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Pharmacological treatment for attention deficit hyperactivity disorder (ADHD) in children with comorbid tic disorders (Review)

Osland ST, Steeves TDL, Pringsheim T

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[Intervention Review]

Pharmacological treatment for attention deficit hyperactivity disorder (ADHD) in children with comorbid tic disorders

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A B S T R A C T

Background

This is an update of the original Cochrane Review published in Issue 4, 2011.

Attention deficit hyperactivity disorder (ADHD) is the most prevalent of the comorbid psychiatric disorders that complicate tic disorders. Medications commonly used to treat ADHD symptoms include stimulants such as methylphenidate and amphetamine; non-stimulants, such as atomoxetine; tricyclic antidepressants; and alpha agonists. Alpha agonists are also used as a treatment for tics. Due to the impact of ADHD symptoms on the child with tic disorder, treatment of ADHD is often of greater priority than the medical management of tics. However, for many decades, clinicians have been reluctant to use stimulants to treat children with ADHD and tics for fear of worsening their tics.

Objectives

To assess the effects of pharmacological treatments for ADHD in children with comorbid tic disorders on symptoms of ADHD and tics.

Search methods

In September 2017, we searched CENTRAL, MEDLINE, Embase, and 12 other databases. We also searched two trial registers and contacted experts in the field for any ongoing or unpublished studies.

Selection criteria

We included randomized, double-blind, controlled trials of any pharmacological treatment for ADHD used specifically in children with comorbid tic disorders. We included both parallel-group and cross-over study designs.

Data collection and analysis

We used standard methodological procedures of Cochrane, in that two review authors independently selected studies, extracted data using standardized forms, assessed risk of bias, and graded the overall quality of the evidence by using the GRADE approach.

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Main results

We included eight randomized controlled trials (four of which were cross-over trials) with 510 participants (443 boys, 67 girls) in this review. Participants in these studies were children with both ADHD and a chronic tic disorder. All studies took place in the USA and ranged from three to 22 weeks in duration. Five of the eight studies were funded by charitable organizations or government agencies, or both. One study was funded by the drug manufacturer. The other two studies did not specify the source of funding. Risk of bias of included studies was low for blinding; low or unclear for random sequence generation, allocation concealment, and attrition bias; and low or high for selective outcome reporting. We were unable to combine any of the studies in a meta-analysis due to important clinical heterogeneity and unit-of-analysis issues.

Several of the trials assessed multiple agents. Medications assessed included methylphenidate, clonidine, desipramine, dextroamphetamine, guanfacine, atomoxetine, and deprenyl. There was low-quality evidence for methylphenidate, atomoxetine, and clonidine, and very low-quality evidence for desipramine, dextroamphetamine, guanfacine and deprenyl in the treatment of ADHD in children with tics. All studies, with the exception of a study using deprenyl, reported improvement in symptoms of ADHD. Tic symptoms also improved in children treated with guanfacine, desipramine, methylphenidate, clonidine, and a combination of methylphenidate and clonidine. In one study, tics limited further dosage increases of methylphenidate. High-dose dextroamphetamine appeared to worsen tics in one study, although the length of this study was limited to three weeks. There was appetite suppression or weight loss in association with methylphenidate, dextroamphetamine, atomoxetine, and desipramine. There was insomnia associated with methylphenidate and dextroamphetamine, and sedation associated with clonidine.

Authors' conclusions

Following an updated search of potentially relevant studies, we found no new studies that matched our inclusion criteria and thus our conclusions have not changed.

Methylphenidate, clonidine, guanfacine, desipramine, and atomoxetine appear to reduce ADHD symptoms in children with tics though the quality of the available evidence was low to very low. Although stimulants have not been shown to worsen tics in most people with tic disorders, they may, nonetheless, exacerbate tics in individual cases. In these instances, treatment with alpha agonists or atomoxetine may be an alternative. Although there is evidence that desipramine may improve tics and ADHD in children, safety concerns will likely continue to limit its use in this population.

P L A I N   L A N G U A G E   S U M M A R Y

Medications for attention deficit hyperactivity disorder (ADHD) in children with tics

Review question

In children with ADHD and tics, how do medications for ADHD affect symptoms of both disorders?

Background

As many as half of all children with tic disorders (a combination of repetitive motions vocalizations), also have ADHD (issues with hyperactivity, impulsivity and maintaining attention). Symptoms of ADHD are often more disabling for children than their tics. Historically, the reported ability of stimulant medications to worsen tics has limited their use in children who have both a chronic tic disorder (lasting over a year since the first tic onset) and ADHD. To evaluate evidence for this reported phenomenon, we searched for clinical trials of medications for ADHD used specifically in children with tic disorders.

Search date

The evidence is current to September 2017.

Study characteristics

We included eight studies with 510 participants (443 boys, 67 girls) in our review. Participants in these studies were children with both ADHD and a chronic tic disorder. The included studies evaluated several different medications for ADHD, including stimulants (methylphenidate, dextroamphetamine) and non-stimulants (clonidine, guanfacine, desipramine, atomoxetine, and deprenyl). All studies took place in the USA and ranged from three to 22 weeks in duration.

Study funding sources

Five of the eight studies were funded by charitable organizations or government agencies, or both. One study was funded by the drug manufacturer. The other two studies did not specify the source of funding for the study.

Key results

The trials in this review suggested that several stimulant and non-stimulant medications may improve ADHD symptoms in children with ADHD and tics. At high doses, dextroamphetamine may initially worsen tics in some children, and dose increases of both dextroamphetamine and methylphenidate may be limited due to tic exacerbation. However, for most children, both tics and ADHD symptoms can improve with use of stimulant medications.

Quality of evidence

There is low-quality evidence for methylphenidate, atomoxetine, and clonidine, and very low-quality evidence for desipramine, dextroamphetamine, guanfacine, and deprenyl in the treatment of ADHD in children with tics. The evidence was limited by the small number of trials, small number of participants, and risk of bias of the included studies.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.   Methylphenidate compared with placebo for attention deficit hyperactivity disorder (ADHD) in children with comorbid tic disorders

Methylphenidate compared with placebo for attention deficit hyperactivity disorder (ADHD) in children with comorbid tic disorders

Patient or population: children with ADHD and comorbid tic disorders

Intervention: methylphenidate

Comparison: placebo

Outcomes	Effect of treatment	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
ADHD symptom-related behavior Measured by standardized rating scales: Conners' Abbreviated Teacher Rating Scale, Conners' Abbreviated Parent Rating Scale, IOWA Conners' Teacher Rating Scale, Mothers' Objective Method for Subgrouping, Continuous Performance Task, Conners' Teacher Rating Scale, Conners' Continuous Performance Task	Tourette's Syndrome Study Group 2002 showed a significant treatment effect using the Conners' Abbreviated Teacher Rating Scale (3.3 points, 98.3% CI −0.2 to 6.8; P = 0.02). Gadow 2007 showed that all doses (0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg) of methylphenidate were superior to placebo on all rating scales (Conners' Abbreviated Teacher/Parent Rating Scale, IOWA Conners' Teacher Rating Scale, Mothers' Objective Method for Subgrouping, Continuous Performance Test), with a dose-dependent effect (F = 24.7; P = 0.001) Castellanos 1997 showed significantly decreased hyperactivity at all doses (15 mg, 25 mg, 45 mg).	229 (3 studies)	⊕⊕⊖⊖ **Low**[a]	–
Tic severity Measured by standardized rating scales: Yale Global Tic Severity Scale, Tourette Syndrome Severity Scale, Tourette Syndrome Clinical Global Impression Scale, Global Tic Rating Scale, 2-Minute Tic and Habit Count, Tic Symptom Self-Report	Tourette's Syndrome Study Group 2002 found a significant treatment effect using the Yale Global Tic Severity Scale (11.0 points, 98.3% CI 2.1 to 19.8; P = 0.003). Gadow 2007 found no difference on the Yale Global Tic Severity Scale but found an improvement in tic severity at all doses (0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg) on the Global Tic Rating Scale completed by teachers (F = 5.33; P = 0.002) Castellanos 1997 found no effect of drug on tic severity for second and third cohorts. Tic severity was significantly greater during week 2 in the first cohort (P < 0.01)	229 (3 studies)	⊕⊕⊖⊖ **Low**[a]	–

ADHD: attention deficit hyperactivity disorder; **CI:** confidence interval.

GRADE Working Group grades of evidence
High quality: we are very confidence that the true effect lies close to that of the estimate of the effect.

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Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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[a]Downgraded two levels due to limitations in study design and implementation, and imprecision of results.

Summary of findings 2.   Clonidine compared with placebo for attention deficit hyperactivity disorder (ADHD) in children with comorbid tic disorders

Clonidine compared with placebo for attention deficit hyperactivity disorder (ADHD) in children with comorbid tic disorders

Patient or population: children with ADHD and comorbid tic disorders

Intervention: clonidine

Comparison: placebo

Outcomes	Effect of treatment	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
ADHD symptom-related behavior Measured by standardized rating scales: Conners' Abbreviated Teacher Rating Scale, Conners' Abbreviated Parent Rating Scale, IOWA Conners' Teacher Rating Scale, Conners' Continuous Performance Task, Child Behaviour Checklist, Gordon Diagnostic System, Clinical Evaluation of Language Function, Matching Familial Figures Test, Porteus Maze Test, Restricted Academic Test	Tourette's Syndrome Study Group 2002 found a significant treatment effect using the Conners' Abbreviated Teacher Rating Scale (3.3 points, 98.3% CI −0.2 to 6.8; P = 0.02). Singer 1995 found no significant difference on any ADHD outcome measures, except the nervous/overactive subscale of the Child Behaviour Checklist (boys aged 6-11 years).	170 (2 studies)	⊕⊕⊖⊖ **Low**[a]	–
Tic severity Measured by standardized rating scales: Yale Global Tic Severity Scale, Tourette Syndrome Severity Scale, Global Tic Rating Scale, Tic Symptom Self-Report, Hopkins Motor/Vocal Scale	Tourette's Syndrome Study Group 2002 showed a significant treatment effect using the Yale Global Tic Severity Scale (10.9 points, 98.3% CI 2.1 to 19.7; P = 0.003). Singer 1995 found no significant difference on measures of tic severity.	170 (2 studies)	⊕⊕⊖⊖ **Low**[a]	–

ADHD: attention deficit hyperactivity disorder; **CI:** confidence interval.

GRADE Working Group grades of evidence

High quality: we are very confidence that the true effect lies close to that of the estimate of the effect.

Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

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Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

*a*Downgraded two levels due to limitations in study design and implementation, and imprecision of results.

Summary of findings 3.   Desipramine compared with placebo for attention deficit hyperactivity disorder (ADHD) in children with comorbid tic disorders

Desipramine compared with placebo for attention deficit hyperactivity disorder (ADHD) in children with comorbid tic disorders

Patient or population: children with ADHD and comorbid tic disorders

Intervention: desipramine

Comparison: placebo

Outcomes	Effect of treatment	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
ADHD symptom-related behavior Measured by standardized rating scales: Child Behaviour Checklist, Gordon Diagnostic System, Clinical Evaluation of Language Function, Matching Familial Figures Test, Porteus Maze Test, Restricted Academic Test, ADHD Rating Scale IV - Parent Version; ADHD Parent Linear Analogue Scale	Spencer 2002 showed a decrease in scores on the ADHD Rating Scale IV - Parent Version (week 0 = 46 (SD 5.9) points; week 6 = 24 (SD 12) points; $P < 0.001$). Singer 1995 showed that desipramine was superior to placebo on the Parent Linear Analogue Scale for Hyperactivity (desipramine: 32.8 (SD 1.3) points; placebo: 64.4 (SD 0.6) points; $P < 0.05$). Hyperactivity subscale of the Child Behavior Checklist showed drug effects for males aged 6 to 11 years (desipramine: 68.6 (SD 1.4) points; placebo: 75.8 (SD 1.0) points; $P < 0.05$).	75 (2 studies)	⊕⊖⊖⊖ **Very low**[a]	–
Tic severity Measured by standardized rating scales: Yale Global Tic Severity Scale, Tourette Syndrome Severity Scale, Hopkins Motor/Vocal Scale; ADHD Parent Linear Analogue Scale	Spencer 2002 showed a decrease in scores on the Yale Global Tic Severity Scale (week 0 = 63 (SD 18) points; week 6: 43 (SD 23) points; $P < 0.001$). Singer 1995 showed that desipramine was superior to placebo on the Parent Linear Analogue Scale of tic severity (desipramine: 30.0 (SD 0.7) points; placebo: 47.4 SD 1.8 points; $P < 0.05$). There were no differences on the other measures of tic severity (Tourette Syndrome Severity Scale, Hopkins Motor/vocal scale, Yale Global Tic Severity Scale).	75 (2 studies)	⊕⊖⊖⊖ **Very low**[a]	–

ADHD: attention deficit hyperactivity disorder; **SD:** standard deviation.

GRADE Working Group grades of evidence

High quality: we are very confidence that the true effect lies close to that of the estimate of the effect.

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Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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*a*Downgraded two levels due to limitations in study design and implementation, and imprecision of results.

Pharmacological treatment for attention deficit hyperactivity disorder (ADHD) in children with comorbid tic disorders (Review)

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BACKGROUND

Description of the condition

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,* currently recognizes three chronic tic disorders: Tourette syndrome, chronic motor tic disorder, and chronic vocal tic disorder (APA 2013). Tourette syndrome consists of multiple motor tics and one or more vocal tics that have persisted for longer than one year. In both chronic motor tic disorder and chronic vocal disorder, tics must also persist for longer than one year but the spectrum of tics is limited to either motor or vocal subtypes, respectively. Together these disorders affect just over 2% of children (Knight 2012). They fall within a clinical spectrum, with a presumed shared underlying neurobiology.

Chronic tic disorders are frequently complicated by the presence of comorbid psychiatric disorders, of which attention deficit hyperactivity disorder (ADHD) is one of the most prevalent (Martino 2013). The clinical implications of a comorbid diagnosis of ADHD in children with tic disorders are significant. The risk for aggressive and delinquent behavior, and conduct difficulties in children with tic disorders is posed largely by the presence of ADHD (Cavanna 2009), and the greatest independent predictor of psychosocial quality of life in children with tic disorders is ADHD symptom severity (Pringsheim 2007). In contrast, the presence of a tic disorder has limited impact on ADHD outcomes (Spencer 2001).

Rates of association between tic disorders and ADHD are much higher than would be expected due to chance alone. Kurlan 2002 used direct interviews in a community-based study of school children to determine the prevalence of tic disorders and any comorbid psychopathology. They included 1596 children aged nine to 17 years from 10 New York state school districts over a four-year period. In this study, 38% of children with tics had a comorbid diagnosis of ADHD. Clinic-based studies yield even higher rates of comorbid ADHD. In a review of a multi-site, international database of 3500 people with tic disorders, Freeman 2000 reported that 60% of children with tic disorders also had ADHD, with a range of 33% to 91% among sites reporting more than 50 cases.

The association between tic disorders and ADHD is a compelling one and a number of investigators have proposed that the disorders share a common pathophysiology, reflecting alterations in noradrenergic and dopaminergic transmission inadequately modulating corticostriatal circuits, and thus failing to inhibit intrusive thoughts, sensory input, and motor responses (Steeves 2008). Neurochemical models based on dopaminergic and noradrenergic dysfunction have likewise guided considerations for their treatment.

Description of the intervention

Medications most commonly used to treat ADHD symptoms include the stimulants methylphenidate and amphetamine, followed by non-stimulants (such as atomoxetine), tricyclic antidepressants, and alpha agonists (Wilens 2006). Due to the impact of ADHD on the child with a tic disorder, treatment for ADHD symptoms is a greater priority than medical treatment for tics. For many decades, clinicians were reluctant to use stimulants to treat symptoms of ADHD in children with tics for fear of worsening the tics. In the 1970s and early 1980s, several case reports and small case series were published of children who experienced the onset or worsening of tics after the use of stimulants for the treatment of ADHD (Golden 1974; Lowe 1982). Despite new evidence that suggests that this relationship was temporal and not causal (Tourette's Syndrome Study Group 2002), package inserts and advertising for US Food and Drug Administration-approved stimulants for ADHD continue to include warnings against the use of these medications for children with comorbid tic disorders.

How the intervention might work

There appears to be some commonality in the mechanisms of action of medications used for ADHD that may be related to either direct or indirect modulation of dopamine and norepinephrine neurotransmission. Stimulants block the reuptake of dopamine and norepinephrine into the presynaptic neuron (methylphenidate) or increase the release of these monoamines into the extraneuronal space (amphetamines) (Seiden 1993). Atomoxetine specifically inhibits presynaptic reuptake of norepinephrine, resulting in increased norepinephrine levels in the synapse (Bymaster 2002). The efficacy of tricyclic antidepressants in the treatment of ADHD is likewise thought to be mediated by their action on catecholamine reuptake, particularly on norepinephrine. The alpha-2 adrenergic agonists appear to alter basal adrenergic tone (Buccafusco 1992). Clonidine stimulates alpha-2A, -2B, and -2C receptors, while guanfacine is selective for alpha-2A receptors. Alpha-2A and -2C receptors are mainly found in the central nervous system, while the alpha-2B receptors are in vascular smooth muscle. Alpha-2 agonism inhibits norepinephrine release from the presynaptic neuron, resulting in a reduction of activity in noradrenergic pathways and an attenuation of the sympathetic stress response.

