NKR1_ADHD_PICO8_Atomoxetine

Characteristics of studies

Characteristics of included studies

Allen 2005

Methods	See NICE guideline "Attention deficit hyperactivity disorder: diagnosis and management" 2018
Participants	
Interventions	
Outcomes	*ADHD kernesymptomer, obsevatørbedømt* ● **Outcome type**: ContinuousOutcome *Frafald pga bivirkninger* ● **Outcome type**: DichotomousOutcome *Appetitforstyrrelser* ● **Outcome type**: DichotomousOutcome
Identification	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Judgement Comment: Randomization done by computerized Interactive voice response system
Allocation concealment (selection bias)	Low risk	Judgement Comment: All clinical material was blinded All clinical material was blinded
Blinding of participants and personnel (performance bias)	Unclear risk	Judgement Comment: The drug labeling system was available for the investigator Quote: " Patients were assigned in a1:1 ratio to double-blind treatment consisting of either placebo oratomoxetine (0.5 to 1.5 mg/kg/day""All clinical trial materials were blinded when provided tothe investigative site, and emergency codes, generated by a computerizeddrug-labeling system, were available to the investigator"
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: Nothing mentioned
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: Last-observation-carried-forward was used. No apparent sources of bias
Selective reporting (reporting bias)	Low risk	Judgement Comment: No apparent sources of bias
Other bias	Low risk	Judgement Comment: No apparent sources of bias

Biederman 2002

Methods	See NICE guideline "Attention deficit hyperactivity disorder: diagnosis and management" 2018
Participants	
Interventions	●
Outcomes	*ADHD kernesymptomer, obsevatørbedømt, CI* ● **Outcome type**: ContinuousOutcome *ADHD kernesymptomer, forældrebedømt, CI* ● **Outcome type**: ContinuousOutcome *Frafald pga bivirkninger, n* ● **Outcome type**: DichotomousOutcome *Appetitforstyrrelser, n* ● **Outcome type**: DichotomousOutcome *Søvnforstyrrelser, n* ● **Outcome type**: DichotomousOutcome
Identification	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization schedules were generated by validated software and implemented in a blinded manner by using an interactive voice-response tele- phone system to dispense study medication."
Allocation concealment (selection bias)	Low risk	Quote: "Study drug materials for all treatment groups were identical in appearance."
Blinding of participants and personnel (performance bias)	Unclear risk	Judgement Comment: Mentioned as blinded, but not specified

Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: Mentioned as blinded, but not specified Parents were blinded to the intervention and it is therefore reasonable to think that bias is balanced equally between the groups. However, this is self-reported outcomes.
Incomplete outcome data (attrition bias)	Low risk	Quote: "All statistical tests were performed using a 2-tailed, .05 signif- icance level using an intent-to-treat principle. Treatment" Judgement Comment: No apparent sources of bias
Selective reporting (reporting bias)	Low risk	Judgement Comment: No apparent sources of bias
Other bias	Low risk	Quote: "This research was funded by Eli Lilly and Company." Judgement Comment: No apparent sources of bias

Block 2009

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention 1 ● *Mean age, years*: 8.8 ● *Male %*: 67.7 Intervention 2 ● *Mean age, years*: 9.1 ● *Male %*: 76.3 Control ● *Mean age, years*: 8.9 ● *Male %*: 74.2 **Included criteria:** Age 6-12 years old. Symptom severity of 1.5 above age and gender norms in ADHD-RS rating **Excluded criteria:** Serious medicall illness, history of phycosis or bipolar disorder, weight 20kg or >65kg, uncontrolled hypertension, previous nonresponse to atomoxetine, alcohol or drug abuse **Pretreatment:** Baseline characteristics were similar
Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: Morning atomoxetine ● *Length of treatment*: 6 weeks Intervention 2 ● *Description*: Evening atomoxetine ● *Length of treatment*: 6 weeks Control ● *Description*: Placebo ● *Length of treatment*: 6 weeks
Outcomes	*Frafald pga bivirkninger* ● **Outcome type**: DichotomousOutcome *Vægttab* ● **Outcome type**: ContinuousOutcome *Appetitforstyrrelser* ● **Outcome type**: DichotomousOutcome
Identification	**Sponsorship source:** Funded by Lilly **Country:** USA **Setting:** 14 outpatient sites **Authors name:** Stan L Block **Institution:** Kentucky Pediatric Research **Email:** slblock@pol.net **Address:** Kentucky Pediatric Research 201 S. 5th street Bardstown, KY 40004
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Allocation concealment (selection bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Blinding of participants and personnel (performance bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Blinding of outcome assessment (detection bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Incomplete outcome data (attrition bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Selective reporting (reporting bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Other bias	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017

Brown 2006

Methods	See NICE guideline "Attention deficit hyperactivity disorder: diagnosis and management" 2018
Participants	
Interventions	
Outcomes	*ADHD kernesymptomer, lærerbedømt* ● **Outcome type**: ContinuousOutcome *ADHD kernesymptomer, forældrebedømt* ● **Outcome type**: ContinuousOutcome *Livskvalitet* ● **Outcome type**: ContinuousOutcome
Identification	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement Comment: Not fully described:The study was a randomized,double-blind, placebo-controlled, parallel design multisite trial thatwas conducted at 10 investigationalsites in the United States
Allocation concealment (selection bias)	Low risk	Judgement Comment: placebo medication was identical to intervention in appearance placebo medication was identical to intervention in appearance
Blinding of participants and personnel (performance bias)	Unclear risk	Judgement Comment: Mentioned as blinded, unclear who was blinded
Blinding of outcome assessment (detection bias)	Low risk	Judgement Comment: As this is a double-blinded study we can assume that bias is equal distributed and not a problem. - However this is self-reported meausrements Mentioned as blinded, unclear who was blinded
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: No apparent sources of bias 83% of the randomized children completed the study
Selective reporting (reporting bias)	Low risk	Judgement Comment: Selective reporting not suggested - however no protocol registered No apparent sources of bias
Other bias	Low risk	Judgement Comment: No apparent sources of bias

DellAgnello 2009

Methods	See NICE guideline "Attention deficit hyperactivity disorder: diagnosis and management" 2018
Participants	
Interventions	
Outcomes	*ADHD kernesymptomer, lærerbedømt* ● **Outcome type**: ContinuousOutcome *ADHD kernesymptomer, forældrebedømt* ● **Outcome type**: ContinuousOutcome *Adfærdsforstyrrelser, lærerbedømt* ● **Outcome type**: ContinuousOutcome *Adfærdsforstyrrelser, forældrebedømt* ● **Outcome type**: ContinuousOutcome *Vægttab* ● **Outcome type**: DichotomousOutcome *Appetitforstyrrelser* ● **Outcome type**: DichotomousOutcome *Søvnforstyrrelser* ● **Outcome type**: DichotomousOutcome *Livskvalitet* ● **Outcome type**: ContinuousOutcome
Identification	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "At the beginning of this period, patients who did not respond to the 6-week period of parent support were randomly assigned to treatment with atomoxetine or placebo in a ratio of 3:1 (i.e. with approximately 75% of patients receiving atomoxetine and 25% of patients receiving placebo). Patients" Judgement Comment: Not fully described how the randomization eas performed
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: Nothing mentioned
Blinding of participants and personnel (performance bias)	Unclear risk	Judgement Comment: Mentioned as double-blinded. Unclear who was blinded. The II period was open - label- however the III period was double blinded, placebo controlled trial.

Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: Mentioned as double-blinded. Unclear who was blinded Not clear if the outcome assessors were blined
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: No apparent sources of bias Only five participants discontinued after randomization and they use LOCF in their analyses
Selective reporting (reporting bias)	Low risk	Judgement Comment: No apparent sources of bias
Other bias	Low risk	Judgement Comment: No apparent sources of bias

Dittmann 2011

Methods	See NICE guideline "Attention deficit hyperactivity disorder: diagnosis and management" 2018
Participants	
Interventions	
Outcomes	*ADHD kernesymptomer, obsevatørbedømt* ● **Outcome type**: ContinuousOutcome *Frafald pga bivirkninger* ● **Outcome type**: DichotomousOutcome *Appetitforstyrrelser* ● **Outcome type**: DichotomousOutcome *Alvorlige bivirkninger total* ● **Outcome type**: DichotomousOutcome
Identification	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Judgement Comment: Randomization was based on a computer-generated random sequence using interactive voice response system, stratified by patients age
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: not described
Blinding of participants and personnel (performance bias)	Unclear risk	Judgement Comment: Mentioned as double-blinded. Unclear who was blinded.
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: Mentioned as double-blinded. Unclear who was blinded.
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: No difference between groups at baseline. However only 62.7% from the placebo groups completed the study. They do however conduct analyses to look at difference in dropout. No apparent sources of bias.
Selective reporting (reporting bias)	Low risk	Judgement Comment: No apparent sources of bias No reason to suspect selective outcome reporting. Not reffering to a registered protocol
Other bias	Low risk	Judgement Comment: No apparent sources of bias.

Escobar 2009

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention 1 ● *Mean age, years*: 10.3 (2.5) mean SD ● *Male %*: 79 Control ● *Mean age, years*: 10.3 (2.4) mean SD ● *Male %*: 80.4 **Included criteria:** Patients with the age og 6-15 years, met the DSM-IV-TR criteria of ADHD and had a ADHDRS-IV-parent:Inv total score > =1.5 SD above the age norm **Excluded criteria:** History of bipolar disorder, psychosis or pervasive developmental disoorder, any other relevant nonpsychiatric condition, general impairments of intelligence, alcohol or drug abuse, were involved in psychotherapy, were taking any medication with sympthomimetic activity or deemed to have difficulties to follow study procedures or to communicate with site personnel. **Pretreatment:** Baseline characteristics were similar in teh atomoxetine and placebo group
Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: Atomoxetine 0.5-1.2mg/kg ● *Length of treatment*: 12 weeks ● *Longest follow-up after end of treatment*: Control ● *Description*: Placebo ● *Length of treatment*: 12 weeks ● *Longest follow-up after end of treatment*:

Outcomes	*ADHD kernesymptomer, obsevatørbedømt* ● **Outcome type**: ContinuousOutcome *Appetitforstyrrelser* ● **Outcome type**: DichotomousOutcome *Livskvalitet* ● **Outcome type**: ContinuousOutcome
Identification	**Sponsorship source:** Lilly research **Country:** Spain **Comments:** Protocol: NCT00191945 **Authors name:** Escobar **Institution:** Lilly research laboratory **Email:** escobar_rodrigo@lilly.com **Address:** Lilly research laboratory, Evenida Industria 30
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Judgement Comment: Randomization was done via a centralized computer-generated random sequence
Allocation concealment (selection bias)	Low risk	Judgement Comment: Study medication was packed in such a way that dose adjustment did not compromise the double-blind design
Blinding of participants and personnel (performance bias)	Unclear risk	Judgement Comment: Mentioned as double blinded. Unclear who was blinded
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: Insufficient information on blinding of the outcome assessors
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: The analyses of effects were carried out by intention to treat. Single missing-item were imputed by the mean score of the remaining items when computing subscale and total score
Selective reporting (reporting bias)	High risk	Judgement Comment: The study protocol has been registered in clinicaltrials.gov, identifier: NCT00191945. The protocol refers the following secondary outcomes, which was not reported in the present study:Vital Signs - Systolic Blood Pressure [Time Frame: Baseline and 12 weeks]Vital Signs - Diastolic Blood Pressure [Time Frame: Baseline and 12 weeks]Vital Signs - Pulse [Time Frame: Baseline and 12 weeks] Vital Signs - Weight [Time Frame: Baseline and 12 weeks]
Other bias	Low risk	Judgement Comment: The study appears to be free from other sources of bias

Gau 2007

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention 1 ● *Mean age, years*: 9.1 ● *Male %*: 90.3 Control ● *Mean age, years*: 9.5 ● *Male %*: 85.3 **Included criteria:** A total score on the ADHD-RS-IV of at least 25 for boys and 22 for girls. Normal intellegence, no ADHD medication **Excluded criteria:** Weight 20kg or >60kg. Serious medical illness, history og bipolar I or II disorder, pervasive developmental disorder, anxiety dosorder, history of seizure, or EEG abnormalities, alcohol or drug abuse or other psychoactive medication other then the study drug during the study **Pretreatment:** No apparent differences at baseline
Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: Atomoxetine 1.8 mg/kg ● *Length of treatment*: 6 weeks Control ● *Description*: Plabebo ● *Length of treatment*: 6 weeks
Outcomes	*ADHD kernesymptomer* ● **Outcome type**: ContinuousOutcome *ADHD kernesymptomer* ● **Outcome type**: ContinuousOutcome *ADHD kernesymptomer* ● **Outcome type**: ContinuousOutcome *Adfærdsforstyrrelser* ● **Outcome type**: ContinuousOutcome *Adfærdsforstyrrelser* ● **Outcome type**: ContinuousOutcome *Vægttab* ● **Outcome type**: ContinuousOutcome

	Apetitforstyrrelser ● **Outcome type**: DichotomousOutcome *Søvnforstyrrelser* ● **Outcome type**: DichotomousOutcome
Identification	**Sponsorship source:** Eli Lilly Co **Country:** Taiwan **Setting:** 3 outpatient sites **Authors name:** Susan Gau **Institution:** Dep. of psychiatry **Email:** lee_pjil@lilly.com **Address:** 11F, 365, Fu Hsin N. Road
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Allocation concealment (selection bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Blinding of participants and personnel (performance bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Blinding of outcome assessment (detection bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Incomplete outcome data (attrition bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Selective reporting (reporting bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Other bias	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017

Geller 2007

Methods	See NICE guideline "Attention deficit hyperactivity disorder: diagnosis and management" 2018
Participants	
Interventions	
Outcomes	*ADHD kernesymptomer, obsevatørbedømt* ● **Outcome type**: ContinuousOutcome *Vægttab, mean change* ● **Outcome type**: ContinuousOutcome *Appetitforstyrrelser* ● **Outcome type**: DichotomousOutcome *Søvnforstyrrelser* ● **Outcome type**: DichotomousOutcome *Livskvalitet* ● **Outcome type**: ContinuousOutcome
Identification	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement Comment: Mentioned as randomized. Unclear how it was done.
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: Nothing mentioned.
Blinding of participants and personnel (performance bias)	Low risk	Judgement Comment: Quote:"Patients assigned to the placebo group received placebo twicedaily""Patients and site personnelwere informed of the 2-week placebo period, but were blinded to itstiming and duration; investigational review boards were provided arationale in a supplement to the protocol and informed of timingand duration. All of the investigational review boards and all of theinvestigators accepted this condition."
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: Mentioned as blinded. Unclear who was blinded.
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: Last observation carried forward (LOCF) was used in the statistical analyses. No apparent sources of bias
Selective reporting (reporting bias)	Low risk	Judgement Comment: No apparent sources of bias.
Other bias	Low risk	Judgement Comment: No apparent sources of bias.

Hervas 2014

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention ● *AGE IN YEARS, MEAN (SD)*: 10.5 ● *MALE GENDER (%)*: 77.7 Placebo ● *AGE IN YEARS, MEAN (SD)*: 11.0 ● *MALE GENDER (%)*: 77.5 **Included criteria:** Male and female children/adolescents (6–17 years old) with adiagnosis of ADHD of at least moderate severity, as defined by abaseline ADHD-RS-IV with a total score of 32 or higher and aminimum Clinical Global Impression-Severity (CGI-S) score of 4,were enrolled in the study. Those with age-appropriate intellectualfunctioning; blood pressure measurements within the 95th percen-tile for age, sex and height; and the ability to swallow tablets orcapsules were included. Girls of childbearing potential had to havea negative urine pregnancy test at screening and baseline and tocomply with any protocol contraceptive requirements. In addition,participants and their parent/legal guardian had to be willing, able and likely to fully comply with the study procedures and restrictionsdefined in the protocol. Subjects who took between 80% and 120%of their total medication were considered to be compliant with thestudy protocol. **Excluded criteria:** Exclusion criteria included: clinically significantillness, including a clinically significant abnormal screening visit;current, comorbid psychiatric diagnosis (except oppositional defiantdisorder [ODD]); history/presence of cardiac abnormalities, cardi-ovascular or cerebrovascular disease, serious heart rhythm abnorm-alities, syncope, tachycardia, cardiac conduction problems,exercise-related cardiac events or clinically significant bradycardia;orthostatic hypotension and/or a known history of hypertension;seizures; and glaucoma. In addition, those with a family history ofsudden cardiac death, ventricular arrhythmia or QT prolongation, apatient history of alcohol or substance abuse and those patientswith serious tic disorder, including Tourette's syndrome, wereexcluded. In addition, enrollment was managed to ensure thatapproximately 25% of those enrolled were adolescents and at least25% were female. Furthermore, at least 70% of those enrolled wereto come from European centers and the remaining 30% from USA/Canada **Pretreatment:** Baseline characteristics were similar across treatmentgroups
Interventions	**Intervention Characteristics** Intervention ● *DESCRIPTION*: For ATX, either oneATX or matching placebo capsule (if optimized to up to 60 mg/day)or two capsules (if optimized to more than 60 mg) were taken. ATXdosing was initiated at 0.5 mg/kg/day in children and adolescentsweighing less than 70 kg at baseline and increased to the target ofapproximately 1.2 mg/kg/day and, if well tolerated after a mini-mum of 1 week, to a maximum of 1.4 mg/kg/day. ATX dosing inchildren and adolescents weighing 70 kg or more at baseline (Visit2) was initiated at 40 mg/day. This was increased to 80 mg/day andthen, following 1 week at 80 mg/day, increased again to 100 mg/day, if required; this was the total permitted maximum daily dose.ATX was titrated as supported by the prescribing information/Summary of Product Characteristics European lab. ● *LENGTH OF INTERVENTION (WEEKS)*: 13 weeks Placebo ● *DESCRIPTION*: Placebo ● *LENGTH OF INTERVENTION (WEEKS)*: 13 weeks
Outcomes	*ADHD kernesymptomer, observatør/kliniker bedømt* ● **Outcome type**: ContinuousOutcome *ADHD kernesymptomer, forældre* ● **Outcome type**: ContinuousOutcome *Frafald pga. bivirkninger* ● **Outcome type**: DichotomousOutcome *Alvorlige bivirkninger-totalt* ● **Outcome type**: DichotomousOutcome *ADHD kernesymptomer, observatør/kliniker bedømt* ● **Outcome type**: ContinuousOutcome *Appetitforstyrrelser* ● **Outcome type**: DichotomousOutcome *Søvnforstyrrelser* ● **Outcome type**: DichotomousOutcome *Angst/nervousness* ● **Outcome type**: DichotomousOutcome *Total severe adverse event* ● **Outcome type**: DichotomousOutcome
Identification	**Sponsorship source:** Funding for this study was provided by Shire Development, LLC.Shire Development, LLC was involved in the study design, collec-tion, analyses and interpretation of the data, and checking theinformation for scientific accuracy **Country:** Spain **Setting:** Multicenter **Comments:** ClinicalTrials.gov identifier: NCT01244490 and EudraCT: 2010-018579 **Authors name:** Amaia Hervas **Institution:** Child and Adolescent Mental Health Unit, University Hospital Mútua de Terrassa, UETD, Hospital SantJoan de Deu, Barcelona, Spain **Email:** 32989ahz@comb.cat
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization occurred at baseline (day 0) and eligible participants were rando- mized, using a 1: 1:1 ratio, to GXR, ATX or placebo (automatically, randomly assigned by the interactive voice response system). Alloca- tion to treatment was stratified within age group (6–12 or 13–17 years) and country."
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: Nothing mentioned
Blinding of participants and personnel (performance bias)	Unclear risk	Judgement Comment: Nothing mentioned
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: Nothing mentioned
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: No apparent sources of bias
Selective reporting (reporting bias)	Low risk	Judgement Comment: Matches study protocol
Other bias	Low risk	Judgement Comment: No other apparent sources of bias

Kaplan 2004

Methods	See NICE guideline "Attention deficit hyperactivity disorder: diagnosis and management" 2018
Participants	
Interventions	
Outcomes	*ADHD kernesymptomer, obsevatørbedømt, CI* ● **Outcome type**: ContinuousOutcome *Adfærdsforstyrrelser, forældrebedømt, SD* ● **Outcome type**: ContinuousOutcome *Frafald pga bivirkninger, n* ● **Outcome type**: DichotomousOutcome *Appetitforstyrrelser, n* ● **Outcome type**: DichotomousOutcome
Identification	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Judgement Comment: Randomization was generated by validated software and implemented using a voice-response phone system to dispense study medication.
Allocation concealment (selection bias)	Low risk	Judgement Comment: Drug materials for all treatment groups in the study were identical in apperance.
Blinding of participants and personnel (performance bias)	Unclear risk	Judgement Comment: Mentioned as blinded. Unclear who was blinded.
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: Mentioned as blinded. Unclear who was blinded.
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: No apparent sources of bias. low droupout
Selective reporting (reporting bias)	Low risk	Judgement Comment: No apparent sources of bias. No reason to suspect slective outcome reporting
Other bias	Low risk	Judgement Comment: No other apparent sources of bias.

