
Comparing the efficacy of stimulants for ADHD in children and adolescents using meta-analysis

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CRD summary

The authors concluded that amphetamine products may be moderately more efficacious than methylphenidate products for children and adolescents with attention deficit hyperactivity disorder. Lack of direct comparison combined with inadequate reporting of review methods and limited validity assessment means that the authors' conclusions should be interpreted with caution.

Authors' objectives

To compare the efficacy of methylphenidate and amphetamine for children and adolescents with attention deficit and hyperactivity disorder (ADHD) using evidence from double-blind placebo-controlled randomised trials (RCTs).

Searching

PubMed, ERIC, EMBASE, CINAHL, The Cochrane Library, E-Psyche and Social Sciences Abstracts were searched for studies published in English after 1979. Search terms were not reported.

Study selection

Double-blind placebo-controlled RCTs were eligible if they evaluated stimulant medication for treatment of children and adolescents with ADHD (defined using criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM), DSM-II, DSM-III, DSM-III-R or DSM-IV). The minimum duration of treatment needed to be two weeks. Studies had to report the mean and standard deviation (SD) of either change or end point scores for all treatment groups. Studies were excluded if they were conducted in laboratories, examined doses for future studies or selected participants with comorbid conditions.

The included studies compared either methylphenidate or amphetamine with placebo. Studies used fixed or "best" dosing methods. Most amphetamine studies evaluated mixed amphetamine salts, mixed amphetamine salts extended release or dextroamphetamine; others evaluated dextroamphetamine extended release and lisdexamphetamine dimesylate. Most methylphenidate studies evaluated methylphenidate; others evaluated osmotic release oral system methylphenidate, dexamethylphenidate, methylphenidate transdermal system and methylphenidate long acting. Mean age of participants ranged from eight to 15 years. Most participants were male (range 60% to 100%). Most were diagnosed using DSM-IV criteria. Studies assessed 19 different measures of ADHD symptoms.

The reviewers did not state how studies were selected for inclusion.

Assessment of study quality

Only double-blind RCTs were included. Other than this, the authors did not state that they assessed validity.

Data extraction

Where studies evaluated more than one fixed dose, data were extracted for the highest dose group. Measures of ADHD symptoms were categorised into three subgroups: total ADHD symptoms scores; inattention subscale scores; and hyperactivity-impulsivity subscale scores. Effect sizes were calculated as standardised mean differences (SMD), either as differences in change scores or differences between end point scores.

The authors did not state how many reviewers performed data extraction.

Methods of synthesis

Pooled effect sizes were calculated using a random-effects model with studies weighted by sample size. Heterogeneity was assessed using the I^2 statistic. In the meta-analyses, each outcome within each study was entered separately;

estimates were adjusted using Huber's formula (as implemented in STATA) to account for statistical dependency variance. The number needed to treat (NNT) to achieve one successful outcome was calculated. Meta-regression was used to examine the influence of 12 different variables.

Results of the review

Twenty-three RCTs were included. Some studies were cross-over studies. Several studies evaluated more than one active stimulant drug. Amphetamine versus placebo was evaluated in 405 patients who received amphetamine and 482 who received placebo. Methylphenidate versus placebo was evaluated in 1,603 patients who received methylphenidate and 1,253 who received placebo.

The authors calculated 99 study-level standardised mean differences (total ADHD symptoms 73 effect sizes, inattention subscale nine effect sizes and hyperactivity-impulsivity 17 effect sizes).

Standardised mean differences were greater for: children compared with adolescents (SMD 0.89 versus 0.64, $p < 0.001$); and teacher-rated (SMD 0.92) and physician-rated (SMD 0.96) versus parent-rated (SMD 0.73) and self-rated (SMD 0.47) scores (0.47, $p < 0.001$); and outcome scores versus change scores (SMD 0.93 versus 0.75, $p = 0.03$). After controlling for these potential confounders, standardised mean differences for amphetamine studies were significantly greater than SMDs for methylphenidate studies ($p = 0.008$). No other variables examined showed any significant influence.

There was evidence of significant publication bias for studies of methylphenidate ($p = 0.03$), but not for amphetamine studies. After adjusting standardised mean differences using the trim and fill method, standardised mean differences for amphetamine studies remained significantly greater than for methylphenidate studies (SMD 0.99 versus 0.72, $p = 0.01$)

Standardised mean differences for amphetamine studies were significantly greater than standardised mean differences for methylphenidate studies for all ADHD symptoms (SMD 1.03 versus 0.77, $p = 0.02$ and NNT 2.0, 95% CI 1.7 to 2.2 for amphetamine versus 2.6, 95% CI 2.4 to 2.8 for methylphenidate) and for hyperactivity-impulsivity symptoms (SMD 1.20 versus 0.91, $p = 0.01$). Only one amphetamine study evaluated inattentive symptoms. There was substantial heterogeneity for ADHD total scores for both amphetamine ($I^2 = 74.5\%$) and methylphenidate ($I^2 = 45.4\%$) and hyperactivity-impulsivity scores for methylphenidate ($I^2 = 68.5\%$).

Authors' conclusions

Amphetamine products may be moderately more efficacious than methylphenidate products for children and adolescents with ADHD even after controlling for potential confounding factors.

CRD commentary

The review question was clearly stated. Inclusion criteria were appropriately defined. Several relevant sources were searched, but no attempts were made to minimise language bias and no specific attempts to minimise publication bias were reported. Potential for publication bias was assessed and analyses adjusted for findings. Methods used to select studies, assess validity and extract data were not described and so any efforts made to reduce reviewer errors and bias were unknown. Only double-blind RCTs were eligible, but validity was not otherwise assessed and so results from these studies and any synthesis may not be reliable. Information on study duration, drug doses and methods used to assess outcomes was lacking. Data were pooled using meta-analysis; multiple effect sizes were used from individual studies and statistical methods were used to adjust for the resulting statistical dependency. Significant heterogeneity was found, which meant that summary measures did not reflect findings from individual studies. The influence of many potential confounders was examined and analyses adjusted for significant confounders. The main analyses involved comparison of amphetamine versus placebo with methylphenidate versus placebo; the drugs of interest were not compared directly. This lack of direct comparison combined with inadequate reporting of review methods and limited validity assessment means that the authors' conclusions should be interpreted with caution.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that future research should "review studies of time course such as analogue school laboratory paradigm", which would provide information about peak and trough effects.

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