

Cochrane for Clinicians

Putting Evidence into Practice

Amphetamines for Attention-Deficit/Hyperactivity Disorder in Adults

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The Cochrane Abstract on the next page is a summary of a review from the Cochrane Library. It is accompanied by an interpretation that will help clinicians put evidence into practice. Drs. Saguil and Sheridan present a clinical scenario and question based on the Cochrane Abstract, followed by an evidence-based answer and a critique of the review. The practice recommendations in this activity are available at <http://summaries.cochrane.org/CD007813>.



This clinical content conforms to AAFP criteria for evidence-based continuing medical education (EB CME). See CME Quiz on page 408.

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A collection of Cochrane for Clinicians published in AFP is available at <http://www.aafp.org/afp/cochrane>.

Clinical Scenario

A 36-year-old man who is enrolled in a master's degree program presents to your office stating that he is having difficulty focusing and concentrating on class material, and is afraid he will not be able to graduate. He reports a history of attention-deficit/hyperactivity disorder (ADHD) that was successfully treated with amphetamines in middle and high school. You wonder if this patient would benefit from amphetamines as an adult.

Clinical Question

Are amphetamines effective for the treatment of adult ADHD?

Evidence-Based Answer

Amphetamines improve ADHD symptom severity but, when compared with placebo, they are associated with increased discontinuation rates because of adverse effects. There does not appear to be a difference among dosages or between the immediate- and sustained-release formulations.¹ (Strength of Recommendation: A, based on consistent, good-quality, patient-oriented evidence.)

Practice Pointers

ADHD is a neurodevelopmental disorder that typically begins in childhood and often persists into adulthood. Adults may demonstrate both hyperactivity and inattention. Symptoms of inattention, such as difficulty sustaining attention, dislike of tasks requiring attention, and easy distractibility, are more common than hyperactive symptoms in adults with ADHD.² The disorder affects an estimated 4.4 percent of adults in the

United States,³ and has been associated with unemployment, divorce, depression, post-traumatic stress disorder, and substance abuse.⁴ Treatment has been associated with higher employment rates⁵ and reduced substance abuse.⁶ Some pharmacotherapies, notably bupropion (Wellbutrin), target ADHD and comorbid mood and anxiety disorders.⁷

This Cochrane review focused on the use of amphetamines (dextroamphetamine, lisdexamfetamine [Vyvanse], and mixed amphetamine salts) in seven trials with a total of 1,091 patients and a mean study length of 8.1 weeks.¹ Amphetamines improved ADHD symptom severity when compared with placebo in five out of six studies; when results were pooled, the standardized mean difference with treatment was -0.72 (95% confidence interval [CI], -0.87 to -0.57). In the four studies that incorporated a Clinical Global Impression—Improvement scale, more patients taking amphetamines achieved a score of “very much improved” or “improved” than did those taking placebo (pooled risk ratio [RR] = 2.30 ; 95% CI, 1.84 to 2.87). In the six studies that evaluated treatment retention, amphetamines were not associated with improved retention (pooled RR = 1.06 ; 95% CI, 0.96 to 1.18); on the other hand, in two of four studies, amphetamines were associated with an increase in drop-out rates secondary to adverse effects (pooled RR = 3.03 ; 95% CI, 1.52 to 6.05).

Common adverse effects of amphetamine use included dry mouth, decreased appetite, insomnia, and headache, as well as an increase in heart rate and blood pressure.⁸⁻¹⁰ Because of the effect amphetamines had on

Cochrane Abstract

Background: Attention-deficit/hyperactivity disorder (ADHD) is a childhood-onset disorder that can persist into adulthood. Amphetamines are used to treat adult ADHD, but uncertainties persist about their efficacy and safety.

Objectives: To examine the efficacy and safety of amphetamines for adults with ADHD, as well as the influence of dose, drug type, and release formulation type.

Search Strategy: The authors searched CENTRAL, PubMed, EMBASE, CINAHL, PsycINFO, ClinicalTrials.gov, UK Clinical Trials Gateway, and also references obtained from articles and experts in the field. The authors conducted the electronic searches on February 25, 2010.

