

Does Stimulant Treatment Lead to Substance Use Disorders?

Stephen V. Faraone, Ph.D., and Timothy Wilens, M.D.

The authors examine the relationship between the treatment of attention-deficit/hyperactivity disorder (ADHD) with stimulants and substance use disorders by reviewing their published meta-analysis of 6 studies and adding preliminary data from a seventh study. Despite some discrepancies among the findings of the 7 studies, the meta-analysis demonstrated that exposure to stimulant therapy for ADHD does not increase the risk for developing substance use disorders but is, in fact, protective against it. Stimulant treatment of ADHD appears to reduce the risk for substance use disorders by 50%, thus reducing the risk for substance use disorders in ADHD youth to levels well within the normal population risk. The implication of this finding is unquestionably one with enormous value both clinically and as a matter of public health. *(J Clin Psychiatry 2003;64[suppl 11]:9-13)*

One of the most common neuropsychiatric disorders of childhood, attention-deficit/hyperactivity disorder (ADHD), occurs in an estimated 3% to 6% of children¹ and accounts for as many as 30% to 50% of child referrals to mental health services.² Over the past 40 years, this common disorder has also been one of the most aggressively studied, with particular attention to the treatment that has been its mainstay: more than 200 randomized clinical trials have consistently documented the efficacy of stimulant therapy in the treatment of ADHD.³

The use of stimulants to treat ADHD has been controversial for some years, in part as a result of speculation that exposure to stimulant therapy somehow leads directly to substance abuse. This persistent fear has been generated somewhat by the fact that stimulants have a potential for abuse.¹ In spite of the fact that there is little responsible evidence that this is actually the case, the assumption persists, especially in the popular press, that stimulant therapy inevitably puts patients at risk for developing substance use disorders including dependence or addiction.^{4,5} To date, only 3 published accounts of cases in which ado-

lescents with ADHD have abused their prescribed stimulants have appeared in the literature.⁶⁻⁸

The association between pharmacotherapy for ADHD with stimulant medications and substance use disorders has been studied, with particular emphasis on any risk for substance use disorders that might develop from exposure to psychotropic medication. In one such study, pharmacotherapy for ADHD was shown to protect children with ADHD from substance use disorders rather than inducing them to abuse substances.⁹ The findings of another study published at about the same time illustrated the reverse: cocaine and nicotine abuse were associated with previous stimulant treatment.¹⁰

In an ongoing attempt to reconcile these discrepant findings, we have undertaken a meta-analysis of the available studies that have sought to measure the extent to which childhood exposure to stimulant pharmacotherapy is associated with substance use disorders in adolescence or adulthood. In its original form, this meta-analysis³ was applied to the 6 longer-term studies (> 4 years) then available,⁹⁻¹⁴ in which pharmacologically treated and untreated groups of ADHD patients were examined for substance use disorder outcomes, using a random effects meta-analysis to analyze odds ratios, using the method of Carlin. For the purposes of this review, we have incorporated some preliminary data from a seventh study, recently reported, where appropriate.¹⁵

METHOD

For the analysis, a random effects meta-analysis was used. Each study provided a 2 × 2 table classifying subjects by treatment status—pharmacotherapy or not—and the subsequent development of substance use disorders—

From Harvard Medical School, Boston, Mass., and Massachusetts General Hospital, Boston.

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Corresponding author and reprints: Stephen V. Faraone, Ph.D., Pediatric Psychopharmacology Research, Massachusetts General Hospital, WRN 705, 55 Fruit St., Boston, MA 02114-3139 (e-mail: sfaraone@hms.harvard.edu).

present or not—from which to compute the odds ratio. In this instance, the odds ratio estimated the increase in the odds of *not* developing substance use disorders (the “protective effect”) among those ADHD subjects treated pharmacologically, compared with untreated subjects. Under this measure, an odds ratio of 2, for example, meant that a subject was twice as likely not to develop substance use disorders if given medication, whereas an odds ratio of less than 1 would mean that a history of taking stimulant medication had inclined the subject to develop substance use disorders. We conducted a sensitivity analysis by re-computing the meta-analysis after deleting one study at a time. If one study accounted for the positive findings, the sensitivity analysis would be nonsignificant when that study was deleted. Meta-analysis regression was further used to evaluate differential effects on specific drug or alcohol use disorders and the potential effects of covariates. To avoid paradoxical findings in which greater treatment intensity predicts worse outcome, the studies were assessed for evidence of baseline severity differences between treated and untreated groups.

