ARTICLE

Effect of Prior Stimulant Treatment for Attention-Deficit/Hyperactivity Disorder on Subsequent Risk for Cigarette Smoking and Alcohol and Drug Use Disorders in Adolescents

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Objective: To examine the effects of early stimulant treatment on subsequent risk for cigarette smoking and substance use disorders (SUDs) in adolescents with attention-deficit/hyperactivity disorder (ADHD).

Design: Case-controlled, prospective, 5-year follow-up study.

Setting: Massachusetts General Hospital, Boston.

Participants: Adolescents with and without ADHD from psychiatric and pediatric sources. Blinded interviewers determined all diagnoses using structured interviews.

Intervention: Naturalistic treatment exposure with psychostimulants for ADHD.

Main Outcome Measures: We modeled time to onset of SUDs and smoking as a function of stimulant treatment.

Results: We ascertained 114 subjects with ADHD (mean age at follow-up, 16.2 years) having complete medication and SUD data; 94 of the subjects were treated with stimulants. There were no differences in SUD risk factors between naturalistically treated and untreated groups other than family history of ADHD. We found no increased risks for cigarette smoking or SUDs associated with stimulant therapy. We found significant protective effects of stimulant treatment on the development of any SUD (hazard ratio [HR], 0.27; 95% confidence interval [CI], 0.13-0.60; $\chi^2_{113}=10.57$, $P=.001$) and cigarette smoking (HR, 0.28; 95% CI, 0.14-0.60; $\chi^2_{111}=10.05$, $P=.001$) that were maintained when controlling for conduct disorder. We found no effects of time to onset or duration of stimulant therapy on subsequent SUDs or cigarette smoking in subjects with ADHD.

Conclusion: Stimulant therapy does not increase but rather reduces the risk for cigarette smoking and SUDs in adolescents with ADHD.

Arch Pediatr Adolesc Med. 2008;162(10):916-921

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ATTENTION-DEFICIT/HYPERactivity disorder (ADHD) is a prevalent neurobehavioral disorder occurring in 6% to 8% of children and in 4% to 5% of adults worldwide.[1-3] Although it is more prevalent in boys than in girls[3] and most of the extant literature on ADHD is based on findings in boys, it is clear that ADHD affects a sizeable number of girls and is as much a source of morbidity and disability for girls as has been documented for boys.[4,5] Attention-deficit/hyperactivity disorder is now considered more long-term, with 40% to 60% of children continuing to manifest prominent ADHD symptoms and impairment through adolescence into adulthood.[6-9] Across the life span, ADHD has been shown to be associated with high risk for comorbid disruptive, mood, and anxiety disorders.[4,10] Likewise, a high risk for cigarette smoking and substance use disorders (SUDs), including drug and alcohol abuse and dependence, has been shown in individuals with ADHD while growing up.[11-15]

Among treatments for ADHD, stimulants remain among first-line treatments for the disorder.[16,17] Because ADHD is a well-known risk for SUDs[12,13,18] and because stimulants are potential drugs of abuse,[19] concerns remain as to the possibility for stimulants to increase the subsequent risk for cigarette smoking and SUDs in individuals treated for ADHD.[20] Along those lines, although one group found that cigarette smoking and cocaine hydrochloride abuse were associated with previous stimulant treatment,[21] others reported that stimulant treatment in youth with ADHD does not increase subsequent cigarette smoking or SUDs,[22] with other studies[23-25] and a meta-analysis[26] showing that stimulant treatment may exert a protective effect against subsequent cigarette smoking or SUDs.

Despite the implications of the effects of early stimulant treatment on later SUDs, important limitations in the literature exist. For example, previous investigations have not generally examined the length of stimulant exposure and later SUDs, severity of SUD outcomes, or comorbidity with conduct disorder (CD).[21] In addition, there is limited literature that specifically examines the association between stimulant treatment and SUDs relative to sex. However, data suggest that adolescents with ADHD compared with boys with ADHD may have substantially higher age-matched risk for cigarette smoking and SUDs in early adolescence.[27-29] Moreover, differences may exist between boys and girls with ADHD in terms of SUD risk associated with prior stimulant treatment. For instance, Katusic et al[24] reported a difference in SUD risk reduction associated with stimulant treatment in boys with ADHD but not in girls with ADHD.

