Comparative efficacy and acceptability of methylphenidate and atomoxetine in treatment of attention deficit hyperactivity disorder in children and adolescents: a meta-analysis

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CRD summary
The review found that methylphenidate and atomoxetine have comparable efficacy and acceptability for treating attention deficit hyperactivity disorder in children and adolescents but that osmotically-released methylphenidate was more effective than atomoxetine. The authors’ conclusions require some caution due to limitations in the review, including insufficient information about study quality, potential publication bias and questionable prominence given to subgroup findings.

Authors' objectives
To compare the efficacy and acceptability of methylphenidate and atomoxetine for treating attention deficit hyperactivity disorder in children and adolescents.

Searching
PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Database of Systematic reviews were searched from 1995 to December 2010 for published studies in any language. Search terms were reported. The reference lists of selected articles were checked.

Study selection
Eligible studies were open-label or double-blinded randomised controlled trials (RCTs) that compared the efficacy of methylphenidate and atomoxetine for treating children and adolescents diagnosed with attention deficit hyperactivity disorder using Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM IV) criteria. The primary review outcome was efficacy (most commonly measured by the attention deficit hyperactivity disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored). Other outcomes of interest were response rate and acceptability (measured by all-cause discontinuation rates).

Participants in the included studies were aged six to 16 years and were predominantly male (78%) and Caucasian (67%). Most had a combined attention deficit hyperactivity disorder subtype, 47% had prior stimulant use, and 36% had comorbid oppositional defiant disorder. Baseline illness severity ranged from 37.4 to 45.5 on the attention deficit hyperactivity disorder Rating Scale. Most studies excluded individuals with tics or other comorbidities. Drug formulations and regimens differed across studies. All studies used a version of the attention deficit hyperactivity disorder Rating Scale-IV to measure efficacy and most also used it to measure response rates, though cut-off points for defining response varied. Study duration ranged from three to 12 weeks.

Two reviewers independently selected the studies, with disagreement resolved by discussion or by a third reviewer.

Assessment of study quality
Study quality was assessed with the Detsky Quality Scale for Randomised Trials, which allocates up to 21 points for randomisation, description of outcome measures, inclusion and exclusion criteria and description of therapy and of statistics.

Data extraction
Standardised mean differences (SMDs) were calculated for continuous outcomes and relative risks (RRs) for dichotomous outcomes, both with 95% confidence intervals (CIs). Only first-phase data were used for one of the two trials that used a crossover design. Missing standard deviations were calculated from the data available or were requested from study authors. Two reviewers independently extracted the data.

Methods of synthesis
Studies were combined using a DerSimonian and Laird random-effects model to calculate pooled efficacy scores and a random-effects Mantel Haenszel model to calculate relative risks for response rates, with 95% confidence intervals.
Inclusion in meta-analysis was apparently restricted to studies scoring at least 12 points on the Detsky scale. Heterogeneity was assessed with the Q test and I² statistic. Subgroup analyses were used to assess the effect of methylphenidate formulation (osmotically released versus immediate release), and sensitivity analyses investigated the effect of study design (cross-over versus parallel) and quality (double-blind versus open-label). Funnel plots were planned to assess publication bias, but there were insufficient studies.

**Results of the review**

Nine RCTs were included in the review (2,762 participants, range 25 to 1,323), five double-blinded and four open-label. All scored at least 12 points on the Detsky scale.

There was no significant difference between methylphenidate and atomoxetine in attention deficit hyperactivity disorder Rating Scale scores (SMD 0.09, 95% CI -0.08 to 0.26; nine RCTs), response rates (RR 0.93, 95% CI 0.76 to 1.14; eight RCTs), or all-cause discontinuation (RR 1.22, 95% CI 0.87 to 1.71; seven RCTs). There was significant heterogeneity (p=0.002, Ι²=67%) for the primary outcome which was attributed to differences between the open-label studies.

In subgroup analysis of attention deficit hyperactivity disorder Rating Scale scores there was a significant benefit from osmotically-released methylphenidate compared to atomoxetine (SMD 0.32, 95% CI 0.12 to 0.53). The findings of other subgroup analyses did not differ substantially from the main findings.

**Authors' conclusions**

Methylphenidate and atomoxetine had comparable efficacy and acceptability for treating attention deficit hyperactivity disorder in children and adolescents. Osmotically-released methylphenidate was more effective than atomoxetine.

**CRD commentary**

The review question and inclusion criteria were clear and relevant sources were searched for studies in any language. The review was limited to published studies so some may have been missed, but there were too few studies to formally assess the risk of publication bias. It was unclear whether quality assessment was carried out with sufficient attempts to minimise reviewer bias and error. Study quality assessment results were not provided for individual studies, which made it hard to determine the reliability of the review findings. Detailed data were presented for only one review outcome and it was unclear which studies were included in other analyses or whether they were statistically homogeneous.

The authors noted that the studies were heterogeneous, several were unblinded, the choice of rating scales may have influenced findings, the largest study only lasted three weeks and subgroups included few studies. The findings about osmotically-released methylphenidate were based on subgroup analysis so were of questionable reliability. The authors' conclusions require some caution due to limitations in the review, including insufficient information about study quality, potential publication bias and questionable prominence given to subgroup findings.

**Implications of the review for practice and research**

**Practice:** The authors stated that osmotically-released methylphenidate could be considered first-line treatment for attention deficit hyperactivity disorder in children and adolescents and that atomoxetine may be used in those with poor response to methylphenidate or at risk of stimulant abuse. Higher doses of atomoxetine, given twice daily, may be beneficial.

**Research:** The authors did not state any implications for research.

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**Bibliographic details**

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