Kelsey 2004

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention 1 ● *Mean age, years*: 9.5 ● *Male %*: 70.7 Control ● *Mean age, years*: 9.4 ● *Male %*: 70.3 **Included criteria:** Children 6 to 12 years of age who metDiagnostic and StatisticalManual of Mental Disorders(4th ed.) criteria for ADHD, as assessedin clinical interviews and confirmed in parent interviews using theKiddie Schedule for Affective Disorders and Schizophrenia forSchool-Aged Children–Present and Lifetime Version,19were eli-gible to participate. All patients were required to meet a symptomseverity threshold, with a symptom severity score at least 1.5 SDsabove age and gender normative values, as assessed with theAttention-Deficit/Hyperactivity Disorder Rating Scale-IV-ParentVersion: Investigator-Administered and Scored (ADHD RS),20,21for the total score or either of the inattentive or hyperactive/impulsive subscales. Important exclusion criteria included seriousmedical illness, a history of psychosis or bipolar disorder, alcoholor drug abuse within the past 3 months, and ongoing use ofpsychoactive medications other than the study drug. Patients wererecruited by referral and by advertisement

Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: Atomoxetine 1.8mg/kg ● *Length of treatment*: 8 weeks Control ● *Description*: Placebo ● *Length of treatment*: 8 weeks
Outcomes	*ADHD kernesymptomer, obsevatørbedømt* ● **Outcome type**: ContinuousOutcome *Frafald pga bivirkninger* ● **Outcome type**: DichotomousOutcome *Appetitforstyrrelser* ● **Outcome type**: DichotomousOutcome
Identification	**Sponsorship source:** Lilly technology **Country:** USA **Setting:** 12 outpatient sites **Authors name:** Douglas Kelsey **Institution:** Lilly research laboratory **Email:** Kelsey_douglas_K@lilly.com
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Allocation concealment (selection bias)	Unclear risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Blinding of participants and personnel (performance bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Blinding of outcome assessment (detection bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Incomplete outcome data (attrition bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Selective reporting (reporting bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Other bias	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017

Martenyi 2010

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention 1 ● *Mean age, years*: 9.9 ● *Male %*: 87.5 Control ● *Mean age, years*: 9.6 ● *Male %*: 81.8 **Included criteria:** Patients were eligible to participate if they met the following criteria: at both visits, 1 and 2(screening and randomization), had a minimum score of 25for boys and 22 for girls, or[12 for their diagnostic sub-type on the Attention-Deficit/Hyperactivity Disorder Rat-ing Scale-IV-Parent Version: Investigator-Administeredand Scored [7], as well as a score ofC4 on the ClinicalGlobal Impressions-ADHD-Severity (CGI-ADHD-S [10])scale; had not taken any medication for the treatment ofADHD or completed washout procedures; had no signifi-cant abnormalities in laboratory results and baseline ECG;and were able to communicate suitably with the investi-gator and study coordinator. **Excluded criteria:** Patients were excluded if they weighed\20 kg or[60 kg at study entry; experienced no clinical benefitafter an adequate trial with methylphenidate or amphet-amine (all patients were psychostimulant naive, but it wasnot required by the protocol); had been treated, within the previous 30 days, with a drug (not including study drug) that had not received a regulatory approval for any indication at the time of study entry; had a history of bipolar Ior II disorder, psychosis, or pervasive developmentaldisorder; met DSM-IV criteria for an anxiety disorder (asassessed by the investigator and confirmed by theK-SADS-PL); had a history of any seizure disorder (otherthan febrile seizures) or prior electroencephalogram abnormalities related to epilepsy; had taken (or were taking) anticonvulsants for seizure control; were at serious suicidal risk or had a serious medical illness; or were pregnant or breast-feeding.
Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: Atomoxetine 1.8mg/kg ● *Length of treatment*: 6 weeks Control ● *Description*: Placebo ● *Length of treatment*: 6 week

Outcomes	*ADHD kernesymptomer, obsevatørbedømt* ● **Outcome type**: ContinuousOutcome *Adfærdsforstyrrelser, forældrebedømt* ● **Outcome type**: ContinuousOutcome *Frafald pga bivirkninger* ● **Outcome type**: DichotomousOutcome *Vægttab* ● **Outcome type**: DichotomousOutcome *Appetitforstyrrelser* ● **Outcome type**: DichotomousOutcome
Identification	**Sponsorship source:** Financial disclosureDrs. Martenyi and Jarkova are employees andstockholders of Eli Lilly and Company. Dr. Zavadenko is a memberof the Lilly ADHD advisory board. The rest of the authors do not haveany financial disclosures to report. This study was funded by Eli Lillyand Company. **Country:** USA **Comments:** Clinical Trials Registry: NCT00386581,http://www.clinicaltrials.gov/. **Authors name:** Ferenc Martenyi **Institution:** Lilly Corporate Center, Lilly Research Laboratories **Email:** martenyi_ferenc@lilly.com **Address:** Lilly Corporate Center, Lilly Research Laboratories, Indianapolis, IN 46285, USA
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Allocation concealment (selection bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Blinding of participants and personnel (performance bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Blinding of outcome assessment (detection bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Incomplete outcome data (attrition bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Selective reporting (reporting bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Other bias	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017

Michelson 2001

Methods	See NICE guideline "Attention deficit hyperactivity disorder: diagnosis and management" 2018
Participants	
Interventions	
Outcomes	*ADHD kernesymptomer, obsevatørbedømt* ● **Outcome type**: ContinuousOutcome *ADHD kernesymptomer, forældrebedømt* ● **Outcome type**: ContinuousOutcome *Adfærdsforstyrrelser, forældrebedømt* ● **Outcome type**: ContinuousOutcome *Frafald pga bivirkninger* ● **Outcome type**: DichotomousOutcome *Vægttab, mean change* ● **Outcome type**: ContinuousOutcome *Appetitforstyrrelser* ● **Outcome type**: DichotomousOutcome *Søvnforstyrrelser* ● **Outcome type**: DichotomousOutcome
Identification	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized using computer-generated codes via an interactive voice response system. The"

Allocation concealment (selection bias)	Low risk	Quote: "Each patient's genotype was reported to the investigative sites in a sealed envelope for blinding purposes, not to be opened except in the case of emergency." Quote: "The study drug for all treatment groups was identical in appearance."
Blinding of participants and personnel (performance bias)	Unclear risk	Judgement Comment: Insufficient information on blinding
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: Insufficient information on blinding
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: Reason for missing outcome data was balanced accrossed groups No apparent sources of bias.
Selective reporting (reporting bias)	Low risk	Judgement Comment: No reference to study protocol, but appears to be from selective outcome reporting
Other bias	Low risk	Judgement Comment: The study appears to be free from other sources of bias

Michelson 2002

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention 1 ● *Mean age, years*: ● *Male %*: 70.6 Control ● *Mean age, years*: ● *Male %*: 70.6 **Included criteria:** Children and adolescents, 6–16 years of age, who met DSM-IVcriteria for ADHD, as assessed by clinical interview and confirmedby the Schedule for Affective Disorders and Schizophrenia forSchool-Age Children—Present and Lifetime Version (K-SADS-PL)(7), were eligible to participate. All patients were required to meeta symptom severity threshold: a score at least 1.5 standard devia-tions above age and gender norms as assessed by the investigator-administered and -scored parent version of the ADHD Rating Am J Psychiatry 159:11, November 20021897MICHELSON, ALLEN, BUSNER, ET AL.Scale–IV (8). Comorbid psychiatric conditions were assessed clin-ically and with the K-SADS-PL **Excluded criteria:** Important exclusion criteria in-cluded serious medical illness, a history of psychosis or bipolardisorder, alcohol or drug abuse within the past 3 months, and on-going use of psychoactive medications other than the study drug.Patients were recruited by referral and by advertisement
Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: Atomoxetine. Study drug was administered as a singledaily dose in the morning. Patients in the atomoxetine treatmentarm began treatment at 0.5 mg/kg/day for 3 days, followed by 0.75mg/kg/day for the remainder of the first week. The daily dose wasthen increased to 1.0 mg/kg/day. Four weeks after randomiza-tion, patients with a Clinical Global Impression (CGI) severityscore >2 (more than minimal symptoms) had a further dose in-crease to 1.5 mg/kg/day. ● *Length of treatment*: 6 weeks Control ● *Description*: Placebo ● *Length of treatment*: 6 weeks
Outcomes	*ADHD kernesymptomer, lærerbedømt* ● **Outcome type**: ContinuousOutcome *ADHD kernesymptomer, obsevatørbedømt* ● **Outcome type**: ContinuousOutcome *ADHD kernesymptomer, forældrebedømt* ● **Outcome type**: ContinuousOutcome *Appetitforstyrrelser* ● **Outcome type**: DichotomousOutcome
Identification	**Sponsorship source:** Lilly Corporate Center **Country:** USA **Authors name:** David Michelson **Institution:** Lilly Corporate Center **Email:** dmichelson@lilly.com **Address:** Lilly Corporate Center, Indianapolis, IN46285
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Allocation concealment (selection bias)	Unclear risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Blinding of participants and personnel (performance bias)	Unclear risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Blinding of outcome assessment (detection bias)	Unclear risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017

Incomplete outcome data (attrition bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Selective reporting (reporting bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Other bias	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017

Montoya 2009

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention 1 ● *Mean age, years*: 10.3 ● *Male %*: 79.0 Control ● *Mean age, years*: 10.3 ● *Male %*: 80.4 **Included criteria:** The study focused on newly diagnosed (time since diag-nosis3 months), treatment-naı¨ve cases of ADHDdefined according to the criteria of the revised fourth edi-tion of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)2. The Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version (K-SADS-PL) 20 was used at screening stage to confirm the diagnosis. Other inclusion criteria were: age between 6 and 15 years, and an ADHDRS-IV-Parent:Inv total score1.5 standard deviations above the age norm21for their diagnostic subtype **Excluded criteria:** Exclusion criteria were patients with history of bipolar disorder, psychosis,pervasive developmental disorder or seizure disorder, glau-coma or hypertension, intelligence quotient (IQ) below 70at investigator's judgment, any pervasive developmental disorder, alcohol or drug abuse within the past 3 months,planned start of structured psychotherapy at any time during the study, and taking any regular psychoactive or sympathomimetic medication. **Pretreatment:** Baseline characteristics were similar in both groups
Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: Atomoxetine. The atomox-etine starting dose was 0.5 mg/kg/day during the first2 weeks and was increased to a target dose of 1.2 mg/kg/dayfor the remaining 10 weeks. Study medication was packedin capsules labeled at 5, 10, 15, 20, 25, and 40 mg regardlessof whether or not they contained atomoxetine or placeboto allow dose adjustments without compromising thedouble-blind design. Because the medication was formu-lated in capsules, only discrete (not continuous) dosingwas possible; thus, patients were divided into six weightranges to approximate the target doses, resulting in anactual dosing range of 0.4 to 0.9 mg/kg/day for the0.5 mg/kg/day dose, and of 0.8 to 1.4 mg/kg/day for thetarget dose of 1.2 mg/kg/day in the extremes of weightintervals. All doses were given once daily. ● *Length of treatment*: 12 weeks Control ● *Description*: Placebo ● *Length of treatment*: 12 weeks
Outcomes	*ADHD kernesymptomer, obsevatørbedømt, CI* ● **Outcome type**: ContinuousOutcome *Adfærdsforstyrrelser, forældrebedømt SE* ● **Outcome type**: ContinuousOutcome *Appetitforstyrrelser, n* ● **Outcome type**: DichotomousOutcome
Identification	**Sponsorship source:** This clinical trial has been funded by Lilly Research Laboratories,Alcobendas, Spain **Country:** Spain **Setting:** 12 specialized outpatient settings **Comments:** study internal code: B4Z-XM-LYDM, identifier: NCT00191945 **Authors name:** Alonso Montoya **Institution:** Lilly Research Laboratories **Email:** escobar_rodrigo@lilly.com **Address:** Rodrigo Escobar. EU Medical Lilly ResearchLaboratories. Avenida Industria, 30. 28108 Alcobendas, Spain
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Allocation concealment (selection bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Blinding of participants and personnel (performance bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Blinding of outcome assessment (detection bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Incomplete outcome data (attrition bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017