The main objective of the present study was to examine the effects of early stimulant treatment on subsequent risk for cigarette smoking and SUDs in adolescents with ADHD. Based on previous work in a similarly aged sample of boys with ADHD,[23] we hypothesized primarily that stimulants would be associated with a reduction in the risk for SUDs and cigarette smoking. Secondarily, we hypothesized that the duration of treatment would be directly related to the reduction in risk for SUDs.[25,30]

METHODS

SUBJECTS

Subjects were derived from a longitudinal case-control family study of adolescents with and without ADHD as described previously in detail.[5] Briefly, the baseline study evaluated female subjects aged 6 to 18 years with ADHD (n=140) and without ADHD (n=122) ascertained from pediatric and psychiatric sources. Potential subjects were excluded if they had been adopted, if their nuclear family was unavailable for study, or if they had autism, psychosis, a full-scale IQ of less than 80, inadequate command of the English language, or major sensorimotor handicaps (paralysis, deafness, or blindness). All of the subjects with ADHD met full *Diagnostic and Statistical Manual of Mental Disorders* (Third Edition Revised) (*DSM-III-R*) diagnostic criteria for ADHD at the time of the clinical referral, and at recruitment they all had active symptoms of the disorder. The present study reports on the 5-year follow-up of the subjects with ADHD.[5] Parents and adult offspring provided written informed consent to participate, and parents gave consent for offspring younger than 18 years. Children and adolescents provided written assent to participate. The human research committee at Massachusetts General Hospital approved this study protocol.

A 3-stage ascertainment procedure was used to select subjects. In the first stage, psychiatric or pediatric clinics conducted screening and referred subjects. In the second stage, we confirmed screening by administering a telephone questionnaire to each subject's mother. In the third stage, we assessed subjects using diagnostic structured interviews. Because the study had begun before finalization of the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) (*DSM-IV*), the baseline assessment used *DSM-III-R*–based structured interviews, but we supplemented these with questions that would allow us to make *DSM-IV* diagnoses. Psychiatric assessments at the 5-year follow-up relied on the Schedule for Affective Disorders and Schizophrenia for School-Aged Children–Epidemiologic Version (K-SADS-E) for subjects younger than 18 years and the Structured Clinical Interview for *DSM-IV* (supplemented with modules from the K-SADS-E to assess childhood diagnoses) for subjects 18 years and older. We considered a disorder positive if *DSM-IV* diagnostic criteria were unequivocally met in either interview. For diagnostic modules, including those assessing all SUDs and ADHD, the interviewer asked the subject to characterize the degree of impairment caused by the symptoms in question on her daily functioning as minimal, moderate, or severe.

A committee of 9 board-certified child and adult psychiatrists (including T.E.W. and J.B.) who were blinded to the subject's ADHD status, referral source, and all other data resolved diagnostic uncertainties. Diagnoses presented for review were considered positive only if a consensus was achieved that criteria were met to a degree that would be considered clinically meaningful. Based on 500 assessments from interviews of children and adults, the median κ coefficient was 0.98. κ Coefficients for individual diagnoses were 0.88 for ADHD, 1.0 for CD, 1.0 for major depression, 0.95 for mania, 1.0 for separation anxiety, 1.0 for agoraphobia, 0.95 for panic, 1.0 for SUD, and 0.89 for tics or Tourette syndrome.

SUBSTANCE USE MEASURES

Our diagnostic interviews collected data on the lifetime use of nicotine, alcohol, marijuana, and other drugs. All substances except for alcohol and nicotine are referred to as drugs. For every substance used by a given subject, we derived the age at first use, lifetime diagnosis of *DSM-IV* abuse or dependence, and age at onset from structured interview data. Cigarette smoking refers to age-appropriate diagnosis of *DSM-IV* smoking dependence.

STATISTICAL ANALYSIS

We compared subjects having ADHD with and without a lifetime history of stimulant medication use relative to follow-up demographic factors. We used the *t* test for age, Wilcoxon rank sum test for socioeconomic status, and Pearson product moment correlation χ^2 test for binary outcomes. We controlled for demographic confounders if an outcome was significantly predicted by group membership at $\alpha=0.1$.

We used Cox proportional hazards models to estimate the lifetime risk for SUDs associated with stimulant therapy. For each outcome, rates are defined as a positive response at any assessment (baseline or follow-up) vs a negative response at both assessments. These models use all available data for each subject, including those not assessed at follow-up. Therefore, all 140 subjects are included, using as many waves of follow-up data as are available. We used the earliest age at onset as the survival time for cases and the age at the most recent interview as the time of censoring for noncases.