RESULTS

Seven studies have been included in the current review (Table 1).^{9–15} Five of the original studies were prospective and longitudinal^{9–13} and 1 was a retrospective report, capturing data from adults with ADHD.¹⁴ Of the 766 medicated subjects in the 7 studies combined, 98% had been treated with stimulants (methylphenidate or amphetamine). Five of those studies demonstrated similar levels of severity and psychiatric comorbidity between the medicated and unmedicated subject groups at baseline. One study¹¹ did not report findings on overall substance abuse but only reported data on cocaine abuse; for the purposes of the meta-analysis, we used the cocaine data to stand for overall substance abuse.

Overall Meta-Analysis

The meta-analysis showed a statistically significant pooled odds ratio of 2.0 ($z = 2.4$, $p = .02$), indicating an overall protective effect of stimulant treatment on subsequent substance abuse. A sensitivity analysis showed that this finding could not be accounted for by any one observation (all p values $< .05$). There were no significant differences between the odds ratios for drug and alcohol outcomes (2.4 vs. 4.0, $z = 1.1$, $p = .3$).

The odds ratio concerning overall drug abuse calculated for each of the 7 studies is shown in Figure 1, which incorporates data from the initial meta-analysis³ as well as added data from the recent study.¹⁵ The odds ratio of 1, indicated by the dotted line, should be taken to mean that stimulant therapy for ADHD had zero effect on subsequent development of drug abuse, while numbers higher than 1 suggest that stimulant medication had a protective

Table 1. Seven Studies of Attention-Deficit/Hyperactivity Disorder Subjects Included in the Meta-Analysis

Author(s) and Study	Year of Publication	Number of Treated Subjects	Number of Untreated Patients
Loney ¹¹	1998	182	37
Lambert and Hartsough ¹⁰	1998	93	81
Biederman et al ⁹	1999	145	45 + controls
Molina et al ¹²	1999	53	73
Huss ¹⁴	1999	103	103
Barkley et al ¹³	2003	98	21
Huss ¹⁵	2003	92	69
Total		766	429

effect and numbers less than 1 suggest the opposite. In this figure, it is clear that 4 studies (Molina et al.,¹² Biederman et al.,⁹ and the 2 Huss studies^{14,15}) suggested medication to have a protective effect, 3 of them individually significant ($p < .05$).^{9,12,15} Two studies, Barkley et al.¹³ and Loney,¹¹ suggested no effect, while the Lambert and Hartsough study¹⁰ showed a small deleterious effect, but was not statistically significant.