Why it is important to do this review

Given the high frequency of comorbidity of chronic tic disorders and ADHD, the effects of ADHD symptoms on psychosocial quality of life in people with tics, and the concern amongst clinicians about the potential of worsening tics with use of stimulant medications, an up-to-date systematic review of pharmacological treatments of ADHD in children with tics is needed. We synthesized the existing evidence for clinicians serving this patient population on the efficacy of these agents for treatment of symptoms of ADHD and their effect on tics. While physicians specializing in this area of practice may already be aware of this literature, children and families affected by ADHD and comorbid tic disorders frequently have concerns about the use of medications and potential worsening of the symptoms of either condition, and often seek advice on these points.

OBJECTIVES

To assess the effects of pharmacological treatments for ADHD in children with comorbid tic disorders on symptoms of ADHD and tics.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized, double-blind, controlled trials of any pharmacological treatment for ADHD used specifically in children with comorbid tic disorders. The term double-blind implies that

trial participants, clinicians, and outcome assessors were blinded to treatment allocation. We included both parallel-group and cross-over study designs.

Types of participants

Children aged 18 years or younger with a clinical diagnosis of ADHD and a chronic tic disorder (Tourette syndrome, chronic motor tic disorder, or chronic vocal tic disorder). With respect to diagnostic classification systems, acceptable ADHD diagnoses included:

- attention-deficit/hyperactivity disorder (APA 1987; APA 2000; APA 2013);
- attention deficit disorder (APA 1980); and
- hyperkinetic disorder (WHO 2005).

Types of interventions

Any pharmacological treatment for ADHD (stimulant and non-stimulant), at any dose, taken orally alone or in combination with another drug, compared to placebo.

Types of outcome measures

Primary outcomes

- ADHD and tic symptom severity measured by validated clinician, teacher, or parent report scales. Specifically, we evaluated:
  - ADHD symptom-related behavior in the home setting assessed with, for example, Conners Abbreviated Symptom Questionnaire (ASQ) for Parents (Conners 1990), or ADHD Rating Scale (DuPaul 2016);
  - ADHD symptom-related behavior in the school setting assessed with, for example, Conners ASQ for Teachers (Conners 1990); and
  - tic severity assessed with, for example, Yale Global Tic Severity Scale (TGTSS) (Leckman 1989), Tic Symptom Self-Report Scale (Leckman 1998), or the Tourette Syndrome Severity Scale (Shapiro 1988).

Secondary outcomes

- Adverse effects, including:
  - cardiovascular effects such as changes in heart rate, blood pressure, or the electrocardiogram; and
  - weight changes.

Search methods for identification of studies

We ran searches for this update in June 2016 and again on 20 September 2017. Search strategies for each database are reported in Appendix 1. Search strategies from the previous version of this review are in Appendix 2.

Electronic searches

For this update, we searched the electronic databases and trial registers listed below. Some new databases have been added since the previous review and others were no longer available to us. These changes are reported in Differences between protocol and review.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 8), in the Cochrane Library, and which includes the Cochrane Developmental, Psychosocial and Learning Problem Specialised Register (searched 20 September 2017).

- MEDLINE Ovid (1946 to September week 1 2017).
- MEDLINE In-Process and Other Non-Indexed Citations Ovid (searched 20 September 2017).
- MEDLINE E-pub Ahead of Print Ovid (searched 20 September 2017).
- Embase Ovid (1974 to 19 September 2017).
- CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature; 1937 to 20 September 2017).
- PsycINFO Ovid (1806 to September week 2 2017).
- Science Citation Index - Expanded Web of Science (SCI; 1970 to 19 September 2017).
- Social Sciences Citation Index Web of Science (SSCI; 1970 to 19 September 2017).
- Conference Proceedings Citation Index - Science Web of Science (1990 to 19 September 2017).
- Conference Proceedings Citation Index - Social Science and Humanities Web of Science (1990 to 19 September 2017).
- *Cochrane Database of Systemic Reviews* (CDSR; 2017, Issue 9) part of the Cochrane Library (searched 20 September 2017).
- Database of Abstracts and Reviews of Effects (DARE; 2015, Issue 2. Final Issue) part of the Cochrane Library (searched 6 July 2016).
- Epistemonikos (www.epistemonikos.org; searched 20 September 2017).
- WorldCat (www.worldcat.org; searched 20 September 2017).
- ClinicalTrials.gov (clinicaltrials.gov; searched 20 September 2017).
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP; www.who.int/ictrp/en; searched 20 September 2017).

Searching other resources

We contacted the Tourette Syndrome Study Group (based in North America) and other experts in the field, including investigators from all review articles and primary studies identified through searches for this review, to determine if there were any ongoing trials or unpublished results in this area.

Data collection and analysis

Selection of studies

Two review authors (TP and TS) independently assessed titles and abstracts of references retrieved from the searches and selected all potentially relevant studies. Next, they retrieved copies of these articles, which they read in detail and assessed for eligibility (Criteria for considering studies for this review). We resolved any disputes regarding the fulfilment of inclusion criteria by discussion. Review authors were not blinded to the names of the trial authors, institutions, or journals of publication.

We recorded our decisions in a study flow diagram (Moher 2009).

Data extraction and management

Two review authors (TP and TS) independently extracted the following data from each included study and entered it into predesigned summary forms.

- Study procedures, including recruitment, diagnosis, medication, dosage, duration, and clinical setting.

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- Study design (i.e. randomized or quasi-randomized).
- Randomization method.
- Method of allocation concealment.
- Method of blinding.
- Inclusion and exclusion criteria for participants.
- Number of participants (total/per group).
- Age distribution.
- Gender.
- Loss of follow-up.
- Premature discontinuation of study, and reasons for discontinuation.
- Outcome.
- Method of analysis (intention-to-treat, per protocol).
- Comparability of groups at baseline.

They then compared the extracted data to ensure accuracy. Next, one review author (TP) entered the data into Review Manager 5 (RevMan 5) (Review Manager 2014), and a second review author (TS) checked them. We resolved discrepancies by consensus. As no further studies were included following the July 2016 search, this process was not repeated.

Assessment of risk of bias in included studies

Two review authors (TP and TS) independently assessed the risk of bias in the included studies for each of the seven domains in Appendix 3, and assigned ratings of low risk of bias, high risk of bias, and unclear risk of bias (Higgins 2017). We resolved any discrepancies by consensus.

Measures of treatment effect

Due to significant clinical heterogeneity (differences between studies in the interventions used and how they were administered, and differences in outcomes measured), and incomplete reporting of the results from cross-over trials, we were unable to conduct a meta-analysis of study data. We attempted to obtain additional information from authors, but, due to the length of time since many of the trials were performed, this information was either not available or our queries went unanswered. Thus, we have presented the results for studies individually. We recorded the methods that were not pertinent to this version of the review in Appendix 4, for use in an update. See our protocol (Pringsheim 2009).

Unit of analysis issues

Unit-of-analysis issues occurred in this review as none of the included cross-over studies presented paired data for analysis but rather provided the means and standard deviations (SD) for each treatment type. See Appendix 4 and Pringsheim 2009.

Dealing with missing data

We attempted to obtain missing information directly from study authors; however, this did not yield the missing information. We contacted Castellanos regarding additional results from his trial (Castellanos 1997), but, due to the long period which had elapsed since his study was performed, the information was no longer accessible. We also contacted the authors of Tourette's Syndrome Study Group 2002 and Feigin 1996 requesting more information on

results but received no replies to our letters. See Appendix 4 and Pringsheim 2009.

Assessment of heterogeneity

We assessed clinical heterogeneity by comparing the distribution of important participant factors between trials and methodological heterogeneity by comparing trial designs. See also Appendix 4 and Pringsheim 2009.

Assessment of reporting biases

As there was an insufficient number of studies found for each treatment type, we did not create funnel plots to assess publication bias. See Appendix 4 and Pringsheim 2009.

Data synthesis

We did not synthesize results in a meta-analysis by treatment type because of important clinical heterogeneity and unit-of-analysis issues (see the Results section for descriptions of the nature of the heterogeneity encountered). Thus, we have presented the data for each study individually. See Appendix 4 and Pringsheim 2009.

'Summary of findings' table

We created 'Summary of findings' tables using Review Manager 2014, which report the effect estimate for our primary outcomes (ADHD and tic symptom severity) measured at study endpoint, the number of participants, and our ratings for the quality of the evidence. Two review authors (TP and SO) used the GRADE method to assess the quality of the body of evidence for each outcome. While randomized trials are considered high-quality evidence, we downgraded the level of evidence to moderate or low for all outcomes due to the presence of limitations in the design of available studies, and the overall small number of studies and participants included in studies in this area. This means it is likely that further research could have an important impact on our confidence in the estimate of the effect and may change the estimate.

Subgroup analysis and investigation of heterogeneity

We did not perform a subgroup analysis. See Appendix 4 and Pringsheim 2009.

Sensitivity analysis

We did not perform a sensitivity analysis due to the small number of trials and the inability to conduct a meta-analysis. See Appendix 4 and Pringsheim 2009.

R E S U L T S

Description of studies

Results of the search

In the original review, we found 599 citations, of which 21 qualified for further review. Of these, eight met our inclusion criteria (Criteria for considering studies for this review). Of the remaining 13, eight were republications of data already presented in the eight studies included in the review and were listed as secondary publications. The remaining five studies were excluded with reasons (see Excluded studies).

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For this update, our search yielded 508 records, once duplicates were removed. We excluded 507 records at title and abstract stage, and retrieved one full-text report for further inspection. This was subsequently excluded due to lack of double-blinding (see Excluded studies).

The study review process is summarized in a PRISMA flow diagram (Figure 1).

Figure 1.   Study flow diagram illustrating the process for inclusion of studies.
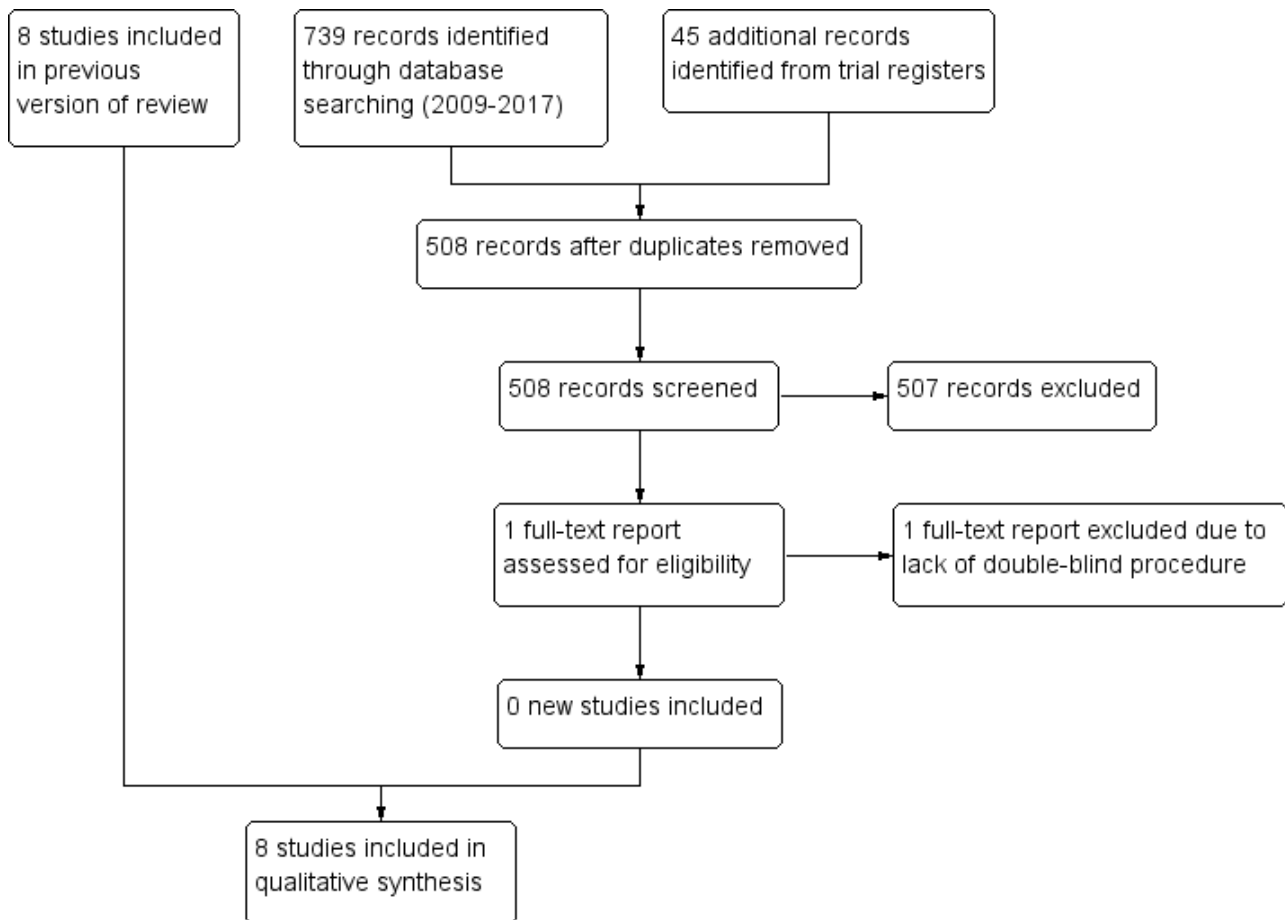
Included studies

See Characteristics of included studies tables.

Study designs

We included eight randomized controlled trials (RCTs) of pharmacological treatments for ADHD in children with comorbid tic disorders (Allen 2005; Castellanos 1997; Feigin 1996; Gadow 2007; Scahill 2001; Singer 1995; Spencer 2002; Tourette's Syndrome Study Group 2002), four of which were cross-over trials (Castellanos 1997; Feigin 1996; Gadow 2007; Singer 1995).

Location

All studies took place in the USA (Allen 2005; Castellanos 1997; Feigin 1996; Gadow 2007; Scahill 2001; Singer 1995; Spencer 2002; Tourette's Syndrome Study Group 2002).

Participants

The studies included 510 children (443 boys, 67 girls) with diagnoses of ADHD and Tourette syndrome or chronic motor or vocal tic disorder. Sample sizes ranged from 22 in Castellanos 1997 to 148 in Allen 2005.

Interventions

Three trials assessed multiple agents (Castellanos 1997; Singer 1995; Tourette's Syndrome Study Group 2002), and ranged in duration from three (Castellanos 1997) to 22 weeks (Singer 1995).

- Castellanos 1997 was a complex placebo-controlled, cross-over study, which randomized 22 children into three cohorts, each sequentially receiving for three weeks either placebo or one of three different dosage titrations of methylphenidate (low: 15 mg, medium: 25 mg, high: 45 mg), and one of three different dosage titrations of dextroamphetamine (low: 7.5 mg, medium: 15 mg, high: 22.5 mg).
- Singer 1995 was a placebo-controlled, three-phase cross-over study in 34 children, of clonidine, desipramine, and placebo. Each treatment was taken four times daily for six weeks, separated by a one-week washout period.
- Tourette's Syndrome Study Group 2002 was a parallel-group trial, which randomized 136 children to a flexible dose

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of methylphenidate (37 children), clonidine (34 children), clonidine plus methylphenidate (33 children), or placebo (32 children) for 16 weeks each (see Table 1).

The remaining five trials assessed single agents.

- Allen 2005 assessed atomoxetine 0.5 mg/kg per day to 1.5 mg/kg per day (76 children), a highly selective, non-stimulant noradrenergic reuptake inhibitor, versus placebo (72 children) in a parallel-group trial of 18 weeks' duration with 148 children (131 boys, 17 girls). Participants considered to be clinical non-responders at week 12 of the study were allowed to withdraw early from the double-blind study and enter an open-label study of the drug.
- Feigin 1996 assessed the effects of deprenyl, a type B monoamine oxidase inhibitor, compared to placebo in 24 children (21 boys, 3 girls). Children were randomized to treatment with deprenyl 5 mg or matching placebo, given twice daily, for eight weeks and then crossed over to the alternate treatment after a six-week washout period.
- Gadow 2007 assessed methylphenidate in a single agent, cross-over trial with placebo in which 71 children (57 boys, 14 girls) were randomized to three sequential doses of methylphenidate (0.1 mg/kg, 0.3 mg/kg, and 0.5 mg/kg), given twice daily, seven days a week for two weeks each.
- Scahill 2001 assessed guanfacine 1.5 mg to 3 mg per day (an alpha-2 receptor agonist), divided into three daily doses, versus placebo in a parallel-group trial of eight weeks' duration. The study randomized 34 children (31 boys, 3 girls) to guanfacine or placebo.
- Spencer 2002 compared desipramine versus placebo in 41 children (34 boys, 7 girls) in a parallel-group trial in which desipramine was titrated weekly up to 3.5 mg/kg per day and given twice daily for six weeks.