Selection Criteria: Randomized controlled trials comparing the efficacy of amphetamine derivatives against placebo or an active intervention.

Data Collection and Analysis: Two authors extracted data from each of the included studies. The authors used the standardized mean difference (SMD) and the risk ratio (RR) to assess continuous and dichotomous outcomes, respectively. They conducted a stratified analysis to determine the influence of moderating variables. They assessed the trials for risk of bias and drew a funnel plot to investigate the possibility of publication bias.

Main Results: The authors included seven studies, which enrolled 1,091 participants. All studies were placebo-controlled and three

included an active comparator: guanfacine, modafinil, and paroxetine. Most studies had short-term follow-up, with a mean study length of 8.1 weeks. Amphetamines improved ADHD symptom severity (SMD = -0.72 ; 95% confidence interval [CI], -0.87 to -0.57) but did not improve retention in treatment overall and were associated with an increased drop-out rate due to adverse events (RR = 3.03 ; 95% CI, 1.52 to 6.05). The three amphetamine derivatives investigated (dextroamphetamine, lisdexamfetamine, and mixed amphetamine salts) were all efficacious for reducing ADHD symptoms, but mixed amphetamine salts also increased retention in treatment. Different doses did not appear to be associated with differences in efficacy. The authors investigated immediate- and sustained-release formulations but found no differences between them on any outcome. When amphetamines were compared with other drug interventions, no differences were found. The authors did not find any study to be at low risk of bias overall, mainly because amphetamines have powerful subjective effects that may reveal the assigned treatment.

Authors' Conclusions: Amphetamines improved short-term ADHD symptom severity. Mixed amphetamine salts also increased retention in treatment. Amphetamines were associated with higher attrition due to adverse events. The short study length and the restrictive inclusion criteria limit the external validity of these findings. Furthermore, the possibility that the results of the included studies were biased was high, which could have led to an overestimation of amphetamine efficacy.



These summaries have been derived from Cochrane reviews published in the Cochrane Database of Systematic Reviews in the Cochrane Library. Their content has, as far as possible, been checked with the authors of the original reviews, but the summaries should not be regarded as an official product of the Cochrane Collaboration; minor editing changes have been made to the text (<http://www.cochrane.org>).

cardiovascular parameters, caution should be exercised in patients with, or at high risk of, circulatory disease. Mixed amphetamine salts alone were associated with fewer treatment withdrawals in one of three studies; in the other two studies, there was a trend toward treatment retention (pooled RR = 1.19 ; 95% CI, 1.06 to 1.35).¹

Most clinicians use the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., text revision (DSM-IV-TR) criteria to diagnose ADHD in adults. However, the DSM-IV-TR criteria focus on childhood findings, which may not be present or may be attenuated in adults. Instead of reporting typical inattention and hyperactivity, adult patients may, through aging and maturation, report developmentally attenuated symptoms such as organizational problems, mood lability, and difficulties with home and social functioning. As a result, clinicians should take a thorough psychosocial history, look intently for clues to the diagnosis in the patients' early childhood recollections, and screen for DSM-IV-TR criteria that may have been diminished by normal adult maturation (e.g., eliciting a history of internal restlessness as opposed to external fidgeting).¹¹

Amphetamines are one of several pharmaceutical options for adults with ADHD. The U.K. National Institute for Health and Clinical Excellence (NICE) Clinical Practice Guideline recommends methylphenidate (Ritalin; a nonamphetamine stimulant)—in conjunction with a comprehensive mental health, educational, and occupational treatment program—as first-line therapy for ADHD in adults. NICE also recommends that other stimulant medications, including amphetamines, be used if there are intolerable adverse effects or if there is a lack of effectiveness.¹² The American Psychiatric Association and American Academy of Child and Adolescent Psychiatry ADHD Parents Medication Guide, although targeting children, echoes the NICE guidelines in listing methylphenidate, alone or in combination with behavioral therapy, first among pharmaceutical treatments for ADHD.¹³

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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Cochrane Briefs

Weight Loss for Patients with Nonalcoholic Fatty Liver Disease

Clinical Question

Is weight loss an effective treatment for nonalcoholic fatty liver disease?