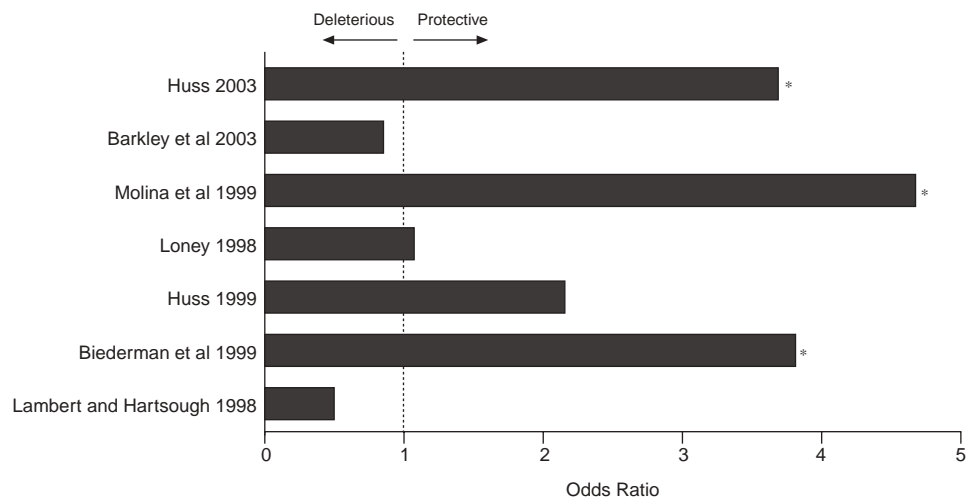
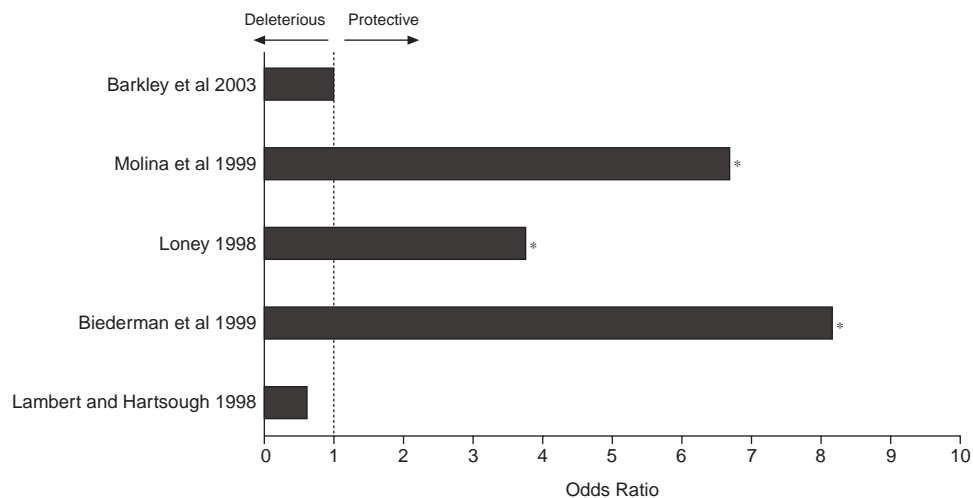
Figure 2 shows equivalent findings with regard to alcohol abuse, as reported in five studies.^{9–13} In this case, 3 studies showed a statistically significant protective effect—Loney,¹¹ Biederman et al.,⁹ and Molina et al.¹²—while the study by Barkley et al.¹³ suggested no effect and Lambert and Hartsough’s study¹⁰ showed a nonsignificant deleterious effect. No effect of type of substance—drug or alcohol—was found ($z = 1.1$, $p = .3$).

Age Effect

As we have reported previously,³ studies that reported follow-up into adolescence showed a greater protective effect (OR = 5.8) than those following subjects into adulthood (OR = 1.7, $z = 4.4$, $p < .0001$), as shown in Figure 3.

Baseline Severity

When data from the 4 studies^{9,11,12,14} that had similar baseline severity between treated and untreated groups were analyzed, larger and therefore more protective odds ratios were computed than those applying to the 2 studies with dissimilar baseline severity ($z = 2.9$, $p = .004$).^{10,13} As a group, the data from studies with similar baseline severity showed a statistically significant protective effect (OR = 4.3). Data points from the 2 studies that did not have similar baseline severity between treatment groups suggest that stimulants increased the risk for substance use disorders outcomes (OR = 0.7). Such a difference in baseline severity between treated and untreated subjects is clearly a potential source of bias and distortion, because more severe illness is clearly associated with poorer outcome and more treatment, both of which can emerge in study results as poorer outcome. Because all of the studies used in the meta-analysis were naturalistic rather than randomized, any attempt to untangle positive or deleterious

Figure 1. Odds Ratio Calculated for Association Between Pharmacotherapy and Subsequent Drug Abuse^a^aData in part from Wilens et al.³*Indicates $p < .05$.Figure 2. Odds Ratio Calculated for Association Between Pharmacotherapy and Subsequent Alcohol Abuse^a^aData from Wilens et al.³*Indicates $p < .05$.

effects of treatment from the severity of the condition being treated are potentially confounded.

Publication Bias

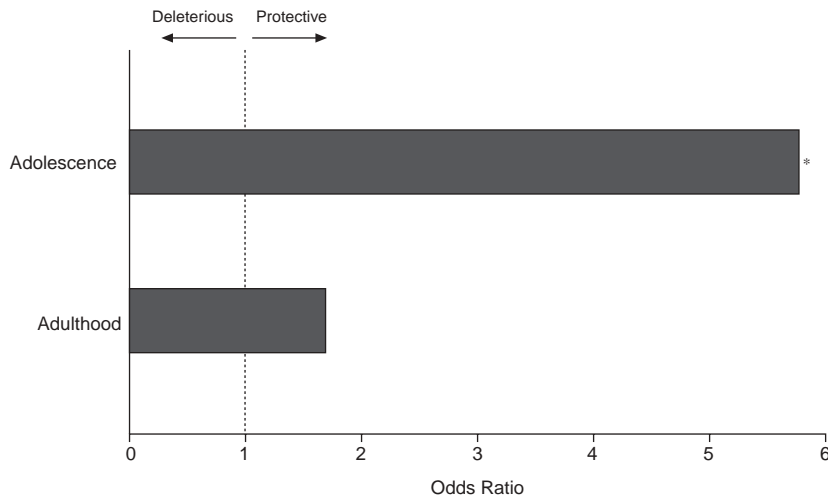
The possibility that the group of studies that controlled for baseline severity overestimated the protective effect because of publication bias was assessed, using the method of Egger. This method regresses the standard normal deviate of the odds ratio (odds ratio divided by its standard error) against the precision of the odds ratio (inverse of its standard error). We found that the publication