Outcome measures

All trials included both ADHD and tic outcomes. Most trials did not specify a primary outcome. The scales chosen to measure ADHD severity varied considerably between studies (Table 2). All studies used the YGTSS for one measure of tic severity. Table 3 lists other measures of tic severity that the studies used. A description of each scales' items and scoring is included in Table 4.

Excluded studies

We excluded six studies from this review. See Characteristics of excluded studies tables.

In the original review, we excluded five studies (Howson 2004; Law 1999; Niederhofer 2003; Nolan 1999; Sallee 1994). We excluded:
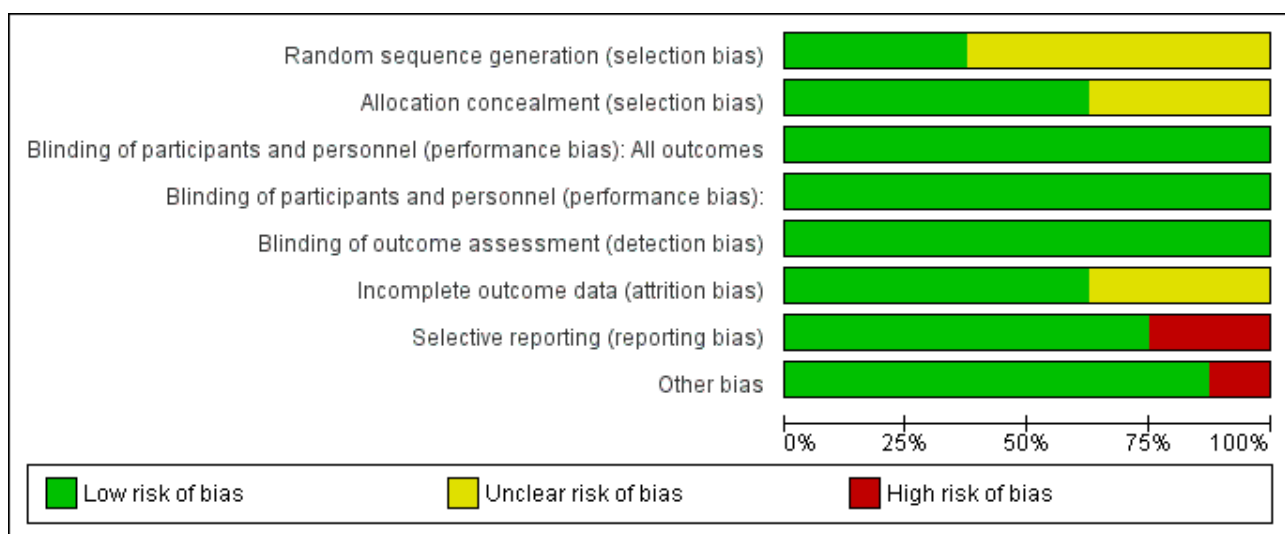
- one study of iofexidine in children with tic disorders and ADHD, as the manuscript was retracted from the journal due to plagiarism and possible fraudulent results (Niederhofer 2003);
- one study of methylphenidate in children with ADHD, which excluded children with severe motor or vocal tics and Tourette syndrome from the study and did not report the effects of methylphenidate on ADHD symptoms (Law 1999);
- one study that looked at the effects of stimulant withdrawal on tics in children with ADHD (Nolan 1999), and therefore did not meet the inclusion criteria (Criteria for considering studies for this review);
- two studies that assessed the effects of pharmacological treatments on cognition and attention but not the primary outcomes of ADHD or tic severity (Howson 2004; Sallee 1994).

In this update, we excluded one study because it did not utilize a double-blind protocol (Lyon 2010).

Risk of bias in included studies

See also 'Risk of bias' tables, in the Characteristics of included studies tables, and Figure 2.

Figure 2.   Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

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Allocation

We judged sequence generation to be at low risk of bias for three studies (Feigin 1996; Spencer 2002; Tourette's Syndrome Study Group 2002). The remaining five studies did not describe sequence generation and we judged these studies at unclear risk of bias on this domain.

Five studies adequately described allocation concealment (Allen 2005; Gadow 2007; Singer 1995; Spencer 2002; Tourette's Syndrome Study Group 2002). The remaining three studies inadequately described allocation concealment, preventing us from making a judgement on whether or not it was adequate.

Blinding

Blinding of participants, clinicians, and outcome assessors were evaluated separately and was a requirement for inclusion. Therefore, all included studies were at low risk of performance and detection bias.

Incomplete outcome data

Three of the eight studies did not adequately addressed incomplete outcome data. Feigin 1996 had a very high dropout of study participants after the first period of the study, especially in the treatment group, and it was unclear if data from participants who dropped out of the study were included in the analysis. Gadow 2007 did not explain how they handled incomplete data sets in the analysis. Castellanos 1997 provided few raw data from study results; the reported only F scores and P values for analysis of variance tests. In addition, all of the above studies, which were cross-over studies, did not provide paired data for analysis. Rather, each study provided only means and SDs for each treatment type and, with the exception of Castellanos 1997, did not provide original data. The remaining five studies adequately addressed incomplete outcome data.

Selective reporting

Singer 1995 did not provide outcome data for many variables described as collected in the Methods section, only presenting data for those scales showing significant changes. Also, they often reported 'male only' results. Consequently, we judged this study at high risk of reporting bias. Castellanos 1997 was at high risk of bias as very few data were presented on the results of the analysis. We judged the remaining five studies at low risk of reporting bias.

Other potential sources of bias

Allen 2005 had a high rate of early treatment termination at 12 weeks in both treatment groups and thus was at high risk of other bias. None of the other studies appeared to have other potential sources of bias and thus were at low risk of other bias.

Effects of interventions

See: **Summary of findings for the main comparison** Methylphenidate compared with placebo for attention deficit hyperactivity disorder (ADHD) in children with comorbid tic disorders; **Summary of findings 2** Clonidine compared with placebo for attention deficit hyperactivity disorder (ADHD) in children with comorbid tic disorders; **Summary of findings 3** Desipramine compared with placebo for attention deficit hyperactivity disorder (ADHD) in children with comorbid tic disorders

All treatments, with the exception of deprenyl, were efficacious in treating the symptoms of ADHD. Tic symptoms improved in children treated with methylphenidate, clonidine, methylphenidate plus clonidine, guanfacine and desipramine (see Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3). Fear of worsening tics limited dose increases of methylphenidate in one study (Tourette's Syndrome Study Group 2002). High-dose dextroamphetamine appeared to worsen tics in one study (Castellanos 1997), although the length of this study was only three weeks.

Primary outcomes: attention deficit hyperactivity disorder and tic symptom severity

Methylphenidate

The Tourette's Syndrome Study Group 2002 parallel-group study randomized children to: clonidine, flexible dose of methylphenidate, clonidine plus methylphenidate, or placebo, for 16 weeks each. The primary outcome was the change from baseline to week 16 in the ADHD Conners ASQ for Teachers; the main secondary outcome was the change from baseline in the YGTSS. On the ASQ, there was a statistically significant treatment effect in comparison to placebo with methylphenidate alone (3.3 points, 98.3% confidence interval (CI) −0.2 to 6.8; P = 0.02, reported in study) and with clonidine plus methylphenidate (6.3 points, 98.3% CI 2.8 to 9.8; P < 0.001). YGTSS scores also improved compared to placebo, with a statistically significant treatment effect observed for methylphenidate alone (11.0 points, 98.3% CI 2.1 to 19.8; P = 0.003), and for methylphenidate plus clonidine (11.0 points, 98.3% CI 2.1 to 19.8; P = 0.003).

The lowest rate of reported adverse effects occurred in the methylphenidate-only group: 20% of participants treated with methylphenidate reported a worsening of tics as an adverse event compared to 22% receiving placebo (and 26% treated with clonidine alone). Paradoxically, however, tics limited further dosage increases more often for participants assigned to methylphenidate alone (35%) than for participants assigned to methylphenidate plus clonidine (15%), clonidine alone (18%), or placebo (19%).

In the Gadow 2007 cross-over trial, which randomized children to three different doses of methylphenidate and placebo for two weeks each, the primary outcome was the YGTSS score. Regarding ADHD symptoms, all three doses of methylphenidate were superior to placebo on all rating scales used, including the ASQ. There was a dose-dependent effect, with methylphenidate 0.5 mg/kg showing superiority to the lower doses of methylphenidate on the ASQ. Mean scores on the ASQ were: 11.6 (SD 6.9) points during placebo treatment; 8.0 (SD 6.0) points with methylphenidate 0.1 mg/kg; 7.3 (SD 5.8) points with methylphenidate 0.3 mg/kg; and 5.7 (SD 5.1) points with methylphenidate 0.5 mg/kg (F = 24.7; P < 0.001).

On the YGTSS, there was no difference in tic severity between treatments with respect to mean total motor, total phonic, impairment, or global severity scores. The teacher ratings on the Global Tic Rating Scale, however, indicated an improvement in tic severity with methylphenidate treatment compared to placebo with all doses (F ratio 5.33; P = 0.002); although one measure, the two-minute tic/habit count, found an increase in simple motor tics during treatment with methylphenidate 0.3 mg/kg and methylphenidate 0.5 mg/kg compared to placebo (F = 3.96; P = 0.009).

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In the Castellanos 1997 cross-over trial in which children were randomized to three weeks each of methylphenidate, dextroamphetamine, and placebo, methylphenidate significantly decreased hyperactivity at all doses. In the first cohort of 10 participants, analysis of variance of total tic severity showed that tic severity was significantly greater during the second week of methylphenidate treatment (P < 0.01) than during any of the placebo weeks, or during the third week of methylphenidate treatment. In the second and third cohorts of participants, there was no significant main effect of drug on tic severity.

A meta-analysis of studies evaluating methylphenidate was not possible for several reasons. First, the cross-over trial by Gadow 2007 presented data as means and SDs for each methylphenidate dosage and placebo, rather than providing a paired analysis. Meta-analysis of these data, therefore, runs the risk of a unit-of-analysis error. Second, the manuscript for Castellanos 1997 only provided F scores from the analysis of variance of tic severity as it related to drug and dosage. No other raw data were provided and, on contacting the study author, these data were no longer available.

Dextroamphetamine

Castellanos 1997 was a placebo-controlled, cross-over study of dextroamphetamine, which randomized 20 children into three cohorts. Each child received one of three different dosage titrations of dextroamphetamine to a target dosage of 7.5 mg, 15 mg, or 22.5 mg, twice daily for three weeks. In all cohorts, dextroamphetamine significantly decreased hyperactivity, measured by teachers using the Conners 39-item Teacher Rating Scale, but there was no significant interaction between drug and dose, indicating that additional improvements in hyperactivity were not observed for higher doses.

In the first cohort of 10 participants, tic severity was significantly greater during the second (15 mg twice daily) and third (22.5 mg twice daily) weeks of dextroamphetamine treatment compared to the weeks on placebo (F = 3.50, 98.3% CI 4 to 36; P = 0.03, reported in study). In the second cohort of six participants, there was no significant main effect of the drug on tic severity. In the third cohort of four participants, there was a trend for tic severity to be greater with dextroamphetamine, but this did not reach statistical significance.

Clonidine

In the Tourette's Syndrome Study Group 2002, in comparison to placebo, there was a statistically significant treatment effect on the ASQ with clonidine alone (3.3 points, 98.3% CI –0.2 to 6.8; P = 0.02), and with clonidine plus methylphenidate (6.3 points, 98.3% CI 2.8 to 9.8; P < 0.0001). YGTSS scores also improved compared to placebo, with a statistically significant treatment effect observed for clonidine alone (10.9 points, 98.3% CI 2.1 to 19.7; P = 0.003), and for clonidine plus methylphenidate (11.0 points, 98.3% CI 2.1 to 19.8; P = 0.003).

Singer 1995 was a three-arm cross-over study comparing clonidine 0.05 mg, given four times daily, to placebo and desipramine 25 mg given four times daily. The authors did not define a primary outcome and presented data for only those scales showing significant changes. In this study, clonidine did not show a significant difference compared to either placebo or desipramine on any of the outcome measures of ADHD and tic severity, with the exception of the nervous/overactive subscale of the Child Behavior

Checklist in a subgroup of boys aged six to 11 years, in which clonidine was superior to placebo.

We were unable to perform a meta-analysis of the two studies evaluating clonidine for two reasons. The Tourette's Syndrome Study Group 2002 trial presented data as means and SDs for each treatment type rather than in a paired analysis, creating a risk for a unit-of-analysis error. The studies also had significant clinical heterogeneity: duration of treatment of six weeks in Singer 1995 versus 16 weeks for Tourette's Syndrome Study Group 2002. As clinical response times for clonidine can take several months, a difference of 10 weeks of treatment time between studies is likely to be clinically significant.

Guanfacine

Scahill 2001 was an eight-week, parallel-group trial of guanfacine versus placebo in 34 children; there was no primary outcome defined. After eight weeks of treatment, guanfacine significantly reduced symptoms of ADHD and tics measured by the ADHD Rating Scale Total Score completed by the teacher (guanfacine: 37.2 (SD 8.4) points at baseline, 23.6 (SD 13.6) points at endpoint; placebo: 34.4 (SD 9.3) points at baseline, 31.7 (SD 11.2) points at endpoint (t = 2.80, df = 32; P < 0.01)), and the YGTSS total tic score (guanfacine: 15.2 (SD 6.6) points at baseline, 10.7 (SD 7.0) points at endpoint; placebo: 15.4 (SD 7.0) points at baseline, 15.4 (SD 5.5) points at endpoint (t = 2.02, df = 30; P = 0.05)).

Atomoxetine

In Allen 2005, a parallel-group study of atomoxetine in 148 children (0.5 mg/kg/day to 1.5 mg/kg/day), the primary stated objective was to test the hypothesis that atomoxetine does not worsen tics in participants with ADHD and a comorbid tic disorder (i.e. is non-inferior relative to placebo). The primary efficacy measure was the YGTSS total tic score and secondary assessment measures included the ADHD Rating Scale total score, parent version. With respect to measures of ADHD severity, children in the atomoxetine group had a mean decrease of 10.9 (SD 10.9) points on the ADHD Rating Scale total score compared to a decrease of 4.9 (SD 10.3) points in the placebo group (P = 0.002).

On the primary outcome measure, tic severity measured using the YGTSS, atomoxetine was non-inferior relative to placebo after 18 weeks of treatment. The lower limit of the one-sided CI for the difference in mean change between the two treatment groups (placebo and atomoxetine) was 0.27, which, being greater than the prespecified lower limit of –3.7, indicated non-inferiority. The atomoxetine group showed a greater mean improvement in the YGTSS at the endpoint (–5.5 (SD 6.9) points) compared to placebo (–3.0 (SD 8.7) points), but this difference was not statistically significant (P = 0.06).

Desipramine

Two studies evaluated desipramine in children with ADHD and a chronic tic disorder: the Spencer 2002 parallel-group study of 41 children, comparing placebo to desipramine titrated weekly up to 3.5 mg/kg/day for six weeks, and the Singer 1995 cross-over study comparing desipramine to both placebo and clonidine.

Spencer 2002 did not specify a primary outcome, although they assessed ADHD severity using the ADHD rating scale and tic severity with the YGTSS. At week six, compared to baseline, both

ADHD symptoms and tic severity significantly improved in children treated with desipramine whereas they did not in children treated with placebo. The ADHD rating scale score decreased from 46 (SD 5.9) points at week zero to 24 (SD 12) points at week six (P < 0.001), and the YGTSS score decreased from 63 (SD 18) points at week zero to 43 (SD 23) points at week six (P < 0.001). There were no changes in measures of anxiety, obsessive-compulsive behaviors, or depression between desipramine and placebo.

In the study by Singer 1995, with respect to ADHD symptoms, desipramine was superior to placebo (and clonidine) in the Parent Linear Analogue Scale for Hyperactivity (P < 0.05), with a mean score of 32.8 (SD 1.3) points during desipramine treatment compared to 64.4 (SD 0.6) points during placebo treatment (and 51.6 (SD 2.2) during clonidine treatment). The hyperactivity subscale of the Child Behavior Checklist demonstrated a statistically significant drug effect only for boys aged six to 11 years for desipramine compared to both clonidine and placebo treatment (P < 0.05). Hyperactivity subscale scores were 68.6 (SD 1.4) points during desipramine treatment compared to 75.8 (SD 1.0) points during placebo treatment (and 70.7 (SD 1.2) points during clonidine treatment).

With respect to effect on tic severity, desipramine was superior to both placebo and clonidine (P < 0.05) on the Parent Linear Analogue Scale. Mean scores were 30.0 (SD 0.7) points during desipramine treatment compared to 47.4 (SD 1.8) points during placebo treatment (and 41.4 (SD 1.1) points during clonidine treatment). Other measures of tic severity, including the Tourette Syndrome Severity Scale and the YGTSS, did not demonstrate significant differences between treatment groups.