We created an indicator variable for each SUD outcome. This indicator is positive for a subject if (1) she reported a lifetime history of treatment with any stimulant and (2) she did not meet criteria for the substance use outcome before the onset of treatment. Untreated subjects and subjects who began stimulant treatment after the onset of the substance use were scored as negative on this binary variable. Subjects whose treatment and substance outcome began at the same age were impossible to categorize and were excluded from the analysis of that outcome. The statistical significance of each covariate in these regression models was determined using the linear Wald test, and $\alpha=.05$ was considered significant. All tests were 2-tailed.

Table 1. Demographic and Stimulant Treatment Characteristics of Adolescents With Attention-Deficit/Hyperactivity Disorder (ADHD) at 5-Year Follow-up

Characteristic	No Stimulant Therapy (n=20)	Stimulant Therapy (n=94)	Statistic	*P* Value
Age, mean (SD)	16.55 (4.15)	16.12 (3.55)	t=0.48[a]	.60
Socioeconomic status, mean (SD)	1.89 (0.83)	1.97 (1.03)	z=−0.03[b]	>.99
Family intact, No. (%)	15 (75.0)	62 (66.0)	χ^2=0.62[b,c]	.40
Full conduct disorder, No. (%)	7 (35.0)	38 (40.4)	χ^2=0.20[b,c]	.70
Level of ADHD impairment, No. (%)[d]			χ^2=1.26[b,c]	.50
Mild	1 (5.6)	8 (8.7)		
Moderate	14 (77.8)	59 (64.1)		
Severe	3 (16.7)[e]	25 (27.2)[e]		
Parental history, No. (%)				
ADHD	3 (15.0)	35 (37.2)	χ^2=3.67[b,c]	.06
Substance use disorder	11 (55.0)	65 (69.1)	χ^2=1.49[b,c]	.20
Source of ascertainment, No. (%)	5 (25.0)	41 (43.6)	χ^2=2.37[b,c]	.10

[a] *t* Test.
[b] Wilcoxon rank sum test.
[c] Pearson product moment correlation χ^2 test.
[d] As assessed on an ordinal scale by the subject about the effect on daily functioning.
[e] The values do not sum to the subsample size because some data points are missing.

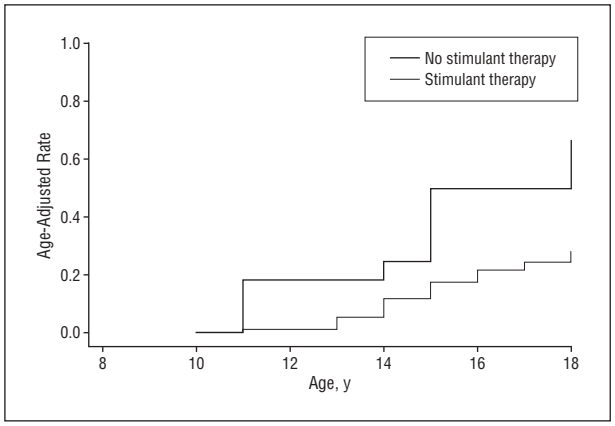

Figure 1. The effects of prior stimulant exposure on risk for subsequent substance use disorder (curves truncated at 18 years).

RESULTS

We ascertained 114 subjects with ADHD having complete medication and SUD data. These subjects ranged in age from 10 to 24 years at the 5-year follow-up (mean age at follow-up, 16.2 years). One hundred eight subjects (94.7%) identified themselves as white and 5 (4.4%) identified themselves as African American. One subject (0.9%) was of unknown race/ethnicity. We found no differences between exposed and unexposed subjects in age, rates of CD, socioeconomic status, source of ascertainment, parental history of SUDs, frequency of family intactness, or severity of ADHD impairment (**Table 1**). We found that subjects with ADHD receiving stimulant treatment were significantly more likely to have parents with a lifetime history of ADHD; all further analyses controlled for parental history of ADHD.

