treatments..., administered once daily for 5 weeks...”
Blinding of participants and personnel (performance bias)	Low risk	Not described, no impact.
Blinding of outcome assessment (detection bias)	Low risk	Not described, no impact.
Incomplete outcome data (attrition bias)	Low risk	8/221 lost to follow up, ITT population 218/221
Selective reporting (reporting bias)	Low risk	All scales reported
Other bias	High risk	COI not declared, non responders excluded

Tennenbaum 2002

Methods	Double-blind, randomized, crossover design
Participants	Adults age 24-53 years meeting DSM-IV ADHD combined subtype criteria. Exclusion criteria were significant medical conditions, active substance use and dependence within 6 months, pregant and nursing females, people with neurological trauma or disorders, chronic diseases, poor physical health, poor vision, people taking psychoactive medication and psychiatric disorders contraindicating treatment with MPH (panic disorder, major depression) or who were clinically unstable (suicidal, psychotic, crimnality/violence, bipolar disorder)
Interventions	The treatment phase was a double-blind, randomized, crossover design comparing Pycnogenol with methylphenidate and with placebo. Each participant received a 3 weeks period on each treatment and 1 week washout to minimize carry over effects.
Outcomes	ADHD symptoms, anxiety, depression

Notes	Ref ID 1637

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Low risk	”Weekly supplies of pills were dispensed by the participating pharmacy in identical opaque, hard shell capsules in blister packs...”
Blinding of outcome assessment (detection bias)	Low risk	”Weekly supplies of pills were dispensed by the participating pharmacy in identical opaque, hard shell capsules in blister packs...”
Incomplete outcome data (attrition bias)	High risk	9/33 excluded based on compliance.
Selective reporting (reporting bias)	High risk	No description of adverse events
Other bias	Low risk	None detected

Weisler 2012

Methods	Randomized double-blind placebo and active-controlled parallel-group multicentre study
Participants	The study included men and women (aged 18–55 years) who met the following inclusion criteria: (a) an established DSM-IV-TR diagnosis of ADHD as confirmed by the Conners Adult ADHD Diagnostic Interview for DSM-IV (CAADID);[25] (b) a Clinical Global Impression-Severity (CGI-S) score of ‡4 at screening and baseline;[26] and (c) a Conners Adult ADHD Rating Scale Self-Report: Screening Version (CAARS-S:SV) DSM-IV ADHD H3Receptor Antagonist for the Treatment of Adult ADHD 423 Adis ª 2012 Springer International Publishing AG. All rights reserved. CNS Drugs 2012; 26 (5)Total Symptoms subscale score depending on age and gender (18–39 years: ‡26 men and ‡32 women; ‡40 years: ‡29 men and ‡27 women) to ensure adequate symptom severity at baseline.[25]
Interventions	Atomoxetin
Outcomes	ADHD symptoms, adverse events
Notes	Ref ID 1717

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generate randomizing 4:10 women and menn
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Low risk	Double blinded
Blinding of outcome assessment (detection bias)	Low risk	Double blinded
Incomplete outcome data (attrition bias)	Low risk	almost equal attrition in MPH and Placebo
Selective reporting (reporting bias)	High risk	Lack e.g. CGI scores for active comparisons ATX and MPH
Other bias	High risk	Strict inclusion no comorbidity.Excluded if ealier responders to MPH.

Wender 1985

Methods	The design was a random-assignment, double-blind crossover of methylphenidate and placebo, with a 2-week trial of each agent and a 1-week intervening washout period. Medication and placebo were dispensed in identical 10mg tablets. DSM-III residual type was a diagnosis of ADHD in adulthood. Initial number of patients randomized not described.
Participants	Adults age 21-45 who met childhood and adulthood criteria for Attention deficit disorder with hyperactivity (DSM-III) and in adulthood met criteria for ADD w. hyperactivity, residual type. Case were excluded if: met criteria for schizophrenia or schizoaffective disorder, had personality disorder features, current affective disorder (also mild cases), IQ below 90, no history of substance abuse in the preceeding 6 months, if pregnant or nursing.
Interventions	The initial dose was 5 mg at 8:00 a.m. and noon, increased by 5 mg per dose every 2-3 days on the basis of the patient’s report. The maximum dose was set at three tablets three times a day (90 mg/day).
Outcomes	Adverse events, functioning, anxiety, depression
Notes	Ref ID 1638

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Low risk	”Medication and placebo were dispensed in identical 10-mg tablets.”

Blinding of outcome assessment (detection bias)	Low risk	”Medication and placebo were dispensed in identical 10-mg tablets.”
Incomplete outcome data (attrition bias)	Unclear risk	Initial number of patients randomized not described
Selective reporting (reporting bias)	Low risk	Measures reported
Other bias	High risk	Non-responders not included

Winhusen 2010

Methods	
Participants	Adults age 18-55 in good physical health who met DSM-IV criteria for ADHD and had an ADHD-RS score of at least score of 22, smoked at least 10 cigarettes a day and had been a regular smoker for at least 3 months. Exclusion criteria was significant suicidal/homocidal risk, used other tobacco products than cigarettes, positive urine test for drugs, met criteria for DSM-IV abuse or dependence of drugs other than nicotine, had current major depression, anxiety (except phobias), antisocial personality disorder, lifetime diagnosis of bipolar disorder or psychosis. Further exclusion criteria were history of narrow angle glaucoma or seizure disorder, tics and family history of Tourettes, past treatment for ADHD with psychomotor stimulants, used smoking cessation counseling programs or medications the past 30 days know to affect treatment with OROS-MPH, women who were pregnant, breastfeeding or unwilling to use an adequate method of birth control.
Interventions	OROS-MPH 18 mg/d up to a maximum of 72 mg/d or to highest dose tolerated
Outcomes	ADHD symptoms, substance abuse, adverse events
Notes	ref ID 1723

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	”Randomization...stratified by site, and completed by computer at a centralized location.
Allocation concealment (selection bias)	Low risk	”Randomization...stratified by site, and completed by computer at a centralized location.
Blinding of participants and personnel (performance bias)	Low risk	Placebo and medication once daily
Blinding of outcome assessment (detection bias)	Low risk	Placebo and medication once daily
Incomplete outcome data (attrition bias)	Low risk	Minimal attrition, attrition equal for MPH and placebo
Selective reporting (reporting bias)	Low risk	None detected
Other bias	Low risk	None detected

Footnotes

Characteristics of excluded studies

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Footnotes

Summary of findings tables

Additional tables

References to studies

Included studies

Adler 2009

[Other: Ref ID 1621]

[Empty]

Biederman 2006

[Other: Ref ID]

[Empty]

Biederman 2010

[Other: Ref ID 1652]

[Empty]

Bouffard 2003

[Other: Ref ID 1623]

[Empty]

Carpentier 2005

[Other: Ref ID]

[Empty]

Casas 2013

[Other: Ref Id 1658]

[Empty]

Ginsberg 2012

[Other: ; Other: Ref ID 1673]

[Empty]

Ginsberg 2012 A

[Other: Ref ID 1672]

[Empty]

Gualtieri 1985

[Other: Ref ID 1625]

[Empty]

Huss 2014

[Other: Ref ID 1748]

[Empty]

Jain 2007

[Other: Ref ID 1641]

[Empty]

Konstenius 2010

[Other: Ref ID 1684]

[Empty]

Konstenius 2013

[Other: Ref ID 1855]

[Empty]

Kooij 2004

[Other: Ref ID 1639]

[Empty]

Kuperman 2001

[Other: Ref ID 1627]

[Empty]

Levin 2006

[Other: Ref ID 1628]

[Empty]

Levin 2007

[Other: Ref ID 1629]

[Empty]

Medori 2008

[Other: Ref ID 1630]