Singer 1995 was a cross-over trial that presented data as means and SDs for each treatment type, rather than in a paired analysis. We were unable to perform a meta-analysis of Singer 1995 and Spencer 2002 because of the risk of a unit-of-analysis error.

Deprenyl

In the Feigin 1996 cross-over trial of deprenyl versus placebo, the primary outcome measure for ADHD was the total score on the DuPaul ADHD Scale, and the primary outcome measure for tics was the total score on the YGTSS. The primary analysis revealed no significant improvement on the DuPaul ADHD Scale with deprenyl (mean improvement 1.3 points, 95% CI –2.7 to 5.3; P = 0.50). The YGTSS total score improved by a mean of 9.3 points with deprenyl (95% CI –0.4 to 19.0; P = 0.06), but this was not statistically significant. Nine of the 24 participants dropped out of the study before entering the second treatment period (six who had received deprenyl and three who had received placebo).

Secondary outcomes: adverse effects

Methylphenidate

In Gadow 2007, there were higher levels of somatic symptoms (sleep and appetite problems, headache, stomach upset, dizziness) on the Stimulant Side Effects Checklist during methylphenidate treatment than with placebo (F = 8.1; P < 0.001). Diastolic blood pressure was higher during treatment with methylphenidate 0.5 mg/kg or 0.1 mg/kg compared with placebo; and heart rate was higher during treatment with methylphenidate 0.3 mg/kg and 0.5 mg/kg compared to placebo.

In Castellanos 1997, appetite suppression with transient weight loss occurred in three children during methylphenidate treatment, and initial insomnia occurred in two children with methylphenidate.

Dextroamphetamine

In Castellanos 1997, appetite suppression with transient weight loss occurred in four children on dextroamphetamine. Initial insomnia occurred in 10 children on dextroamphetamine.

Clonidine

In Tourette's Syndrome Study Group 2002, sedation was common in children receiving clonidine, with 48% of the clonidine-treated participants reporting this adverse effect compared to 14% of participants treated with methylphenidate and 6% with placebo.

In Singer 1995, specific adverse effects were not reported. The authors reported that 15/34 children experienced at least one drug-related problem during placebo treatment, compared to 28/34 children during clonidine treatment.

Guanfacine

In Scahill 2001, there was no significant difference between the guanfacine and placebo groups in any adverse effects, including laboratory test results, weight, or cardiovascular parameters. One participant in the guanfacine group withdrew at week four of the study due to sedation.

Atomoxetine

In Allen 2005, rates of decreased appetite and nausea were significantly higher in participants treated with atomoxetine than with placebo (decreased appetite: 16% with atomoxetine versus 3% with placebo; P = 0.01; nausea: 16% with atomoxetine versus 1% with placebo; P = 0.002). The atomoxetine group showed a mean decrease of bodyweight at endpoint (–0.9 (SD 1.9) kg) that was significantly different from the weight gain seen in the placebo group (1.6 (SD 2.3) kg). Participants receiving atomoxetine also had a significant increase in heart rate (+8.3 (SD 12.0) beats per minute) compared to the decrease in heart rate seen in the placebo group (–1.2 (SD 12.7) beats per minute). Electrocardiography revealed a decrease in QT interval in the atomoxetine group versus a slight increase in the placebo group.

Desipramine

In Spencer 2002, there were no serious adverse events. Children treated with desipramine had significantly higher rates of appetite suppression (24%) compared to placebo (0%) (P < 0.02). Mild but statistically significant increases in diastolic blood pressure and pulse rate also occurred in the desipramine-treated participants.

In Singer 1995, specific adverse effects were not reported. The authors stated that 15/34 children reported at least one drug-related problem during placebo treatment compared to 26/34 children during desipramine treatment.

Deprenyl

In Feigin 1996, adverse events were not reported to have occurred more frequently with treatment with deprenyl than with placebo; however, the authors did not include a description of adverse events by treatment group.

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DISCUSSION

Summary of main results

The findings of this review suggest that there are a number of medicines available to treat children with ADHD and comorbid tic disorders. All the agents, with the exception of deprenyl, reported improvements in symptoms of ADHD in children with tic disorders, however, the quality of evidence available was low.

The data from Tourette's Syndrome Study Group 2002 suggest that methylphenidate and clonidine have similar efficacy in treating symptoms of ADHD, and their combination is superior to either treatment alone. These findings may be seen as contrary to clinical experience, which has traditionally proposed that stimulants are more effective in treating ADHD symptoms than alpha agonists (Connor 1999). This unexpected result may have been due to the doses of methylphenidate used in the study which, at 25 mg/day, is lower than doses used in clinical practice for all but very young children. In Singer 1995, desipramine was superior to clonidine for the treatment of ADHD symptoms. However, this trial has limited applicability for two reasons. First, in general, the effects of clonidine may take several months to become apparent and a six-week trial of this medication would likely be inadequate to evaluate efficacy. Second, desipramine is now used only on rare occasions in children because of concerns about cardiac toxicity (Amitai 2006).

The three studies of methylphenidate suggested that this drug does not worsen tics in the majority of children. It should be noted that the dose of methylphenidate in Tourette's Syndrome Study Group 2002 was on the lower end of what is used in clinical practice (mean 26 mg daily). There has been only one study of dextroamphetamine on tic symptoms. Castellanos 1997 found worsening of tics during the second (15 mg twice daily) and third (22.5 mg twice daily) weeks of dextroamphetamine treatment compared to the weeks on placebo. As treatment was for only three weeks, it is not clear if worsening of tic symptoms would have resolved over time. The dosages used in this study are on the high end of what is used in clinical practice. There was no further clinical benefit for ADHD symptoms with the higher doses of dextroamphetamine compared to the lower dosage used (7.5 mg twice daily), which did not worsen tics. The result from this single study suggested that the lower dosage of dextroamphetamine could be considered when treating children with comorbid ADHD and tics.

Tics do not appear to worsen with alpha agonists, and the majority of studies reported an improvement in tic severity with this class of drug. Tics significantly improved in both trials studying desipramine (Singer 1995; Spencer 2002); however, safety concerns have meant that it is no longer routinely used in children (Riddle 1993). The effect of atomoxetine on tic severity was non-inferior to placebo (Allen 2005).

Overall completeness and applicability of evidence

Overall, there was a small number of trials assessing pharmacological treatments for ADHD in children with tic disorders. There are some gaps in the current available evidence, with no trials of long-acting stimulants in children with tic disorders or trials using a number of newer ADHD treatments (see Implications for research). As ADHD and tic disorders frequently occur together, the evidence is applicable clinically. The evidence is limited by the short duration of the majority of trials.

Quality of the evidence

Important methodological limitations reduced the impact of most of the trials included in this review, with the body of evidence considered low for methylphenidate, atomoxetine, and clonidine, and very low for desipramine, dextroamphetamine, guanfacine, and deprenyl. Many of the trials were small, selective outcome reporting was occasionally an issue, and reporting of results from cross-over trials was generally poor with no studies presenting paired data for analysis.

Potential biases in the review process

We did not identify any potential biases in the review process.

Agreements and disagreements with other studies or reviews

Bloch 2009 conducted a meta-analysis on the treatment of ADHD in children with comorbid tic disorders. Their study included the same trials as those reported in our review but they double counted one trial as two, mistaking a separate report, Gadow 2007, as an additional trial. They have drawn similar conclusions to our systematic review but elected to perform a meta-analysis of the data, despite the degree of clinical heterogeneity and the unit-of-analysis issues identified above, which, in our view, would preclude such an analysis. Additionally, Cohen 2015 conducted a meta-analysis of RCTs of psychostimulants for ADHD, focusing specifically on data related to the onset of tics reported in these trials. They concluded that the use of psychostimulants was not associated with new onset of, or increase in, the severity of pre-existing tics. Their study included 22 trials, none of which are included in our review, and their findings supported our conclusions.

AUTHORS' CONCLUSIONS

Implications for practice

Drugs of the stimulant class have generally been thought to provide the most reliable and robust treatment responses for symptoms of ADHD in children with tics. Given the methodological difficulties inherent in comparing effect sizes across studies with divergent inclusion criteria, efficacy measures, and designs, this review can provide no evidence-based recommendations for choosing between treatment options. Stimulants will likely continue to be considered as first-line treatment for children with moderate-to-severe symptoms of ADHD in children with tic disorders. Although, overall, stimulants have not been shown to worsen tics in most participants with tic disorders, they may still exacerbate tics in individual cases. In these instances, treatment with alpha agonists or atomoxetine could be considered as alternatives. Although there is evidence that desipramine may improve both tics and ADHD in children, safety concerns will likely continue to limit its use.

Implications for research

This study highlights the need for adherence to minimal common standards of study design and efficacy measures of pharmacological treatments of tics and ADHD for different agents to enable subsequent comparison of results. A variety of newer agents appear to improve symptoms of ADHD and therefore are candidates for double-blind, placebo-controlled, head-to-head trials in children with tic disorders and ADHD. These agents include: lisdexamfetamine, a long-acting stimulant prodrug (Biederman

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2007); the newer antidepressant bupropion, a dual norepinephrine and dopamine reuptake inhibitor (Conners 1996); the novel non-stimulant, modafinil, an agent with both dopaminergic and postsynaptic alpha-1 adrenergic effects (Kahbazi 2009); and nicotine, which enhances noradrenergic and dopaminergic transmission (Potter 2004; Shytle 2002).

Larger, confirmatory studies with the existing agents used for treatment of ADHD would be desirable, including studies of guanfacine and clonidine, as well as studies of the established stimulants in the longer-acting forms that are now more commonly used, and the long-acting form of guanfacine. Longer-term evaluation of dextroamphetamine would also be warranted given ongoing concerns over its ability to exacerbate tics in a small number of participants.

The agents used to treat isolated ADHD may improve ADHD symptoms in participants with comorbid tic disorders. This suggests that the pathophysiology of ADHD may be similar in both groups. Each of the agents reviewed in this study has a different mechanism of action or has preferential effects on different receptor subtypes. A more detailed analysis of the interaction between the specific mechanism of action of each agent and its symptomatic effects on ADHD and tics may provide further insights into the underlying pathophysiology of both conditions.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Allen 2005

Methods	Double-blind, parallel-group study
Participants	**Country:** USA
	Inclusion criteria: children aged 7-17 years, meeting APA 2000 criteria for ADHD and TS or chronic motor tic disorder
	Mean age: 11.2 (SD 2.5) years
	Sample size: 148 (placebo = 72, atomoxetine = 76)
	Sex: 131 boys, 17 girls
Interventions	**Intervention:** atomoxetine
	Dose: 0.5-1.5 mg/kg per day
	Control: placebo
	Administration: administered in a divided dose, once in the morning and once in the late afternoon, for 18 weeks under double-blind conditions
Outcomes	• Yale Global Tic Severity Scale (primary outcome) • ADHD Rating Scale-IV: Parent Version
Notes	**Study start and end dates:** no information
	Funding: funded by Eli Lilly and Company
	Author affiliations:
	• Drs Allen, Feldman, and Kelsey, and DR Milton and LL Layton are from the Lilly Research Laboratories Indianapolis, IN.

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Allen 2005 *(Continued)*

- Dr Kurlan is from the Department of Neurology, University of Rochester School of Medicine and Dentistry, NY.
- Drs Gilbert and Sallee are from the Department of Pediatrics, Cincinnati Children's Hospital Medical Center, OH.
- Dr Coffey is from the New York University Child Study Center, NY.
- Dr Linder is from Dallas Pediatric Neurology Associates, Dallas, TX.
- Dr Lewis is from Monarch Research Associates, Norfolk, VA.
- Dr Winner is from Premiere Research Institute, Palm Beach Neurology, West Palm Beach, FL.
- Dr Dunn is from Riley Child and Adolescent Psychiatry Clinic, Indianapolis, IN.
- Dr Dure is from the Department of Pediatrics, Division of Neurology, University of Alabama at Birmingham, AL.
- Dr Mintz is from Bancroft NeuroHealth, Cherry Hill, NJ.
- Dr Ricardi is from the Arizona Family Resource Counseling Center, Phoenix, AZ.
- Dr Spencer is from the Pediatric Psychopharmacology Unit, Massachusetts General Hospital/Harvard Medical School, Boston, MA.

Conflicts of interest:

- Drs Allen, Feldman, and Kelsey, and DR Milton and LL Layton are employees of, and shareholders in, Eli Lilly and Company.
- Dr Gilbert receives research support from the Tourette Syndrome Association, Lilly, NINDS, and NIMH. He does no consulting, advising, or speaker's bureaus.
- Dr Sallee receives research support from Shire, Otsuka, Lilly, and NINDS. He is a member of the speaker's bureau for Pfizer and Lilly and is on the advisory board of Shire and Pfizer.
- Dr Coffey receives research support from NIMH, NINDS, Tourette Syndrome Association, Bristol Myers Squibb, and Lilly. She is a member on the advisory board and speaker's bureau for Lilly.
- Dr Linder currently receives research support from Lilly, Abbott, and Johnson & Johnson. He is on the speaker's bureau for Lilly, Astra-Zeneca, McNeil, and Valeant. He is not on any advisory boards at this time.
- Dr Lewis receives research support from Lilly, Astra-Zeneca, McNeil, and Abbott Labs.
- Dr Winner is on the speaker's bureau for Pfizer, Glaxo, Merck, McNeil, and Astra-Zeneca. He is also on the Advisory Board for Glaxo, Merck, Allergan, McNeil, Astra-Zeneca, and Excel. In addition, he does research with Glaxo, McNeil, and Astra-Zeneca.
- Dr Dunn receives research support from Astra-Zeneca, Lilly, and Shire. He is a member of the speaker's bureau for Lilly, McNeil, and UCB Pharma.
- Dr Mintz receives research support from UCB Pharma, Lilly, Glaxo, McNeil, and National Institutes of Health (NIH). He is a member of the speaker's bureau for Lilly and UCB Pharma.
- Dr Ricardi is a speaker for Lilly and receives research support from Lilly.
- Dr Erenberg is a member of the speaker's bureau for Lilly, McNeil, Shire, and UCB Pharma.
- Dr Spencer receives research support from Shire, Lilly, Janssen, Pfizer, McNeil, Novartis, and NIMH. He is a member of the speaker's bureau for Lilly, Novartis, Shire, and McNeil. Dr Spencer is on the advisory boards for Shire, Lilly, McNeil, Novartis, Janssen, and Johnson & Johnson.
- Drs Kurlan, Gilbert, Linder, Lewis, Winner, Dunn, Dure, Sallee, Mintz, Ricardi, Erenberg, and Spencer have received grants from Eli Lilly in excess of USD 10,000.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** no details provided
Allocation concealment (selection bias)	Low risk	**Comment:** randomization carried at visit 2 by a computerized interactive voice response system

Allen 2005 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Comment:** double blinded
Blinding of participants and personnel (performance bias)	Low risk	**Comment:** double blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment:** double blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** incomplete outcome data addressed
Selective reporting (reporting bias)	Low risk	**Comment:** all expected outcomes included
Other bias	High risk	**Comment:** high rate of early treatment termination in both treatment groups at 12 weeks

Castellanos 1997

Methods	Double-blind, placebo-controlled, cross-over study of methylphenidate and dextroamphetamine
Participants	**Country:** USA **Inclusion criteria:** children aged 6-13 years, meeting APA 1987 criteria for ADHD and Tourette syndrome **Mean age:** 9.4 (SD 2.0) years **Sample size:** 22 **Sex:** all boys
Interventions	**Intervention:** methylphenidate and dextroamphetamine, each at 3 possible doses **Dose:** methylphenidate: 15 mg (low), 25 mg (medium) and 45 mg (high); dextroamphetamine: 7.5 mg (low), 15 mg (medium) and 22.5 mg (high) **Control:** placebo **Administration:** doses were given twice daily at breakfast and lunch for a 1-week period for each sequence. 1 group of 12 boys was given drug dosages in a low, medium, and high sequence for 1 week each. 1 group of 6 boys was given drug dosages in a low, medium, and medium sequence for 1 week each. 1 group of 4 boys was given drug dosages in a low, high, and high sequence for 1 week each.
Outcomes	• Conners Teacher Rating Scale - Hyperactivity Scale • Yale Global Tic Severity Scale • Tourette Syndrome Unified Rating Scale
Notes	**Study start and end dates:** no information **Funding:** no information

Castellanos 1997 *(Continued)*

Author affiliations:

- all authors, with the exception of Dr Elia and Ms Ritchie are with the Child Psychiatry Branch, NIMH, Bethesda, MD
- Dr Elia is with the Medical College of Pennsylvania, Philadelphia, PA
- Ms Ritchie is with the Center for Mental Health Services, Substance Abuse and Mental Health Services Administration, Rockville, MD