Selective reporting (reporting bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Other bias	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017

Newcorn 2008

Methods	See NICE guideline "Attention deficit hyperactivity disorder: diagnosis and management" 2018
Participants	
Interventions	●
Outcomes	*ADHD kernesymptomer, obsevatørbedømt, CI* ● **Outcome type**: ContinuousOutcome *ADHD kernesymptomer, forældrebedømt, CI* ● **Outcome type**: ContinuousOutcome *Frafald pga bivirkninger, n* ● **Outcome type**: DichotomousOutcome *Appetitforstyrrelser, n* ● **Outcome type**: DichotomousOutcome *Søvnforstyrrelser, n* ● **Outcome type**: DichotomousOutcome
Identification	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "After two pretreatment assess- ment visits, patients were randomly assigned to receive one of three treatments: atomoxetine (0.8–1.8 mg/kg per day, adminis- tered as a divided twice-daily dose), osmotically released meth- ylphenidate (18–54 mg/day, administered as a single morning dose), or placebo. The randomization ratio was 3:3:1 for atomox- etine, osmotically released methylphenidate, and placebo, re- spectively." Judgement Comment: Mentioned as randomized. Unclear how it was done.
Allocation concealment (selection bias)	Low risk	Quote: "The study drugs were administered by using a double-dummy design. Patients in each treatment arm took three identically ap- pearing capsules consisting of atomoxetine, osmotically released methylphenidate, or placebo"
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "In addition, both the site investiga- tors and subjects were blinded to the response criterion used in the initial trial and to when that phase ended and the next phase began. These design features all served to protect the blind during the crossover phase of the study." Judgement Comment: Nothing mentioned
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: Unclear if outcome assessors were blinded
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: No apparent sources of bias conducts ITT
Selective reporting (reporting bias)	Low risk	Judgement Comment: No apparent sources of bias.
Other bias	Low risk	Judgement Comment: No apparent sources of bias.

Spencer 2002

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention 1 ● *Mean age, years*: 9.7 ● *Male %*: 98 (n) Control ● *Mean age, years*: 10.0 ● *Male %*: 103 (n) **Included criteria:** Should meet the DSM-IV criteria for ADHD. Have a ADHD-RS:IV of at least 1.5 standard deviation above the gender and age norm **Excluded criteria:** Poor metabolizers of CYP2D6. Weight 25kg at study entry. Documented history of bipolar I or II disorder or any history of seizure, organic brain disease, alcohol and drug abuse, prior medical condition or taking any osychotropic medication.
Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: Atomoxetine. 2mg/kg ● *Length of treatment*: 12 weeks Control ● *Description*: Placebo ● *Length of treatment*: 12 weeks

Outcomes	*ADHD kernesymptomer, obsevatørbedømt* ● **Outcome type**: ContinuousOutcome *Frafald pga bivirkninger* ● **Outcome type**: DichotomousOutcome *Vægttab* ● **Outcome type**: ContinuousOutcome *Appetitforstyrrelser* ● **Outcome type**: DichotomousOutcome *Appetitforstyrrelser* ● **Outcome type**: DichotomousOutcome *Søvnforstyrrelser* ● **Outcome type**: DichotomousOutcome
Identification	**Sponsorship source:** Eli Lilly Company **Country:** USA **Authors name:** Thomas Spencer **Institution:** Eli Lilly Company **Email:** heilig@lilly.com
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Allocation concealment (selection bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Blinding of participants and personnel (performance bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Blinding of outcome assessment (detection bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Incomplete outcome data (attrition bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Selective reporting (reporting bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Other bias	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017

Spencer 2008

Methods	See NICE guideline "Attention deficit hyperactivity disorder: diagnosis and management" 2018
Participants	
Interventions	
Outcomes	*ADHD kernesymptomer, obsevatørbedømt* ● **Outcome type**: ContinuousOutcome *Frafald pga bivirkninger* ● **Outcome type**: DichotomousOutcome *Appetitforstyrrelser* ● **Outcome type**: DichotomousOutcome
Identification	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement Comment: See Allen 2005 "Atomoxetine treatment in children and adolescents with ADHD and comorbid tic disorders"
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: See Allen 2005 "Atomoxetine treatment in children and adolescents with ADHD and comorbid tic disorders"
Blinding of participants and personnel (performance bias)	Unclear risk	Judgement Comment: See Allen 2005 "Atomoxetine treatment in children and adolescents with ADHD and comorbid tic disorders"
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: See Allen 2005 "Atomoxetine treatment in children and adolescents with ADHD and comorbid tic disorders"
Incomplete outcome data (attrition bias)	Unclear risk	Judgement Comment: See Allen 2005 "Atomoxetine treatment in children and adolescents with ADHD and comorbid tic disorders"
Selective reporting (reporting bias)	Unclear risk	Judgement Comment: See Allen 2005 "Atomoxetine treatment in children and adolescents with ADHD and comorbid tic disorders"

Other bias	Unclear risk	Judgement Comment: See Allen 2005 "Atomoxetine treatment in children and adolescents with ADHD and comorbid tic disorders"

Svanborg 2009

Methods	See NICE guideline "Attention deficit hyperactivity disorder: diagnosis and management" 2018
Participants	
Interventions	
Outcomes	*ADHD kernesymptomer, obsevatørbedømt* ● **Outcome type**: ContinuousOutcome
Identification	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement Comment: See Svanborg, P.; Thernlund, G.; Gustafsson, P. A.; Hagglof, B.; Poole, L.; Kadesjo, B. Efficacy and safety of atomoxetine as add-on to psychoeducation in the treatment of attention deficit/hyperactivity disorder: a randomized, double-blind, placebo-controlled study in stimulant-naive Swedish children and adolescentsEuropean child & adolescent psychiatry 2009;18(4):240-249 Germany 2009
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: See Svanborg, P.; Thernlund, G.; Gustafsson, P. A.; Hagglof, B.; Poole, L.; Kadesjo, B. Efficacy and safety of atomoxetine as add-on to psychoeducation in the treatment of attention deficit/hyperactivity disorder: a randomized, double-blind, placebo-controlled study in stimulant-naive Swedish children and adolescentsEuropean child & adolescent psychiatry 2009;18(4):240-249 Germany 2009
Blinding of participants and personnel (performance bias)	Unclear risk	Judgement Comment: See Svanborg, P.; Thernlund, G.; Gustafsson, P. A.; Hagglof, B.; Poole, L.; Kadesjo, B. Efficacy and safety of atomoxetine as add-on to psychoeducation in the treatment of attention deficit/hyperactivity disorder: a randomized, double-blind, placebo-controlled study in stimulant-naive Swedish children and adolescentsEuropean child & adolescent psychiatry 2009;18(4):240-249 Germany 2009
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: See Svanborg, P.; Thernlund, G.; Gustafsson, P. A.; Hagglof, B.; Poole, L.; Kadesjo, B. Efficacy and safety of atomoxetine as add-on to psychoeducation in the treatment of attention deficit/hyperactivity disorder: a randomized, double-blind, placebo-controlled study in stimulant-naive Swedish children and adolescentsEuropean child & adolescent psychiatry 2009;18(4):240-249 Germany 2009
Incomplete outcome data (attrition bias)	Unclear risk	Judgement Comment: See Svanborg, P.; Thernlund, G.; Gustafsson, P. A.; Hagglof, B.; Poole, L.; Kadesjo, B. Efficacy and safety of atomoxetine as add-on to psychoeducation in the treatment of attention deficit/hyperactivity disorder: a randomized, double-blind, placebo-controlled study in stimulant-naive Swedish children and adolescentsEuropean child & adolescent psychiatry 2009;18(4):240-249 Germany 2009
Selective reporting (reporting bias)	Unclear risk	Judgement Comment: See Svanborg, P.; Thernlund, G.; Gustafsson, P. A.; Hagglof, B.; Poole, L.; Kadesjo, B. Efficacy and safety of atomoxetine as add-on to psychoeducation in the treatment of attention deficit/hyperactivity disorder: a randomized, double-blind, placebo-controlled study in stimulant-naive Swedish children and adolescentsEuropean child & adolescent psychiatry 2009;18(4):240-249 Germany 2009
Other bias	Unclear risk	See Svanborg, P.; Thernlund, G.; Gustafsson, P. A.; Hagglof, B.; Poole, L.; Kadesjo, B. Efficacy and safety of atomoxetine as add-on to psychoeducation in the treatment of attention deficit/hyperactivity disorder: a randomized, double-blind, placebo-controlled study in stimulant-naive Swedish children and adolescentsEuropean child & adolescent psychiatry 2009;18(4):240-249 Germany 2009

Svanborg 2009a

Methods	See NICE guideline "Attention deficit hyperactivity disorder: diagnosis and management" 2018
Participants	
Interventions	●
Outcomes	● Livskvalitet
Identification	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization using an interactive voice system, stratified by site, was performed at visit 2 (week 0)."
Allocation concealment (selection bias)	Low risk	Quote: "identical placebo capsules were available"
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "In addition to pharmacotherapy, treatment in- cluded a psychoeducational program for the patients' caregivers of both treatment groups." Judgement Comment: Mentioned as blinded. Unclear who was blinded.
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: Unclear if outcome assessors are blinded

Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: No apparent sources of bias. LOCF analyses
Selective reporting (reporting bias)	Low risk	Judgement Comment: No apparent sources of bias.Not refering to a registered protocol
Other bias	Low risk	Judgement Comment: No apparent sources of bias.

