Cochrane for Clinicians

Putting Evidence into Practice

Use of Amphetamines for Attention-Deficit/Hyperactivity Disorder in Adults

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Clinical Question

Are amphetamines safe and effective in adults with attention-deficit/hyperactivity disorder (ADHD)?

Evidence-Based Answer

Amphetamines provide a clinician-rated 30% or greater reduction in ADHD symptoms when compared with placebo (number needed to treat = 5).[1] (Strength of Recommendation: B, based on inconsistent or limited-quality patient-oriented evidence.)

Practice Pointers

ADHD is a neurodevelopmental disorder with a mean onset at six years of age. Approximately one-third of affected children will carry the disorder into adulthood; the current prevalence of ADHD in U.S. adults is 4.4%.[2] ADHD symptoms present differently in adults than in children. Hyperactivity and impulsivity in adults often appear as restlessness, talkativeness, and emotional dysregulation (i.e., irritability, emotional lability, and emotional reactivity). Inattention manifests similarly in childhood and adulthood. The use of amphetamines for the treatment of adult ADHD has increased, and this Cochrane review analyzed their safety and effectiveness.[1]

The review included 19 randomized controlled trials (2,521 adults with ADHD) comparing dextroamphetamine, lisdexamfetamine (Vyvanse), or mixed amphetamine salts with placebo. Studies lasted on average 5.3 weeks (range: one to 20 weeks), with only three studies (N = 542) lasting more than eight weeks. The participants had a mean age of 35.3 years, and most (57.2%) were men; 78.8% had combined-type ADHD. The primary outcome was the severity of ADHD symptoms, assessed by clinicians or participants using the standardized ADHD Rating Scale-IV (ADHD-RS-IV). Secondary outcomes included clinical impressions of ADHD symptom severity and improvement at study end based on the Clinical Global Impression Severity and Impression Scales (CGI-S and CGI-I, respectively); percentage of participants with a 30% reduction in ADHD symptoms (measured by the ADHD-RS-IV) and/or a CGI-I score of 1 or 2; global functioning based on the CGI-S; symptoms of depression and anxiety per standardized instruments chosen by the individual study; treatment adherence; and adverse effects. The review had several limitations: no study had a low risk of bias, 16 of the 19 studies were funded by pharmaceutical companies, there was attrition bias because adverse effects of amphetamines may have been present, and the reviewers were to rule out carryover effects in studies with a crossover design.[1]

Low- to very low-quality evidence demonstrated that amphetamines, as a group, were effective in reducing the severity of ADHD symptoms as rated by clinicians (standardized mean difference [SMD] = −0.90; 95% CI, −1.04 to −0.75; $P < .00001$; 13 studies; 2,028 participants) and participants (SMD = −0.51; 95% CI, −0.75 to −0.28; $P < .000021$; six studies; 120 participants) using the ADHD-RS-IV. Not all amphetamines performed equally. Lisdexamfetamine (SMD = −1.06; 95% CI, −1.26 to −0.85; seven studies; 896 participants) and mixed amphetamine salts (SMD = −0.80; 95% CI, −0.93 to −0.66; five studies; 1,083 participants) reduced clinician-rated severity of symptoms, whereas dextroamphetamine did not. The review also found that dextroamphetamine and lisdexamfetamine, but not mixed amphetamine salts, significantly reduced participant-rated severity of ADHD symptoms compared with placebo (dextroamphetamine: SMD = −0.77; 95% CI, −1.14 to −0.40; two studies; 35 participants; lisdexamfetamine: SMD = −0.33; 95% CI, −0.65 to −0.01; three studies; 67 participants; and mixed amphetamine salts: SMD = −0.45; 95% CI, −1.02 to 0.12; one study; 18 participants).[1]

Amphetamines were not effective at improving global functioning based on the CGI-S Scale or at reducing symptoms of depression and anxiety (based on various standardized instruments used across different studies). Low vs. high dose (low dose defined as less than 16 mg per day for dextroamphetamine, 53.4 mg per day for lisdexamfetamine, and 50 mg per day for mixed amphetamine salts), type of formulation (immediate or sustained release), and the presence of a comorbidity (drug-use disorder or

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depression) did not affect the severity of ADHD symptoms as assessed by clinicians or participants. A meta-analysis of 17 studies (N = 2,409) found a greater risk of dropout from any adverse effect with amphetamines than with placebo (relative risk = 2.69; 95% CI, 1.63 to 4.42), although withdrawal by participants treated with amphetamines was considered low at 7.6% (placebo drop-out rate was 2.4%).[1] Adverse effects leading to withdrawal included anxiety, depressed mood, nausea/vomiting, headache, fatigue, insomnia, increased blood pressure, flushing, and affective dullness.[3-9] Most reported adverse effects were considered mild to moderate.

The National Institute for Health and Care Excellence (NICE) guidelines for managing adult ADHD recommend implementing environmental modifications initially, and offering medications such as lisdexamfetamine or methylphenidate (Ritalin) only in a shared decision-making model with routine follow-up.[10] When adults are taking amphetamines, it is recommended that weight, heart rate, blood pressure, and sleep patterns be monitored with every medication change and every six months because of potential cardiovascular events. This Cochrane review supports the NICE guidelines.[1,10]

The practice recommendations in this activity are available at http://www.cochrane.org/CD007813.