Conflicts of interests: no information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** not described
Allocation concealment (selection bias)	Unclear risk	**Comment:** not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Comment:** double blinded
Blinding of participants and personnel (performance bias)	Low risk	**Comment:** double blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment:** double blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** little raw data provided
Selective reporting (reporting bias)	High risk	**Comment:** did not include all expected outcomes. No measure of ADHD inattentive symptoms or parent report of ADHD symptoms included
Other bias	Low risk	**Comment:** no other bias apparent

Feigin 1996

Methods	Randomized, double-blind, placebo-controlled, cross-over study
Participants	**Country:** USA **Inclusion criteria:** children aged 7-16 years, meeting APA 1987 criteria for Tourette syndrome and ADHD **Mean age:** 12 years **Sample size:** 24 **Sex:** 21 boys, 3 girls
Interventions	**Intervention:** deprenyl

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Feigin 1996 *(Continued)*

Dose: 5 mg twice daily

Control: placebo

Administration: 2 × 8-week treatment periods separated by 6-week washout period. Participants given deprenyl or placebo for 8 weeks, followed by cross-over to the alternate treatment after a washout period of 6 weeks

Outcomes	• DuPaul ADHD Scale • Achenbach Child Behavioural Checklist - Parent • Leyton Obsessional Inventory • Children's Yale Brown Obsessive Compulsive Scale • Yale Global Tic Severity Scale
Notes	**Study start and end dates:** no information **Funding:** no information **Author affiliations:** • Drs Feigin, Kurlan, McDermott, Dimitsopulos, Trinidad, and Como and Ms Brower are from the University of Rochester Medical Center, Rochester, NY • Drs Chapieski and Jankovic and Ms Beach are from Baylor College of Medicine, Houston, TX **Conflicts of interest:** no information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** randomization plan generated by a Fortran program
Allocation concealment (selection bias)	Unclear risk	**Comment:** not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Comment:** double blinded
Blinding of participants and personnel (performance bias)	Low risk	**Comment:** double blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment:** double blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** not clear if those who dropped out of the study had their data included in the analysis. Very high dropout rate after first period, especially in treatment group
Selective reporting (reporting bias)	Low risk	**Comment:** all expected outcomes included
Other bias	Low risk	**Comment:** no other bias apparent

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Gadow 2007

Methods	Double-blind, cross-over study
Participants	**Country:** USA **Inclusion criteria:** children aged 6-12 years, meeting APA 1987 or APA 2000 criteria for ADHD and chronic motor tic disorder or TS **Mean age:** 8.95 (± 1.4) years **Sample size:** 71 **Sex:** 57 boys, 14 girls
Interventions	**Intervention:** methylphenidate **Dose:** 0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg **Control:** placebo **Administration:** participants received placebo and 3 doses of methylphenidate (0.1 mg/kg, 0.3 mg/kg, and 0.5 mg/kg) for 2 weeks each. Medication was administered twice daily in the aforementioned dose, 3.5 hours apart, 7 days per week for 2 weeks
Outcomes	• Yale Global Tic Severity Scale (primary outcome) • Shapiro Tourette Syndrome Severity Scale • TS measured with the Clinical Global Impression scale • Global Tic Rating Scale • 2-Minute Tic Count • Conners Abbreviated Teacher/Parent Rating Scale • IOWA Conners Teacher Rating Scale • Mothers' Objective Method for Subgrouping • Continuous Performance Test
Notes	**Study start and end dates:** no information **Funding:** funded, in part, by a research grant from the Tourette Syndrome Association and United States Public Health Service grant number MH 45358 from the NIMH. **Author affiliations:** all of the authors are with the Department of Psychiatry and Behavioral Science, State University of New York, Stony Brook, NY **Conflicts of interests:** no information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** dose schedules assigned on a random basis
Allocation concealment (selection bias)	Low risk	**Comment:** details provided in paper referenced in the methods section of study manuscript
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Comment:** double blinded

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Gadow 2007 *(Continued)*

Blinding of participants and personnel (performance bias)	Low risk	**Comment:** double blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment:** double blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** did not explain how incomplete data sets were handled
Selective reporting (reporting bias)	Low risk	**Comment:** all expected outcomes included
Other bias	Low risk	**Comment:** no other bias apparent

Scahill 2001

Methods	Randomized, placebo-controlled, parallel-group study of guanfacine versus placebo
Participants	**Country:** USA
	Inclusion criteria: children aged 7-15 years, meeting APA 2000 criteria for ADHD and a chronic tic disorder
	Mean age: 10.4 (SD 2.0) years
	Sample size: 34 (placebo = 17, guanfacine = 17)
	Sex: 31 boys, 3 girls
Interventions	**Intervention:** guanfacine
	Dose: 1.5-3 mg per day
	Control: placebo
	Administration: divided into 3 daily doses, for 8 weeks
Outcomes	• ADHD Rating Scale • Clinical Global Impressions Scale - Global Improvement score • Yale Global Tic Severity Scale • Children's Yale Brown Obsessive Compulsive Scale • Continuous Performance Task
Notes	**Study start and end dates:** no information
	Funding: funded, in part, by grant number MO1-RR-06022, from the Children's Clinical Research Center; Mental Health Research Center grant number MH-30929; and grant from the Tourette Syndrome Association
	Author affiliations: authors from the Yale Child Study Center, New Haven, CT
	Conflicts of interests: no information

Risk of bias

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Scahill 2001 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** not described
Allocation concealment (selection bias)	Unclear risk	**Comment:** not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Comment:** double blinded
Blinding of participants and personnel (performance bias)	Low risk	**Comment:** double blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment:** double blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** incomplete outcome data addressed
Selective reporting (reporting bias)	Low risk	**Comment:** all expected outcomes included
Other bias	Low risk	**Comment:** no other bias apparent

Singer 1995

Methods	Randomized, placebo-controlled, cross-over study of clonidine and desipramine
Participants	**Inclusion criteria:** children aged 7-14 years, meeting APA 1980 and APA 1987 criteria for TS and ADHD **Mean age:** 10.6 years **Sample size:** 34 **Sex:** 31 boys and 3 girls
Interventions	**Country:** USA **Intervention:** clonidine, desipramine **Dose:** clonidine 0.05 mg, desipramine 25 mg **Control:** placebo **Administration:** given 4 times daily for 6 weeks. 1-week washout period between treatments
Outcomes	• Child Behavior Checklist • Gordon Diagnostic System • Clinical Evaluation of Language Function • Matching Familial Figures Test • Porteus Maze Test

Singer 1995 *(Continued)*

- Restricted Academic Test
- Tourette Syndrome Severity Scale
- Hopkins Motor/vocal Scale
- Yale Global Tic Severity Scale
- Leyton Obsessional Inventory

Notes	**Study start and end dates:** no information
	Funding: funded by grants from the Tourette Syndrome Association and the United States Public Health Service (grant numbers NS 27327 and HD 25806)
	Author affiliations: authors from the Departments of Neurology and Pediatrics at Johns Hopkins University School of Medicine, Baltimore, MD
	Conflicts of interest: no information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** not described
Allocation concealment (selection bias)	Low risk	**Comment:** medications, prepared by the Johns Hopkins Hospital pharmacy, provided as uniform-appearing capsules in numbered containers
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Comment:** double blinded
Blinding of participants and personnel (performance bias)	Low risk	**Comment:** double blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment:** double blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** incomplete outcome data addressed
Selective reporting (reporting bias)	High risk	**Comment:** not all expected outcomes included. Outcome data not provided for many variables. Often reported 'male only' results
Other bias	Low risk	**Comment:** no other bias apparent

Spencer 2002

Methods	Double-blind, parallel-group trial of desipramine versus placebo
Participants	**Country:** USA
	Inclusion criteria: children aged 5-17 years, with APA 2000 diagnosis of ADHD and TS or chronic motor tic disorder

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Spencer 2002 *(Continued)*

	Mean age: not provided for overall sample; desipramine: 10.6 (SD 2.4) years, placebo: 11.3 (SD 3.0) years
	Sample size: 41 (placebo = 20, desipramine = 21)
	Sex: 34 boys, 7 girls
Interventions	**Intervention:** desipramine
	Dose: titrated weekly up to 3.5 mg/kg
	Control: placebo
	Administration: given twice daily (maximum dose split into two doses) for 6 weeks
Outcomes	• Clinical Global Impression Scale • ADHD Rating Scale • Yale Global Tic Severity Scale • Children's Yale Brown Obsessive Compulsive Scale • Children's Depression Inventory • Revised Children's Manifest Anxiety Scale
Notes	**Study start and end dates:** no information
	Funding: funded partly by the Tourette Sydrome Association and grant number R29 MH57511 from the NIMH, Bethesda, MD
	Author affiliations:
	• Drs Spencer, Biederman, Crawford, and Faraone, Ms Bearman, and Ms Tarazi are from the Pediatric Psychopharmacology Unit, Psychiatry Service, Massachusetts General Hospital, Boston, MA • Drs Spencer, Biederman, Coffey, Geller, and Faraone are from the Department of Psychiatry, Harvard Medical School, Boston, MA • Dr Coffey is with the Tourette's Disorder Clinic and Dr Geller is from the Obsessive Compulsive Disorders Clinic at the McLean Hospital, Belmont, MA • Dr Faraone is also from the Harvard Institute of Psychiatric Epidemiology and Genetics, Harvard Medical School, Boston, MA
	Conflicts of interest: no information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "Pharmacy randomized participants using separate balanced randomization"
Allocation concealment (selection bias)	Low risk	**Quote:** "Randomization codes were kept in sealed envelopes in the medical records. Medication was given in identical appearing 25 mg capsules."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Comment:** double blinded
Blinding of participants and personnel (performance bias)	Low risk	**Comment:** double blinded

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Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment:** double blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** incomplete outcome data addressed
Selective reporting (reporting bias)	Low risk	**Comment:** all expected outcomes included
Other bias	Low risk	**Comment:** no other bias apparent

Tourette's Syndrome Study Group 2002

Methods	Randomized, controlled, parallel-group study of clonidine, methylphenidate, clonidine plus methylphenidate or placebo
Participants	**Country:** USA **Inclusion criteria:** children aged 7-14 years, meeting DSM-IV criteria for ADHD and a chronic tic disorder **Mean age:** not provided for overall sample; placebo: 9.7 (SD 1.8) years, methylphenidate: 10.7 (SD 2.0) years, clonidine: 9.7 (SD 1.8) years, clonidine plus methylphenidate: 10.6 (SD 1.9) years **Sample size:** 136 (placebo = 32, methylphenidate = 37, clonidine = 34, clonidine plus methylphenidate = 33) **Sex:** 85% boys
Interventions	**Intervention:** clonidine, methylphenidate **Dose:** flexible. Mean dose: • clonidine: 0.25 mg per day (alone), 0.28 mg per day (with methylphenidate) • methylphenidate: 25.7 mg per day (alone), 26.1 mg per day (with clonidine) **Control:** placebo **Administration:** 2-3 times per day for 16 weeks
Outcomes	• Conners Abbreviated Symptom Questionnaire for Teachers (ADHD) • Yale Global Tic Severity Scale • Continuous Performance Task • Child Global Assessment Scale • Global Tic Rating Scale • Tic Symptom Self Report
Notes	**Study start and end dates:** no information **Funding:** • NINDS (National Institute of Neurological Disorders and Stroke) grant #1R01NS33654 • The General Clinical Research Center (GCRC) grant from the National Center for Research Resources, National Institutes of Health • Tourette Syndrome Association (Bayside, NY)

Tourette's Syndrome Study Group 2002 *(Continued)*

Author affiliations: no information

Conflicts of interest: no information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** randomly assigned by central co-ordinating center. Computer-generated randomization plan
Allocation concealment (selection bias)	Low risk	**Comment:** central co-ordinating center
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Comment:** double blinded
Blinding of participants and personnel (performance bias)	Low risk	**Comment:** double blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment:** double blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** incomplete outcome data addressed
Selective reporting (reporting bias)	Low risk	**Comment:** all expected outcomes included
Other bias	Low risk	**Comment:** no other bias apparent

ADHD: attention deficit hyperactivity disorder; APA: American Psychiatric Association; CGI: Clinical Global Impression; DSM-III-R: *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*; DSM-IV: *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; IOWA: inattention/overactivity with aggression; NIMH: National Institute of Mental Health; NINDS: National Institute of Neurological Disorders and Stroke; SD: standard deviation; TS: Tourette syndrome.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Howson 2004	Primary outcome to assess immediate effect of a single transdermal dose of nicotine on tics and objective indices of sustained attention. Participants did not have to have ADHD to participate in study
Law 1999	Study excluded participants with Tourette syndrome
Lyon 2010	Study did not use double-blind procedures
Niederhofer 2003	Study retracted from journal due to suspicion of fraudulent results and plagiarism

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Study	Reason for exclusion
Nolan 1999	Study looked at the effect of stimulant withdrawal on tics rather than the effect of the medication on ADHD and tic symptom severity
Sallee 1994	Study on the effect of pimozide on cognition. Not all participants had ADHD

ADHD: attention deficit hyperactivity disorder.

ADDITIONAL TABLES

Table 1. Comparisons

Comparisons	Trial(s)
Methylphenidate versus placebo	Castellanos 1997
	Gadow 2007
	Tourette's Syndrome Study Group 2002
Clonidine versus placebo	Singer 1995
	Tourette's Syndrome Study Group 2002
Methylphenidate plus clonidine versus placebo	Tourette's Syndrome Study Group 2002
Dextroamphetamine versus placebo	Castellanos 1997
Guanfacine versus placebo	Scahill 2001
Atomoxetine versus placebo	Allen 2005
Desipramine versus placebo	Singer 1995
	Spencer 2002
Deprenyl versus placebo	Feigin 1996
Desipramine versus clonidine	Singer 1995

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Table 2.   Attention deficit hyperactivity disorder symptom severity scales used in this review

Scale/measure	Allen 2005	Castellanos 1997	Feigin 1996	Gadow 2007	Scahill 2001	Singer 1995	Spencer 2002	Tourette's Syndrome Study Group 2002
Conners Abbreviated Teacher Rating Scale	–	–	–	Yes	–	–	–	Yes
Conners Abbreviated Parent Rating Scale	–	–	–	Yes	–	–	–	Yes
IOWA Conners Teacher Rating Scale	–	–	–	Yes	–	–	–	Yes
Mothers' Objective Method for Subgrouping	–	–	–	Yes	–	–	–	–
Continuous Performance Task	–	–	–	Yes	Yes	–	–	–
ADHD Rating Scale-IV: Parent Version	Yes	–	–	–	Yes	–	Yes	–
Clinical Global Impression Scale – Overall – Severity	Yes	–	–	–	Yes	–	–	–
Clinical Global Impression Scale – ADHD/Psychiatric Symptoms	Yes	–	–	–	–	–	–	–
ADHD Teacher 39-Item Conners Rating Scale	–	Yes	–	–	–	–	–	–
DuPaul ADHD Scale	–	–	Yes	–	–	–	–	–
Parent Conners Questionnaire Hyperactivity Index	–	–	–	–	Yes	–	–	–
Child Behaviour Checklist	–	–	–	–	–	Yes	–	–
Gordon Diagnostic System	–	–	–	–	–	Yes	–	–
Clinical Evaluation of Language Function	–	–	–	–	–	Yes	–	–
Matching Familial Figures Test	–	–	–	–	–	Yes	–	–
Porteus Maze Test	–	–	–	–	–	Yes	–	–
Restricted Academic Test	–	–	–	–	–	Yes	–	–

Conners Continuous Performance Task	–	–	–	–	–	–	–	Yes

ADHD: attention deficit hyperactivity disorder; IOWA: inattention/overactivity with aggression.

