Efficacy and safety of atomoxetine for attention-deficit/hyperactivity disorder in children and adolescents: meta-analysis and meta-regression analysis

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CRD summary
The authors concluded that atomoxetine reduced attention-deficit/hyperactivity disorder symptoms in children and adolescents. The evidence presented appeared to support the authors’ conclusion, but poor reporting of review methods, the lack of information about individual studies, and differences between the studies make it difficult to adequately assess the robustness of the authors’ conclusions.

Authors’ objectives
To evaluate the efficacy and safety of atomoxetine for attention-deficit/hyperactivity disorder (ADHD) in children and adolescents.

Searching
MEDLINE, PubMed, PsycINFO and the Cochrane CENTRAL Register (Issue 3, 2006) were searched from 1985 to September 2006; the search terms were reported. In addition, reference lists were screened.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion in the review.

Specific interventions included in the review
Studies that compared atomoxetine (single or different doses) with placebo were eligible for inclusion.

Participants included in the review
Studies of children and adolescents with any subtype of ADHD were eligible for inclusion. Some of the included studies were in patients with ADHD with or without oppositional defiant disorder (ODD); other studies were in patients with co-morbid ADHD plus ODD.

Outcomes assessed in the review
Studies that assessed the severity of ADHD using the validated Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV), adverse events, withdrawals or drop-outs were eligible for inclusion. Studies had to present sufficient data to enable the calculation of effect sizes. The primary review outcomes were ADHD-RS-IV Total, Inattentive symptom and Hyperactive/impulsive symptom scores. Other outcomes included Connors’ Parent and Teacher Rating Scales-Revised: Short Form (CPRS-R:S and CTRS-R:S), the Clinical Global Impression-Severity (CGI-S), the Oppositional Index of the CPRS-R:S (for ODD symptoms) and the psychosocial summary score on the parent-administered Child Health Questionnaire (CHQ; used to measure quality of life and functional outcomes). The review also assessed treatment response, relapse prevention.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Validity was assessed and scored using the Jadad scale, which considers reporting of randomisation, blinding and withdrawals. The maximum possible score was 5 points. The authors did not state how the validity assessment was performed.

Data extraction
Two reviewers independently extracted the data and resolved any disagreements through discussion. For each study, standardised mean differences (SMDs) between atomoxetine and placebo were calculated with 95% confidence
Methods of synthesis
How were the studies combined?
The main analyses included patients with ADHD with and without ODD. Weighted averages of SMDs were calculated using a random-effects model. The number-needed-to-treat (NNT) to prevent one relapse or result in one treatment response and the number-needed-to-harm (NNH) to result in one adverse event were calculated. Fisher’s exact test was used to examine differences in adverse events between atomoxetine and placebo. Publication bias was assessed using a funnel plot and Begg’s and Egger’s tests.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared statistic. Analyses were repeated for only patients with co-morbid ADHD plus ODD. Meta-regression was used to examine the influence on treatment efficacy of potential covariates: study characteristics, patient characteristics and study quality. Meta-regression analyses were used to examine the influence on adverse events of drug dose, treatment duration, and patient and dose characteristics.

Results of the review
Nine RCTs (1,828 patients) were included in the review: seven RCTs in patients with ADHD with or without ODD (1,615 patients) and two RCTs in patients with co-morbid ADHD plus ODD (213 patients). All of the included studies provided information about withdrawals and drop-outs. Five studies were reported as having appropriate randomisation. Eight studies were double-blinded. The Jadad scores ranged from 3 to 5.

ADHD with or without ODD
Compared with placebo, atomoxetine significantly improved ADHD-RS-IV Total scores (SMD -0.638, 95% CI: -0.761, -0.516), Inattentive symptom scores (SMD -0.558, 95% CI: -0.658, -0.457) and Hyperactive/impulsive symptom scores (SMD -0.548, 95% CI: -0.727, -0.369). Statistically significant heterogeneity was detected for Hyperactive/impulsive symptom scores (p=0.01; I-squared 67%) but not for the other two analyses. The results were similar after adjusting for significant confounding factors.

Compared with placebo, atomoxetine significantly improved CPRS/CTRS-R:S, CGI-S scores, and quality of life and function (results were reported).

The NNT to result in one treatment response was 3.43 (95% CI: 2.79, 4.45) and the NNT to prevent one relapse was 10.30 (95% CI: 5.89, 40.62).

ADHD with ODD
Compared with placebo, atomoxetine significantly reduced or improved ADHD-RS-IV Total, Inattentive symptom scores, Hyperactive/impulsive symptom scores, CGI, parent-rated CPRS-R:S and ODD symptoms in patients with co-morbid ADHD plus ODD (results were reported).

Adverse events. The following adverse events were significantly more common for patients receiving atomoxetine compared with placebo: decrease in appetite (NNH=8.81), somnolence (NNH=19.41), abdominal pain (NNH=22.48), vomiting (NNH=29.96), dyspepsia (NNH=49.38), dizziness (NNH=53.03), fatigue (NNH=62.24), infection (NNH=75.32) and pruritus (NNH=119.5).

Begg’s test showed no evidence of publication bias (p=0.28) but Egger’s test did (p=0.04).

The results of meta-regression analyses were also reported.

Authors’ conclusions
Atomoxetine reduced ADHD symptoms in children and adolescents and may be effective in patients with co-morbid ODD or depression or anxiety.
CRD commentary
The review addressed a clear question that was defined in terms of the participants, interventions, outcomes and study design. Several relevant sources were searched but no specific attempts to minimise publication or language bias were reported, so other studies might have been missed; the potential for publication bias was assessed but results from the two tests were inconsistent. Validity was assessed using specified criteria and the results of this assessment reported. Methods were used to minimise reviewer error and bias in the extraction of data, but it is unclear whether similar steps were taken at the study selection and validity assessment stages. There was little information about the individual studies: patient characteristics, drug dose, treatment duration and results data were not reported, which makes it difficult to know how generally applicable the results from the review are. The data were pooled in meta-analyses, statistical heterogeneity was assessed, and meta-regression used to examine the influence of potential confounders. The evidence presented appears to support the authors’ conclusion, but incomplete reporting of review methods, lack of information about individual studies, and differences between the studies make it difficult to adequately assess the robustness of the authors’ conclusions.

Implications of the review for practice and research
Practice: The authors stated that atomoxetine may be considered for children with co-morbid anxiety who meet the criteria of the European Treatment Guideline on ADHD. Specifically: strong preference for a non-stimulant; strong preference for 24-hour action; failure to respond to immediate-release methylphenidate; or adverse effects with immediate-release methylphenidate.

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

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