[Empty]

Reimherr 2007

[Other: Ref ID 1640]

[Empty]

Retz 2012

[Other: Ref ID]

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Rösler 2009

[Other: Ref Di 1632]

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Rösler 2010

[Other: Ref ID 1698]

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Rösler 2013

[Other: Ref ID 1697]

[Empty]

Schubiner 2002

[Other: Ref ID 1633]

[Empty]

Spencer 1995

[Other: Ref ID 1634]

[Empty]

Spencer 2005

[Other: Ref Id 1635]

[Empty]

Spencer 2007

[Other: Ref ID 1636]

[Empty]

Tennenbaum 2002

[Other: Ref ID 1637]

[Empty]

Weisler 2012

[Other: ref ID 1717]

[Empty]

Wender 1985

[Other: Ref ID]

[Empty]

Winhusen 2010

[Other: Ref ID 1723]

[Empty]

Excluded studies

Studies awaiting classification

Ongoing studies

Other references

Additional references

Other published versions of this review

Data and analyses

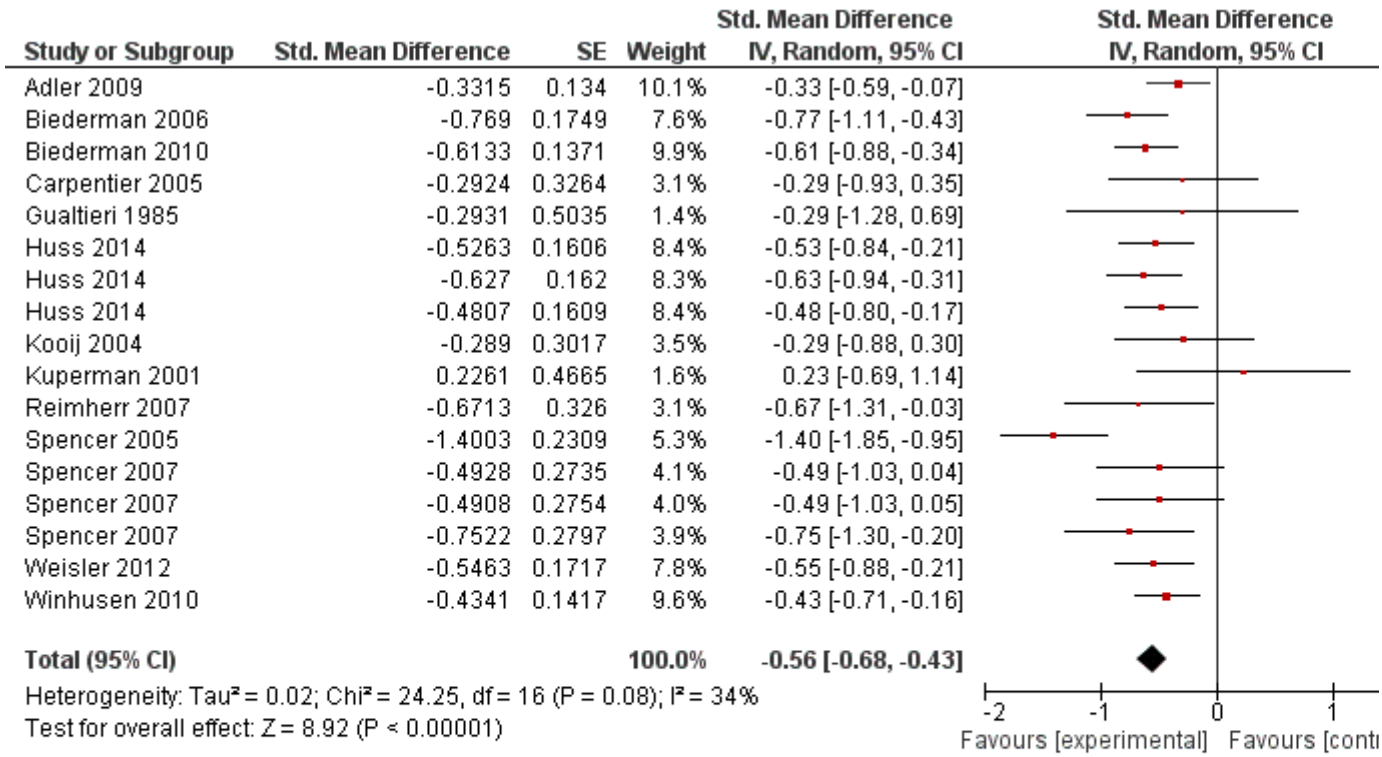
1 Methylphenidate versus placebo

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 ADHD Symptoms (ADHD RS)	13		Std. Mean Difference (IV, Random, 95% CI)	-0.56 [-0.68, -0.43]
1.2 ADHD Symptoms (Connor's Adult ADHD Rating Scale)	8		Std. Mean Difference (IV, Random, 95% CI)	-0.50 [-0.69, -0.32]
1.3 ADHD Function (Global Assessment of Function)	4		Std. Mean Difference (IV, Random, 95% CI)	-0.87 [-1.20, -0.55]
1.4 ADHD Function (CGI Investigator rated)	4		Std. Mean Difference (IV, Random, 95% CI)	-0.36 [-0.53, -0.19]
1.5 Depression	11		Std. Mean Difference (IV, Random, 95% CI)	0.10 [-0.08, 0.28]

1.6 Anxiety	10		Std. Mean Difference (IV, Random, 95% CI)	0.05 [-0.16, 0.25]
1.7 Any drug use	3	167	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.34, 2.23]
1.8 Systolic blood pressure	14		Std. Mean Difference (IV, Random, 95% CI)	0.15 [0.06, 0.25]
1.9 Diastolic blood pressure	13		Std. Mean Difference (IV, Random, 95% CI)	0.15 [0.05, 0.24]
1.10 Pulse	14		Std. Mean Difference (IV, Random, 95% CI)	0.38 [0.27, 0.48]
1.11 Insomnia	17	3222	Odds Ratio (M-H, Random, 95% CI)	2.13 [1.66, 2.73]
1.12 Decreased appetite (+"anorexia")	17	3278	Odds Ratio (M-H, Random, 95% CI)	4.95 [3.87, 6.33]
1.13 Dry mouth	14	2959	Odds Ratio (M-H, Random, 95% CI)	5.53 [4.01, 7.62]
1.14 Nausea	9	2013	Odds Ratio (M-H, Random, 95% CI)	2.79 [1.90, 4.10]
1.15 Cardiovascular complications	7	944	Odds Ratio (M-H, Random, 95% CI)	3.25 [1.85, 5.73]
1.16 Sexual (reduced libido, erectile dysfunction)	3	532	Odds Ratio (M-H, Random, 95% CI)	4.10 [1.20, 14.05]
1.17 Urinary difficulties	4	569	Odds Ratio (M-H, Random, 95% CI)	2.45 [0.83, 7.24]
1.18 Palpitations	7	1778	Odds Ratio (M-H, Random, 95% CI)	3.72 [1.83, 7.56]

