Childhood Stimulant Treatment and Risk for Later Substance Abuse

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Conflicting studies of the relationship between therapeutic use of psychostimulant medication and substance abuse have long been a subject of concern among clinicians and researchers. One controlled longitudinal study examined this relationship in 147 patients who were diagnosed with hyperactivity as young children and were surveyed with regard to their substance use both as adolescents and as adults. This study found that stimulant therapy for attention-deficit/hyperactivity disorder in childhood is not associated with increased risk of adolescent experimentation with substance use, frequency of such use, or the risk of developing psychoactive substance use disorders by young adulthood. Moreover, stimulant therapy in high school may well have provided a protective effect against hallucinogen abuse by adulthood. A possible explanation for contradictory findings previously published was suggested by the existence of a number of potentially confounding variables, particularly conduct disorders, for which prior studies have failed to control.

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A controversy about the use of stimulants to treat attention-deficit/hyperactivity disorder (ADHD) has been described by several researchers,[1–4] and is related in part to fears of a purported risk that such treatment might lead to later psychoactive substance use disorders. Although the most sensational charges concerning such a risk have been made in the popular press, targeted to parents of children with ADHD,[5,6] the topic also has been addressed in the professional literature.[4,7] Many observers have found no conclusive evidence thus far to support the claims made by critics that treatment for ADHD is harmful; moreover, there is little evidence that the availability of stimulants has had an appreciable effect on rates of abuse.[4] Observers also have noted, however, that existing studies have yielded conflicting conclusions regarding the question of whether the therapeutic use of psychostimulants increases the risk for drug abuse.[4,8] Researchers view these conflicting and disparate conclusions as having created a need for prospective, controlled studies carried into adulthood of the risks and benefits of stimulant therapy.[4,7]

Such a study has been underway for 13 years.[9,10] In this longitudinal study of individuals diagnosed with hyperactivity as young children, a significant cohort of these children and their parents were questioned about substance use at age 15 years and again at young adult follow-up (mean age = 21 years; range, 19–25 years).[9,10] This important undertaking has sought to fill an acknowledged gap in existing evidence concerning the actual risks of developing psychoactive substance use disorders among stimulant-treated children with ADHD, a gap created by the fact that only a handful of similar studies have so far been published, with conflicting results. Among them is a study that reported a relationship between stimulant therapy in childhood and increased risk for psychoactive substance use disorders,[11] whose conclusions are at odds with those of other studies. Accordingly, one of the goals of the 13-year longitudinal follow-up study[10] has been to attempt to replicate the disparate findings of the Lambert and Hartsough study.[11]

Of those studies that have addressed the question of the relationship between stimulant treatment for ADHD and psychoactive substance use disorders to date, the most rigorously controlled and largest of these are summarized in Table 1.

DESCRIPTION OF FOLLOW-UP STUDY

The longitudinal study followed 158 hyperactive children for 13 years. A matched normal community control group of 81 children, none of whom had ever been diagnosed with hyperactivity or treated with stimulant medication, also were followed contemporaneously with the

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Table 1. Studies Examining Relationship Between Stimulant Treatment for Attention-Deficit/Hyperactivity Disorder (ADHD) and Risk of Psychoactive Substance Use Disorders (SUD)

Study Author(s)	Year of Publication	Subjects (N)	Chief Finding(s)	Limitation(s)
Burke et al[12]	2001	177	Youths with ADHD more likely to use tobacco, marijuana, alcohol, and other drugs, but this association was not significant once comorbid conduct disorders were statistically controlled for in analysis; however, adolescent inattention was independently associated with tobacco use after controlling for conduct disorder	No control for the effects of having been exposed to the use of tobacco by others, particularly within the same household, while growing up
Chilcoat and Breslau[13]	1999	717	ADHD associated with increased frequency of drug use by adolescence, especially in association with high level of conduct disorder	Young age (11 y) of subjects at follow-up may have limited their exposure to substances
Loney[14]	1998	295	No relationship between stimulant therapy and extent of drug use for most drugs; protective effect noted for tobacco, stimulants, glue-sniffing, opiates, and alcoholism	Only boys included
Biederman et al[15]	1999	212	Unmedicated adolescents at increased risk for SUD at 4-year follow-up; medicated adolescents at significantly reduced risk	Study only addressed risk for SUD associated with psychopharmacologic treatment in general rather than stimulants in specific; did not evaluate risk for SUD by adulthood
Paternite et al[16]	1999	219	No association of stimulant duration or dosage with alcoholism or SUD at young adulthood	Analyses not reported for relationship of stimulant treatment variables to specific forms of SUD other than alcohol
Lambert and Hartsough[11]	1998	492	Stimulant treatment in childhood for > 1 year correlated with increased risk for SUD, especially cocaine and tobacco	Study failed to control for impact of severity of ADHD and symptoms of conduct disorder
Milberger et al[17]	1997	260	No relationship between treatment (counseling and medication) and adolescent tobacco use, although adolescents still in treatment for ADHD less likely to smoke	No distinction made between stimulant therapy and counseling

hyperactive children. The original subjects were first evaluated from 1979 to 1980 at ages 4 through 12 years. The first follow-up evaluation took place in 1987 and 1988,[9] when the 123 hyperactive subjects then available were aged 12 through 20 years (mean age = 15 years), and a subsequent follow-up evaluation was conducted between 1992 and 1996, when 147 available hyperactive subjects were aged 19 through 25 years (mean age = 21 years). Most of the participants in both groups were located for that 13-year follow-up: 147 (93%) of 158 hyperactive subjects were located, as were 73 (90%) of 81 controls.[10] Because of the nature of the inquiry, the data described here were collected from the initially hyperactive cohort of subjects only.