Takahashi 2009

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention 1 ● *Mean age, years*: 10.25 ● *Male %*: 83.9 Intervention 2 ● *Mean age, years*: 10.60 ● *Male %*: 86.7 Intervention 3 ● *Mean age, years*: 10.51 ● *Male %*: 86.9 Control ● *Mean age, years*: 10.76 ● *Male %*: 83.9 **Included criteria:** This multicenter study was conducted in 245 Japanese pe-diatric patients with ADHD at 41 study centers in Japan.Japanese children and adolescents who were at least 6 yearsold but younger than 18 years of age were eligible to partici-pate if: (1) they met the DSM-IV criteria for ADHD by clinicalassessment (American Psychiatric Association 1994) and (2)their diagnosis was confirmed in structured interviews withinvestigators using the behavior module for ADHD of theKiddie Schedule for Affective Disorders and Schizophreniafor School- Aged Children–Present and Lifetime Versions (K-SADS-PL) (Kaufman et al. 1997). Also, patients had to have aClinical Global Impressions–ADHD-Severity (CGI-ADHD-S)assessment score3 (Guy 1976; National Institute of MentalHealth 1985) and a symptom severity score at least 1.5 stan-dard deviations (SD) above Japanese pediatric age and gendernorms on the Attention-Deficit=Hyperactivity Disorder Rat-ing Scale-IV–Parent Version:Investigator Administered andScored=Translated and Validated in Japanese (ADHD RS-IV-J:I) (DuPaul et al. 1998; Yamazaki et al. 2001).Patients were also required to be of normal intelligence (IQ80). For patients younger than 17 years of age, this wasassessed by the Wechsler Intelligence Scale for Children–Third Edition (WISC-III). Individual investigators determinednormal intelligence in patients 17 years and older. **Excluded criteria:** Important exclusion criteria included patients who tookany antipsychotic medication within 26 weeks of study visit 1,had a history of bipolar disorder or psychosis, or were de-termined by the investigator to be at suicidal risk
Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: Atomoxetine 0.5mg/kg ● *Length of treatment*: 8 weeks Intervention 2 ● *Description*: Atomoxetine 1.2mg/kg ● *Length of treatment*: 8 weeks ● *Longest follow-up after end of treatment*: Intervention 3 ● *Description*: Atomoxetine 1.8mg/kg ● *Length of treatment*: 8 weeks Control ● *Description*: Placebo ● *Length of treatment*: 8 weeks
Outcomes	*ADHD kernesymptomer, obsevatørbedømt* ● **Outcome type**: ContinuousOutcome *Frafald pga bivirkninger* ● **Outcome type**: DichotomousOutcome *Appetitforstyrrelser* ● **Outcome type**: DichotomousOutcome
Identification	**Sponsorship source:** This research was funded by Eli Lilly Japan K.K **Country:** Japan **Authors name:** Michihiro Takahashi, **Institution:** Lilly Research Laboratories Japan, Kobe, Japan. **Email:** Takahashi_michihiro@lilly.com **Address:** Dr. Michiro TakahashiLilly Research Laboratories JapanEli Lilly Japan K.K.Sannomiya Plaza Bldg.7-1-5, Isogamidori, Chuo-kuKobe, 651-0086 Japa
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Allocation concealment (selection bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017

Blinding of participants and personnel (performance bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Blinding of outcome assessment (detection bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Incomplete outcome data (attrition bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Selective reporting (reporting bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Other bias	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017

Wehmeier 2011

Methods	See NICE guideline "Attention deficit hyperactivity disorder: diagnosis and management" 2018
Participants	
Interventions	
Outcomes	*Frafald pga bivirkninger* ● **Outcome type**: DichotomousOutcome *Alvorlige bivirkninger total* ● **Outcome type**: DichotomousOutcome
Identification	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Judgement Comment: Computer-randomization
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: Insufficient information on sequence generation, but capsules identical in appearance
Blinding of participants and personnel (performance bias)	Unclear risk	Judgement Comment: Mentioned as blinded. Unclear who was blinded.
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: Insufficient information on blinding of the outcome assessors
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: Missing data replaced with last observation carried forward
Selective reporting (reporting bias)	Low risk	Judgement Comment: The study protocol was registered in clinicaltrials.gov (NCT00546910) and there was consistency in the reporting
Other bias	Unclear risk	Judgement Comment: Financed by medcine industry and it is unclear which role the Funding had in the study. No apparent sources of bias.

Wehmeier 2012

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Overall ● *Mean age, years*: 9.0 ● *Male %*: 77.6 **Included criteria:** 6-12 years of age. ADHD diagnosis according to diagnostic and statistical manual of mental disorder **Excluded criteria:** Previous treatment with atomoxetine, clinical over- or underweight, history of bipolar disorder, psychosis, pervasive developmental disorder, seizure disorder, serious suicidal risk and other acute/unstable medical condition **Pretreatment:** Treatment groups were comparable at baseline
Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: Atomoxetine 1.2 mg/kg ● *Length of treatment*: 8 weeks Control ● *Description*: Placebo ● *Length of treatment*: 8 weeks
Outcomes	*ADHD kernesymptomer, obsevatørbedømt* ● **Outcome type**: ContinuousOutcome *Vægttab* ● **Outcome type**: DichotomousOutcome *Appetitforstyrrelser* ● **Outcome type**: DichotomousOutcome *Alvorlige bivirkninger - total* ● **Outcome type**: DichotomousOutcome

Identification	**Sponsorship source:** Lilly Deutschland **Country:** Germany **Comments:** NCT00546910 **Authors name:** Peter M. Wehmeier **Institution:** Dep. of child and adolescent Psychiatry **Email:** Peter.Wehmeier@vitos-weilmuenster.de
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Allocation concealment (selection bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Blinding of participants and personnel (performance bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Blinding of outcome assessment (detection bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Incomplete outcome data (attrition bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Selective reporting (reporting bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Other bias	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017

Wehmeier 2014

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention ● *AGE IN YEARS, MEAN (SD)*: 9.1 ● *MALE GENDER (%)*: 47, n Placebo ● *AGE IN YEARS, MEAN (SD)*: 8.9 ● *MALE GENDER (%)*: 50 **Included criteria:** Girls and boys aged 6 to 12 years with a diagnosis ofADHD according to Diagnostic and Statistical Manual ofMental Disorders (4th ed., text rev.; DSM-IV-TR; APA,2000) criteria (APA, 2000) were eligible. The diagnosiswas confirmed using the “Diagnose-ChecklisteHyperkinetische Störungen” (Diagnostic Checklist forHyperkinetic Disorders [DCL-HKS]), a structured instrumentthat is routinely used for the diagnostic assessment ofADHD in Germany (Döpfner Lehmkuhl, 2000). Theitems of this instrument correspond to those of theADHD-RS (DuPaul et al., 1998; Faries et al., 2001). Thepresence of comorbid disorders frequently associated withADHD was not exclusionary. **Excluded criteria:** The exclusion criteria comprisedprevious treatment with ATX, treatment with psychotropicmedication other than the study drug, clinicallyrelevant over- and underweight, a history of bipolar disorder,psychosis, pervasive developmental disorder, seizuredisorder (other than febrile seizures), serious suicidal risk,and other relevant acute or unstable medical conditions.Psychotherapy initiated prior to the study was acceptable. **Pretreatment:** The two treatment groups were comparable in terms of baseline characteristicsand baseline ADHD severity as measured by theADHD-RS
Interventions	**Intervention Characteristics** Intervention ● *DESCRIPTION*: Eligible patients were randomizedto 8 weeks of treatment with ATX starting at 0.5mg/kg/day for 1 week, followed by 7 weeks on the standardtarget dose of 1.2 mg/kg/day ● *LENGTH OF INTERVENTION (WEEKS)*: 8 weeks Placebo ● *DESCRIPTION*: placebo (administered incapsules looking identical to the study drug) ● *LENGTH OF INTERVENTION (WEEKS)*: 8 weeks
Outcomes	*ADHD kernesymptomer, observatør/kliniker bedømt* ● **Outcome type**: ContinuousOutcome *ADHD kernesymptomer, forældre* ● **Outcome type**: ContinuousOutcome *Frafald pga. bivirkninger* ● **Outcome type**: DichotomousOutcome *Alvorlige bivirkninger-totalt* ● **Outcome type**: DichotomousOutcome
Identification	**Sponsorship source:** The author(s) disclosed receipt of the following financial supportfor the research and/or authorship of this article: The study wasfunded by Lilly Deutschland, the German affiliate of Eli Lilly andCompany **Country:** Germany **Setting:** Multicenter study **Comments:** Clinical trial: NCT00546910 **Authors name:** Peter M. Wehmeier

	Institution: Department of Child and Adolescent Psychiatry, Central Institute of Mental Health **Email:** peter.wehmeier@vitos-weilmuenster.de **Address:** Peter M. Wehmeier, Department of Child and Adolescent Psychiatry,Central Institute of Mental Health, Post Box 12 21 20, 68072 Mannheim,Germany.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement Comment: No information on sequence generation has been provided
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: No information on allocation concealment has been provided
Blinding of participants and personnel (performance bias)	Low risk	Judgement Comment: This is a randomized, double-blind, placebo-controlled, two-arm, multicenter study
Blinding of outcome assessment (detection bias)	Low risk	Judgement Comment: This is a randomized, double-blind, placebo-controlled, two-arm, multicenter study
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: Information on attrition is provided, and reasons for exclusions given.Ittention to treat analysis were performed.
Selective reporting (reporting bias)	Low risk	Judgement Comment: Study is registered in clinicaltrial.gov.There are no apperant risk of bias in relation to selective outcome reporting.
Other bias	Low risk	Judgement Comment: Funding source has been reported and the study apparently seem free of other sources of bias

Weiss 2005

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention 1 ● *Mean age, years*: 9.9 ● *Male %*: 82.2 Control ● *Mean age, years*: 9.9 ● *Male %*: 40 **Included criteria:** Age 8-12 years old. ADHD diagnosis, symptom severity least 1.0 SD above gender and age norm. Mean Conners Parent rating scale index score at least 1.5 SD above sex and age norm **Excluded criteria:** Unavailability of a primary treacher willing to keep telefone appointments and to provide ratings. Evidence of significant intelectual deficits, serious medical illness or use of psychotropic medication. **Pretreatment:** Baseline characteristics across groups were similar
Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: Atomoxetine 1.8mg/kg ● *Length of treatment*: 7 weeks Control ● *Description*: Placebo ● *Length of treatment*: 7 weeks
Outcomes	*ADHD kernesymptomer, obsevatørbedømt* ● **Outcome type**: ContinuousOutcome *Adfærdsforstyrrelser, forældrebedømt* ● **Outcome type**: ContinuousOutcome *Frafald pga bivirkninger* ● **Outcome type**: DichotomousOutcome *Vægttab* ● **Outcome type**: DichotomousOutcome *Appetitforstyrrelser* ● **Outcome type**: DichotomousOutcome
Identification	**Sponsorship source:** Eli Lilly and company **Country:** USA **Authors name:** Margaret Weiss **Institution:** Lilly research laboratory **Email:** allenaj@lilly.com
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Allocation concealment (selection bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017

