Aetiology

Review: stimulant pharmacotherapy for children with ADHD is associated with a reduced risk of later substance abuse disorder


Question
In children with attention deficit hyperactivity disorder (ADHD), what is the relation between stimulant pharmacotherapy and later substance use disorder (SUD)?

Data sources
Studies were identified by searching PubMed with the terms ADHD, pharmacotherapy, stimulants, and SUD and by seeking data from presentations at national and international scientific meetings.

Study selection
Prospective and retrospective studies were included if they evaluated children, adolescents, and adults who had received stimulant pharmacotherapy in childhood and if they reported on SUD outcome (overall rates of any non-nicotine drug and alcohol use disorder) in adolescence or adulthood.

Data extraction
Data were extracted on baseline severity of ADHD, patient age at follow up, length of follow up, use of stimulants, and incidence of alcohol use disorder and drug use disorder. Odds ratios for developing SUD were pooled in a meta-analysis using the random effects model.

Main results
6 studies from the US and Germany were included. Of 5 prospective longitudinal studies, 2 followed children for ≥ 4 years and 3 followed children into young adulthood (range of follow up 4 to > 10 y). The studies included 674 participants who received stimulants (mostly methylphenidate and amphetamine) and 360 participants who did not. Meta-analysis showed that stimulant pharmacotherapy was associated with a reduction in the risk of developing SUD (odds ratio 1.9, 95% CI 1.1 to 3.6). Statistically significant heterogeneity existed among the studies (p < 0.001). Sensitivity analysis showed that no one study had more influence than any other on the pooled estimate.

Conclusion
In children who had childhood attention deficit hyperactivity disorder, the use of stimulant pharmacotherapy is associated with a reduced risk of developing substance use disorder in adolescence or adulthood.

COMMENTARY
The review by Wilens et al is a careful analysis of the highest quality available, longitudinal studies to assess the possible association between stimulant treatment and later risk of substance abuse among children with ADHD. The report constitutes a major step forward and is the most sophisticated exposition on this issue to date.

In 1998, the National Institutes of Health conducted a Consensus Conference on ADHD to address this and other controversial or misunderstood aspects of ADHD. After reviewing all available studies at that time, an impartial scientific panel concluded, “Although an increased risk of drug abuse and cigarette smoking is associated with childhood ADHD, existing studies come to conflicting conclusions as to whether use of psychostimulants increases or decreases the risk of abuse. A major limitation of inferences from observational databases is the inability to examine independently the use of stimulant medication, the diagnosis and severity of ADHD, and the effect of coexisting conditions.”

Since then, a half dozen additional studies have become available, which are reviewed here by Wilens et al. As they note, all recent evidence has pointed to the likelihood of a protective effect of treatment on later risk of substance use.

In addition, Wilens et al responded to the challenge from the Consensus panel by ascertaining the extent to which studies controlled for (or at least examined) the baseline severity of treated compared with untreated children with ADHD. 4 of 6 studies in fact did this. To the best extent possible therefore, one major possible confounding variable has been accounted for. In the only study suggesting a treatment–substance abuse linkage, stimulant treated children were more severe at baseline than untreated children, suggesting that the study’s conclusions were flawed.

So has “no linkage” been definitely established? Not yet, but the evidence is suggestive. As Wilens et al note, selection factors may still account for the lack of association in studies finding no linkages, if families that sought medication for their children were more motivated or had higher education status. What is needed? Control for such potential confounders, ideally through random assignment.

Fortunately, we should not have long to wait: the National Institute of Mental Health’s Multimodal Treatment Study of ADHD was in part designed to address these long term outcomes. It initially randomly assigned children to medication or psychotherapy. Thus this study may be able to address possible selection factor confounders as well as other factors of importance—not just whether a child ever took medication, but for how long, for what reasons, and in combination with which other treatments.

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