Comparative efficacy of guanfacine extended release versus atomoxetine for the treatment of attention-deficit/hyperactivity disorder in children and adolescents: applying matching-adjusted indirect comparison methodology

Sikirica V, Findling RL, Signorovitch J, Erder MH, Dammerman R, Hodgkins P, La M, Xie J, Wu EQ

CRD summary
This review concluded that guanfacine extended release appeared to be more efficacious than atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents. Concerns about the reporting, the limited number of trials, and the validity of the statistical analysis, mean that these results should be interpreted with caution.

Authors' objectives
To compare the efficacy of guanfacine extended release versus atomoxetine, for the treatment of attention deficit hyperactivity disorder (ADHD), in children and adolescents.

Searching
Five databases, including MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL), were searched in December, 2012, for primary studies published in English. ClinicalTrials.gov and relevant reviews, meta-analyses and post hoc analyses were searched. Search terms were reported.

Study selection
Randomised, double-blind, controlled clinical trials, comparing the efficacy of guanfacine extended release versus atomoxetine, for the treatment of ADHD, in participants aged six to 18 years, were included. The primary outcome was the mean change from baseline in ADHD Rating Scale IV (ADHD-RS-IV) score; secondary outcomes were the scores on the hyperactivity/impulsivity and inattention sub-scales. Trials focusing on subgroups of patients with ADHD were excluded, as were trials with combination or additional therapy, and those in which ADHD symptoms were reported by teachers.

All of the included trials were placebo controlled. Two trials investigated guanfacine extended release, at doses ranging from 1mg to 4mg per day. Four trials investigated atomoxetine, at doses ranging from 0.5mg to 2mg per kg per day. Half of the trials had multiple arms receiving different doses of the same drug. ADHD Rating Scale IV scores were the primary outcome in all of the trials. The mean age of participants was nine years for the guanfacine trials, and 11 years for the atomoxetine trials. The mean percentage of female participants was 24 in the guanfacine trials, and 29 in the atomoxetine trials.

The authors did not state how many reviewers selected trials for inclusion in the review.

Assessment of study quality
The authors did not report a quality assessment.

Data extraction
Only aggregate data on the outcomes were available from the trials of atomoxetine, but individual patient data were available from the trials of guanfacine extended release.

The number of reviewers who extracted the data was not reported.

Methods of synthesis
For the primary comparison of the two treatments, the dose was the maximum recommended target effective dosage on the US Food and Drug Administration (FDA) label. An unadjusted comparison was performed, in which selected individual patient data for guanfacine were pooled and compared with the summary results for atomoxetine.

A matching-adjusted indirect comparison (MAIC) was performed, in which individual patient data for guanfacine were
matched for baseline characteristics and placebo responses to the aggregate data for atomoxetine. The efficacy outcomes were then compared, using a bootstrap procedure (with 1,000 iterations) to estimate statistical significance. The results were presented as differences between the two treatments with their standard errors and probabilities of statistical significance.

Sensitivity analyses were conducted by comparing the results across different dosage ranges, and by repeating the MAIC for a larger number of trials (to include a more heterogeneous population). Further details were reported.

**Results of the review**
Six trials were included in the review (1,537 participants); two were trials of guanfacine (631 participants) and four were trials of atomoxetine (906 participants).

In the main MAIC with atomoxetine, guanfacine extended release (at a dose of 0.09mg to 1.12mg/kg/day) demonstrated statistically significant greater reductions in mean ADHD-RS-IV score from baseline to endpoint (-7.0; SE 2.2; p<0.01; three trials).

Similar results were shown for the hyperactivity/impulsivity (-3.8; SE 1.2; p<0.01; three trials) and inattention (-3.2; SE 1.3; p<0.05; three trials) sub-scales, and in the sensitivity analyses of other dosage ranges and more heterogeneous trial populations (the differences between treatment groups were not always statistically significant). Further results were reported.

**Authors’ conclusions**
After adjustments, guanfacine extended release appeared to be more efficacious than atomoxetine for the treatment of ADHD; the results were consistent across a variety of dosages and various trial populations.

**CRD commentary**
The review question and inclusion criteria were clearly defined. Various relevant data sources were searched; the restriction to articles in English means that some relevant trials may have been missed. It was unclear whether the study selection and data extraction processes were carried out by more than one person, so there was potential for reviewer error and bias. The authors did not report any quality assessment, so it was unclear how reliable the results of each trial were.

A novel statistical approach was used, and it did not appear to retain the randomisation in the trials; the results may therefore be subject to bias; it was unclear whether the matching corrected for any such bias. Some results appeared to differ from those of a conventional unadjusted analysis. The authors acknowledged that cross-trial differences in unrecorded characteristics could have biased their results, and that it was not possible to assess or address any response or intolerance differences across individuals and subgroups.

The review included comparatively few trials and patients, and the authors acknowledged that many trials had to be excluded. Given the various concerns, the results and conclusions should be treated with caution.

Conflict of Interests: This review was funded by the manufacturers of guanfacine extended release; four authors were employed by the manufacturer and own stock in the company.

**Implications of the review for practice and research**
**Practice:** The authors stated that a seven-point reduction in ADHD-RS-IV score with guanfacine extended release, compared with atomoxetine, might be clinically meaningful. This was based on the results of another published analysis.

**Research:** The authors stated that the potential clinical impact of the findings from this review should be investigated, and that patient-centred research was needed to better define the associations between patient characteristics and treatment efficacy. Research comparing the safety, tolerability and long-term efficacy of guanfacine extended release and atomoxetine was recommended. The authors stated that matching-adjusted indirect comparisons should be made between these two treatments and clonidine extended release.

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