Blinding of participants and personnel (performance bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Blinding of outcome assessment (detection bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Incomplete outcome data (attrition bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Selective reporting (reporting bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Other bias	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017

Wilens 2011

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention 1 ● *Mean age, years*: 8.7 ● *Male %*: 69 Control ● *Mean age, years*: 8.6 ● *Male %*: 61 **Included criteria:** Males and females, aged 6–12 years (inclusive), with a DSM-IV diagnosis of any ADHDsubtype, confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia forSchool-Age Children-Present and Lifetime Version (K-SADS-PL),15 and a rating of 4 orhigher on the Clinical Global Impression-ADHD-Severity Scale (CGI-ADHD-S) wereenrolled at 23 sites (Study 1: 10; Study 2: 3; Studies 1 and 2: 10) in the United States(September 2007 - July 2008). For all sites, an institutional review board approved the studyprotocol. A parent/caregiver of each youth provided informed consent, and subjects ages 7–12 provided written assent **Excluded criteria:** aged 6 to 12 years, treated with ABT-089. We hypothesized that ABT-089 would besuperior to placebo in the treatment of ADHD symptomatology. Secondarily, wehypothesized improvement in functional outcomes and examined the tolerability and safetyof ABT-089 in this pediatric population.METHODSStudy PatientsMales and females, aged 6–12 years (inclusive), with a DSM-IV diagnosis of any ADHDsubtype, confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia forSchool-Age Children-Present and Lifetime Version (K-SADS-PL),15 and a rating of 4 orhigher on the Clinical Global Impression-ADHD-Severity Scale (CGI-ADHD-S) wereenrolled at 23 sites (Study 1: 10; Study 2: 3; Studies 1 and 2: 10) in the United States(September 2007 - July 2008). For all sites, an institutional review board approved the studyprotocol. A parent/caregiver of each youth provided informed consent, and subjects ages 7–12 provided written assent. **Pretreatment:** Baseline characteristics did not differ between treatment groups within or between studies
Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: Atomoxetine 1.2mg/kg ● *Length of treatment*: 6 weeks Control ● *Description*: Placebo ● *Length of treatment*: 6 weeks
Outcomes	*ADHD kernesymptomer, obsevatørbedømt* ● **Outcome type**: ContinuousOutcome *Frafald pga bivirkninger* ● **Outcome type**: DichotomousOutcome *Søvnforstyrrelser* ● **Outcome type**: DichotomousOutcome
Identification	**Sponsorship source:** Abbott **Country:** USA **Comments:** M06-888 (Study 1): A Safety and Efficacy Study of ABT-089 in Children With Attention-Deficit/Hyperactivity Disorder (ADHD), Clinicaltrials.gov, NCT00528697; M10-345 (Study 2): Safety and Tolerability Study ofABT-089 in Children With Attention-Deficit/Hyperactivity Disorder (ADHD), Clinicaltrials.gov, NCT00640419 **Authors name:** Timothy E. Wilens, **Institution:** Massachusetts General Hospital, Pediatric Psychopharmacology Unit **Email:** twilens@partners.org **Address:** Massachusetts General Hospital, Pediatric Psychopharmacology Unit, 55 Fruit Street,YAW 6A, Boston, MA 02114,
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Allocation concealment (selection bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Blinding of participants and personnel (performance bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017

Blinding of outcome assessment (detection bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Incomplete outcome data (attrition bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Selective reporting (reporting bias)	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017
Other bias	Low risk	See Joseph et al "Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison" 2017

Footnotes

Summary of findings tables

Additional tables

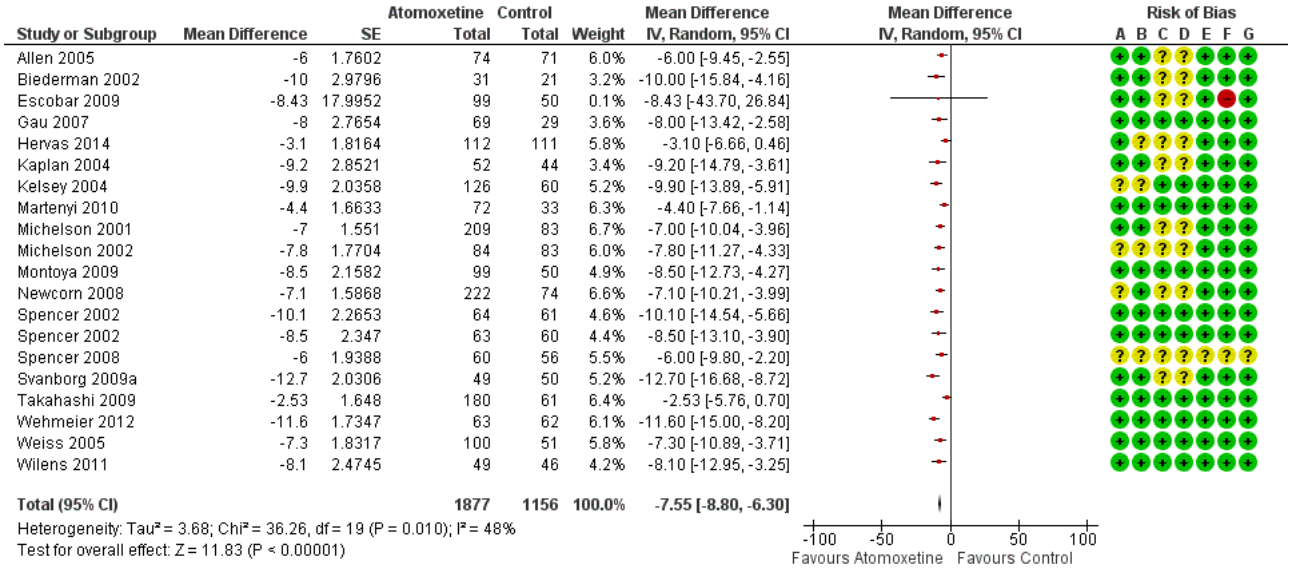
Data and analyses

1 Atomoxetine vs Control

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 ADHD kernesymptomer (ADHD-RS-IV total score) Obsevatørbedømt	19	3033	Mean Difference (IV, Random, 95% CI)	-7.55 [-8.80, -6.30]
1.3 ADHD kernesymptomer, lærerbedømt	4	542	Std. Mean Difference (IV, Random, 95% CI)	-0.43 [-0.72, -0.14]
1.4 ADHD kernesymptomer, forældrebedømt	7	1160	Std. Mean Difference (IV, Random, 95% CI)	-0.66 [-0.90, -0.43]
1.5 Adfærdsforstyrrelser (Conners oppositional), lærerbedømt	2	225	Mean Difference (IV, Random, 95% CI)	-2.30 [-6.42, 1.81]
1.6 Adfærdsforstyrrelser (Conners oppositional), forældrebedømt	7	1010	Mean Difference (IV, Random, 95% CI)	-1.45 [-2.18, -0.71]
1.7 Livskvalitet (CHIP, satisfaction)	3	385	Mean Difference (IV, Random, 95% CI)	-0.90 [-3.86, 2.06]
1.8 Livskvalitet (Child health questionaire, psychosocial))	4	842	Mean Difference (IV, Random, 95% CI)	5.40 [3.12, 7.68]
1.11 Vægttab, mean change SD	5	1121	Mean Difference (IV, Random, 95% CI)	-1.71 [-2.22, -1.20]
1.12 Frafald pga bivirkninger	18	3184	Risk Ratio (IV, Random, 95% CI)	1.44 [0.88, 2.35]
1.13 Vægttab	4	475	Risk Ratio (IV, Random, 95% CI)	3.36 [0.91, 12.43]
1.14 Søvnforstyrrelser	7	1205	Risk Ratio (IV, Random, 95% CI)	1.17 [0.66, 2.08]
1.16 Angst/nervousness	2	476	Risk Ratio (IV, Random, 95% CI)	2.14 [1.22, 3.75]
1.17 Appetitforstyrrelser	22	3897	Risk Ratio (IV, Random, 95% CI)	3.18 [2.51, 4.02]
1.19 Alvorlige bivirkninger	6	950	Risk Ratio (IV, Random, 95% CI)	0.21 [0.02, 1.80]

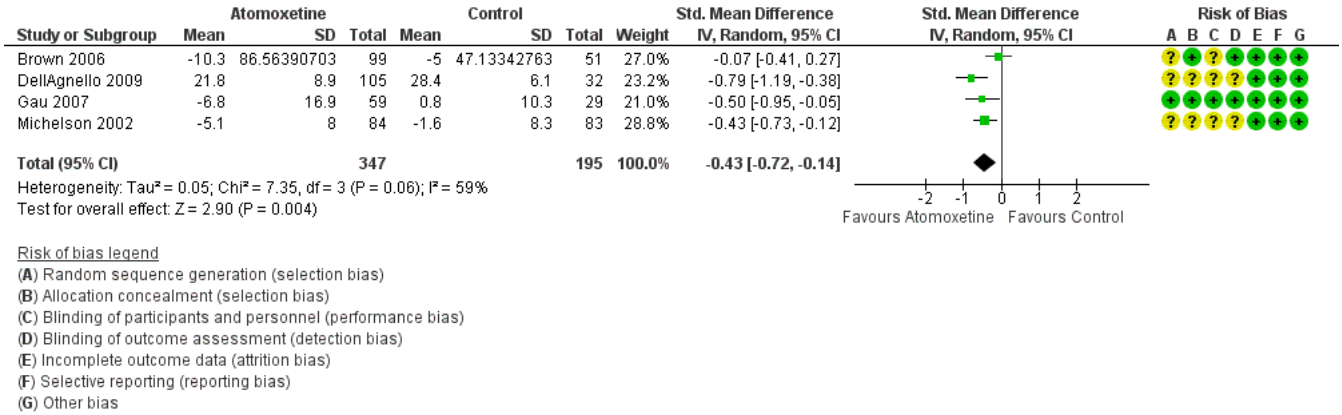
Figures

Figure 1 (Analysis 1.1)



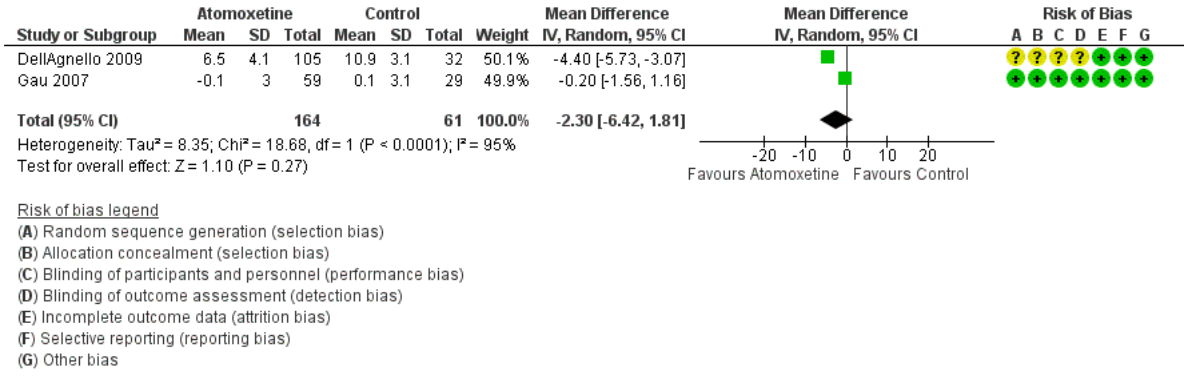
Forest plot of comparison: 1 Atomoxetine vs Control, outcome: 1.1 ADHD kernesymptomer (ADHD-RS-IV total score) Obsevatørbedømt.