Figures

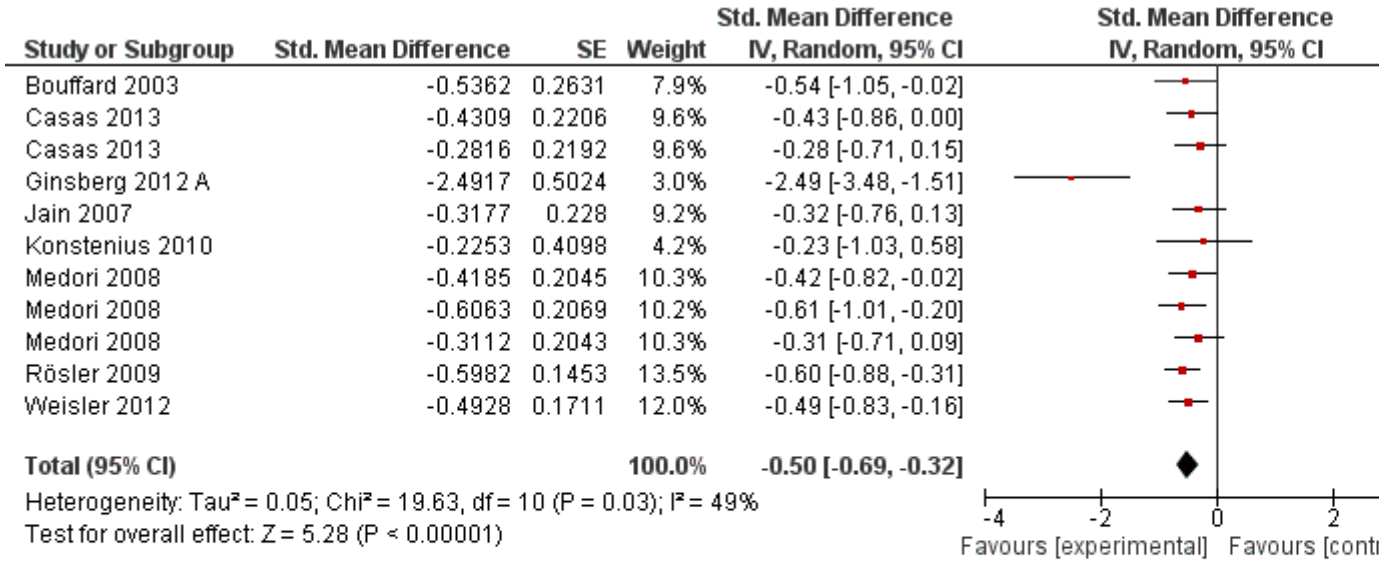
Figure 1 (Analysis 1.1)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Forest plot of comparison: 1 Methylphenidate versus placebo, outcome: 1.1 ADHD Symptoms (ADHD RS).

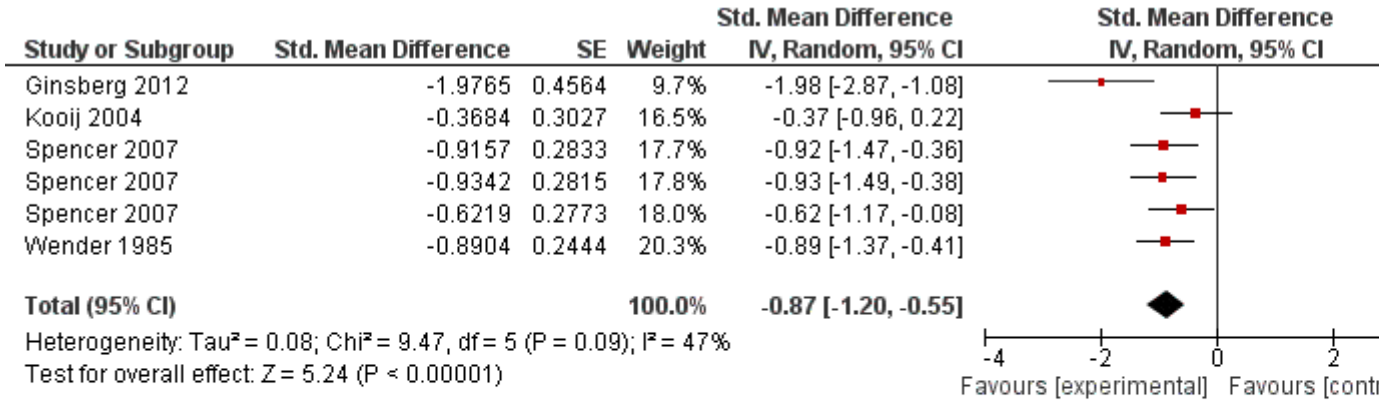
Figure 2 (Analysis 1.2)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Forest plot of comparison: 1 Methylphenidate versus placebo, outcome: 1.2 ADHD Symptoms (Connor's Adult ADHD Rating Scale).

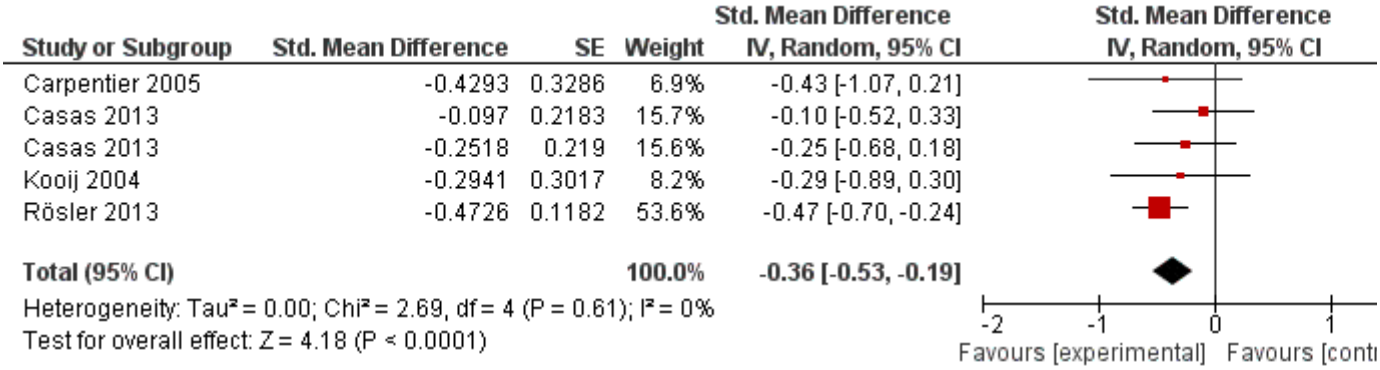
Figure 3 (Analysis 1.3)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Forest plot of comparison: 1 Methylphenidate versus placebo, outcome: 1.3 ADHD Function (Global Assessment of Function).

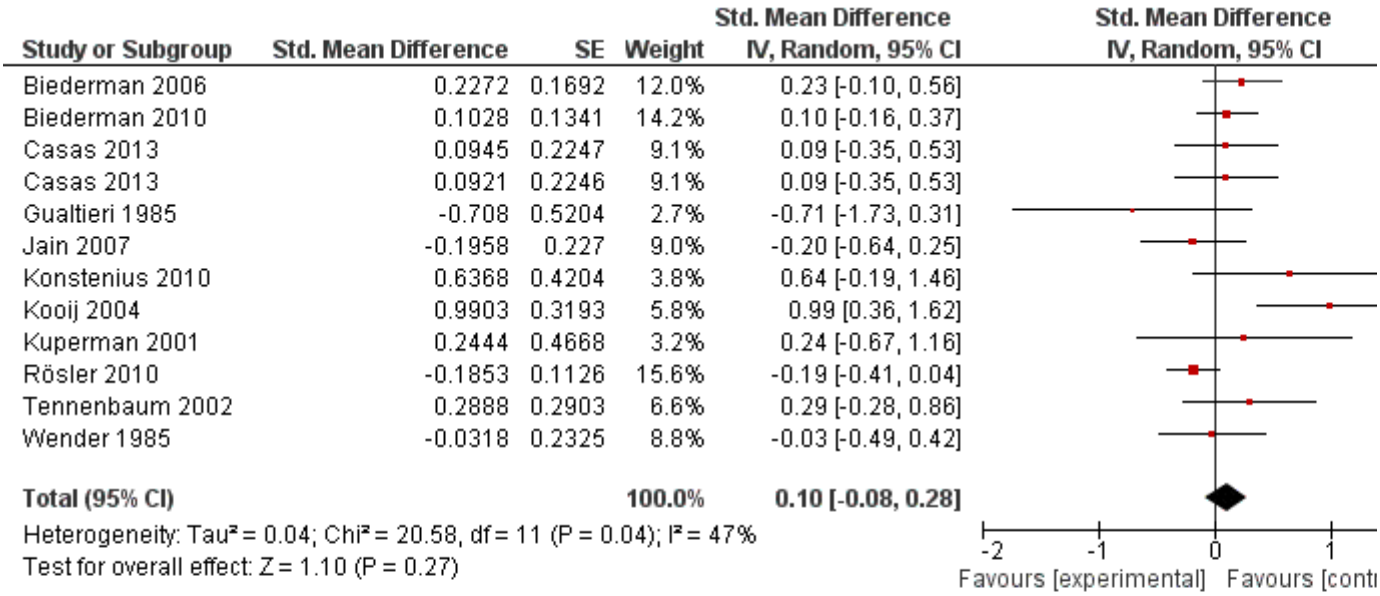
Figure 4 (Analysis 1.4)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Forest plot of comparison: 1 Methylphenidate versus placebo, outcome: 1.4 ADHD Function (CGI Investigator rated).

