Pharmacotherapy of Attention-deficit/Hyperactivity Disorder Reduces Risk for Substance Use Disorder

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ABSTRACT. *Objective.* **To assess the risk for substance use disorders (SUD) associated with previous exposure to psychotropic medication in a longitudinal study of boys with attention-deficit/hyperactivity disorder (ADHD).**

Methods. **The cumulative incidence of SUD throughout adolescence was compared in 56 medicated subjects with ADHD, 19 nonmedicated subjects with ADHD, and 137 non-ADHD control subjects.**

Results. **Unmedicated subjects with ADHD were at a significantly increased risk for any SUD at follow-up compared with non-ADHD control subjects (adjusted OR: 6.3 [1.8–21.6]). Subjects with ADHD medicated at baseline were at a significantly reduced risk for a SUD at follow-up relative to untreated subjects with ADHD (adjusted OR: 0.15 [0.04–0.6]). For each SUD subtype studied, the direction of the effect of exposure to pharmacotherapy was similar to that seen for the any SUD category.**

Conclusions. **Consistent with findings in untreated ADHD in adults, untreated ADHD was a significant risk factor for SUD in adolescence. In contrast, pharmacotherapy was associated with an 85% reduction in risk for SUD in ADHD youth.** *Pediatrics* **1999;104(2). URL: http://www.pediatrics.org/cgi/content/full/104/2/e20;** ***ADHD, pharmacotherapy substance use disorders.***

ABBREVIATIONS. ADHD, attention-deficit/hyperactivity disorder; SUD, substance use disorder; A/D, abuse or dependence; CD, conduct disorder; SES, socioeconomic status.

As recently highlighted by Goldman et al,[1] the association between pharmacologic intervention in youth with attention-deficit/hyperactivity disorder (ADHD) and subsequent substance use disorder (SUD) remains a source of clinical and public health concern. Goldman et al[1] questioned whether exposure to stimulant medication in youth with ADHD could lead to prescription drug abuse or serve as a gateway to the abuse of other drugs. The focus on the stimulants as a potential risk for SUD in ADHD youth is understandable, because stimulants are the drugs prescribed most commonly for this disorder. Given their well documented abuse potential, their use by many youth with ADHD has been of concern to both parents and clinicians.

Whether pharmacotherapy leads to SUD in ADHD children has serious clinical implications. If such a link were documented, clinicians, patients, and families would need to weigh carefully the risk of SUD against the therapeutic benefit of medication. On the other hand, if pharmacotherapy does not lead to SUD, clinicians, patients, and families could approach pharmacologic treatment issues without ungrounded fears. Decreased apprehension toward appropriate pharmacotherapy in turn may lead to earlier intervention for affected youth with its attendant benefits of avoiding the academic, psychiatric, and interpersonal complications of ADHD.

Unfortunately, as reviews of the literature show, no controlled studies of subjects with ADHD have evaluated adequately the putative link between SUD and pharmacotherapy,[1,2] and there are only two published case reports of stimulant abuse by adolescents with ADHD receiving these compounds therapeutically.[3,4] Despite this dearth of data, the idea that pharmacotherapy increases the risk for SUD persists in diagnostic and treatment conferences[5,6] and in the popular press.[7,8]

The purpose of this study was to assess the risk for SUD associated with previous exposure to psychotropic medication in our longitudinal follow-up of psychiatrically and pediatrically referred boys with ADHD attending to co-morbidity with conduct disorder (CD), a well documented risk factor for SUD.[9–13] We examined three competing hypotheses. The first is the null hypothesis that psychotropics would have no effect on the development of SUD in children with ADHD. The alternative hypothesis is that exposure to pharmacotherapy will be associated with higher risk for SUD in general and stimulant abuse in particular. Because SUD in children and adolescents with ADHD may arise from an attempt at self-medication, the third competing hypothesis posited that pharmacologic management would diminish the risk for SUD by controlling the core features of ADHD and promoting adaptive behavior and academic success.

METHODS

Subjects

We analyzed data from a longitudinal family genetic study of ADHD that we have presented in previous publications.[14] The original sample included a total of 260 families chosen from psychiatric and nonpsychiatric settings based on the ADHD status of

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an index child (140 subjects with ADHD and 120 normal control subjects). All index children were white, non-Hispanic males 6 and 17 years of age at first assessment. We obtained informed consent for all subjects before their enrollment in the protocol.