Figure 3 (Analysis 1.3)



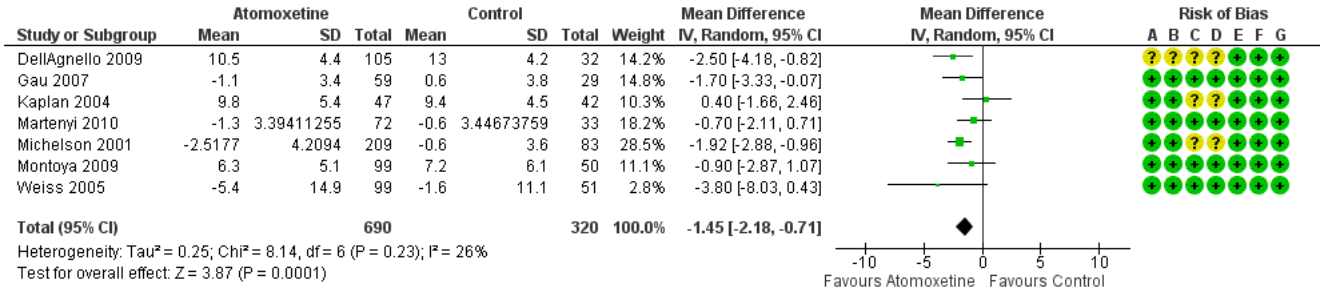
Forest plot of comparison: 1 Atomoxetine vs Control, outcome: 1.3 ADHD kernesymptomer, lærerbedømt.

Figure 4 (Analysis 1.5)



Forest plot of comparison: 1 Atomoxetine vs Control, outcome: 1.5 Adfærdsforstyrrelser (Conners oppositional), lærerbedømt.

Figure 5 (Analysis 1.6)



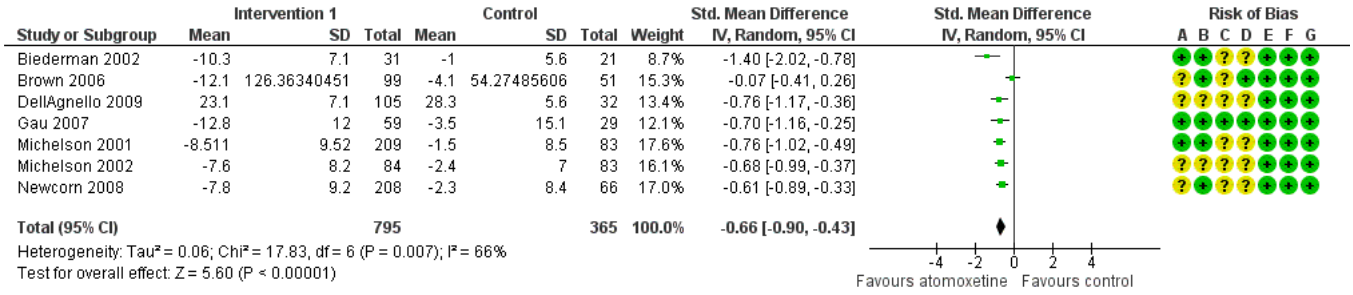
Study or Subgroup	Atomoxetine Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
DellAgnello 2009	10.5	4.4	105	13	4.2	32	14.2%	-2.50 [-4.18, -0.82]
Gau 2007	-1.1	3.4	59	0.6	3.8	29	14.8%	-1.70 [-3.33, -0.07]
Kaplan 2004	9.8	5.4	47	9.4	4.5	42	10.3%	0.40 [-1.66, 2.46]
Martenyi 2010	-1.3	3.39411255	72	-0.6	3.44673759	33	18.2%	-0.70 [-2.11, 0.71]
Michelson 2001	-2.5177	4.2094	209	-0.6	3.6	83	28.5%	-1.92 [-2.88, -0.96]
Montoya 2009	6.3	5.1	99	7.2	6.1	50	11.1%	-0.90 [-2.87, 1.07]
Weiss 2005	-5.4	14.9	99	-1.6	11.1	51	2.8%	-3.80 [-8.03, 0.43]
Total (95% CI)			**690**			**320**	**100.0%**	**-1.45 [-2.18, -0.71]**

Heterogeneity: Tau² = 0.25; Chi² = 8.14, df = 6 (P = 0.23); I² = 26%
Test for overall effect: Z = 3.87 (P = 0.0001)

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 Atomoxetine vs Control, outcome: 1.6 Adfærdsforstyrrelser (Conners oppositional), forældrebedømt.

Figure 6 (Analysis 1.4)



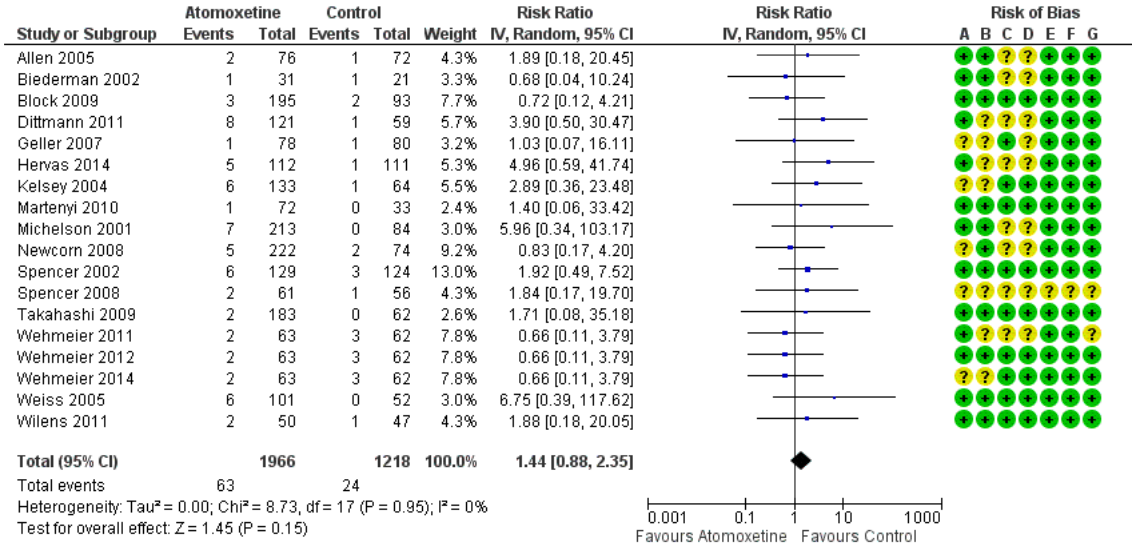
Study or Subgroup	Intervention 1 Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Biederman 2002	-10.3	7.1	31	-1	5.6	21	8.7%	-1.40 [-2.02, -0.78]
Brown 2006	-12.1	126.36340451	99	-4.1	54.27485606	51	15.3%	-0.07 [-0.41, 0.26]
DellAgnello 2009	23.1	7.1	105	28.3	5.6	32	13.4%	-0.76 [-1.17, -0.36]
Gau 2007	-12.8	12	59	-3.5	15.1	29	12.1%	-0.70 [-1.16, -0.25]
Michelson 2001	-8.511	9.52	209	-1.5	8.5	83	17.6%	-0.76 [-1.02, -0.49]
Michelson 2002	-7.6	8.2	84	-2.4	7	83	16.1%	-0.68 [-0.99, -0.37]
Newcorn 2008	-7.8	9.2	208	-2.3	8.4	66	17.0%	-0.61 [-0.89, -0.33]
Total (95% CI)			**795**			**365**	**100.0%**	**-0.66 [-0.90, -0.43]**

Heterogeneity: Tau² = 0.06; Chi² = 17.83, df = 6 (P = 0.007); I² = 66%
Test for overall effect: Z = 5.60 (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 Atomoxetine vs Control, outcome: 1.4 ADHD kernesymptomer, forældrebedømt.

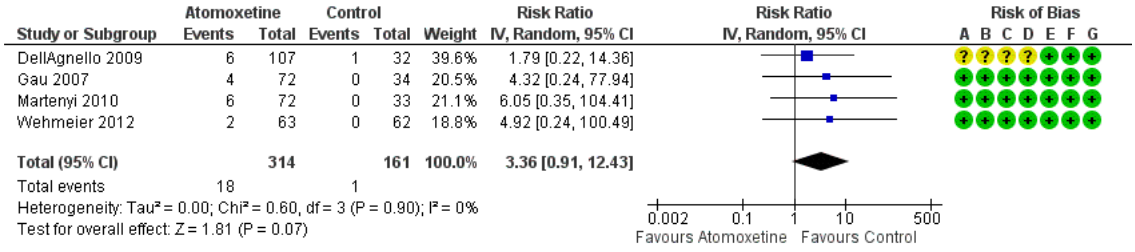
Figure 7 (Analysis 1.12)



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 Atomoxetine vs Control, outcome: 1.12 Frafald pga bivirkninger.

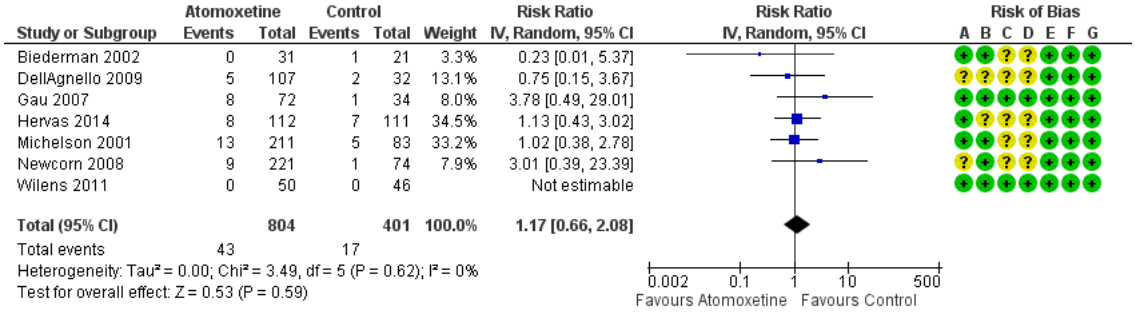
Figure 8 (Analysis 1.13)



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 Atomoxetine vs Control, outcome: 1.13 Vægttab.