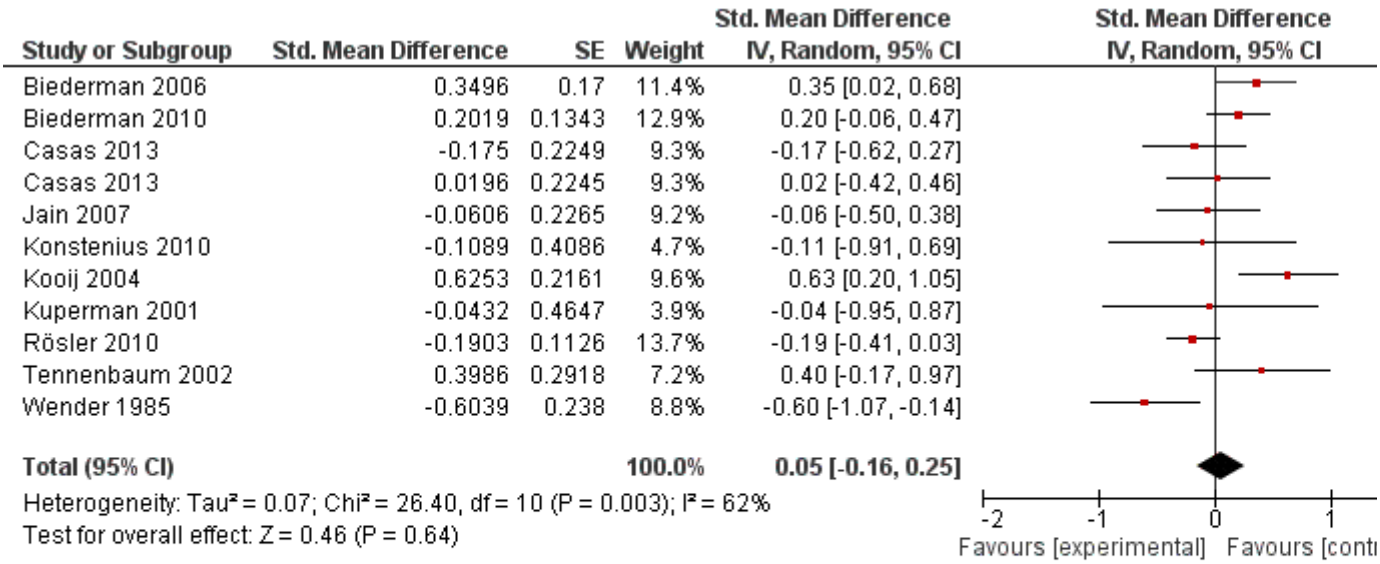
Figure 5 (Analysis 1.5)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Forest plot of comparison: 1 Methylphenidate versus placebo, outcome: 1.5 Depression (Hamilton, Beck, and SCL-90 scales).

Figure 6 (Analysis 1.6)

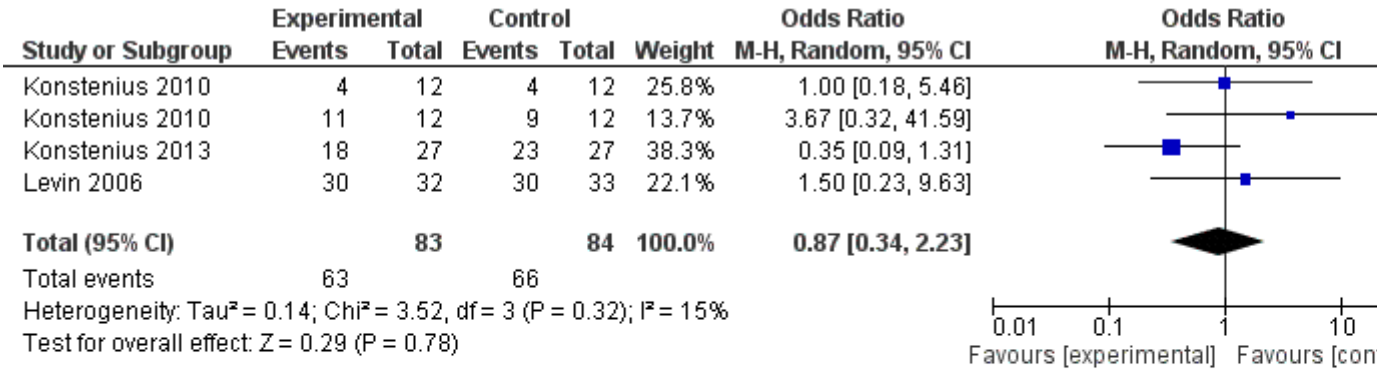


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Forest plot of comparison: 1 Methylphenidate versus placebo, outcome: 1.6 Anxiety (HAM-A, Beck, SLC-90 scales)

.

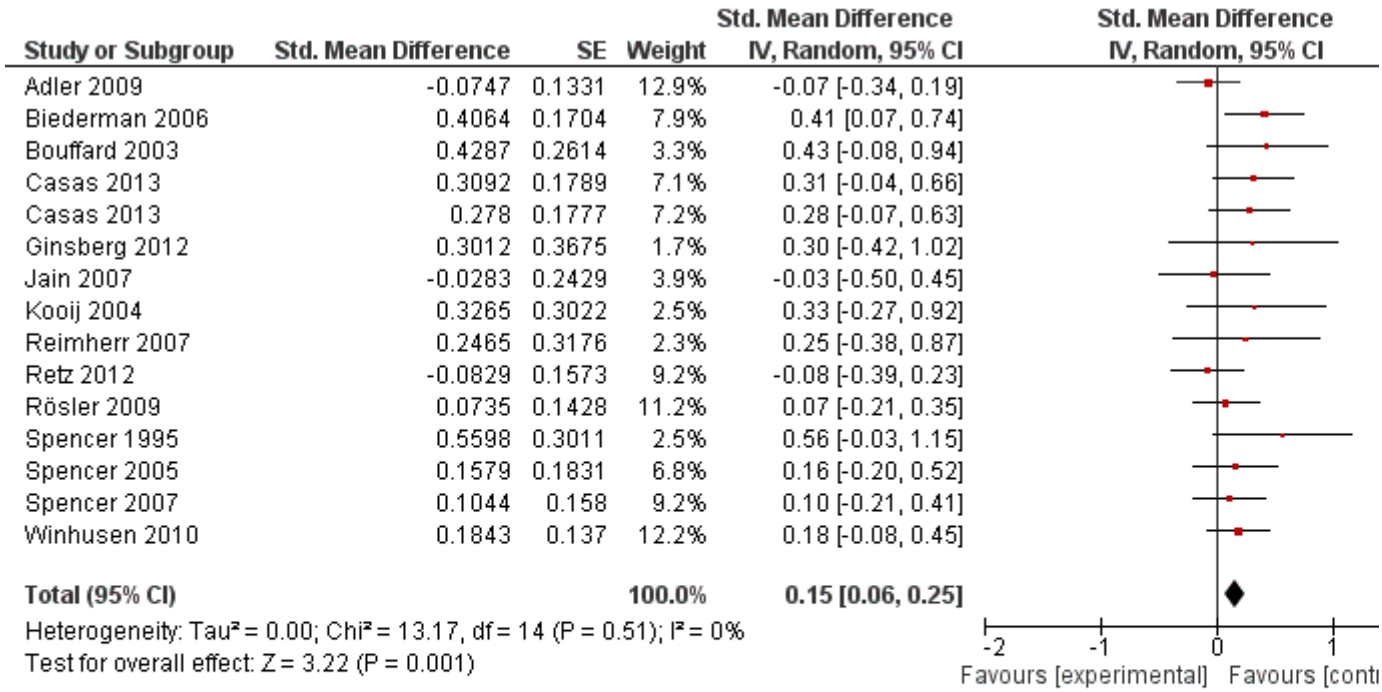
Figure 7 (Analysis 1.7)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Forest plot of comparison: 1 Methylphenidate versus placebo, outcome: 1.7 Any drug use.