At the 4-year follow-up, 91% of the 140 ADHD families and 91% of the 120 control families seen at baseline were reevaluated successfully and provided 280 and 226 subjects, respectively, for analysis. Subjects meeting criteria for ADHD were asked what forms of treatment, if any, they had received. Of the 280 children of families ascertained via an ADHD proband, 56% ($n = 156$) met criteria for ADHD, of which 75% ($n = 117$) reported previous pharmacotherapy. A small proportion (3% [$n = 6$]) of the 226 children of families ascertained via a non-ADHD control child met criteria for ADHD, with none receiving pharmacotherapy. From the available subjects, three groups were defined 1) medicated subjects with ADHD ($n = 117$); 2) nonmedicated subjects with ADHD ($n = 45$); and 3) non-ADHD subjects ($n = 344$).

However, because the groups with ADHD were composed of predominantly male subjects (97% medicated male subjects with ADHD [$n = 114$]; 84% nonmedicated of nonmedicated male subjects with ADHD [$n = 38$]) and because the non-ADHD group had significantly fewer males (64% [$n = 221$]; $\chi^2_{(2)} = 35.1$; $P < .001$), females were excluded from this analysis. Similarly, because the medicated subjects with ADHD were significantly younger than both the nonmedicated subjects with ADHD and the non-ADHD control subjects (15.7 ± 3.6 and 16.8 ± 5.5 years old), only subjects ≥15 years were included in this analysis. Thus, we analyzed: 1) 56 medicated subjects with ADHD; 2) 19 nonmedicated subjects with ADHD; and 3) 137 non-ADHD subjects. Although these exclusion criteria reduced our sample size considerably, restricting our analysis to males older than 15 years of age was the most complete method of controlling for potential confounding by these variables.

Measures

All diagnostic assessments used DSM-III-R-based structured interviews. Psychiatric assessments of children relied on the Schedule of Affective Disorder and Schizophrenia for School-Age Children Epidemiologic Version.[15] Diagnoses were based on independent interviews with the mothers and direct interviews with children, except for those younger than 12 years of age who were not interviewed directly. At baseline and the 1-year follow-up, the structured interviews assessed lifetime history of psychopathology; at year 4, these assessments reflected the interval since the previous assessment. The assessment personnel were blind to family status (ADHD or control) and ascertainment site (psychiatric or pediatric). All follow-up assessments were made blind to previous assessments of the same subjects and their family members.

The interviewers had undergraduate degrees in psychology and were trained to high levels of interrater reliability. We computed κ coefficients of agreement by having experienced, board-certified child and adult psychiatrists diagnose subjects from audiotaped interviews conducted by the assessment staff. Based on 173 interviews, the median κ statistic was 0.86. In addition, a committee of board-certified child and adult psychiatrists chaired by the senior author resolved all diagnostic uncertainties. The committee members were blind to each subject's ascertainment group, ascertainment site, data collected from other family members, and all other information.

Diagnoses were considered positive if, based on the interview results, DSM-III-R criteria were met unequivocally to a clinically meaningful degree. From the structured diagnostic interviews, diagnoses were made for alcohol A/D. DSM-III-R criteria for substance dependence requires at least three of the following symptoms: substance taken in increasingly larger amounts; unsuccessful attempts at reducing substance use; expending a great deal of time acquiring/using/recovering from substance; frequent intoxication; reduction in frequency of other activities; continued use despite the functional complications of substance use; increased tolerance to the effects of substance; symptoms of withdrawal; or use of substance to avoid symptoms of withdrawal. Abuse requires either continued use despite the functional complications associated with substance use or recurrent use of substances in physically hazardous situations. Diagnoses are analyzed here as any SUD, alcohol A/D, marijuana A/D, hallucinogen A/D, stimulant A/D, and cocaine A/D. Tobacco A/D was collected only at our follow-up assessment. Based on previous reports,[9–13] CD was considered a known risk factor for SUD and is also analyzed here.