EXPOSURE TO STIMULANTS

Risk for SUDs

We compared subjects having ADHD with and without exposure to stimulants on age-adjusted rates of developing SUDs. We failed to find any evidence of a significantly higher risk for any SUD among subjects exposed to stimulant medication. Instead, we found evidence for a significant protective effect of stimulant exposure on the subsequent development of any SUD (hazard ratio [HR], 0.27; 95% confidence interval [CI], 0.13-0.60; $\chi^2_{1|13}$=10.57, *P*=.001) (**Figure 1**). Stimulant-exposed adolescents with ADHD were 73% less likely to manifest an SUD compared with adolescents who were not exposed to stimulants (**Table 2**).

We also failed to find any evidence for increases in the risks for class or severity of dependence associated with stimulant treatment. Instead, we found evidence of specific SUD risk reduction associated with prior stimulant treatment. More specifically, we found a significant protective effect of stimulant exposure on the age-adjusted rate of development of drug abuse (n=112) and, although not statistically significant, a lesser effect of stimulant exposure on drug dependence (n=112). Likewise, we found no significant effect of stimulant exposure on alcohol abuse (n=114) or on alcohol dependence (n=114).

Risk for Cigarette Smoking

We also evaluated stimulant exposure in relation to the development of cigarette smoking (dependence). We failed to find a significantly higher risk for cigarette smoking (dependence) and prior exposure to stimulant medication. Instead, we found a significant protective effect of stimulant exposure on the age-adjusted rate of smoking development in our sample (HR, 0.28; 95% CI, 0.14-0.60; $\chi^2_{1|11}$=10.05, *P*=.001) (**Figure 2**). Subjects with ADHD who were previously treated with stimulants had a 72% lower risk and a later onset of cigarette smoking relative to subjects with ADHD without stimulant treatment.

Because comorbidity with CD is a potent predictor of subsequent risk for SUDs and cigarette smoking in subjects with ADHD,[31] we repeated each analysis controlling for the effect of CD, which did not change any of the results. As expected, the effect of CD was significant for overall SUDs, drug abuse (112 subjects; HR, 3.61; 95% CI, 1.13-11.50; *P*=.03), and drug dependence (112 subjects; HR, 5.00; 95% CI, 1.41-17.50; *P*=.01).

ONSET AND DURATION

We found no effect of age at onset of stimulant therapy on the development of any SUD or smoking. Likewise, there was no effect of stimulant duration on the development of cigarette smoking (HR, 1.02; 95% CI, 0.87-

Table 2. Rates of Substance Use Disorders in Adolescents With Attention-Deficit/Hyperactivity Disorder at 5-Year Follow-up

Variable	No. (%)		Hazard Ratio (95% Confidence Interval)
	No Stimulant Therapy (n=20)	Stimulant Therapy (n=94)	
Substance use disorder	11 (55.0)	19 (20.2)	0.31 (0.14-0.68)
Alcohol			
Abuse	5 (25.0)	11 (11.7)	0.61 (0.20-1.89)
Dependence	2 (10.0)	3 (3.2)	0.29 (0.05-1.80)
Substance			
Abuse	8 (40.0)	11 (11.7)	0.30 (0.12-0.75)
Dependence	4 (20.0)	9 (9.6)	0.57 (0.16-1.96)

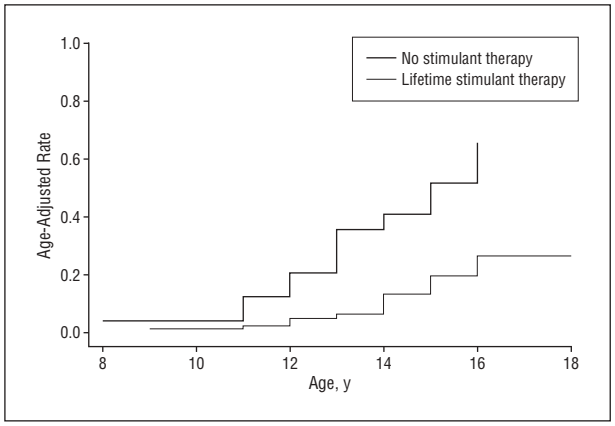

Figure 2. The effects of prior stimulant exposure on risk for subsequent cigarette smoking dependence (curves truncated at 18 years).