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the U.S. Army Medical Department or the U.S. Army Service at large.

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Treatment of Threatened Miscarriage with Progestogens

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Clinical Question

Are progestogens a safe and effective treatment option for patients with threatened miscarriage?

Evidence-Based Answer

Progestogens reduce the risk of miscarriage when compared with placebo in patients with threatened miscarriage (number needed to treat [NNT] = 10.) Use of progestogens poses no significant risks to mother or baby.[1] (Strength of Recommendation: A, based on consistent, good-quality patient-oriented evidence.)

Practice Pointers

Miscarriage occurs in 15% to 20% of pregnancies and is associated with significant physical and psychological morbidity. Threatened miscarriage is defined as any vaginal bleeding, with or without abdominal pain, with a closed cervix and a viable fetus inside the uterine cavity. Effective treatment options to increase the chance of a successful pregnancy are lacking. Bed rest, pelvic rest, vitamins, uterine relaxants, and administration of beta subunit of human chorionic gonadotropin are not recommended.[2] Progesterone has physiologic roles in maintaining pregnancy by inducing changes in the endometrium, suppressing uterine contractions, and modulating the maternal immune system. Progestogens—medications that mimic the activity of progesterone—are therefore a rational therapeutic option to treat threatened miscarriage. Early studies had less rigorous methodology, so the authors of this Cochrane review sought to evaluate progestogen using newer data.[1]

This Cochrane review included seven randomized controlled trials and 696 patients from lower middle- to high-income countries, although none of the trials took place in North America.[1] Three of these trials investigated oral

SUMMARY TABLE

Outcomes of Progesterone vs. Placebo or No Treatment for Threatened Miscarriage

Outcomes of pregnancy	Probable outcome with placebo or no treatment	Probable outcome with progesterone treatment (95% CI)	NNT (95% CI)	Participants (studies)	Quality of evidence
Miscarriage	242 per 1,000	138 per 1,000 (102 to 189)	10 (8 to 19)	696 (7)	Moderate
Preterm birth	91 per 1,000	84 per 1,000 (49 to 142)	NA	588 (5)	Low
Congenital abnormalities	13 per 1,000	9 per 1,000 (1 to 62)	NA	337 (2)	Very low

NA = not applicable; NNT = number needed to treat.

progestogens and four trials evaluated vaginal progesterone. The authors assessed the body of evidence to be of moderate quality for the primary outcome of miscarriage vs. successful pregnancy, mainly because of limitations in study design. For example, only three of the seven studies were deemed to be at low risk of selection bias. The authors analyzed only studies that included pregnant women at 23 weeks of gestation or less, presenting with a concern of threatened miscarriage, and in which the viability of the pregnancy had been confirmed before starting treatment. Secondary outcomes were maternal (pain, preterm birth) and fetal (preterm birth, stillbirth, neonatal death, congenital abnormalities, low birth weight, or any other adverse neonatal outcomes reported). Maternal pain was reported in two trials; one double-blind, randomized, placebo-controlled trial included 50 patients and demonstrated significantly decreased maternal pain with use of progesterone. The other single-blind, randomized trial included 60 patients and demonstrated no pain relief with progesterone vs. no treatment.

Although progestogens decreased the risk of miscarriage overall, this was significant only with orally—not vaginally—administered therapies. Women receiving any progestogen therapy had a lower risk of miscarriage than those receiving placebo (absolute risk reduction = 10.4%; 95% CI, 5.3% to 14.0%; NNT = 10). Two of the three trials employing the oral treatment route used dydrogesterone, which is not available in the United States. The third trial (n = 60) used oral micronized progesterone, 400 mg daily for four weeks, starting with the diagnosis of threatened miscarriage and continuing even if vaginal bleeding stopped. These demonstrated consistent effects and reached statistical significance when the data were pooled.

Progestogens as an intervention did not cause any significant harms. When progestogens were compared with placebo, there were no differences in pregnancy-induced hypertension, antepartum hemorrhage, stillbirth, low birth weight, or respiratory distress syndrome. No significant differences were found for preterm birth or congenital abnormalities, although these analyses were limited by low- and very low-quality evidence, respectively. Adverse effects of progestogens are usually mild and include breast tenderness, bloating, and headache. Progestogens should be used with caution in patients who have cardiovascular disease or impaired liver function, including cholestasis.

A guideline from the National Institute for Health and Care Excellence is currently in development.[3] The guideline supports offering women treatment while counseling them that the evidence is not strong. More research is needed to define the most effective preparation, dosing, route and frequency of administration, and duration of therapy.

The practice recommendations in this activity are available at http://www.cochrane.org/CD005943.

Editor's Note: The numbers needed to treat and absolute risk reductions reported in this Cochrane for Clinicians were calculated by the author based on raw data provided in the original Cochrane review.

The opinions and assertions contained herein are the private views of the author and do not reflect the official policy or position of the U.S. Air Force, the Department of Defense, or the U.S. government.

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