Statistical Analysis

Ordinary least squares regression analyzed continuous dependent variables, and logistic regression analyzed binary responses. Because siblings sampled from one family are not independent of each other, standard tests of statistical significance will be incorrect. To account for this bias, we adjusted our analyses by using Huber's[16] formula as implemented in STATA, version 5.0[17] to produce robust statistical tests for both ordinary least squares and logistic regression models. Estimates of variance according to Huber's[16] correction are empiric and do not place any requirement on the distribution of the error terms. This robust estimate of variance enters family cluster scores (not individual scores) into the formula for the estimate of variance resulting in asymptotically unbiased estimates. Therefore, our analyses adjust for the correlation among subjects of the same family and produce unbiased P values. All statistical tests were two-tailed and used the .05 level of statistical significance.

RESULTS

We restricted our analysis to those male subject older than 15 years of age (56 medicated subject with ADHD, 19 nonmedicated subject with ADHD, and 137 non-ADHD subjects). On average, the children treated at baseline were medicated for 4.4 ± 2.7 years of treatment, and none of the nonmedicated subjects with ADHD were treated during our follow-up period. We sampled referred subjects with ADHD from both psychiatric and nonpsychiatric treatment facilities and control subjects from outpatient clinics at the same institution as the source of subjects with ADHD. There was a significant association between source of ascertainment and study group status; 66% of the medicated ADHD group were from the psychiatric clinic, whereas only 16% of the unmedicated ADHD group came from the psychiatric clinic and 30% of the control subjects came from the outpatient pediatric clinic at the same institution as the psychiatric clinic ($\chi^2_{(2)} = 26.4$; $P < .001$). However, the source of ascertainment was not associated with CD ($\chi^2_{(1)} = 0.5$; $P = .5$ and $\chi^2_{(1)} = 0.3$; $P < .6$) in the ADHD groups or with SUD in the control group ($\chi^2_{(1)} = 0.5$; $P < .5$) and, therefore, cannot be a confounder in these data.

There were, however, statistically significant differences in the subjects' age in years (17.2 ± 2.1, 18.5 ± 2.4, and 19.2 ± 4.3, respectively; $F_{(2,146)} = 6.4$; $P = .002$), in socioeconomic status (SES)[18] (2.0 ± 1.0, 1.9 ± 1.1, and 1.6 ± 0.8, respectively; $F_{(2,146)} = 5.2$; $P = .006$), lifetime risk of CD at baseline (27% [$n = 15$], 47% [$n = 9$], and 4% [$n = 6$], respectively, $\chi^2_{(2)} = 26.9$; $P < .001$) and in a lifetime history of SUD in the subjects' parents (59% [$n = 33$], 84% [$n = 16$], and 47% [$n = 64$], respectively; $\chi^2_{(2)} = 10.4$; $P < .006$). Thus, our analyses were corrected for these confounders using multiple logistic regression.

As shown in Table 1, statistically significant differences were identified among the medicated ADHD, nonmedicated ADHD, and non-ADHD groups in rates of SUD at baseline and follow-up and in tobacco A/D at follow-up. For each of the study groups, alcohol and marijuana were the substance abused most frequently, followed distantly by hallucinogens, stimulants, and cocaine. Because at follow-

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TABLE 1. Prevalence of SUD Subtypes

	Medicated ADHD $N = 56$	Non-medicated ADHD $N = 19$	Non-ADHD $N = 137$	$\chi^2_{(2)}$	P Value*
	N (%)	N (%)	N (%)		
Baseline SUD†	0 (0)	7 (37)	18 (13)	19.2‡	<.001
Alcohol A/D	0 (0)	7 (37)	15 (11)	20.7‡	<.001
Marijuana A/D	0 (0)	4 (21)	8 (6)	11.7‡	.001
Hallucinogen A/D	0 (0)	4 (21)	4 (3)	17.9‡	<.001
Stimulant A/D	0 (0)	1 (5)	2 (1)	12.8‡	.2
Cocaine A/D	0 (0)	0 (0)	2 (1)	1.1‡	.6
Follow-up SUD†	14 (25)	14 (75)	25 (18)	19.5	<.001
Alcohol A/D	12 (21)	13 (68)	21 (15)	20.5	<.001
Marijuana A/D	9 (16)	8 (42)	11 (8)	13.6	.001
Hallucinogen A/D	4 (7)	3 (16)	5 (4)	4.7	.09
Stimulant A/D	1 (2)	1 (5)	0 (0)	5.8‡	.06
Cocaine A/D	1 (2)	3 (16)	2 (1)	8.2	.02
Follow-up tobacco A/D	19 (34)	6 (32)	22 (16)	8.8	.012

* Logistic regression model using robust estimates of variance to account for familial associations between siblings.
† SUD subtypes are not mutually exclusive.
‡ Uncorrected P value reported because regression model would not converge due to cell with zero observations.

up, the rates of stimulants and cocaine A/D were very low, we combined these subtypes into a single category (stimulant/cocaine A/D) for pairwise comparisons.