1.18; $\chi^2_{86}=0.04$, $P=.8$) or SUDs (HR, 1.01; 95% CI, 0.90-1.14; $\chi^2_{90}=0.06$, $P=.8$) in subjects with ADHD. We then tested whether stimulant therapy affected the duration of alcohol abuse and dependence, drug abuse and dependence, and cigarette smoking and found no effect of stimulant exposure on duration of SUDs (linear regression $t_{30}=0.81$, $P=.43$) or smoking (linear regression $t_{28}=0.36$, $P=.7$) in subjects who developed SUDs or started smoking.

COMMENT

In a longitudinal sample of adolescents with ADHD followed up for 5 years, we found strong evidence that prior treatment with stimulants was associated with a subsequent decreased risk for SUDs and cigarette smoking. We did not detect any significant association between age at onset or duration of stimulant treatment and subsequent risk of SUDs or cigarette smoking. Similarly, in those who developed SUDs, there was no relationship between stimulant treatment and the severity or duration of SUDs. Although limited by a small sample of adolescents who were unmedicated for their ADHD, our results extend to adolescents with ADHD the previously reported findings in boys with ADHD,[22-25] suggesting that prior stimulant treatment does not increase the risk for subsequent SUDs and cigarette smoking and may instead have a protective effect on the development of SUDs and the start of cigarette smoking.

The present results replicate previous findings in boys with ADHD that suggest a protective effect of stimulant treatment against subsequent alcohol and drug use disorders.[23] The present work adds to a growing body of literature showing general reductions in SUDs among stimulant-treated children with ADHD in their adolescent years.[26] Our results documenting protective effects of stimulants in adolescents with ADHD are not entirely consistent with those of Katusic et al,[24] who found that the protective effect of stimulants against SUDs was limited to boys with ADHD. The reasons for the discrepancy are probably related to the small sample size of girls studied by Katusic et al, which limited their power to detect meaningful differences.

The protective effects of stimulants against the development of SUDs are particularly noteworthy considering that a greater proportion of our adolescents with ADHD were more fully into the age range at risk for SUDs compared with boys with ADHD when they were assessed.[27] Furthermore, girls with ADHD have an almost 2-year earlier age at onset of SUDs relative to boys with ADHD (17 years vs 19 years).[12,32,33]

Investigations examining the effects of stimulant therapy on subsequent SUDs have generally shown more of a protective effect in adolescents and a neutral effect in adults,[26] leading to the notion that stimulants may delay rather than protect against subsequent SUDs. More research is needed to understand this developmental effect of stimulants (eg, persistence of treatment vs underlying biologic effect) on subsequent substance use and to further clarify their protective mechanisms.

Our results are among the first to demonstrate a clinically and statistically significant reduction in the risk and delayed onset of cigarette smoking associated with stimulant treatment in adolescents with ADHD. Our present results are consistent with epidemiological evidence from Germany[25] indicating delays in the onset of smoking and lower rates of smoking associated with stimulant treatment in subjects with ADHD. Our data are also consistent with a recent prospective study[34] that found an association between stimulant therapy and diminished risk for cigarette smoking. However, our findings are in opposition to results of an older naturalistic study by Lambert and Hartsough[21] that showed higher risk for tobacco dependence in treated subjects with ADHD; however, their stimulant-treated group had an overrepresentation of CD, a strong predictor of SUDs and cigarette smoking.[31,35] Our data may be of further importance given prior work in boys with ADHD showing that early cigarette smoking in ADHD is related to a high risk for subsequent SUDs.[36]

Although the mechanism of risk reduction for SUDs and cigarette smoking remains unclear, some recent preclinical data may shed light on this important area. For instance, Augustyniak et al[37] showed that prepubertal exposure of methylphenidate hydrochloride in an animal model of ADHD (spontaneous hypertensive rat) resulted in diminished sensitivity to the incentive proper-

ties of cocaine in adulthood without altering the responses of the mesolimbic dopamine system. Similarly, enduring effects of early exposure to methylphenidate among rat pups resulted in diminished subsequent behaviors among these animals that were synonymous with SUDs.[38] Psychosocial considerations explaining the reduced risk of SUDs associated with stimulant treatment also need to be considered. For instance, decreased risk for SUDs may be related to those families who seek out appropriate treatment for their children. Alternatively, it may be that the necessary supervision and heightened monitoring of youth receiving stimulants are associated with the reduced SUDs. Clearly, more work is necessary to understand if the risk reduction for SUDs and cigarette smoking in adolescents with ADHD treated with stimulants is related to a biologic, psychosocial, or combined mechanism of action.