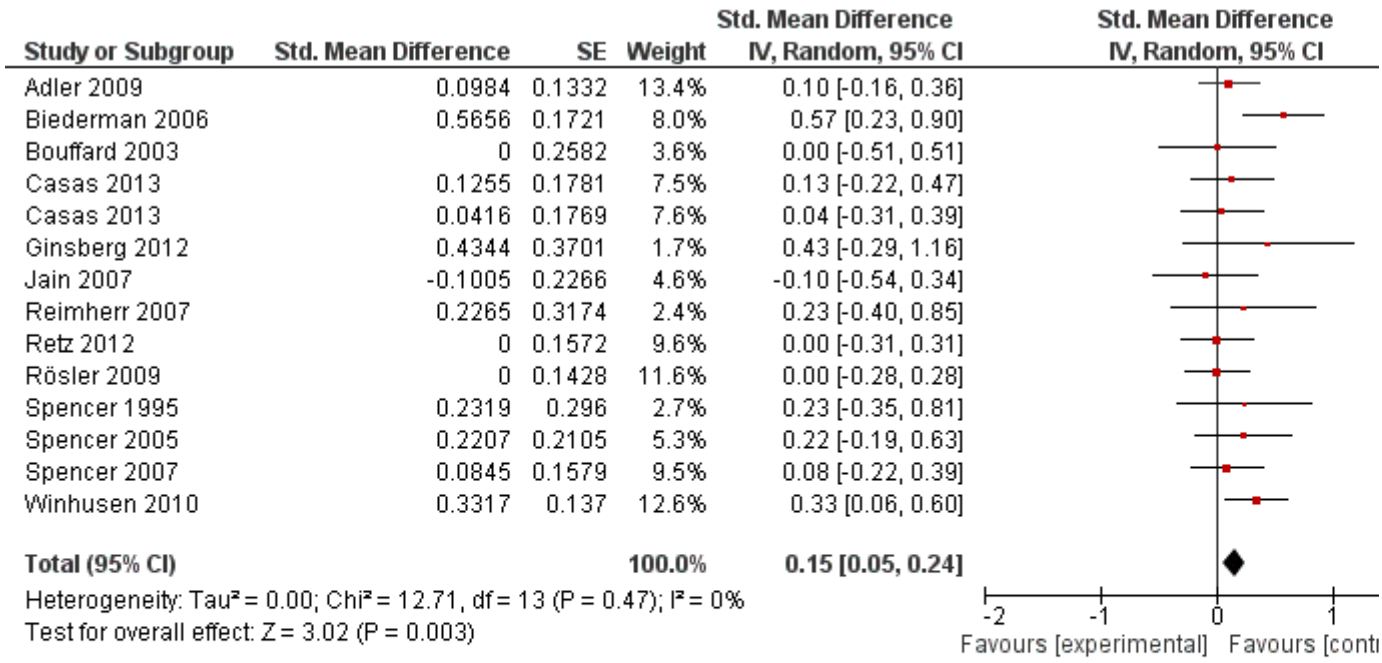
Figure 8 (Analysis 1.8)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Forest plot of comparison: 1 Methylphenidate versus placebo, outcome: 1.8 Systolic blood pressure.

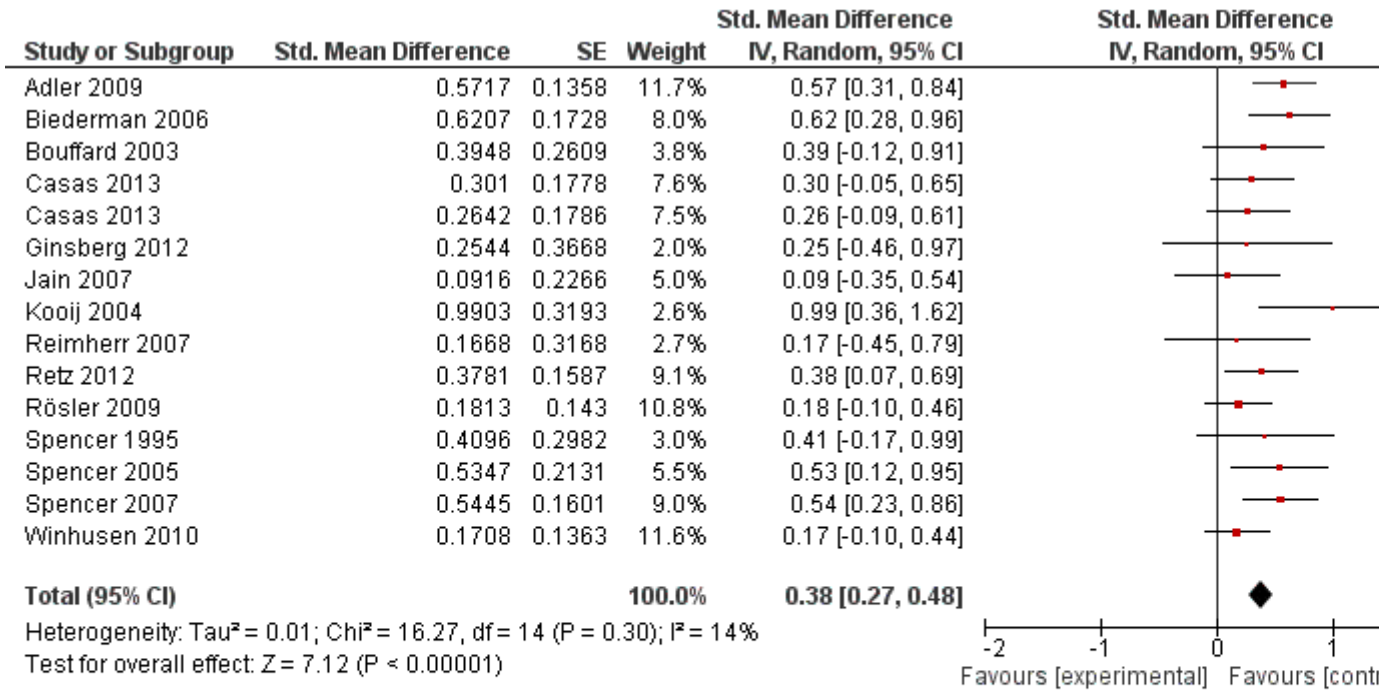
Figure 9 (Analysis 1.9)



Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Forest plot of comparison: 1 Methylphenidate versus placebo, outcome: 1.9 Diastolic blood pressure.