As noted above, we used multiple logistic regression to adjust for potential confounding variables in testing pairwise comparisons. These models estimated the relative risk (OR) for each type of SUD associated with ADHD and with being exposed to pharmacotherapy. The cumulative incidence of SUD during follow-up was predicted from a model containing terms for ADHD, medication status, age at follow-up, SES, diagnosis of CD at baseline, diagnosis of SUD at baseline, and history of SUD in subjects' parents. By using medication status at baseline, a temporal order is established between exposure to medication and our measure of SUD 4 years later. Although this does not necessarily imply causal relationships, it allows us to extend beyond inferences of cross-sectional association and to make predictive conclusions.

The adjusted results from the multiple logistic regression models are presented in Table 2. These analyses showed that unmedicated subjects with ADHD were at a significantly increased risk for any SUD at follow-up compared with non-ADHD control subjects (Table 2). Using ORs <1 (the odds for outcome in exposed subjects being lower than the odds in unexposed subjects) as indicative of a protective association, subjects with ADHD medicated at baseline were at a significantly reduced risk for an SUD outcome at follow-up compared with nonmedicated subjects with ADHD. As expected, CD and parental SUD were also associated with a significant increased risk for an SUD (Table 2). However, there was no statistical interaction between CD and ADHD or medication status ($\chi^2_{(2)} = 3.7$; $P = .15$) indicating that the effect of medication status in subjects with ADHD on subsequent SUD was not modified by the presence of CD.

Although stratification of the sample by specific categories of A/D reduced power, the direction of the effect of exposure to pharmacotherapy for each of the SUD subtypes was similar to that seen for the any SUD category (Table 2). In each case, subjects with ADHD medicated at baseline were at a reduced risk relative to nonmedicated subjects with ADHD, and CD was associated consistently with a significantly increased risk for each type of SUD other than for stimulant/cocaine A/D. For tobacco A/D, the medicated group did not have a significantly different risk than did the unmedicated ADHD group, and the

TABLE 2. The Adjusted Effect of ADHD and Pharmacotherapy on SUD Incidence

	Unmedicated ADHD Versus Controls	Medicated ADHD Versus Unmedicated ADHD	Baseline CD(+) Versus Baseline CD (−)
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Any SUD at follow-up	6.3 (1.8–21.4)	0.15* (0.04–0.6)	5.5 (2.0–15.3)
Alcohol A/D†	5.8 (1.7–19.3)	0.16 (0.05–0.57)	4.9 (1.8–13.5)
Marijuana A/D	3.1 (0.8–12.5)	0.42 (0.11–1.7)	5.4 (1.7–16.9)
Hallucinogen A/D	1.0 (0.1–9.3)	0.76 (0.12–5.0)	9.0 (1.7–46.9)
Cocaine/stimulant A/D	7.5 (0.3–163.4)	0.2 (0.02–2.1)	3.0 (0.2–48.3)
Tobacco A/D	0.85 (0.15–4.8)	2.4 (0.5–12.3)	4.4 (1.5–12.7)

* ORs <1 indicate a protective effect, i.e., that the odds of SUD were smaller in the medicated than in the unmedicated ADHD groups.
† A/D, abuse or dependence.
From separate logistic regression models predicting each SUD subtype as the dependent variable and the following baseline characteristics as independent variables: ADHD, Medication for ADHD, Conduct disorder, age, SES, any SUD at baseline, and parental history of SUD. For simplicity only the results from the terms of most interest (ADHD, Medication for ADHD, & CD) are presented.
Underlining indicates P value <.01 according to Wald's χ^2 using robust estimates of variance to account for familial associations between siblings.