bias was not significant ($t = 0.5$, $p = .6$), indicating that the group of studies that controlled for baseline severity had not overestimated the protective effect.

Study Limitations

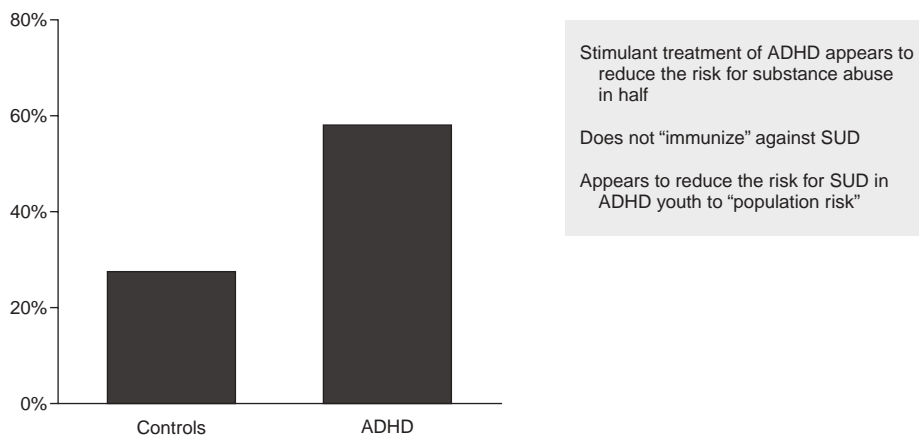
The results of this meta-analysis must be considered in the context of a number of limiting factors inherent in the nature of the project. The number of studies suitable for the initial project was small ($N = 7$), as was the number of subjects ($N = 1195$). Most of the subjects were male. Although all were peer-reviewed, some of the studies were

Figure 3. Odds Ratio Calculated for Association Between Age and the Development of Substance Use Disorders^a



^aData from Wilens et al.³
 *Indicates $p < .05$.

Figure 4. Rates of Substance Use Disorders (SUD) in Untreated Adults With Attention-Deficit/Hyperactivity Disorder (ADHD)^a



^aData from Wilens et al.³

published while others were presented at professional gatherings. The studies themselves were naturalistic rather than randomized, and several confounds—severity of illness, comorbidity, family history of substance use disorders—may have independently affected study outcomes. Similarly, not all subjects treated for ADHD received stimulants; 4% received other medications. Moreover, the duration and adequacy of therapeutic regimens were not delineated. The substance use disorders outcome measures depended on self-report or parental report, as is often the case in research of this sort; and the criteria used to denote substance abuse or dependence varied from study to study. Further studies investigating the

long-term outcome of substance use disorders and mechanisms by which risk of such disorders is reduced in ADHD youth of both sexes who are treated pharmacologically will be needed to clarify these concerns.

CONCLUSIONS

In spite of the acknowledged limitations outlined, the meta-analysis clearly indicated that the pharmacotherapy of ADHD does not increase the risk for subsequent substance use disorders; in fact, the data suggest that stimulant medication has a protective effect on later substance use disorders. The mechanism by which stimulant phar-

macotherapy for ADHD protects against substance use disorders remains unclear. We have speculated that stimulant therapy reduces classic symptoms associated with ADHD such as poor self-esteem, demoralization, and school failure, and, accordingly, such treatment reduces the risk of substance use disorders. It may also be that by reducing conduct-disordered behavior, treatment indirectly reduces the risk of substance use disorders. The close supervision accorded most treated patients may directly intervene in their risk of developing substance use disorders. Furthermore, it may be that parents who seek treatment for their children in the first place are more invested in their children's academic success and therefore more involved in their children's lives.³

Stimulant treatment of ADHD appears to reduce the risk for substance use disorders by half, reducing the risk for substance use disorders in ADHD youth to levels well within accepted population risks, as established by controls.^{3,9,10,16} Figure 4 shows a comparison between the risk for substance use disorders in untreated adults with ADHD and that of controls. Although stimulant treatment for ADHD cannot prevent the subsequent development of substance use disorders, its protective effect is clear.