Evidence-Based Answer

There are insufficient high-quality studies to determine patient-oriented outcomes of weight loss for the treatment of fatty liver disease. Nonetheless, weight loss

remains a reasonable goal because it may reduce liver inflammation and improve comorbidities. In two of the studies reviewed, liver enzyme levels were essentially halved in patients who lost weight with lifestyle changes. (Strength of Recommendation: C, based on consensus, disease-oriented evidence, usual practice, expert opinion, or case series.)

Practice Pointers

Nonalcoholic fatty liver disease encompasses a disease spectrum ranging from simple fatty liver to nonalcoholic steatohepatitis to end-stage cirrhosis. Experts consider steatosis in a person consuming less than 20 to 30 g of alcohol daily (i.e., 1.5 standard alcoholic beverages for women and two standard alcoholic beverages for men) to be a criterion for the diagnosis of nonalcoholic fatty liver disease.¹ More than two-thirds of adults who are obese have fatty liver, and 20 percent may have nonalcoholic steatohepatitis.² More than 90 percent of adults with morbid obesity have fatty liver, and almost one-half have nonalcoholic steatohepatitis.³ According to this Cochrane review, nonalcoholic fatty liver disease has been identified as a cause of cirrhosis, especially cryptogenic cirrhosis.

Weight loss currently has the most supporting evidence for improving liver enzyme levels, compared with other therapies.^{1,4} This Cochrane review analyzed seven randomized trials (373 participants) that investigated weight loss as a treatment for fatty liver disease. One study examined children; the other studies focused on adults. The intensity of lifestyle changes in the intervention groups and counseling in the placebo groups differed among studies. All but one trial were judged to be at high risk of bias, and comparisons were hindered by different end points. Only one trial reported histologic changes. Statistically significant reductions in alanine transaminase (ALT) levels were seen in the treatment arms of two of the four lifestyle intervention trials that measured liver enzyme levels (one of which was the study involving children). In these trials, lifestyle changes were associated with reductions in ALT levels (from 84 to 42 U per L [1.40 to 0.70 μ kat per L] and from 152 to 63 U per L [2.54 to 1.05 μ kat per L]), as well as appreciable weight loss (a loss of 19.33 lb [8.7 kg] and a two-point reduction in body mass index, respectively).

Orlistat (Xenical) was used for weight loss in two other studies, but there was no notable reduction in liver enzyme levels or body mass index compared with patients in placebo groups who were counseled on restrictive diets. However, both the orlistat and placebo groups achieved halving of liver enzyme levels and an approximate weight loss of 17.78 lb (8 kg).

In a 2004 meta-analysis, bariatric surgery was reported to resolve 77 percent of diabetes mellitus cases, 62 percent of hypertension cases, and 70 percent of hyperlipidemia cases.⁵ Although some experts believe that bariatric surgery may also improve fatty liver disease that accompanies metabolic syndrome, no clinical trials have been performed. In addition, there have been some reports of histologic deterioration with rapid weight loss after bariatric surgery, so these patients should be monitored closely.¹

Consensus guidelines on nonalcoholic fatty liver disease have been published in the *Journal of Digestive Diseases* and by the American Gastroenterological Association (AGA).^{4,6} The AGA recommends that the initial target weight loss be 10 percent of baseline weight at a rate of 1 to 2 lb (0.45 to 0.90 kg) per week. An algorithm for the workup of mildly elevated liver enzyme levels can be found at <http://www.aafp.org/afp/2005/0315/p1105.html#afp20050315p1105-f1>.

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The screenshot shows a dual-monitor setup. The left monitor displays a web page titled 'Cost-Effectiveness Analysis of Treatment Options for Acute Otitis Media'. The right monitor displays the 'ANNALS OF FAMILY MEDICINE' journal website. Both pages are in a browser window with various links and navigation menus visible.

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