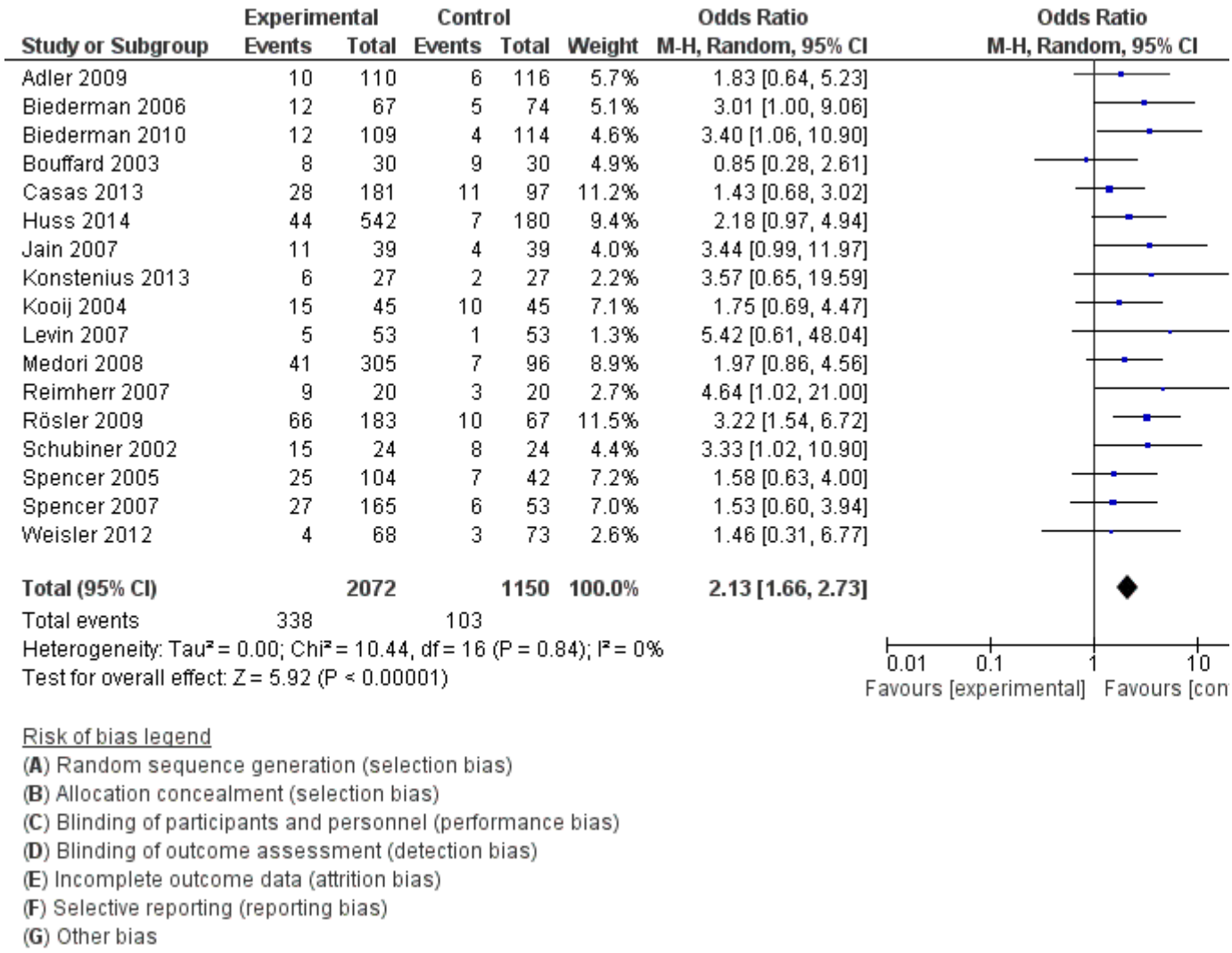
Figure 10 (Analysis 1.10)



Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Forest plot of comparison: 1 Methylphenidate versus placebo, outcome: 1.10 Pulse.

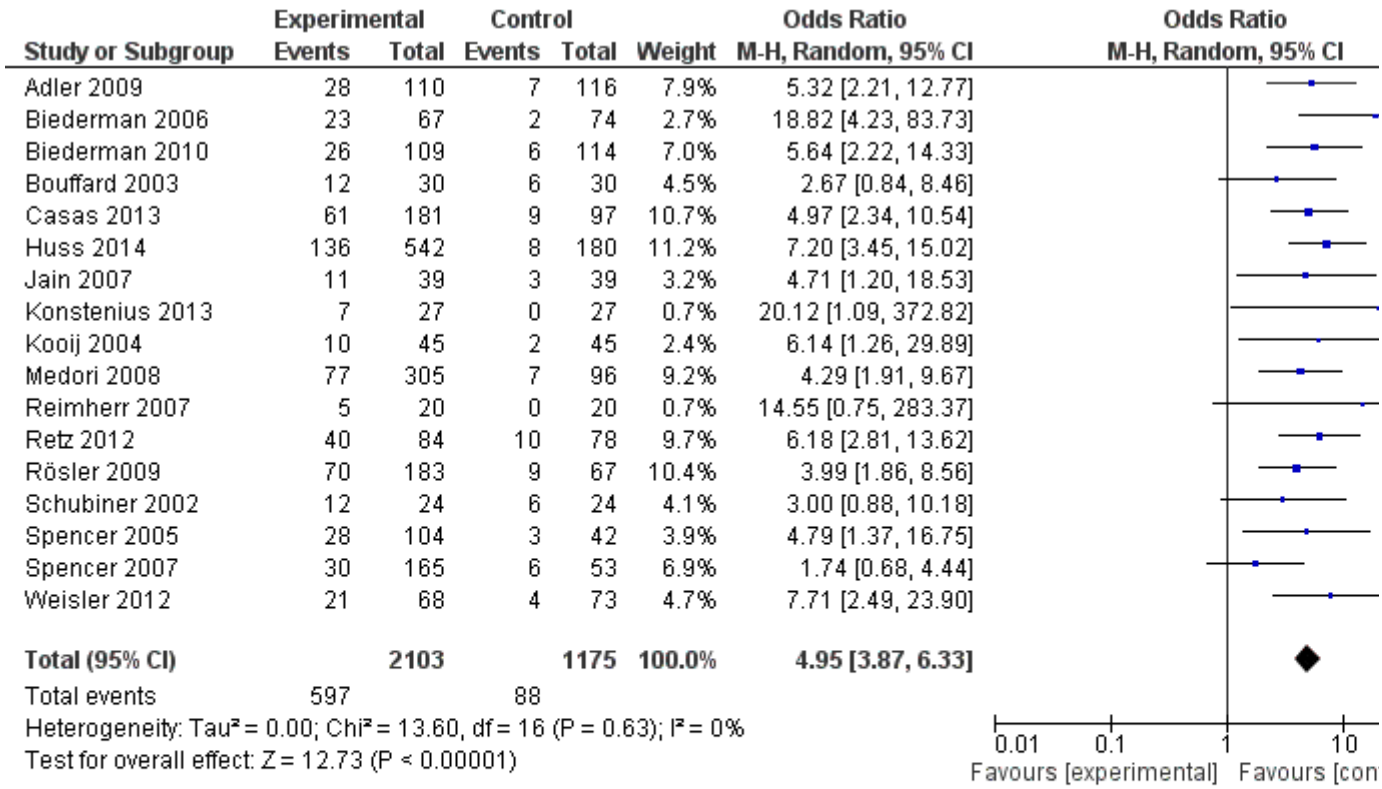
Figure 11 (Analysis 1.11)



Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Forest plot of comparison: 1 Methylphenidate versus placebo, outcome: 1.11 Insomnia.

