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Abstract

OBJECTIVE:
Irritability is listed as a common side effect of psychostimulant medications. However, psychostimulants have been demonstrated as an effective treatment in reducing irritability and aggression in children with attention-deficit/hyperactivity disorder (ADHD). The goal of this study was to quantify the risk of irritability as a side effect of psychostimulant treatment for ADHD.

DATA SOURCES AND STUDY SELECTION:
A PubMed search was conducted on August 18, 2013, to identify all double-blind, randomized, placebo-controlled trials published in English examining the efficacy of psychostimulant medications in the treatment of children with ADHD. Trials were excluded if (1) they required additional psychiatric or medical comorbidity in addition to ADHD, (2) they involved fewer than 20 subjects (parallel group trials), or (3) children received psychostimulant medication for less than 1 week.

DATA EXTRACTION:
A fixed-effects meta-analysis was used to examine the risk ratio of irritability reported as a side effect in children treated with psychostimulants compared to placebo. Stratified subgroup analysis and meta-regression were used to examine the effects of stimulant type, dosage, duration of use, and trial design on the measured risk of irritability.

RESULTS:
From 92 potentially eligible trials, the meta-analysis identified 32 trials involving 3,664 children with ADHD that reported data on irritability as a side effect. The relative risk of irritability significantly differed between psychostimulant classes (test for subgroup differences $\chi^2 = 7.6$, $P = .006$). Methylphenidate derivatives were associated with a significantly decreased risk of irritability compared to placebo (risk ratio [RR] = 0.89 [95% CI, 0.82 to 0.96], $z = -2.87$, $P = .004$, $k = 32$, $I^2 = 50\%$), whereas amphetamine derivatives were associated with a significantly increased risk of irritability (RR = 2.90 [95% CI, 1.26 to 6.71], $z = 2.5$, $P = .01$, $k = 5$, $I^2 = 0\%$).

CONCLUSIONS:
This meta-analysis suggests an increased risk of irritability may be confined to amphetamine-derived psychostimulants. Future meta-analyses examining the effects of amphetamine and methylphenidate derivatives on irritability as a continuous measure, as well as head-to-head trials between methylphenidate and amphetamine derivatives examining effects on irritability, will be important to replicate the findings of this meta-analysis.