Amphetamines for attention deficit hyperactivity disorder in adults

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Background:
Attention deficit hyperactivity disorder (ADHD) is a childhood-onset disorder characterised by inattention, hyperactivity, and impulsivity. ADHD can persist into adulthood and can affects individuals' social and occupational functioning, as well as their quality of life and health. ADHD is frequently associated with other mental disorders such as substance use disorders and anxiety and affective disorders. Amphetamines are used to treat adults with ADHD, but uncertainties about their efficacy and safety remain.

Objectives:
To examine the efficacy and safety of amphetamines for adults with ADHD.

Search strategy:
In August 2017, we searched CENTRAL, MEDLINE, Embase, PsycINFO, 10 other databases, and two trials registers, and we ran citation searches for included studies. We also contacted the corresponding authors of all included studies, other experts in the field, and the pharmaceutical company, Shire, and we searched the reference lists of retrieved studies and reviews for other published, unpublished, or ongoing studies. For each included study, we performed a citation search in Web of Science to identify any later studies that may have cited it.

Selection criteria:
We searched for randomised controlled trials comparing the efficacy of amphetamines (at any dose) for ADHD in adults aged 18 years and over against placebo or an active intervention.

Data collection and analysis:
Two review authors extracted data from each included study. We used the standardised mean difference (SMD) and the risk ratio (RR) to assess continuous and dichotomous outcomes, respectively. We conducted a stratified analysis to determine the influence of moderating variables. We assessed trials for risk of bias and drew a funnel plot to investigate the possibility of publication bias. We rated the quality of the evidence using the GRADE approach, which yielded high, moderate, low, or very low quality ratings based on evaluation of within-trial risk of bias, directness of evidence, heterogeneity of data; precision of effect estimates, and risk of publication bias.

Main results:
We included 19 studies that investigated three types of amphetamines: dexamphetamine (10.2 mg/d to 21.8 mg/d), lisdexamfetamine (30 mg/d to 70 mg/d), and mixed amphetamine salts (MAS; 12.5 mg/d to 80 mg/d). These studies enrolled 2521 participants; most were middle-aged (35.3 years), Caucasian males (57.2%), with a combined type of ADHD (78.8%). Eighteen studies were conducted in the USA, and one study was conducted in both Canada and the USA. Ten were multi-site studies. All studies were placebo-controlled, and three also included an active comparator: guanfacine, modafinil, or paroxetine. Most studies had short-term follow-up and a mean study length of 5.3 weeks.

We found no studies that had low risk of bias in all domains of the Cochrane 'Risk of bias' tool, mainly because amphetamines have powerful subjective effects that may reveal the assigned treatment, but also because we noted attrition bias, and because we could not rule out the possibility of a carry-over effect in studies that used a cross-over design.

Sixteen studies were funded by the pharmaceutical industry, one study was publicly funded, and two studies did not report their funding sources.

Amphetamines versus placebo
Severity of ADHD symptoms: we found low- to very low-quality evidence suggesting that amphetamines reduced the severity of ADHD symptoms as rated by clinicians (SMD $-0.90$, 95% confidence interval (CI) $-1.04$ to $-0.75$; 13 studies, 2028 participants) and patients (SMD $-0.51$, 95% CI $-0.75$ to $-0.28$; six studies, 120 participants).

Retention: overall, we found low-quality evidence suggesting that amphetamines did not improve retention in treatment (risk ratio (RR) 1.06, 95% CI 0.99 to 1.13; 17 studies, 2323 participants).

Adverse events: we found that amphetamines were associated with an increased proportion of patients who withdrew because of adverse events (RR 2.69, 95% CI 1.63 to 4.45; 17 studies, 2409 participants).

Type of amphetamine: we found differences between amphetamines for the severity of ADHD symptoms as rated by clinicians. Both lisdexamfetamine (SMD $-1.06$, 95% CI $-1.26$ to $-0.85$; seven studies, 896 participants; low-quality evidence) and MAS (SMD $-0.80$, 95% CI $-0.93$ to $-0.66$; five studies, 1083 participants; low-quality evidence) reduced the severity of ADHD symptoms. In contrast, we found no evidence to suggest that dexamphetamine reduced the severity of ADHD symptoms (SMD $-0.24$, 95% CI $-0.80$ to 0.32; one study, 49 participants; very low-quality evidence). In addition, all amphetamines were efficacious in reducing the severity of ADHD symptoms as rated by patients (dexamphetamine: SMD $-0.77$, 95% CI $-1.14$ to $-0.40$; two studies, 35 participants; low-quality evidence; lisdexamfetamine: SMD $-0.33$, 95% CI $-0.65$ to $-0.01$; three studies, 67 participants; low-quality evidence; MAS: SMD $-0.45$, 95% CI $-1.02$ to 0.12; one study, 18 participants; very low-quality evidence).

Dose at study completion: different doses of amphetamines did not appear to be associated with differences in efficacy.

Type of drug-release formulation: we investigated immediate- and sustained-release formulations but found no differences between them for any outcome.

Amphetamines versus other drugs

We found no evidence that amphetamines improved ADHD symptom severity compared to other drug interventions.