These results must be considered in light of the methodological limitations. Our naturalistic study design cannot provide evidence so compelling as that produced by a randomized controlled study of stimulant treatment. Because participating subjects were referred and were largely of white race/ethnicity, we do not know if our results will generalize to children with ADHD in the general population or of other racial/ethnic backgrounds. Furthermore, because the adolescents with ADHD in our sample were mostly adolescents, they had not yet fully transitioned through the age range at risk for SUDs and cigarette smoking. The small size of our sample of untreated adolescents with ADHD also limits our statistical power. Although our study was prospective, we depended on retrospectively (ie, within the intervals between assessments) reported ages of treatment and cigarette smoking and SUD onset to establish the temporal sequence. We relied on structured interview data and not on objective measures (eg, urine toxicologic screening results) to determine dependence on cigarette smoking or SUDs and may have underestimated lifetime rates of these disorders. However, recent findings suggest that structured interview–derived substance use data may be more sensitive than objective measures in determining past SUDs.[39] We also did not examine the role of other treatment modalities and SUDs. However, previous work failed to find any relationship between psychotherapy and later SUDs outside of stimulant treatment.[23]

Despite these limitations, this study provides evidence for the first time (to our knowledge) that prior stimulant treatment does not increase the subsequent risk for and may have protective effects against the development of cigarette smoking and SUDs in adolescents with ADHD. These data add to a growing literature documenting that stimulant treatment of ADHD may diminish the risk for cigarette smoking and SUDs in adolescence. These results should allay lingering concerns among clinicians and families about future substance use problems when prescribing stimulants to a child with ADHD. Future research should focus on more salient predictors and moderators of SUDs in adolescents with ADHD, as well as on observing this group fully through the age range of SUD risk.

Accepted for Publication: February 29, 2008.
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Author Contributions: Dr Wilens had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Faraone and Biederman. *Acquisition of data:* Wilens, Schillinger, Westerberg, and Biederman. *Analysis and interpretation of data:* Wilens, Adamson, Monuteaux, Faraone, and Biederman. *Drafting of the manuscript:* Adamson, Faraone, and Biederman. *Critical revision of the manuscript for important intellectual content:* Wilens, Monuteaux, Faraone, Schillinger, Westerberg, and Biederman. *Statistical analysis:* Adamson, Monuteaux, and Faraone. *Obtained funding:* Faraone and Biederman. *Administrative, technical, and material support:* Wilens, Schillinger, Westerberg, and Biederman. *Study supervision:* Wilens, Monuteaux, and Biederman.
Financial Disclosure: Dr Wilens receives grant support from Abbott, McNeil, Eli Lilly & Co, National Institutes of Health (National Institute on Drug Abuse), Merck, and Shire; is on the speaker's bureau for Eli Lilly & Co, McNeil, Novartis, and Shire; and is a consultant for Abbott, McNeil, Eli Lilly & Co, National Institutes of Health (National Institute on Drug Abuse), Novartis, Merck, and Shire. Dr Faraone receives research support from, is on the speaker's bureau for, and has had an advisory or consulting relationship with McNeil and Shire; he also has had an advisory or consulting relationship with Novartis and Eli Lilly & Co. Dr Biederman receives research support from Alza, AstraZeneca, Bristol Myers Squibb, Eli Lilly & Co, Janssen Pharmaceuticals Inc, McNeil, Merck, Organon, Otsuka, Shire, National Institute of Mental Health, and Eunice Kennedy Shriver National Institute of Child Health and Human Development; is a consultant or advisory board member for Janssen, McNeil, Novartis, and Shire; and is on the speaker's bureau for Janssen, McNeil, Novartis, Shire, and UCB Pharma, Inc. Dr Biederman in previous years received research support, consultation fees, or speaker's fees for and from the following additional sources: Abbott, AstraZeneca, Celltech, Cephalon, Eli Lilly & Co, Esai, Forest, Glaxo, Gliatech, National Alliance for Research on Schizophrenia and Depression (NARSAD), National Institute on Drug Abuse, New River, Novartis, Noven, Neurosearch, Pfizer, Pharmacia, The Prechter Foundation, The Stanley Foundation, and Wyeth.
Funding/Support: This study was supported by grants DA R01 DA14419 and K24 DA016264 from the National Institutes of Health (Dr Wilens) and by the Lilly Foundation.

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