Table 3. Tic severity symptom scales used in this review

Scale/measure	Allen 2005	Castellanos 1997	Feigin 1996	Gadow 2007	Scahill 2001	Singer 1995	Spencer 2002	Tourette's Syndrome Study Group 2002
Yale Global Tic Severity Scale	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Tourette Syndrome Severity Scale	–	–	–	Yes	–	Yes	–	–
Tourette Syndrome Clinical Global Improvement	Yes	–	–	Yes	–	–	–	–
Global Tic Rating Scale	–	–	–	Yes	–	–	–	Yes
2-Minute Tic and Habit Count	–	–	–	Yes	–	–	–	–
Tic Symptom Self-Report	Yes	–	–	–	–	–	–	Yes
Goetz Tic Severity Scale	–	–	Yes	–	–	–	–	–
Hopkins Motor/Vocal Scale	–	–	–	–	–	Yes	–	–

Table 4. Description of scales used in included studies

Scale/measure	Number of items	Scoring
Conners' Abbreviated Symptoms Questionnaire for Teachers (ASQ)	10 items pertaining to the child's behavior	Rated on a 4-point Likert scale, ranging from 0 (not at all), 1 (just a little), 2 (pretty much) to 3 (very much true), with a possible total score ranging from 0 to 30. Higher scores indicate worse symptoms
Yale Global Tic Severity Scale (YGTSS)	5 items on the number, frequency, intensity, complexity, and interference from motor tics, and 5 items on the number, frequency, intensity, complexity, and interference from vocal tics, and 1 item on overall impairment	The Total Motor Tic Score is derived by adding the 5 motor tics items (each item ranges from 0 to 5, total motor tic score ranges from 0 to 25). The Total Vocal Tic Score is derived by adding the 5 phonic tics items (each item ranges from 0 to 5, total vocal tic ranges from 0 to 25). The Total Tic Score is a summation of the Total Motor Tic and Total Vocal Tic Scores. The Overall Impairment Rating is rated on a 51-point scale anchored by 0 (no impairment) and 50 (severe impairment). Finally, the Global Severity Score is a summation of the Total Motor Tic Score, Total Vocal Tic Score, and Overall Impairment Rating (range 0 to 100). Higher scores indicate worse symptoms.
Global Tic Rating Scale	9 items, with the first 5 referring to the frequency of motor (3 items) and phonic tics (2 items) according to body region, which are summed to produce motor and phonic tic frequency subscores, respectively	All items are rated on a scale from 0 (never) to 3 (very much). Total score ranges from 0 to 27. Higher scores indicate worse symptoms
ADHD Rating Scale IV - Parent Version	18-item questionnaire. 9 questions each on inattention and hyperactivity-impulsivity, where the odd-numbered items represent the inattention subscale, and the even-numbered items represent the hyperactive/impulsive subscale	Items coded on 4-point Likert scale using scores 1 (never or rarely), 2 (sometimes), 3 (often), or 4 (very often). Total score ranges from 18 to 52. Raw scores are converted to percentiles.
ADHD Parent Linear Analogue Scale	10-cm line on which both the parent and physician separately rank symptoms	The ends of each line represent 0 (no symptoms) and 10 (most severe)
Child Behaviour Checklist (CBCL)	113 items across 8 subscales assessing maladaptive behavioral and emotional problems: • withdrawn • somatic complaints • anxious/depressed • social problems • thought problems • attention problems • delinquent problems • aggressive behavior	Items are coded from 0 to 2, scored 0 (not at all), 1 (somewhat true), or 2 (very true). CBCL profile for each category, with scores below the 95th percentile in the normal range, and above the 98th percentile in the clinical range. Higher scores indicate worse symptoms.
Conners' Abbreviated Parent Rating Scale	48 items across 6 subscales: • conduct problems • learning problems • psychosomatic • impulsive/hyperactive	All items are rated on a scale from 0 (never) to 3 (very much). Total score ranges from 0 to 144. Higher scores indicate worse symptoms

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Table 4. Description of scales used in included studies *(Continued)*

	• anxiety • hyperactivity index	
IOWA Conners' Teacher Rating Scale	10 items. Consists of 5-item subscales designed to assess inattention/overactivity and aggression Inattention/overactivity: • fidgeting • hums and makes other odd noises • excitable, impulsive • inattentive, easily distracted • fails to finish things he starts (short attention span) Aggression: • quarrelsome • acts "smart," • temper outbursts (explosive and unpredictable behavior) • defiant • unco-operative	Scored 0 (not at all), 1 (just a little), 2 (pretty much), or 3 (very much). Total score ranges from 0 to 30. Higher scores indicate worse symptoms
Mothers' Objective Method for Subgrouping	Contains 10 (hyperactivity or ADHD, or both) symptoms arranged in a checklist format. Generates a hyperactivity scale score and an aggression scale score	1 indicates checked and 0 unchecked. Total score ranges from 0 to 10. Higher scores indicate worse symptoms
Continuous Performance Task (CPT)	Computer-administered and scored measure of sustained visual attention and motor response inhibition. The test takes about 15 minutes to administer and yields measures of omissions, commissions, and reaction time.	Omission errors measure inattention, commission errors measure impulsivity
Conners' Teacher Rating Scale	39 items clustered into 5 factors, including conduct problems, daydreaming, inattention, anxious-fearful, and hyperactive behavior ADHD Teacher 39-Item	All items are rated on a scale from 0 (never) to 3 (very much). Total score ranges from 0 to 137. Raw scores for each scale are converted to T scores, incorporating normative adjustments for age and sex, with scores of at least 70 considered clinically elevated
Conners' Continuous Performance Task (CPT)	Visual-motor task. Respondents must rapidly and accurately hit the space bar after every letter presented except the letter 'X'. Several variables may be derived from the Conners' CPT, including errors of omission and commission, mean hit reaction time (RT), mean hit RT standard error.	Omission errors measure inattention, commission errors measure impulsivity
Tourette Syndrome Severity Scale	5-item scale • Are the tics noticeable to others? • Do the tics elicit comments? • Is the patient considered odd or bizarre? • Do the tics interfere with functioning? • Is the patient incapacitated, homebound, or hospitalized?	Higher scores indicates worse symptoms

Table 4. Description of scales used in included studies *(Continued)*

Tourette Syndrome Clinical Global Impression (CGI) Scale	Observer-rated scale that measures illness severity (CGI-S), or global improvement (CGI-I)	7-point scale, with the severity of illness scale (CGI-S) using a range of responses from 1 (normal) to 7 (among the most severely ill people). CGI-I scores range from 1 (very much improved) to 7 (very much worse)
2-Minute Tic and Habit Count	The physician counts separately the number of brief, jerky (i.e. tics) and rhythmic (i.e. stereotypic, habit) movements and vocalizations during quiet conversation in an office setting.	Higher scores indicates worse symptoms
Tic Symptom Self-Report	40-item checklist containing 20 motor tic items and 20 phonic tic items	0–3 scale corresponding with absent (score of 0) to very frequent and forceful (score of 3). Total score ranges from 0 to 120. Higher scores indicate worse symptoms
Goetz Tic Severity Scale	Videotape protocol involving a 10-minute film of people placed in front of a video camera in a quiet room. 2 body views are recorded, full frontal body (far) and head and shoulders only (near), under 2 conditions: relaxed with the examiner in the room, and relaxed with the patient alone in the room 5 domains are rated: • number of body areas involved with tics • motor tic intensity • phonic tic intensity • frequency of motor tics • frequency of phonic tics	0–4 scoring format. For all domains, 0 represents normal function without evidence of tic disability. Higher scores indicate worse symptoms
Hopkins Motor/Vocal Scale	Consists of a series of linear analog scales (10 cm) on which both the parent and physician separately rank each tic (motor and vocal) symptom, taking into consideration its frequency, intensity, degree of interference, and impairment	The ends of each line represent 0 (no tics) and 10 (most severe). The line can be subdivided roughly into 4 ranges: mild, moderate, moderately severe, and severe
Du Paul ADHD Rating Scale	14 items, assessing separate factors of inattention and hyperactivity-impulsivity	Rated on a 0 (normal) to 3 (severe) scale, yielding a total score ranging from 0 to 42. Higher scores indicate worse symptoms
Parent Conners' Questionnaire Hyperactivity Index	10-item rating scale identifying hyperactive children	Each item is rated from 0 to 3 (range 0–30). Higher scores indicate worse symptoms

ADHD: attention deficit hyperactivity disorder.

APPENDICES

Appendix 1. Search strategies from 2009 onwards

Cochrane Central Register of Controlled Trials (CENTRAL)

CENTRAL (2017, Issue 8), searched 20 September 2017 (21 records)
CENTRAL (2016, Issue 6), searched 6 July 2016 (47 records)

#1[mh ^"attention deficit and disruptive behavior disorders"]

#2[mh " attention deficit disorder with hyperactivity"]
#3[mh "conduct disorder"]
#4(ADHD or ADDH or ADHS or "AD/HD" or HKD or TDAH)
#5((attention* or behav*) near/3 (defic* or dysfunc* or disorder*))
#6((disrupt* near/3 disorder*) or (disrupt* near/3 behav*) or (defian* near/3 disorder*) or (defian* near/3 behav*))
#7(impulsiv* or inattentiv* or inattention*)
#8[mh hyperkinesis]
#9(hyperkin* or hyper next kin*)
#10(minimal* near/3 brain near/3 (disorder* or dysfunct* or damage*))
#11(hyperactiv* or hyper next activ*)
#12{or #1-#11}
#13[mh Tics]
#14[mh "tic disorders"]
#15[mh "tourette syndrome"]
#16(tic or tics)
#17Tourette*
#18(habit* near/3 (spasm* or chorea*))
#19{or #13-#18}
#20#12 and #19
#21[mh infant]
#22[mh child]
#23[mh adolescent]
#24(child* or boy* or girl* or infant* or baby or babies or teen* or adolescen* or toddler* or pre-school* or preschool* or schoolchild*)
#25{or #21-#24}
#26#20 and #25 Publication Year from 2009 to 2016, in Trials
#27#20 and #25 Publication Year from 2016 to 2017, in Trials

MEDLINE Ovid

MEDLINE (1946 to September week 1 2017) (43 records)
MEDLINE (1946 to June week 4 2016) (10 records)

1 "attention deficit and disruptive behavior disorders"/
2 attention deficit disorder with hyperactivity/
3 conduct disorder/
4 ADHD.tw,kw.
5 ADDH.tw,kw.
6 ADHS.tw,kw.
7 ("AD/HD" or HKD).tw,kw.
8 TDAH.tw,kw.
9 ((attention$ or behav$) adj3 (defic$ or dysfunc$ or disorder$)).tw,kw.
10 ((disrupt$ adj3 disorder$) or (disrupt$ adj3 behav$) or (defian$ adj3 disorder$) or (defian$ adj3 behav$)).tw,kw.
11 (impulsiv$ or inattentiv$ or inattention$).tw,kw.
12 hyperkinesis/
13 (hyperkin$ or hyper-kin$).tw,kw.
14 (minimal adj3 brain adj3 (disorder$ or dysfunct$ or damage$)).tw,kw.
15 (hyperactiv$ or hyper-activ$).tw,kw.
16 or/1-15
17 tics/
18 tic disorders/
19 tourette syndrome/
20 (tic or tics).tw,kw.
21 Tourette$.tw,kw.
22 (habit$ adj3 (spasm$ or chorea$)).tw,kw.
23 or/17-22
24 infant/
25 exp child/
26 adolescent/
27 (child$ or boy$ or girl$ or infant$ or baby or babies or teen$ or adolescen$ or toddler$ or pre-school$ or preschool$ or schoolchild$).tw,kw.
28 or/24-27
29 exp Antidepressive Agents/
30 antidepress$.tw,kw.

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31 Clonidine/
32 desipramine/
33 exp Dextroamphetamine/
34 Guanfacine/
35 exp Methylphenidate/
36 atomoxetine.mp.
37 catapres$.mp.
38 clonidine.mp.
39 concerta.mp.
40 desipramine.mp.
41 dexamfetamine.mp.
42 dexedrine.mp.
43 dextroamphetamine.mp.
44 dixarit.mp.
45 equasym.mp.
46 guanfacine.mp.
47 medikinet.mp.
48 methylphenidat$.mp.
49 ritalin$.mp.
50 strattera.mp.
51 or/29-50
52 16 and 23 and 28 and 51
53 limit 52 to yr="2009 -Current"
54 limit 52 to ed="20160623 - 20170918"

MEDLINE In-Process and Other Non-Indexed Citations Ovid

MEDLINE In-Process and Other Non-Indexed Citations (19 September 2017) (18 records)
MEDLINE In-Process and Other Non-Indexed Citations (1 July 2016) (14 records)

1 ADHD.tw,kw.
2 ADDH.tw,kw.
3 ADHS.tw,kw.
4 ("AD/HD" or HKD).tw,kw.
5 TDAH.tw,kw.
6 ((attention$ or behav$) adj3 (defic$ or dysfunc$ or disorder$)).tw,kw.
7 ((disrupt$ adj3 disorder$) or (disrupt$ adj3 behav$) or (defian$ adj3 disorder$) or (defian$ adj3 behav$)).tw,kw.
8 (impulsiv$ or inattentiv$ or inattention$).tw,kw.
9 (hyperkin$ or hyper-kin$).tw,kw.
10 (minimal adj3 brain adj3 (disorder$ or dysfunct$ or damage$)).tw,kw.
11 (hyperactiv$ or hyper-activ$).tw,kw.
12 (tic or tics).tw,kw.
13 Tourette$.tw,kw.
14 (habit$ adj3 (spasm$ or chorea$)).tw,kw.
15 (child$ or boy$ or girl$ or infant$ or baby or babies or teen$ or adolescen$ or toddler$ or pre-school$ or preschool$ or schoolchild$).tw,kw.
16 (antidepress$ or anti-depress$).tw,kw.
17 atomoxetine.tw,kw.
18 catapres$.tw,kw
19 clonidine.tw,kw.
20 concerta.tw,kw.
21 desipramine.tw,kw.
22 dexamfetamine.tw,kw.
23 dexedrine.tw,kw.
24 dextroamphetamine.tw,kw.
25 dixarit.tw,kw.
26 equasym.tw,kw.
27 guanfacine.tw,kw.
28 medikinet.tw,kw.
29 methylphenidat$.tw,kw.
30 ritalin$.tw,kw.
31 strattera.tw,kw.
32 or/1-11

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33 or/12-14
34 32 and 33
35 15 and 32 and 33
36 or/17-31
37 35 and 36

MEDLINE Epub Ahead of Print Ovid

MEDLINE Epub Ahead of Print (19 September 2017) (1 record)
MEDLINE Epub Ahead of Print (1 July 2016) (4 records)

1 ADHD.tw,kw.
2 ADDH.tw,kw.
3 ADHS.tw,kw.
4 ("AD/HD" or HKD).tw,kw.
5 TDAH.tw,kw.
6 ((attention$ or behav$) adj3 (defic$ or dysfunc$ or disorder$)).tw,kw.
7 ((disrupt$ adj3 disorder$) or (disrupt$ adj3 behav$) or (defian$ adj3 disorder$) or (defian$ adj3 behav$)).tw,kw.
8 (impulsiv$ or inattentiv$ or inattention$).tw,kw.
9 (hyperkin$ or hyper-kin$).tw,kw.
10 (minimal adj3 brain adj3 (disorder$ or dysfunct$ or damage$)).tw,kw.
11 (hyperactiv$ or hyper-activ$).tw,kw.
12 (tic or tics).tw,kw.
13 Tourette$.tw,kw.
14 (habit$ adj3 (spasm$ or chorea$)).tw,kw.
15 (child$ or boy$ or girl$ or infant$ or baby or babies or teen$ or adolescen$ or toddler$ or pre-school$ or preschool$ or schoolchild $).tw,kw.
16 (antidepress$ or anti-depress$).tw,kw.
17 atomoxetine.tw,kw.
18 catapres$.tw,kw
19 clonidine.tw,kw.
20 concerta.tw,kw.
21 desipramine.tw,kw.
22 dexamfetamine.tw,kw.
23 dexedrine.tw,kw.
24 dextroamphetamine.tw,kw.
25 dixarit.tw,kw.
26 equasym.tw,kw.
27 guanfacine.tw,kw.
28 medikinet.tw,kw.
29 methylphenidat$.tw,kw.
30 ritalin$.tw,kw.
31 strattera.tw,kw.
32 or/1-11
33 or/12-14
34 32 and 33
35 15 and 32 and 33
36 or/17-31
37 35 and 3

Embase Ovid

Embase (1974 to 19 September 2017) (21 records)
Embase (1974 to 2016 week 27) (142 records)

1 attention deficit disorder/
2 hyperactivity/
3 conduct disorder/
4 ADHD.tw.
5 ADDH.tw.
6 ADHS.tw.
7 "AD/HD".tw.
8 "add".tw.
9 (attention$ adj3 (defic$ or dysfunc$ or disorder$)).tw.

Pharmacological treatment for attention deficit hyperactivity disorder (ADHD) in children with comorbid tic disorders (Review)

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10 (behav$ adj3 (dysfunc$ or disorder$)).tw.

11 disruptiv$.tw.

12 (minimal adj3 brain adj3 (disorder$ or dysfunct$ or damage$)).tw.

13 (impulsiv$ or inattentiv$ or inattention$).tw.

14 disruptiv$.tw.

15 (overactiv$ or over-activ$).tw.

16 hyperkinesis/

17 (hyperactiv$ or hyper-activ$).tw.

18 (hyperkin$ or hyper-kin$ or hkd).tw.

19 or/1-18

20 tic/

21 gilles de la tourette syndrome/

22 (tic or tics)tw,kw.

23 Tourette$.tw,kw.

24 (habit$ adj3 (spasm$ or chorea$)).tw,kw.

25 or/20-24

26 19 and 25

27 exp child/

28 adolescence/

29 (child$ or boy$ or girl$ or infant$ or baby or babies or teen$ or adolescen$ or toddler$ or pre-school$ or preschool$ or schoolchild $).tw,kw.

30 or/27-29

31 26 and 30

32 exp antidepressant agent/

33 (antidepress$ or anti-depress$).tw,kw.

34 atomoxetine/

35 clonidine/

36 desipramine/

37 dexamphetamine/

38 methylphenidate/

39 atomoxetine.mp.

40 catapres$.mp.

41 clonidine.mp.

42 concerta.mp.

