Comparing the efficacy of medications for ADHD using meta-analysis

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CRD summary
The authors concluded that the greater efficacy found for stimulants compared with nonstimulants in children with attention-deficit/hyperactivity disorder (ADHD) needs to be interpreted with caution in view of the impact of potential confounding factors. There were limitations in the review process, but the authors’ conclusion appears appropriately cautious given the lack of head-to-head comparisons of different classes of ADHD drugs.

Authors' objectives
To compare the efficacy of drug treatments for attention-deficit/hyperactivity disorder (ADHD) in youths.

Searching
MEDLINE, PREMEDLINE, PubMed, ERIC, CINAHL, the Cochrane CENTRAL Register, e-psyche and Social Science Abstracts were searched for studies published after 1979; the search terms were not reported. In addition, presentations from meetings of two specified associations were screened.

Study selection
Double-blind, placebo-controlled randomised controlled trials (RCTs) with at least 2 weeks’ follow-up that compared drug treatments with placebo in youths with ADHD diagnosed using the American Psychiatric Association's DSM-III-R or DSM-IV criteria, and with at least 20 patients in each treatment group, were eligible for inclusion. Studies had to report means and standard deviations of either change or end point scores for treatment groups. Studies were excluded if behaviour was assessed in laboratory conditions, they were dose-exploration studies, or were in selected samples of patients with co-morbid conditions.

The included studies evaluated 14 drugs using 19 different measures of ADHD symptoms (the abstract stated 15 drugs and 17 different outcomes). In the review, drugs were grouped into three categories: immediate-release stimulants, including mixed amphetamine salts (MAS), dextroamphetamine (d-Amp), methylphenidate (MPH), pemoline and dexmethylphenidate; long-acting stimulants including MAS extended release, d-Amp extended release, MPH modified release, MPH using osmotic-release oral system, MPH transdermal system and MPH-long acting; and nonstimulants or others, including atomoxetine, bupropion and modafinil. The majority of studies comprised predominantly males. The mean age of the patients ranged from 8 to 15 years.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Only double-blind RCTs were included. The authors did not state that they assessed other aspects of validity.

Data extraction
For each study, standardised mean differences were calculated. Each outcome measure within a study was treated as a separate entry in the analysis.

The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
The studies were grouped by class of drug (immediate-release, long-acting stimulant and nonstimulant/other) and pooled standardised mean differences were calculated using the random-effects method of DerSimonian and Laird; the studies were weighted by sample size. Standard statistical procedures were used to adjust for lack of dependence among multiple outcome measures from individual studies.
Meta-regression was used to examine the effects of the following variables on the effect size: study design, type of outcome score (change score or post-treatment score), type of rater (parent, teacher, clinician, self), mean age of the sample, percentage of males, dosing method (fixed or titrated to best dose), exclusion of nonresponders, use of placebo lead-in and year of publication.

Statistical heterogeneity was assessed using the Q statistic. Publication bias was assessed using Egger’s test.

Results of the review
Twenty-nine parallel-group and crossover RCTs were included. These studies provided 157 effect sizes.

Meta-regression found a significant effect of the drug group (p<0.001). The effect sizes for nonstimulants were significantly less than those for immediate-release stimulants (p<0.0001) or long-acting stimulants (p=0.0008). There were no significant differences between immediate-release and long-acting stimulants (p=0.14).

The effect sizes were significantly greater for crossover compared with parallel-group studies (p=0.02), and for studies that reported the post-treatment outcome compared with change score (p=0.04). None of the other variables were found to have a significant association with effect size. After adjusting for the two significant variables, immediate-release and long-acting stimulants were still significantly more effective than nonstimulants (p=0.05). The effects of drugs were significant for post-treatment outcomes from parallel studies, but not significant for post-treatment outcomes from crossover studies or change scores from parallel studies.

There was significant heterogeneity among studies of long-acting stimulants (p=0.02), but not among studies of immediate-release or nonstimulants.

There was no evidence of publication bias for all medication types or for any individual class of drug.

Authors’ conclusions
Studies used different methods to evaluate drugs for youths with ADHD. The finding of greater efficacy for stimulants compared with nonstimulants needs to be interpreted with caution in view of the impact of potential confounding factors in the absence of head-to-head comparisons.

CRD commentary
The review question was stated clearly. Several relevant sources were searched and potential sources of unpublished studies were screened; the reviewers found no evidence of publication bias. However, it was not clear whether any language restrictions had been applied. The methods used to select studies and extract the data were not described, so it is not known whether any efforts were made to reduce reviewer error and bias. Only double-blind RCTs were included but no other aspects of validity were assessed, which makes it difficult to judge the reliability of the results. The data were pooled, heterogeneity was assessed, and the influence of defined factors was examined. The authors’ conclusion appears appropriately cautious in view of the lack of head-to-head comparisons of different classes of ADHD drugs. However, lack of reporting of review methods and an inadequate quality assessment reduce the reliability of any conclusions.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that future studies should ‘review studies of time course such as the analog school laboratory paradigm’.

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