Figure 12 (Analysis 1.12)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Adler 2009	28	110	7	116	7.9%	5.32 [2.21, 12.77]
Biederman 2006	23	67	2	74	2.7%	18.82 [4.23, 83.73]
Biederman 2010	26	109	6	114	7.0%	5.64 [2.22, 14.33]
Bouffard 2003	12	30	6	30	4.5%	2.67 [0.84, 8.46]
Casas 2013	61	181	9	97	10.7%	4.97 [2.34, 10.54]
Huss 2014	136	542	8	180	11.2%	7.20 [3.45, 15.02]
Jain 2007	11	39	3	39	3.2%	4.71 [1.20, 18.53]
Konstenius 2013	7	27	0	27	0.7%	20.12 [1.09, 372.82]
Kooij 2004	10	45	2	45	2.4%	6.14 [1.26, 29.89]
Medori 2008	77	305	7	96	9.2%	4.29 [1.91, 9.67]
Reimherr 2007	5	20	0	20	0.7%	14.55 [0.75, 283.37]
Retz 2012	40	84	10	78	9.7%	6.18 [2.81, 13.62]
Rösler 2009	70	183	9	67	10.4%	3.99 [1.86, 8.56]
Schubiner 2002	12	24	6	24	4.1%	3.00 [0.88, 10.18]
Spencer 2005	28	104	3	42	3.9%	4.79 [1.37, 16.75]
Spencer 2007	30	165	6	53	6.9%	1.74 [0.68, 4.44]
Weisler 2012	21	68	4	73	4.7%	7.71 [2.49, 23.90]
Total (95% CI)		**2103**		**1175**	**100.0%**	**4.95 [3.87, 6.33]**
Total events	597		88			

Heterogeneity: Tau² = 0.00; Chi² = 13.60, df = 16 (P = 0.63); I² = 0%
Test for overall effect: Z = 12.73 (P < 0.00001)

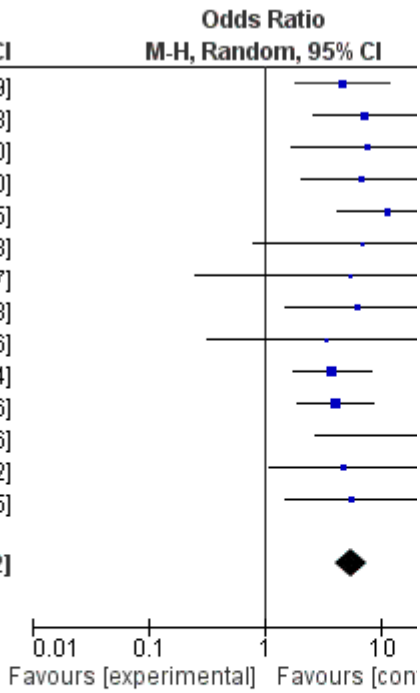
Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Forest plot of comparison: 1 Methylphenidate versus placebo, outcome: 1.12 Decreased appetite (+"anorexia").

Figure 13 (Analysis 1.13)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Adler 2009	22	110	6	116	11.6%	4.58 [1.78, 11.79]
Biederman 2006	23	67	5	74	9.6%	7.21 [2.55, 20.38]
Biederman 2010	20	62	2	34	4.4%	7.62 [1.66, 35.00]
Casas 2013	32	181	3	97	7.0%	6.73 [2.00, 22.60]
Huss 2014	110	542	4	180	10.1%	11.20 [4.07, 30.85]
Jain 2007	6	39	1	39	2.2%	6.91 [0.79, 60.38]
Konstenius 2013	2	27	0	27	1.1%	5.39 [0.25, 117.77]
Medori 2008	36	305	2	96	5.0%	6.29 [1.49, 26.63]
Reimherr 2007	3	20	1	20	1.9%	3.35 [0.32, 35.36]
Retz 2012	32	84	11	78	17.2%	3.75 [1.73, 8.14]
Rösler 2009	70	183	9	67	17.8%	3.99 [1.86, 8.56]
Spencer 2005	36	104	0	42	1.3%	45.29 [2.71, 757.46]
Spencer 2007	26	165	2	53	4.8%	4.77 [1.09, 20.82]
Weisler 2012	14	74	3	73	6.2%	5.44 [1.49, 19.85]
Total (95% CI)		**1963**		**996**	**100.0%**	**5.53 [4.01, 7.62]**
Total events	432		49			

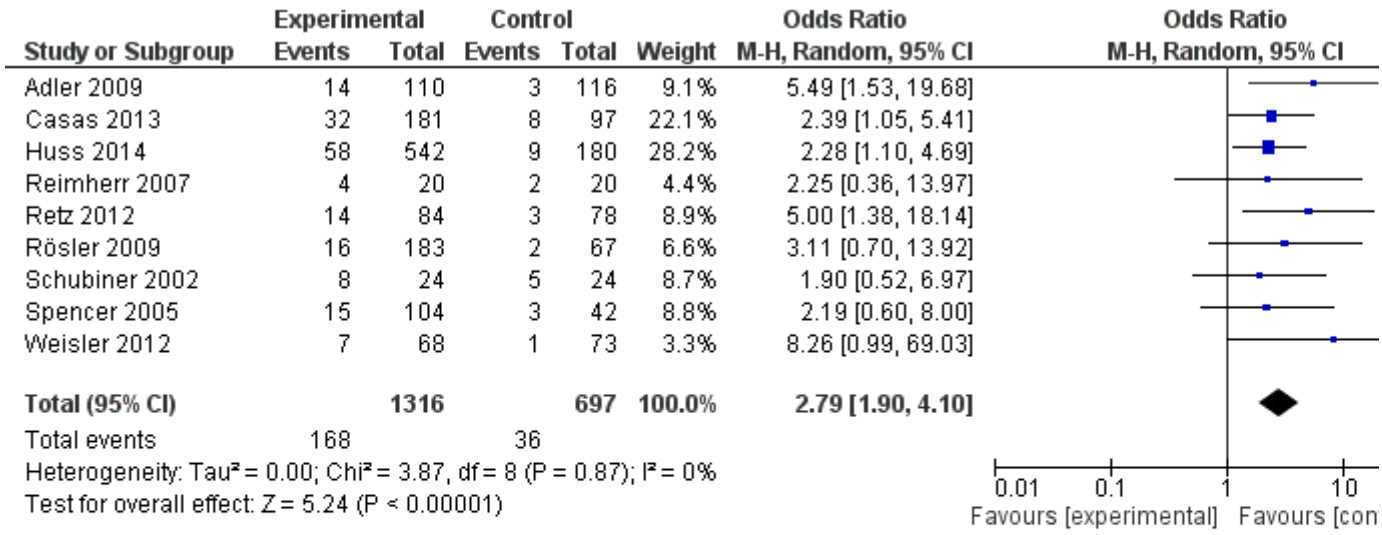
Heterogeneity: Tau² = 0.00; Chi² = 7.10, df = 13 (P = 0.90); I² = 0%
Test for overall effect: Z = 10.42 (P < 0.00001)



Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Forest plot of comparison: 1 Methylphenidate versus placebo, outcome: 1.13 Dry mouth.