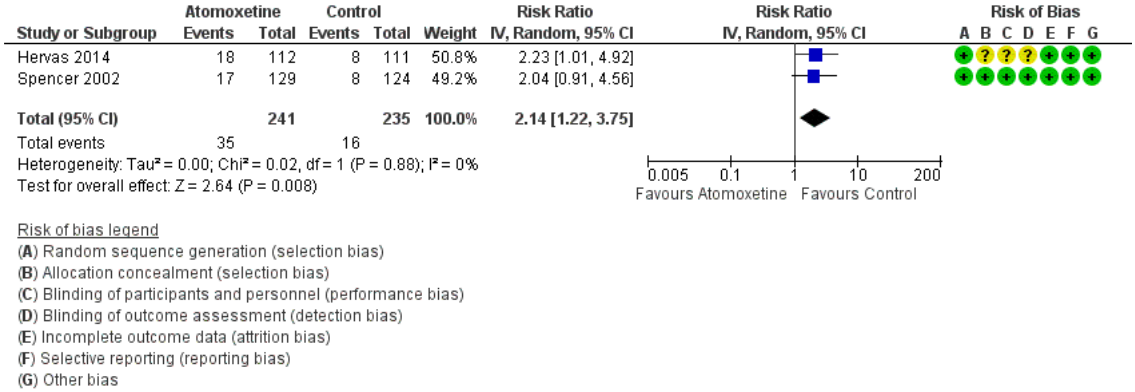
Figure 9 (Analysis 1.14)



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 Atomoxetine vs Control, outcome: 1.14 Søvnforstyrrelser.

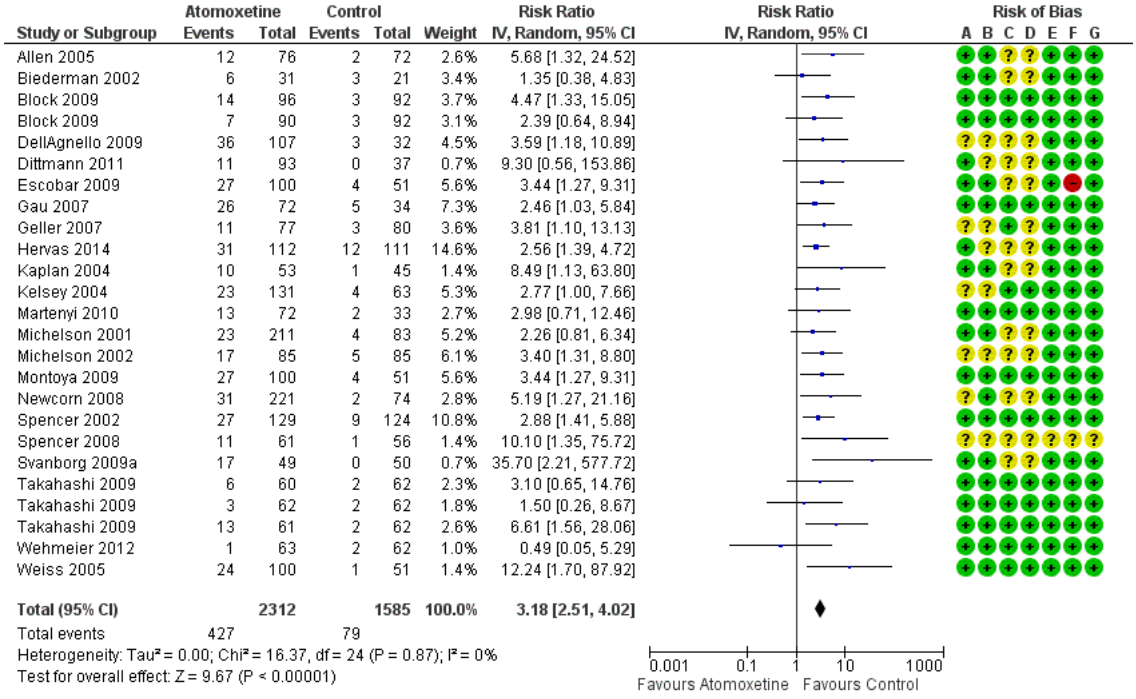
Figure 10 (Analysis 1.16)



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 Atomoxetine vs Control, outcome: 1.16 Angst/nervousness.

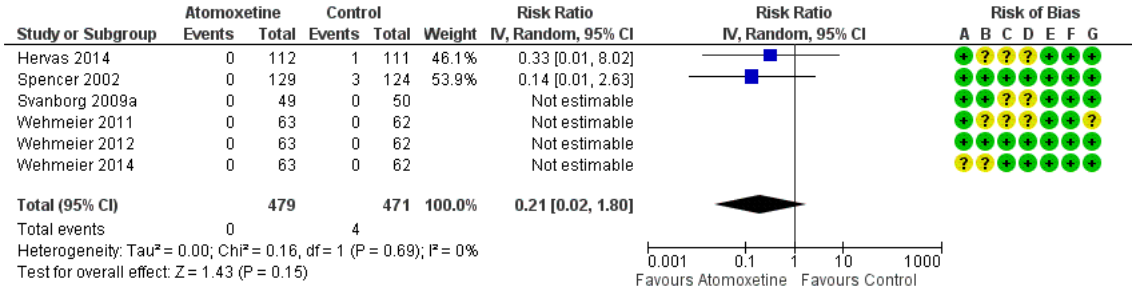
Figure 11 (Analysis 1.17)



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

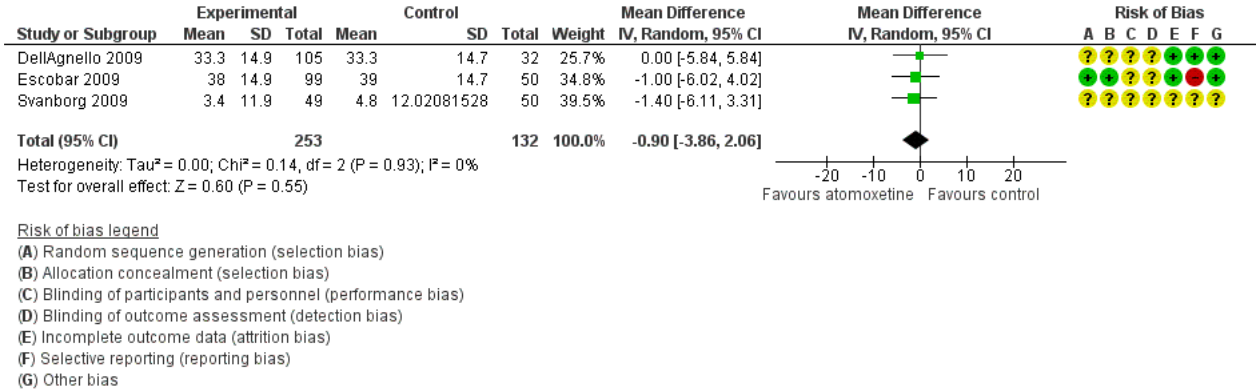
Forest plot of comparison: 1 Atomoxetine vs Control, outcome: 1.17 Appetitforstyrrelser.

Figure 12 (Analysis 1.19)



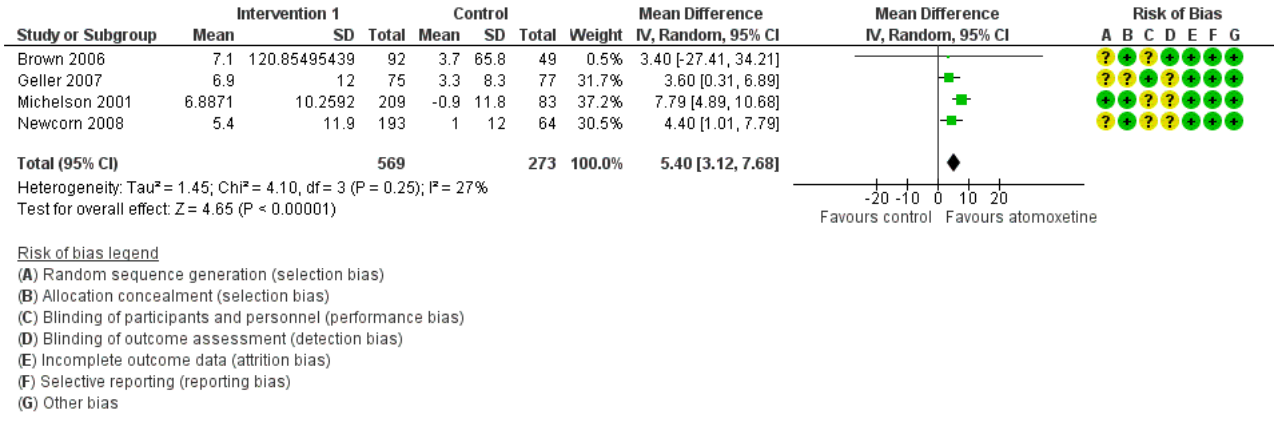
Forest plot of comparison: 1 Atomoxetine vs Control, outcome: 1.19 Alvorlige bivirkninger.

Figure 13 (Analysis 1.7)



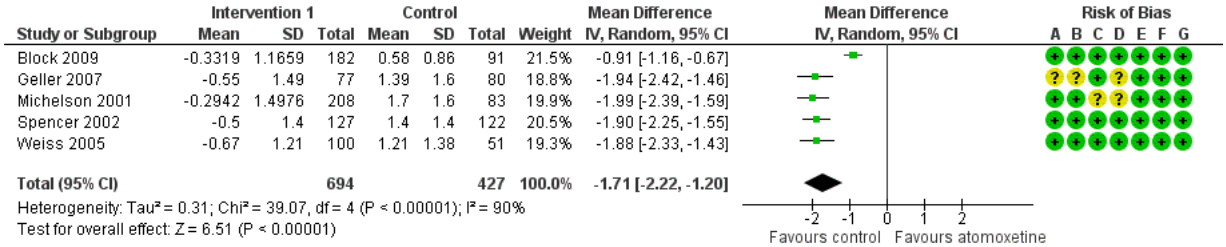
Forest plot of comparison: 1 Atomoxetine vs Control, outcome: 1.7 Livskvalitet (CHIP, satisfaction).

Figure 14 (Analysis 1.8)



Forest plot of comparison: 1 Atomoxetine vs Control, outcome: 1.8 Livskvalitet (Child health questionaire, psychosocial)).

Figure 15 (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 Atomoxetine vs Control, outcome: 1.11 Vægttab, mean change SD.