Limits of meta-analysis: methylphenidate in the treatment of adult attention-deficit hyperactivity disorder

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CRD summary
This meta-analysis showed a significant effect of methylphenidate on the symptoms of adult attention-deficit and hyperactivity disorder compared with placebo. The conclusions of this review may not be reliable due to lack of quality assessment and pooling of heterogeneous data.

Authors' objectives
To review the effectiveness of methylphenidate as a treatment for attention-deficit hyperactivity disorder in adults.

Searching
The following databases were searched from inception to January 2008: MEDLINE, PsycINFO and the Cochrane Central Register of Controlled Trials (CENTRAL). Search strategies and search terms were reported. References from included studies were scanned. Only papers available in English or German were considered for inclusion.

Study selection
Placebo-controlled randomised double-blind trials of methylphenidate for the treatment of adults with attention-deficit and hyperactivity disorder (ADHD) were eligible for inclusion. ADHD had to be diagnosed using either the Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) criteria. Outcomes assessing ADHD symptoms were required. Trials where the population reported a concurrent psychiatric disorder were not excluded.

Included trials were either of parallel or crossover group design and the majority were conducted in the USA, with two trials from the Netherlands and two from Canada. Treatment duration varied across trials ranging from 5 days to 14 weeks. The mean daily dose of methylphenidate ranged from 20 to 82mg, where reported. The mean age of participants ranged from 31 to 42 years and proportion of males in each trial ranged from 44 to 92%. Participant diagnoses were based mainly on DSM-IV criteria.

Two independent reviewers performed the study selection, disagreements were resolved by discussion.

Assessment of study quality
No validity assessment was reported, but only placebo-controlled randomised double-blind trials were included.

Data extraction
Effect sizes for each trial were calculated based on the standard deviation of the post scores for each outcome measure of ADHD symptoms. These effect sizes were corrected for small sample bias (Hedges method). Where more than one relevant outcome measure or several subscales were reported, an average mean effect size for each trial was calculated. Where trials reported single item results without a total score, these items were averaged and treated as a scale. If a trial incorporated multiple group comparisons, the overall treatment effect was averaged.

Two independent reviewers performed the data extraction, disagreements were resolved by discussion.

Methods of synthesis
Random-effects inverse-variance meta-analysis was used to pool individual trial effect sizes. Trials were grouped according to design (parallel or cross-over) and then by outcome type (self-rated or physician-rated). Meta-regression was used to assess the influence of dosage on treatment effect. Publication bias was considered using funnel and normal-quantile plots, and the Begg test. The fail-safe-n was also calculated. The main analysis was repeated excluding each mean trial effect, one at a time, to evaluate the influence of a single trial on the overall result. Post-hoc analyses to
explore the influence of treatment duration and impact of co-morbidity were included.

**Results of the review**
A total of 18 randomised controlled trials (RCTs) met the inclusion criteria. However, only 16 RCTs (six parallel and 10 crossover) reported sufficient data to be included in the meta-analyses. The total number of patients was unclear, but sample sizes ranged from 8 to 221. No evidence of publication bias was found.

The main analysis found a significant overall effect size of 0.42 (95% CI 0.20 to 0.63) across all trial designs. Significant heterogeneity was reported. Effect sizes were similar when trials were grouped by design (crossover $d=0.44$, 95% CI 0.27 to 0.60; parallel $d=0.36$, 95% CI -0.17 to 0.88), although the crossover trials displayed a significant effect. Substantial heterogeneity was reported within the parallel group trials.

Subgroup analysis according to rater (self versus observer) based on seven trials which reported both self and observer rated outcomes. It was reported that the effect sizes in each subgroup were significantly different from zero, but there were no significant differences between self and observer ratings. Significant heterogeneity was noted on in the observer rating subgroup.

Meta-regression found no significant effect of mean daily dose of methylphenidate on attention-deficit and hyperactivity disorder symptoms. The fail-safe N required to nullify the overall effect was 144 trials. The exclusion sensitivity plot found the overall effect size did not change significantly with exclusion of any single trial; some trials reduced the degree of heterogeneity.

The post-hoc analyses found no significant impact of treatment duration on effect size; there was also no change to the overall results when analysing patients with co-morbid substance abuse.

**Authors’ conclusions**
This meta-analysis showed a significant effect of methylphenidate on the symptoms of adult attention-deficit and hyperactivity disorder compared with placebo, but the size of the effect and the results of subgroup analyses contradicted previous findings and challenged treatment guidelines.

**CRD commentary**
This clearly reported systematic review addressed a defined question with appropriate inclusion criteria. The searches were adequate and tests did not indicate publication bias, but the language restrictions may have introduced some bias. Study selection and data extraction were carried out by two independent reviewers, which was likely to reduce the impact of reviewer error/bias.

The lack of a formal quality assessment was acknowledged by the authors, but did make it more difficult to judge the reliability of the primary data. Statistical heterogeneity was reported, but did not appear to be explored. Self and observer ratings appeared to have been pooled in the main analyses, as were cross-over and parallel studies; combining these different types of outcome and study design may have affected the reliability of the results, particularly since only the cross-over trials showed significant differences.

The conclusions of this review may not be reliable due to the lack of quality assessment and pooling of heterogeneous data.

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

**Practice:** The authors did not make any recommendations for practice.

**Research:** The authors stated that further high quality trials of methylphenidate for adult attention-deficit and hyperactivity disorder are required, particularly head-to-head comparisons with other treatment options.

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