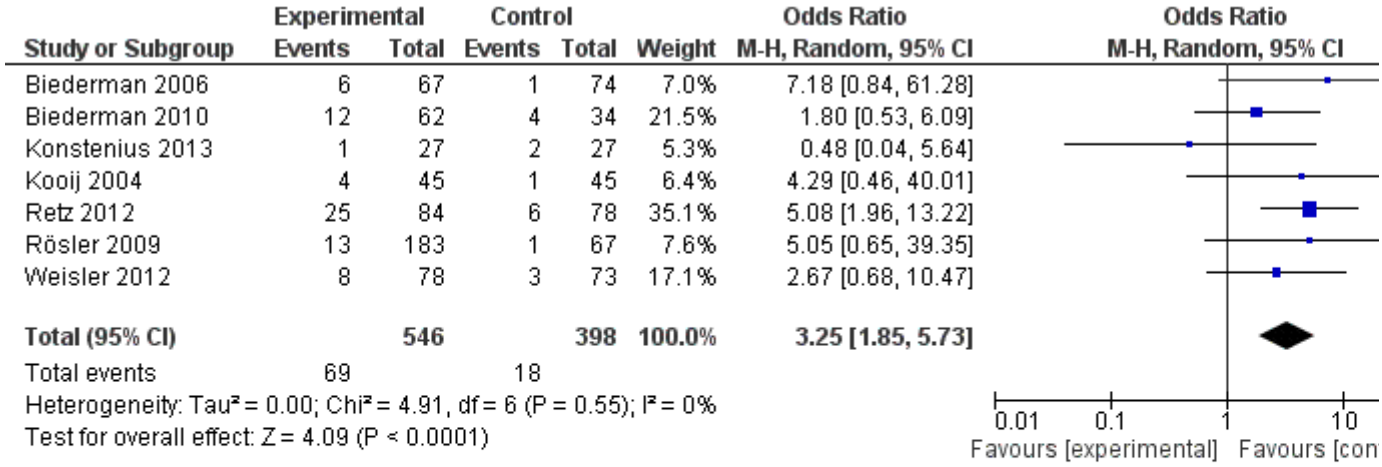
Figure 14 (Analysis 1.14)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Forest plot of comparison: 1 Methylphenidate versus placebo, outcome: 1.14 Nausea.

Figure 15 (Analysis 1.15)

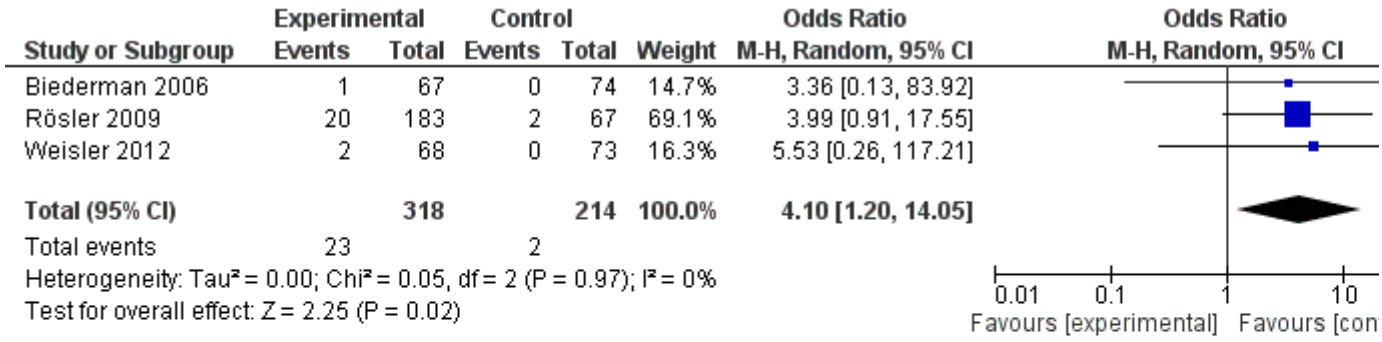


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Forest plot of comparison: 1 Methylphenidate versus placebo, outcome: 1.15 Cardiovascular complications (chest pain where specified)

.

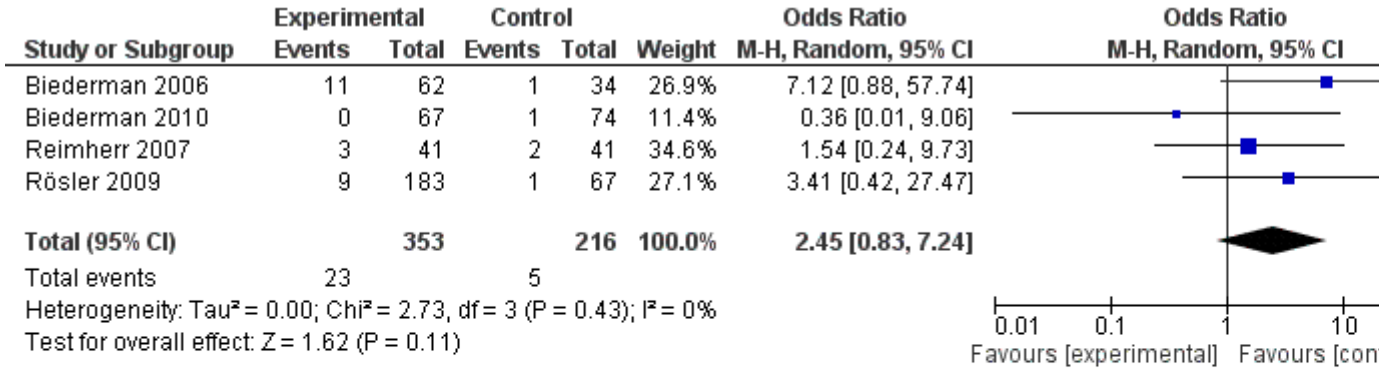
Figure 16 (Analysis 1.16)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Forest plot of comparison: 1 Methylphenidate versus placebo, outcome: 1.16 Sexual (reduced libido, erectile dysfunction).

Figure 17 (Analysis 1.17)



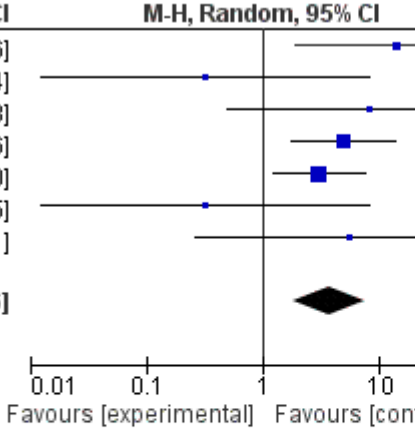
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Forest plot of comparison: 1 Methylphenidate versus placebo, outcome: 1.17 Urinary difficulties.

Figure 18 (Analysis 1.18)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Huss 2014	39	542	1	180	11.2%	13.88 [1.89, 101.76]
Konstenius 2013	0	27	1	27	4.6%	0.32 [0.01, 8.24]
Medori 2008	12	305	0	96	5.9%	8.22 [0.48, 140.13]
Retz 2012	21	84	5	78	31.5%	4.87 [1.73, 13.66]
Rösler 2009	42	183	6	67	37.2%	3.03 [1.22, 7.50]
Schubiner 2002	0	24	1	24	4.5%	0.32 [0.01, 8.25]
Weisler 2012	2	68	0	73	5.1%	5.53 [0.26, 117.21]
Total (95% CI)		**1233**		**545**	**100.0%**	**3.72 [1.83, 7.56]**
Total events	116		14			

Heterogeneity: Tau² = 0.14; Chi² = 7.04, df = 6 (P = 0.32); I² = 15%
Test for overall effect: Z = 3.63 (P = 0.0003)



Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Forest plot of comparison: 1 Methylphenidate versus placebo, outcome: 1.18 Palpitations.

Sources of support

Internal sources

- No sources of support provided

External sources

- No sources of support provided

Feedback

Appendices