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unmedicated subjects with ADHD were not at significantly increased risk relative to the non-ADHD control subjects.

DISCUSSION

In a large, well characterized sample of pediatrically and psychiatrically referred ADHD and non-ADHD youth, pharmacotherapy for ADHD did not predict an increased risk for SUD. We found instead that subjects with ADHD who did not receive pharmacologic treatment were at a significantly increased risk for SUD suggesting that pharmacotherapy may protect children with ADHD from this risk. Although we cannot address potential differences between stimulant and nonstimulant drugs, it is reasonable to assume that the majority of our subjects indeed were exposed to stimulants, because stimulants are the mainstay of the treatment of this disorder.[1,19,20]

Our results are consistent with a small body of literature examining the long-term effects of stimulant therapy on subsequent SUD onset in adolescents with ADHD. In a review of longitudinal studies of treated ADHD children, Hechtman et al[2] found no evidence that stimulant exposure predicted later SUD and weak evidence that stimulant therapy prevented SUD.[21–23] Since this review,[2] there have been no systematic analyses addressing the risks or benefits of stimulant therapy in regards to SUD onset among youth with ADHD. By providing statistical evidence that pharmacotherapy for ADHD may protect children with ADHD from SUD onset, these results augment the equivocal findings of the extant literature.

Our results also indicate that medication status is an essential modifier of the ADHD–SUD association. This finding extends our previous report that the risk for SUD was indistinguishable in ADHD and non-ADHD youth.[24] However, in that analysis we did not account for medication status.[24] As we report now, stratification by medication reveals that untreated ADHD is a significant risk factor for SUD even after correcting for comorbid CD.

The increased risk for SUD in untreated youth with ADHD is consistent with our findings of significant ADHD-SUD associations in adults with ADHD.[25,26] Because these adults had been primarily undiagnosed and untreated as children, they provide retrospective corroboration that ADHD, in the absence of pharmacotherapy, may increase the risk for SUD in subjects with ADHD.[27] Although these findings require prospective confirmation, they suggest that adequate pharmacotherapy for ADHD in childhood may have a significant protective effect for the subsequent development of SUD in adulthood.

Our findings should be viewed in consideration of additional methodologic limitations. The first pertains to the lack of an ideal control group for assessing the independent effect of pharmacotherapy on SUD onset. We did not present the comparison between medicated subjects with ADHD and non-ADHD control subjects, because the control subjects did not have ADHD, and therefore, did not have a comparable baseline risk for SUD. In such a comparison, the protective effect of pharmacotherapy would be commingled with the deleterious effects of ADHD, and the result would be biased with respect to both the effects of ADHD and its pharmacotherapy. Thus, comparisons must be limited to those groups differing in only one potential risk factor (ie, within ADHD subjects, medication vs no medication or within nonmedicated subjects, ADHD vs non-ADHD).

There also were significant differences among medicated ADHD, unmedicated ADHD, and non-ADHD control groups in age, SES, risk of CD, and gender. We limited our analysis to males >15 years of age and corrected for other confounders with multiple logistic regression. Although logistic regression deals with the potential confounding attributable to the variables measured, it does not necessarily correct for the other unmeasured confounders that may be associated with those modeled. However, these unmeasured confounders are not likely to account completely for our findings, because they would need to be more prevalent and more strongly associated with SUD than are SES, CD, and parental history of SUD.

Despite having a large sample of ADHD and non-ADHD children, we lacked adequate statistical power to evaluate fully the effect on different SUD subtypes, especially for stimulant/cocaine use disorder and tobacco A/D. The result of this reduction in power was that our estimates of relative risk were not very precise, and null findings cannot be considered conclusive. Nevertheless, despite the low power to test our hypotheses, it is reassuring to know that only a very small proportion (2%) of many exposed subjects ($n = 56$) suffered stimulant or cocaine use disorders.

Finally, this study cannot make definitive conclusions regarding the risks associated with pharmacotherapy of ADHD beyond the age of our current sample, in females, or in nonwhite subjects. Only follow-up of this and of other samples of children treated for ADHD with stimulants and other medications will provide such answers. Despite these considerations, our results suggest that rather than inducing SUD in youth with ADHD, pharmacotherapy for ADHD may protect children with ADHD from this serious and deleterious outcome.

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