WITHDRAWN: Immediate-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults.

Epstein T, Patsopoulos NA, Weiser M.
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Abstract
BACKGROUND:
Symptoms of attention deficit hyperactivity disorder (ADHD), diagnosed mainly in children, often persist into adulthood. Adults in this group have a high rate of other psychiatric problems and functional difficulties in a number of key areas such as academic achievement, interpersonal relationships, and employment. Although the usefulness of immediate-release methylphenidate in children has been extensively studied, studies in adults, which are few, demonstrate varying results.

OBJECTIVES:
To evaluate the efficacy and tolerability of immediate-release methylphenidate versus placebo in the treatment of adults with ADHD.

SEARCH METHODS:
We searched the following databases in November 2013: CENTRAL, Ovid MEDLINE, EMBASE, PsycINFO, Database of Abstracts of Reviews of Effects (DARE), and two trials registers. Biosis was searched in December 2013. We inspected references of all relevant papers to identify more studies and contacted authors of recently published trials.

SELECTION CRITERIA:
We included all randomized trials comparing immediate-release methylphenidate versus placebo in participants aged 18 years or older with ADHD. We excluded trials conducted on subpopulations of adults with ADHD such as adults with both ADHD and substance dependence.

DATA COLLECTION AND ANALYSIS:
Two review authors independently selected trials, extracted data, and assessed trial risk of bias. We contacted authors of trials to ask for additional and missing data. For dichotomous outcomes, we calculated risk ratios (RRs) and 95% confidence intervals (CIs). For continuous outcomes, we calculated mean differences (MDs) or standardized mean differences (SMDs) with 95% CIs.

MAIN RESULTS:
Results from the 11 randomized controlled trials (474 participants, counting participants from cross-over studies as a single arm, and counting both arms from parallel studies) included in the review demonstrated improvement in core clinical ADHD symptoms of hyperactivity, impulsivity, and inattentiveness, and overall improvement. We were able to pool results from 10 studies, which included 466 participants. Most included studies were judged to have unclear risk of bias for most categories. However, as all studies were randomized, double-blind, and placebo-controlled and, in general, did not contain factors that significantly decreased the quality of the body of evidence, the quality of evidence was assessed as "high" for most outcomes according to the GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) approach. For one outcome-inattentiveness-most information came from studies at unclear risk of bias, and so the quality of evidence for this outcome was judged as "moderate." Results are given as SMD for each of the core clinical symptoms of ADHD. In all cases, participant numbers were calculated by counting participants in a single arm from cross-over studies and in both arms from parallel studies. The SMD for the outcome of hyperactivity was -0.60 (95% CI -1.11 to -0.09, 6 studies, number of participants (n) = 245, high-quality evidence) in favor of immediate-release methylphenidate; the SMD for impulsivity was -0.62 (95% CI -1.08 to -0.17, 5 studies, n = 207, high-quality evidence) in favor of immediate-release methylphenidate; and the SMD for inattentiveness was -0.66 (95% CI -1.02 to -0.30, 7 studies, n = 391, moderate-quality evidence) in favor of immediate-release methylphenidate. Moderate to extreme statistical heterogeneity was detected for all outcomes. Subgroup analysis comparing high versus low doses did not indicate that higher doses of immediate-release methylphenidate were associated with greater efficacy. For overall change,
the SMD was -0.72 (95% CI -1.12 to -0.32, 9 studies, n = 455, high-quality evidence) in favor of immediate-release methylphenidate. The effects of immediate-release methylphenidate on anxiety and depression as parameters of general changes in mental state were equivocal. Some trials reported reduction in depression and anxiety, others detailed no change, and still others described an increase in depressive and anxious symptoms. The most common adverse effect was loss of appetite, in some cases with weight loss. Although no study reported either of these effects as problematic or severe, the included studies were of short duration; thus clinical significance could not be properly assessed. Five studies reported changes in systolic or diastolic blood pressure, and three reported increases in heart rate. None of these results were judged to present cause for concern. No study reported clinically significant adverse effects—cardiovascular or other. Three studies did not mention adverse effects. We were unable to determine whether adverse effects were not discussed by study authors because none occurred, or because no data on adverse effects were collected.

AUTHORS’ CONCLUSIONS:
Data from randomized controlled trials suggest that immediate-release methylphenidate is efficacious for treating adults with ADHD with symptoms of hyperactivity, impulsivity, and inattentiveness, and for improving their overall clinical condition. Trial data suggest that adverse effects from immediate-release methylphenidate for adults with ADHD are not of serious clinical significance, although this conclusion may be limited, certainly in the case of weight loss, by the short duration of published studies.