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[Intervention Review]

Amphetamines for attention deficit hyperactivity disorder (ADHD) in children and adolescents

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ABSTRACT

Background

Attention deficit hyperactivity disorder (ADHD) is one of the most common psychiatric conditions affecting children and adolescents. Amphetamines are among the most commonly prescribed medications to manage ADHD. There are three main classes of amphetamines: dexamphetamine, lisdexamphetamine and mixed amphetamine salts, which can be further broken down into short- and long-acting formulations. A systematic review assessing their efficacy and safety in this population has never been conducted.

Objectives

To assess the efficacy and safety of amphetamines for ADHD in children and adolescents.

Search methods

In August 2015 we searched CENTRAL, Ovid MEDLINE, Embase, PsycINFO, ProQuest Dissertation and Theses, and the Networked Digital Library of Theses and Dissertations. We also searched ClinicalTrials.gov, and checked the reference lists of relevant studies and reviews identified by the searches. No language or date restrictions were applied.

Selection criteria

Parallel-group and cross-over randomized controlled trials (RCTs) comparing amphetamine derivatives against placebo in a pediatric population (< 18 years) with ADHD.

Data collection and analysis

Two authors independently extracted data on participants, settings, interventions, methodology, and outcomes for each included study. For continuous outcomes, we calculated the standardized mean difference (SMD) and for dichotomous outcomes we calculated the risk ratio (RR). Where possible, we conducted meta-analyses using a random-effects model. We also performed a meta-analysis of the most commonly reported adverse events in the primary studies.

Main results

We included 23 trials (8 parallel-group and 15 cross-over trials), with 2675 children aged three years to 17 years. All studies compared amphetamines to placebo. Study durations ranged from 14 days to 365 days, with the majority lasting less than six months. Most studies

were conducted in the United States; three studies were conducted across Europe. We judged 11 included studies to be at a high risk of bias due to insufficient blinding methods, failing to account for dropouts and exclusions from the analysis, and failing to report on all outcomes defined a priori. We judged the remaining 12 studies to be at unclear risk of bias due to inadequate reporting.

Amphetamines improved total ADHD core symptom severity according to parent ratings (SMD -0.57; 95% confidence interval (CI) -0.86 to -0.27; 7 studies; 1247 children/adolescents; very low quality evidence), teacher ratings (SMD -0.55; 95% CI -0.83 to -0.27; 5 studies; 745 children/adolescents; low quality evidence), and clinician ratings (SMD -0.84; 95% CI -1.32 to -0.36; 3 studies; 813 children/adolescents; very low quality evidence). In addition, the proportion of responders as rated by the Clinical Global Impression - Improvement (CGI-I) scale was higher when children were taking amphetamines (RR 3.36; 95% CI 2.48 to 4.55; 9 studies; 2207 children/adolescents; very low quality evidence).

The most commonly reported adverse events included decreased appetite, insomnia/trouble sleeping, abdominal pain, nausea/vomiting, headaches, and anxiety. Amphetamines were associated with a higher proportion of participants experiencing decreased appetite (RR 6.31; 95% CI 2.58 to 15.46; 11 studies; 2467 children/adolescents), insomnia (RR 3.80; 95% CI 2.12 to 6.83; 10 studies; 2429 children/adolescents), and abdominal pain (RR 1.44; 95% CI 1.03 to 2.00; 10 studies; 2155 children/adolescents). In addition, the proportion of children who experienced at least one adverse event was higher in the amphetamine group (RR 1.30; 95% CI 1.18 to 1.44; 6 studies; 1742 children/adolescents; low quality evidence).

We performed subgroup analyses for amphetamine preparation (dexamphetamine, lisdexamphetamine, mixed amphetamine salts), amphetamine release formulation (long acting versus short acting), and funding source (industry versus non industry). Between-group differences were observed for proportion of participants experiencing decreased appetite in both the amphetamine preparation (P < 0.00001) and amphetamine release formulation (P value = 0.008) subgroups, as well as for retention in the amphetamine release formulation subgroup (P value = 0.03).

Authors' conclusions

Most of the included studies were at high risk of bias and the overall quality of the evidence ranged from low to very low on most outcomes. Although amphetamines seem efficacious at reducing the core symptoms of ADHD in the short term, they were associated with a number of adverse events. This review found no evidence that supports any one amphetamine derivative over another, and does not reveal any differences between long-acting and short-acting amphetamine preparations. Future trials should be longer in duration (i.e. more than 12 months), include more psychosocial outcomes (e.g. quality of life and parent stress), and be transparently reported.

PLAIN LANGUAGE SUMMARY

Amphetamines for attention deficit hyperactivity disorder in children and adolescents

Background
Attention deficit hyperactivity disorder (ADHD) is a common problem affecting children and adolescents. ADHD is characterized by inattention (being easily distracted, unable to focus on one task), impulsivity (fidgety; constantly moving), and hyperactivity (impatient; acts without thinking). One of the most common treatments for managing ADHD is the drug class of amphetamines, which are a class of stimulant medications. They are thought to reduce the severity of symptoms associated with ADHD.

Review question

Do children and adolescents (under 18 years of age) diagnosed with ADHD benefit from treatment with amphetamines to reduce the core symptoms of ADHD, compared to other children and adolescents who receive no drug or a fake drug (placebo)?

Study characteristics
As of August 2015, we identified 23 randomized controlled trials (RCTs: a type of scientific experiment in which people are randomly assigned to one of two or more treatments), which included 2675 children and adolescents between three years and 17 years of age. These studies compared amphetamines to placebo. Three different kinds of amphetamines were investigated: dexamphetamine, lisdexamphetamine and mixed amphetamine salts. The duration of the included studies ranged from 14 days to 365 days. The RCTs were conducted in the United States and Europe.

Key results
We found that amphetamines were effective at improving the core symptoms of ADHD in the short term, but that they were also linked to a higher risk of experiencing adverse events such as sleep problems, decreased appetite, and stomach pain. We found no evidence that one kind of amphetamine was better than another, and found no difference between amphetamines that act for longer periods of time versus those that act for shorter periods of time.

Quality of the evidence

The quality of the included studies was low to very low because of problems in their design and large differences between the studies. Well-designed and clearly reported RCTs that are longer in duration are needed, so we may better understand the long-term effects (both positive and negative) of amphetamines.