43 desipramine.mp.

44 dexamfetamine.mp.

45 dexedrine.mp.

46 dextroamphetamine.mp.

47 dixarit.mp.

48 equasym.mp.

49 medikinet.mp.

50 methylphenidat$.mp.

51 ritalin$.mp.

52 strattera.mp.

53 or/32-52

54 31 and 53

55 Randomized controlled trial/

56 controlled clinical trial/

57 Single blind procedure/

58 Double blind procedure/

59 triple blind procedure/

60 Crossover procedure/

61 (crossover or cross-over).tw.

62 ((singl$ or doubl$ or tripl$ or trebl$) adj1 (blind$ or mask$)).tw.

63 Placebo/

64 placebo.tw.

65 prospective.tw.

66 factorial$.tw.

67 random$.tw.

68 assign$.ab.

69 allocat$.tw.

70 volunteer$.ab.

71 or/55-70
72 54 and 71
73 limit 72 to yr="2009 -Current"
74 limit 72 to yr="2016 -Current"

CINAHL EbscoHOST

CINAHL (searched 20 September 2017) 13 records
CINAHL (searched 5 July 2016) 64 records

S1 (MH "Attention Deficit Hyperactivity Disorder")
S2 ADHD
S3 ADDH
S4 ADDH
S5 ADHS
S6 "AD/HD"
S7 ((attention* or behav*) n3 (defic* or dysfunc* or disorder*))
S8 ((disrupt* N3 disorder*) or (disrupt* N3 behav*) or (defian* N3 disorder*) or (defian* N3 behav*))
S9 (impulsiv* or inattentiv* or inattention*)
S10 (MH "Hyperkinesis")
S11 hyperkine*
S12 (minimal N3 brain N3 (disorder* or dysfunct* or damage*))
S13 hyperactiv*
S14 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13
S15 (MH "Tic")
S16 (MH "Tourette Syndrome")
S17 (tic or tics)
S18 Tourette*
S19 (habit* N3 (spasm* or chorea*))
S20 S15 OR S16 OR S17 OR S18 OR S19
S21 S14 AND S20
S22 (MH "Child+")
S23 (MH "Adolescence") OR (MH "Young Adult")
S24 (child* or boy* or girl* or infant* or baby or babies or teen* or adolescen* or toddler* or pre-school* or preschool* or schoolchild*)
S25 S22 OR S23 OR S24
S26 (MH "Clinical Trials+")
S27 MH random assignment
S28 (MH "Meta Analysis")
S29 (MH "Crossover Design")
S30 (MH "Quantitative Studies")
S31 PT randomized controlled trial
S32 PT Clinical trial
S33 trial*
S34 ("follow-up study" or "follow-up research")
S35 (prospectiv* study or prospectiv* research)
S36 placebo*
S37 (MH "Program Evaluation")
S38 (MH "Treatment Outcomes")
S39 TI(single N2 mask* or single N2 blind*) OR AB(single N2 mask* or single N2 blind*)
S40 TI((doubl* N2 mask*) or (doubl* N2 blind*)) OR AB((doubl* N2 mask*) or (doubl* N2 blind*))
S41 TI ((tripl* N2 mask*) or (tripl* N2 blind*)) or ((trebl* N2 mask*) or (trebl* N2 blind*)) OR AB((tripl* N2 mask*) or (tripl* N2 blind*)) or ((trebl* N2 mask*) or (trebl* N2 blind*))
S42 random*
S43 S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42
S44 S21 AND S43
S45 EM 2009-
S46 S44 AND S45
S47 EM 20160701-
S48 S44 AND S47

PsycINFO Ovid

PsycINFO (1806 to September Week 2 2017) 9 records

PsycINFO (1806 to June Week 5 2016) 63 records

1 exp attention deficit disorder/
2 exp Behavior Problems/
3 Impulsiveness/
4 hyperkinesis/
5 adhd.tw.
6 addh.tw.
7 adhs.tw.
8 "ad/hd".tw.
9 TDAH.tw.
10 hyperactiv$.tw.
11 hyper-activ$.tw.
12 overactiv$.tw.
13 over-activ$.tw.
14 hyperkin$.tw.
15 hyper-kin$.tw.
16 hkd.tw.
17 (minimal adj3 brain$ adj3 (damag$ or disorder$ or dysfunc$)).tw.
18 (attention$ adj3 (deficit$ or disorder$ or dysfunc$)).tw.
19 (behav$ adj3 (dysfunc$ or disorder$)).tw.
20 disruptiv$.tw.
21 (impulsiv$ or inattentiv$ or inattentiv$).tw.
22 or/1-21
23 tics/
24 Tourette Syndrome/
25 (tic or tics).tw.
26 tourette$.tw.
27 (habit$ adj3 (spasm$ or chorea$)).tw.
28 or/24-27
29 22 and 28
30 exp antidepressant drugs/
31 (antidepress$ or anti-depress$).tw.
32 ATOMOXETINE/
33 clonidine/
34 desipramine/
35 dextroamphetamine/
36 methylphenidate/
37 atomoxetine.mp.
38 catapres$.mp.
39 clonidine.mp.
40 concerta.mp.
41 desipramine.mp.
42 dexamfetamine.mp.
43 dexedrine.mp.
44 dextroamphetamine.mp.
45 dixarit.mp.
46 equasym.mp.
47 Guanfacine.mp.
48 medikinet.mp.
49 methylphenidat$.mp.
50 ritalin$.mp.
51 strattera.mp.
52 or/30-51
53 29 and 52
54 limit 53 to yr="2009 -Current"
55 limit 53 to yr="2016 -Current"

Science Citation Index - Expanded (SCI-EXPANDED) and Social Sciences Citation Index (SSCI) (Web of Science)

SCI and SSCI (1970 to 19 September 2017) (10 records)
SCI and SSCI (1970 to 5 July 2016) (225 records)

Pharmacological treatment for attention deficit hyperactivity disorder (ADHD) in children with comorbid tic disorders (Review)

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19#17 AND #16 AND #15 AND #12
Indexes=SCI-EXPANDED, SSCI Timespan=2016-2017
# 18#17 AND #16 AND #15 AND #12
Indexes=SCI-EXPANDED, SSCI Timespan=All years
# 17TS=(child* or boy* or girl* or infant* or baby or babies or teen* or adolescen* or toddler* or pre-school* or preschool* or schoolchild*)
Indexes=SCI-EXPANDED, SSCI Timespan=All years
# 16TS=(random* or trial* or control* or blind* or allocat* or assign* or group* or prospective or placebo*)
Indexes=SCI-EXPANDED, SSCI Timespan=All years
# 15#14 OR #13
Indexes=SCI-EXPANDED, SSCI Timespan=All years
# 14TS=(antidepress* OR anti-depress*)
Indexes=SCI-EXPANDED, SSCI Timespan=All years
# 13TS=(atomoxetine OR clonidine OR concerta OR desipramine OR dexamfetamine OR dexedrine OR dextroamphetamine OR dixarit OR equasym OR guanfacine OR medikinet OR methylphenidat* OR ritalin OR strattera)
Indexes=SCI-EXPANDED, SSCI Timespan=All years
# 12#11 AND #8
Indexes=SCI-EXPANDED, SSCI Timespan=All years
# 11#10 OR #9
Indexes=SCI-EXPANDED, SSCI Timespan=All years
# 10TS=(habit* near/3 (spasm* or chorea*))
Indexes=SCI-EXPANDED, SSCI Timespan=All years
# 9TS=(tic OR tics OR Tourette*)
Indexes=SCI-EXPANDED, SSCI Timespan=All years
# 8#7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1Indexes=SCI-EXPANDED, SSCI Timespan=All years
# 7TS=(hyperactiv* or hyper-activ*)
Indexes=SCI-EXPANDED, SSCI Timespan=All years
# 6TS=(minimal* near/3 brain near/3 (disorder* or dysfunct* or damage*))
Indexes=SCI-EXPANDED, SSCI Timespan=All years
# 5TS=(hyperkin* or hyper-kin*)
Indexes=SCI-EXPANDED, SSCI Timespan=All years
# 4TS=(impulsiv* or inattentiv* or inattention*)
Indexes=SCI-EXPANDED, SSCI Timespan=All years
# 3TS=((disrupt* near/3 disorder*) or (disrupt* near/3 behav*) or (defian* near/3 disorder*) or (defian* near/3 behav*))
Indexes=SCI-EXPANDED, SSCI Timespan=All years
# 2TS=((attention* or behav*) near/3 (defic* or dysfunc* or disorder*))
Indexes=SCI-EXPANDED, SSCI Timespan=All years
# 1TS= (ADHD or ADDH or ADHS or "AD/HD" or HKD or TDAH)
Indexes=SCI-EXPANDED, SSCI Timespan=All years

Conference Proceedings Citation Index- Science (CPCI-S) and Conference Proceedings Citation Index- Social Science & Humanities (CPCI-SSH) Web of Science

CPCI-S and CPCI-SSH (1990 to 19 September 2017) (0 records)
CPCI-S and CPCI-SSH (1990 to 5 July 2016) (16 records)

19(#17 AND #16 AND #15 AND #12)
Indexes=CPCI-S, CPCI-SSH Timespan=2016-2017 [Final search line September 2017]
# 18#17 AND #16 AND #15 AND #12 [Final search line July 2016]
Indexes=CPCI-S, CPCI-SSH Timespan=All years
# 17TS=(child* or boy* or girl* or infant* or baby or babies or teen* or adolescen* or toddler* or pre-school* or preschool* or schoolchild*)
Indexes=CPCI-S, CPCI-SSH Timespan=All years
# 16TS=(random* or trial* or control* or blind* or allocat* or assign* or group* or prospective or placebo*)
Indexes=CPCI-S, CPCI-SSH Timespan=All years
# 15#14 OR #13
Indexes=CPCI-S, CPCI-SSH Timespan=All years
# 14TS=(antidepress* OR anti-depress*)
Indexes=CPCI-S, CPCI-SSH Timespan=All years
# 13TS=(atomoxetine OR clonidine OR concerta OR desipramine OR dexamfetamine OR dexedrine OR dextroamphetamine OR dixarit OR equasym OR guanfacine OR medikinet OR methylphenidate OR ritalin OR strattera)
Indexes=CPCI-S, CPCI-SSH Timespan=All years
# 12#11 AND #8
Indexes=CPCI-S, CPCI-SSH Timespan=All years
# 11#10 OR #9

Pharmacological treatment for attention deficit hyperactivity disorder (ADHD) in children with comorbid tic disorders (Review)

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Indexes=CPCI-S, CPCI-SSH Timespan=All years
# 10TS=(habit* near/3 (spasm* or chorea*))
Indexes=CPCI-S, CPCI-SSH Timespan=All years
# 9TS=(tic OR tics OR Tourette*)
Indexes=CPCI-S, CPCI-SSH Timespan=All years
# 8#7 OR # 6 OR #5 OR #4 OR #3 OR #2 OR #1
Indexes=CPCI-S, CPCI-SSH Timespan=All years
# 7TS=(hyperactiv* or hyper-activ*)
Indexes=CPCI-S, CPCI-SSH Timespan=All years
# 6TS=(minimal* near/3 brain near/3 (disorder* or dysfunct* or damage*))
Indexes=CPCI-S, CPCI-SSH Timespan=All years
# 5TS=(hyperkin* or hyper-kin*)
Indexes=CPCI-S, CPCI-SSH Timespan=All years
# 4TS=(impulsiv* or inattentiv* or inattention*)
Indexes=CPCI-S, CPCI-SSH Timespan=All years
# 3TS=((disrupt* near/3 disorder*) or (disrupt* near/3 behav*) or (defian* near/3 disorder*) or (defian* near/3 behav*))
Indexes=CPCI-S, CPCI-SSH Timespan=All years
# 2TS=((attention* or behav*) near/3 (defic* or dysfunc* or disorder*))
Indexes=CPCI-S, CPCI-SSH Timespan=All years
#1 TS= (ADHD or ADDH or ADHS or "AD/HD" or HKD or TDAH)
Indexes=CPCI-S, CPCI-SSH Timespan=All years

Cochrane Database of Systematic Reviews (CDSR) part of the Cochrane Library

CDSR (2017, Issue 9), searched 20 September 2017 (0 records)
CDSR (2016, Issue 7), searched 6 July 2016 (2 records)

#1[mh ^"attention deficit and disruptive behavior disorders"]
#2[mh " attention deficit disorder with hyperactivity"]
#3[mh "conduct disorder"]
#4(ADHD or ADDH or ADHS or "AD/HD" or HKD or TDAH):ti,ab,kw
#5((attention* or behav*) near/3 (defic* or dysfunc* or disorder*)):ti,ab,kw
#6((disrupt* near/3 disorder*) or (disrupt* near/3 behav*) or (defian* near/3 disorder*) or (defian* near/3 behav*)):ti,ab,kw
#7(impulsiv* or inattentiv* or inattention*):ti,ab,kw
#8[mh hyperkinesis]
#9(hyperkin* or hyper next kin*):ti,ab,kw
#10(minimal* near/3 brain near/3 (disorder* or dysfunct* or damage*)):ti,ab,kw
#11(hyperactiv* or hyper next activ*):ti,ab,kw
#12{or #1-#11}
#13[mh Tics]
#14[mh "tic disorders"]
#15[mh "tourette syndrome"]
#16(tic or tics):ti,ab,kw
#17Tourette*:ti,ab,kw
#18(habit* near/3 (spasm* or chorea*)):ti,ab,kw
#19{or #13-#18}
#20#12 and #19
#21[mh infant]
#22[mh child]
#23[mh adolescent]
#24(child* or boy* or girl* or infant* or baby or babies or teen* or adolescen* or toddler* or pre-school* or preschool* or schoolchild*):ti,ab,kw
#25{or #21-#24}
#26#20 and #25 Publication Year from 2009 to 2016, in Cochrane Reviews (Reviews and Protocols)
#27#20 and #25 Online Publication Date from Jun 2016 to Sep 2017, in Cochrane Reviews (Reviews and Protocols)

Database of Abstracts of Reviews of Effect (DARE) part of the Cochrane Library

DARE (2015, Issue 2), searched 6 July 2016 (1 record). This was the final issue of DARE, and so was not searched in 2017.

#1[mh ^"attention deficit and disruptive behavior disorders"]
#2[mh " attention deficit disorder with hyperactivity"]
#3[mh "conduct disorder"]
#4(ADHD or ADDH or ADHS or "AD/HD" or HKD or TDAH):ti,ab,kw

Pharmacological treatment for attention deficit hyperactivity disorder (ADHD) in children with comorbid tic disorders (Review)

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#5((attention* or behav*) near/3 (defic* or dysfunc* or disorder*)):ti,ab,kw
#6((disrupt* near/3 disorder*) or (disrupt* near/3 behav*) or (defian* near/3 disorder*) or (defian* near/3 behav*)):ti,ab,kw
#7(impulsiv* or inattentiv* or inattention*):ti,ab,kw
#8[mh hyperkinesis]
#9(hyperkin* or hyper next kin*):ti,ab,kw
#10(minimal* near/3 brain near/3 (disorder* or dysfunct* or damage*)):ti,ab,kw
#11(hyperactiv* or hyper next activ*):ti,ab,kw
#12{or #1-#11}
#13[mh Tics]
#14[mh "tic disorders"]
#15[mh "tourette syndrome"]
#16(tic or tics):ti,ab,kw
#17Tourette*:ti,ab,kw
#18(habit* near/3 (spasm* or chorea*)):ti,ab,kw
#19{or #13-#18}
#20#12 and #19
#21[mh infant]
#22[mh child]
#23[mh adolescent]
#24(child* or boy* or girl* or infant* or baby or babies or teen* or adolescen* or toddler* or pre-school* or preschool* or schoolchild*):ti,ab,kw
#25{or #21-#24}
#26#20 and #25, in Other Reviews

Epistemonikos

www.epistemonikos.org

Searched 20 September 2017. Limited to systematic reviews added to database between 6 July 2016 and 20 September 2017 (0 records)
Searched 6 July 2016. Limited to systematic reviews (14 records)

(title:(adhd OR hyperactiv* OR attention deficit) OR abstract:(adhd OR hyperactiv* OR attention deficit)) AND (title:(tic* OR Tourette*) OR abstract:(tic* OR Tourette*))

WorldCat

www.worldcat.org

Searched 20 September 2017 (0 records)
Searched 6 July 2016 (1 record)

kw:(adhd OR hyperactiv* OR attention deficit*) AND kw:(TIC* OR tourette*) AND kw:(atomoxetine OR clonidine OR concerta OR desipramine OR dexamfetamine OR dexedrine OR dextroamphetamine OR dixarit OR equasym OR guanfacine OR medikinet OR methylphenidate OR ritalin OR strattera)

ClinicalTrials.gov

clinicaltrials.gov

Searched 20 September 2017. Limited to records first received from 1 July 2016 to 20 September 2017 (3 records)
Searched 6 July 2016 (31 records)

(adhd AND tic) OR (adhd AND tourette) OR (attention deficit AND tic) OR (attention deficit AND tourette) | Interventional Studies

WHO ICTRP

www.who.int/trialsearch/default.aspx

Searched 20 September 2017. Limited to records first received from 1 July 2016 to 20 September 2017 (2 records)
Searched 6 July 2016 (9 records)

Basic search: adhd AND tic OR adhd AND tourette OR attention deficit AND tic OR attention deficit AND tourette

Appendix 2. Search strategies up to 2009

The Cochrane Library

2009, Issue 4.