Implications

The evidence from the meta-analysis confirming the protective effect of stimulant therapy for ADHD against substance use disorders is of great significance, both clinically and from the perspective of public health. Clinicians will be relieved to be in a position to authoritatively reassure parents and patients that the risks and benefits of stimulant therapy for ADHD do not provoke anxiety concerning drug addiction or any other form of substance use disorders. Moreover, the evidence of a protective effect of stimulant therapy for ADHD on the development of substance use disorders is among the strongest within the field of child psychology. This finding is unquestionably one with enormous value in a population and an age cohort vulnerable to the lures of illicit drugs and the culture within which they are used.

Drug names: amphetamine (Adderall, Dextroamp, and others), methylphenidate (Ritalin, Concerta, and others).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

REFERENCES

1. Goldman LS, Genel M, Bezman RJ, et al. Diagnosis and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *JAMA* 1998;279:1100–1107
2. The MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* 1999;56:1073–1086
3. Wilens TE, Faraone SV, Biederman J, et al. Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? a meta-analytic review of the literature. *Pediatrics* 2003;111:179–185
4. Diller L. *Running on Ritalin*. New York, NY: Bantam; 1998
5. Breggin P. *Talking Back to Ritalin*. Monroe, Me: Common Courage Press; 1998
6. Garland EJ. Intranasal abuse of prescribed methylphenidate [letter]. *J Am Acad Child Adolesc Psychiatry* 1998;37:573–574
7. Jaffe SL. Intranasal abuse of methylphenidate by an alcohol and drug abusing adolescent with ADHD. *J Am Acad Child Adolesc Psychiatry* 1991;30:773–775
8. Goyer PF, Davis GC, Rapoport JL. Abuse of prescribed stimulant medication by a 13-year-old boy. *J Am Acad Child Adolesc Psychiatry* 1979;18:170–175
9. Biederman J, Wilens T, Mick E, et al. Pharmacotherapy of attention-deficit/hyperactivity disorder reduces risk for substance use disorder. *Pediatrics* [serial online]. 1999;104:e20. Available at: <http://www.pediatrics.org/cgi/content/full/104/2/e20>. Accessed Jan 20, 2003
10. Lambert NM, Hartsough CS. Prospective study of tobacco smoking and substance dependencies among samples of ADHD and non-ADHD participants. *J Learn Disabil* 1998;31:533–544
11. Loney J. Risk of treatment versus nontreatment. Presented at the National Institute of Health Consensus Development Conference on the Diagnosis and Treatment of Attention Deficit Hyperactivity Disorder. November 16–18, 1998; Bethesda, Md. Available at: http://consensus.nih.gov/cons/110/110_abstract.pdf. Accessed March 13, 2003
12. Molina B, Pelham W, Roth J. Stimulant medication and substance use by adolescents with a childhood history of ADHD [poster]. Presented at the biennial meeting of the International Society for Research in Child and Adolescent Psychopathology; June 17–20, 1999; Barcelona, Spain
13. Barkley RA, Fischer M, Smallish L, et al. Does the treatment of attention-deficit/hyperactivity disorder with stimulants contribute to drug use/abuse? a 13-year prospective study. *Pediatrics* 2003;111:97–109
14. Huss M. ADHD and substance abuse. In: IX Annual European Congress of Psychiatry. Hamburg, Germany; 1999
15. Huss M. The relationship of ADHD and substance abuse. Presented at the International Conference on ADHD; Feb 26–March 1, 2003; Chicago, Ill
16. Wilens T. Attention deficit hyperactivity disorder and substance use disorders: nature of the relationship, subtypes at risk, and treatment issues. In: Jensen PS, Cooper J, eds. *Attention Deficit Hyperactivity Disorder: State of the Science Best Practices*. Kingston, NJ: Civic Research Institute; 2002:1–24