#1MeSH descriptor Tic Disorders explode all trees
#2MeSH descriptor Tics explode all trees
#3(tic or tics)
#4(tourette*)
#5(habit* near/3 spasm*) or (habit* near/3 chorea*)
#6(#1 OR #2 OR #3 OR #4 OR #5)
#7MeSH descriptor Adolescent explode all trees
#8(child* or adolescen* or boy* or girl* or infant* or toddler* or pre-school* or pre school* or schoolchild*)
#9MeSH descriptor Attention Deficit Disorder with Hyperactivity, this term only
#10(adhd)
#11(addh)
#12adhs
#13(hyperactiv*)
#14hyperkin*
#15(attention deficit*)
#16(brain dysfunction)
#17(#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16)
#18(#7 OR #8)
#19MeSH descriptor Methylphenidate, this term only
#20(methylphenidate or ritalin* or concerta or equasym or medikinet)
#21MeSH descriptor Dextroamphetamine, this term only
#22(dexamfetamine or dextroamphetamine or dexedrine or atomoxetine or strattera)
#23MeSH descriptor Clonidine, this term only
#24(clonidine or dixarit or catapres* or guanfacine)
#25MeSH descriptor Guanfacine, this term only
#26(#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25)
#27(#6 AND #17 AND #18 AND #26)

MEDLINE

1950 to July 2009.

1 tic disorders/ or tourette syndrome/
2 Tics/
3 (tic or tics).tw.
4 tourette$.tw.
5 (habit$ adj3 (spasm$ or chorea$)).tw.
6 or/1-5
7 adolescent/ or child/ or child, preschool/ or infant/
8 (child$ or boy$ or girl$ or infant$ or baby or babies or teen$ or adolescen$ or toddler$ or pre-school$ or pre school$ or schoolchild$).tw.
9 or/7-8
10 Attention Deficit Disorder with Hyperactivity/
11 adhd.tw.
12 addh.tw.
13 adhs.tw.
14 hyperactiv$.tw.
15 hyperkin$.tw.
16 attention deficit$.tw.
17 brain dysfunction.tw.
18 or/10-17
19 Methylphenidate/
20 methylphenidate.tw.
21 ritalin$.tw.
22 concerta.tw.
23 equasym.tw.
24 medikinet.tw.
25 Dextroamphetamine/
26 dexamfetamine.tw.

27 dextroamphetamine.tw.
28 dexedrine.tw.
29 atomoxetine.tw.
30 strattera.tw.
31 Clonidine/
32 clonidine.tw.
33 dixarit.tw.
34 catapres$.tw.
35 desipramine/
36 exp Antidepressive Agents/
37 antidepress$.tw.
38 or/19-37
39 6 and 9 and 18 and 38

Embase

1980 to July 2009

1   tic disorders/ or tourette syndrome/
2   Tics/
3   (tic or tics).tw.
4   tourette$.tw.
5   (habit$ adj3 (spasm$ or chorea$)).tw.
6   or/1-5
7   adolescent/ or child/ or child, preschool/ or infant/
8   (child$ or boy$ or girl$ or infant$ or baby or babies or teen$ or adolescen$ or toddler$ or pre-school$ or pre school$ or schoolchild$).tw.
9   or/7-8
10   Attention Deficit Disorder with Hyperactivity/
11   adhd.tw.
12   addh.tw.
13   adhs.tw.
14   hyperactiv$.tw.
15   hyperkin$.tw.
16   attention deficit$.tw.
17   brain dysfunction.tw.
18   or/10-17
19   Methylphenidate/
20   methylphenidate.tw.
21   ritalin$.tw.
22   concerta.tw.
23   equasym.tw.
24   medikinet.tw.
25   Dextroamphetamine/
26   dexamfetamine.tw.
27   dextroamphetamine.tw.
28   dexedrine.tw.
29   atomoxetine.tw.
30   strattera.tw.
31   Clonidine/
32   clonidine.tw.
33   dixarit.tw.
34   catapres$.tw.
35   guanfacine.tw.
36   Guanfacine/
37   or/19-36
38   random$.tw.
39   factorial$.tw.
40   crossover$.tw.
41   cross over$.tw.
42   cross-over$.tw.
43   placebo$.tw.
44   (doubl$ adj blind$).tw.
45   (singl$ adj blind$).tw.

46   assign$.tw.
47   allocat$.tw.
48   volunteer$.tw.
49   Crossover Procedure/
50   Double Blind Procedure/
51   Randomized Controlled Trial/
52   Single Blind Procedure/
53   or/38-52
54   6 and 53 and 18 and 37 and 9

CINAHL (Cumulative Index to Nursing and Allied Health Literature)

1982 to July 2009.

S29 (S28 and S27 and S12 and S6)
S28 S16 or S15 or S14 or S13
S27 S26 or S25 or S24 or S23 or S22 or S21 or S20 or S19 or S18 or S17
S26 clonidine or dixarit or catapres* or guanfacine
S25 (MH "Clonidine")
S24 atomoxetine or strattera
S23 dexamfetamine or dextroamphetamine or dexedrine
S22 (MH "Dextroamphetamine")
S21 medikinet
S20 equasym
S19 concerta
S18 methylphenidate or ritalin
S17 (MH "Methylphenidate")
S16 attention deficit* or brain dysfunction
S15 hyperactiv* or hyperkin*
S14 adhd or addh or adhs
S13 (MH "Attention Deficit Hyperactivity Disorder")
S12 S11 or S10 or S9 or S8 or S7
S11 child* or boy* or girl* or infant* or baby or babies or teen* or adolescen* or toddler* or pre-school* or pre school* or schoolchild*
S10 (MH "Child, Preschool")
S9 (MH "Infant")
S8 (MH "Child")
S7 (MH "Adolescence")
S6 S5 or S4 or S3 or S2 or S1
S5 habit* n3 chorea*
S4 habit* n3 spasm*
S3 tourette*
S2 tic or tics
S1 (MH "Tic+")

PsycINFO

1806 to July week 4 2009.

1   randomi$.tw.
2   singl$.tw.
3   doubl$.tw.
4   trebl$.tw.
5   tripl$.tw.
6   blind$.tw.
7   mask$.tw.
8   (or/2-5) adj3 (or/6-7)
9   clin$.tw.
10   trial$.tw.
11   (clin$ adj3 trial$).tw.
12   placebo$.tw.
13   exp PLACEBO/
14   crossover.tw.
15   exp Treatment Effectiveness Evaluation/
16   exp Mental Health Program Evaluation/

17   random$.tw.
18   assign$.tw.
19   allocate$.tw.
20   (random$ adj3 (assign$ or allocate$)).tw.
21   20 or 16 or 15 or 14 or 13 or 12 or 11 or 8 or 1
22   tourette syndrome/
23   Tics/
24   (tic or tics).tw.
25   tourette$.tw.
26   (habit$ adj3 (spasm$ or chorea$)).tw.
27   or/22-26
28   (child$ or boy$ or girl$ or infant$ or baby or babies or teen$ or adolescen$ or toddler$ or pre-school$ or pre school$ or schoolchild$).tw.
29   Attention Deficit Disorder with Hyperactivity/
30   adhd.tw.
31   addh.tw.
32   adhs.tw.
33   hyperactiv$.tw.
34   hyperkin$.tw.
35   attention deficit$.tw.
36   brain dysfunction.tw.
37   or/29-36
38   Methylphenidate/
39   methylphenidate.tw.
40   ritalin$.tw.
41   concerta.tw.
42   equasym.tw.
43   medikinet.tw.
44   Dextroamphetamine/
45   dexamfetamine.tw.
46   dextroamphetamine.tw.
47   dexedrine.tw.
48   atomoxetine.tw.
49   strattera.tw.
50   Clonidine/
51   clonidine.tw.
52   dixarit.tw.
53   catapres$.tw.
54   guanfacine.tw.
55   Guanfacine/
56   or/38-55
57   56 and 27 and 28 and 37
58   21 and 57

Dissertation Abstracts

methylphenidate AND tic OR tics OR tourettes
ritalin AND tic OR tics OR tourettes
concerta AND tic OR tics OR tourettes
equasym AND tic OR tics OR tourettes
medikinet AND tic OR tics OR tourettes
dexamfetamine AND tic OR tics OR tourettes
dextroamphetamine AND tic OR tics OR tourettes
dexedrine AND tic OR tics OR tourettes
atomoxetine AND tic OR tics OR tourettes
strattera AND tic OR tics OR tourettes
clonidine AND tic OR tics OR tourettes
dixarit AND tic OR tics OR tourettes
catapres AND tic OR tics OR tourettes
guanfacine AND tic OR tics OR tourettes

Appendix 3. Criteria for assigning 'Risk of bias' judgements

Sequence generation

Description: the method used to generate the allocation sequence was described in detail so as to assess whether it should have produced comparable groups.

Review authors' judgment: was the allocation concealment sequence adequately generated?

Allocation concealment

Description: the method used to conceal allocation sequence was described in sufficient detail to assess whether intervention schedules could have been foreseen in advance of, or during, recruitment.

Review authors' judgment: was allocation adequately concealed?

Blinding of participants and personnel

Description: the method used to blind participants and personnel from knowledge of which intervention a participant received was described.

Review authors' judgment: was knowledge of the allocated intervention adequately prevented during the study?

Blinding of outcome assessment

Description: the method used to blind outcome assessors from knowledge of which intervention a participant received was described.

Review authors' judgment: was knowledge of the allocated intervention adequately prevented during the study?

Incomplete outcome data

Description: if studies did not report intention-to-treat analyses, we attempted to obtain missing data by contacting the study authors. We extracted and reported data on exclusions, as well the numbers involved (compared with total randomized) and the reasons for exclusion, when reported or obtained from study investigators.

Review authors' judgment: were incomplete data dealt with adequately by the reviewers?

Selective outcome reporting

Description: attempts were made to assess the possibility of selective outcome reporting by investigators. This was done by checking study protocols when available through trial registries and comparing the outcomes listed in the protocol with the published report. We made comparisons between outcomes listed in the Methods section of the manuscript and those listed in the Results section.

Review authors' judgment: are reports of the study free of suggestion of selective outcome reporting?

Other sources of bias

Description: other concerns about bias not addressed in the domains above, including:

- design-specific risk of bias (i.e. washout adequacy in cross-over trials);
- early stopping;
- baseline imbalance;
- inappropriate administration of a cointervention; and
- used an insensitive instrument to measure outcomes.

Review authors' judgement: was the study apparently free of other problems that could put it at a high risk of bias?

Appendix 4. Methods described in protocol for meta-analysis

Measures of treatment effect

Binary outcome data

We will use risk ratio (RR) estimations with 95% confidence intervals (CIs) for binary outcomes.

Continuous outcome data

We will analyze data on continuous outcomes using either mean differences (MDs), or standardized mean differences (SMDs) if continuous outcomes are measured with similar but not identical instruments across studies. All analyses will include all participants in the treatment groups to which they were allocated, if data permit.

Unit of analysis issues

Cluster-randomized trials

We do not anticipate finding any cluster-randomized trials.

Cross-over trials

When conducting a meta-analysis combining the results of cross-over trials, we will use the inverse variance methods recommended by Elbourne 2002. Where data presented from a cross-over trial are restricted (and more information is not available from the original investigators), we will use the presented data within the first phase only, up to the point of cross-over.

Dealing with missing data

We will attempt to obtain missing information from study authors directly. If we are unable to obtain the missing information, we will impute the missing data with replacement values, and treat these as if they were observed.

Assessment of heterogeneity

We will assess statistical heterogeneity by examining the I^2 statistic, a quantity which describes approximately the proportion of variation in point estimates that is due to heterogeneity rather than sampling error. In addition, we will use a Chi^2 test of homogeneity, to determine the strength of evidence that heterogeneity is genuine.

Assessment of reporting biases

We will draw funnel plots (effect size versus standard error) to assess publication bias if we find sufficient studies. Asymmetry of the plots may indicate publication bias, although they may also represent a true relationship between trial size and effect size. If such a relationship is identified, we will further examine the clinical diversity of the studies as a possible explanation (Egger 1997).

Data synthesis

We will synthesize results using a meta-analysis by treatment type if there is no important clinical heterogeneity. For example, if studies have a very different study design or methodology, or if trial participants are very different between studies, a meta-analysis may not be appropriate. We will use both the random-effects and fixed-effect models. When we report the results of the random-effects model, we will also report tau^2.

Subgroup analysis and investigation of heterogeneity

We will analyze trials in subgroups based on treatment type, for example, methylphenidate, atomoxetine.

Sensitivity analysis

We will conduct sensitivity analyses to assess the impact of risk of bias on our results.

WHAT'S NEW

Date	Event	Description
20 September 2017	New search has been performed	Updated following a new search conducted in July 2016 and September 2017.
29 September 2016	New citation required but conclusions have not changed	Following review of the abstracts for the new citations obtained, which was conducted by TP and SO, it was determined that none of the new citations matched inclusion criteria and thus the conclusions remain unchanged. Formatting was updated to match new review criteria.

CONTRIBUTIONS OF AUTHORS

SO: reviewed abstracts for inclusion in this update of the review and updated the review to meet current methodological standards.

TS: selected which trials to include, extracted data from trials, interpreted the analysis, edited the final review, and will keep the review up-to-date.

Pharmacological treatment for attention deficit hyperactivity disorder (ADHD) in children with comorbid tic disorders (Review)

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TP: drafted the protocol, developed the search strategy (with guidance from Margaret Anderson, CDPLP), selected which trials to include, extracted data from trials, entered data into Review Manager 2014, carried out the analysis, interpreted the analysis, drafted the final review, and will keep the review up-to-date.

DECLARATIONS OF INTEREST

SO works as a Research Associate at the Clinical Neurosciences Department, Cumming School of Medicine, University of Calgary, on projects focused on movement disorders, ADHD, obsessive compulsive disorder (OCD) and other associated conditions.

TS: none known.

TP's institute receives grants from Shire Canada. TP is involved in one of these grants to develop a continuing medical education program for physicians on the management of aggression in youth and attention deficit hyperactivity disorder (ADHD). TP's institution holds the funds for this project and approves all expenditure.

SOURCES OF SUPPORT

Internal sources

- Department of Clinical Neurosciences, University of Calgary, Canada.

  Employer for SO and TP

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- **Authors**
  - Sydney Osland was added as an author to update the review.
- Electronic searches
  - We added two MEDLINE segments, which are update daily, to make our search as up-to-date as possible (MEDLINE In-Process and Other Non-Indexed Citations and MEDLINE EPub Ahead of Print).
  - BIOSIS Previews was not searched for this update as it was no longer available to the review team or editorial base. Instead, we searched four databases from Web of Science (Science Citation Index - Expanded Web of Science, Social Sciences Citation Index Web of Science, Conference Proceedings Citation Index - Science Web of Science, and Conference Proceedings Citation Index - Social Science and Humanities Web of Science) for all years.
  - Dissertation Express was replaced by a theses search using WorldCat because it allows more complex search strings and does not limit the number of hits that are returned.
  - The Current Controlled Trials meta-Register service (mRCT) was under review at the time the searches were run and was replaced with ClinicalTrials.gov (clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp/en).
  - We also searched sources of systematic reviews to check relevant reference lists (Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Effect (DARE), and Epistemonikos).
- Data collection and analysis
  - We included a list of methods that were described in the protocol, Pringsheim 2009, but not used in the review in Appendix 4.
- Assessment of risk of bias in included studies
  - We evaluated blinding of participants and personnel separately to blinding of outcome assessment due the importance of 'triple blinding;' that is, when outcome assessors, participants, and personnel are unaware of treatment assignment.
- Data synthesis
  - We added a new section on 'Summary of findings' tables, and included three 'Summary of findings' tables in the review (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3), as it is now standard to include this feature in all Cochrane Reviews.
- Description of studies
  - The updated review included the addition of a study flow diagram (Figure 1), due to the new methodological requirements for Cochrane Reviews (Lefebvre 2011).

INDEX TERMS

Medical Subject Headings (MeSH)

Atomoxetine Hydrochloride [therapeutic use]; Attention Deficit Disorder with Hyperactivity [*drug therapy]; Central Nervous System Stimulants [adverse effects] [*therapeutic use]; Clonidine [therapeutic use]; Desipramine [therapeutic use]; Dextroamphetamine [therapeutic use]; Guanfacine [therapeutic use]; Methylphenidate [therapeutic use]; Randomized Controlled Trials as Topic; Selegiline; Tic Disorders [*complications] [drug therapy]

MeSH check words

Adolescent; Child; Child, Preschool; Female; Humans; Male