All subjects were referred initially to a clinic specializing in the treatment of hyperactive children. Most of the subjects were male (91%) and white (94%). At the adolescent follow-up (mean age = 15 years), participants were interviewed about their substance use, if any, and their parents were interviewed about the subjects' histories of stimulant therapy, substance use, antisocial behavior, and disruptive behavior disorders. At the young adult follow-up evaluation (mean age = 21 years), subjects were interviewed about self-reported substance use, psychiatric disorders, stimulant therapy received during high school years, current adaptive functioning, and history of antisocial behaviors.[10]

Stimulant Therapy

Table 2 summarizes the data collected from participants and their parents concerning subjects' histories of stimulant therapy.

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Table 2. Stimulant Medication Use Data From Follow-Up of 158 Hyperactive Children[a]

Follow-Up Data	N	Data Source	Subjects Treated With Stimulants, N (%)	Duration of Treatment mean ± SD, mo	Medications Used, N (%)
Adolescent (mean age 15 y)	123	Parental interview	98 (74)	40.2 ± 43.3 (range, 0–156)	Methylphenidate: 96 (98), *d*-amphetamine: 4 (4), pemoline: 24 (24), multiple stimulant medications: 24 (24)
Young adult (mean age 21 y)	147	Self-report	32 (22)[b]	26.6 ± 20	Not specified

[a]Data from Barkley et al.[10]
[b]Seven subjects (5%) currently taking stimulant medication.

Psychoactive Substance Use Disorders

The measures used to identify participants with histories of psychoactive substance use disorders included the following[10]:

- Adolescent self-reports of having tried 10 substances by the time of follow-up (cigarettes, alcohol, marijuana, hashish, cocaine, heroin, hallucinogens, nonprescribed stimulants, sedatives, tranquilizers).
- Adult self-reports of frequency of lifetime use of 10 substances (marijuana, cocaine, acid/LSD/mescaline, stimulants, narcotics, sedatives/barbiturates, other), average weekly alcohol use, and frequency of alcohol and illicit substance use in past 3 months.
- Structured Clinical Interview for DSM-III-R, Nonpatient Edition, psychoactive substance use disorders at young adult follow-up.

Other Measures Used

To assess potential mediators of substance use by the subjects, several ratings of conduct disorder and ADHD were used at all stages of the study[10] to measure the presence and severity of ADHD symptoms and conduct problems. Both parent ratings and self-reports were used. The following measures were included in the study[10]:

- Severity of childhood ADHD symptoms as defined using both the Conners Rating Scale Hyperactivity Index and Werry-Weiss-Peters Activity Rating Scale.
- Severity of childhood conduct problems as identified with the Conners Conduct Problems factor score.
- Severity of adolescent ADHD symptoms as indicated by number of parent-reported DSM-III-R symptoms.
- Severity of adolescent conduct disorder as rated utilizing number of parent-reported DSM-III-R symptoms.
- Severity of current adult ADHD symptoms as based on the number of parent-reported DSM-IV symptoms.
- Severity of lifetime conduct disorder as based on the number of self-reported DSM-III-R symptoms.

RESULTS

Data from the study[10] were analyzed in several ways.

Analysis of Adolescent Self-Reports of Ever Having Tried Drugs

The first set of analyses looked at comparisons of treated and untreated subjects with reference to their adolescent reports of ever having tried 10 illicit substances (cigarettes, alcohol, marijuana, hashish, cocaine, heroin, hallucinogens, nonprescribed stimulants, sedatives, tranquilizers). None of the results of these analyses were significant, as follows:

- A comparison of the 98 subjects treated with stimulants and the 21 subjects not so treated with regard to adolescent reports of ever having tried illicit substances produced no significant results.
- No difference was found between treated and untreated adolescents with regard to the use of illicit stimulants, including cocaine—6% of treated subjects had tried illicit stimulants versus 10% of untreated subjects, which was not significant.
- To see whether stimulant therapy might exert a dose-response effect on future substance use, the group of 98 treated subjects was subdivided into those whose treatment had lasted a year or more (N = 55) and those whose treatment had lasted less than a year (N = 43). This analysis replicated a similar distinction made among subjects by Lambert and Hartsough[11] in their study. There was no increased risk for substance use by adolescence in subjects who had been treated with stimulants for more than 1 year compared with those treated for less than 1 year.

Analysis of Adult Self-Reports of Ever Having Tried Drugs

In this set of analyses, treated subjects were compared with untreated subjects with respect to their young adult

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self-reports of drug use using both categorical and frequency measures. Findings were as follows:

- No statistically significant correlations were found between the duration of stimulant treatment and 10 frequency measures of drug use.
- When treated and untreated subjects were compared on frequency measures of drug use (log-transformed), no significant differences were found; cocaine use was marginal ($p = .06$), but when this finding was reanalyzed with potential mediators being the severity of childhood, adolescent, and adult ADHD and conduct disorder, the results were nonsignificant ($p = .16$).
- When treated and untreated subjects were compared on categorical measures—e.g., "Have you ever tried this drug?"—only cocaine use was significant: 26% of treated subjects had tried cocaine as opposed to 5% of untreated subjects. Total illicit stimulant use (cocaine plus other stimulants) was not significant.
- When the data comparing categorical cocaine use were reanalyzed to control for childhood, adolescent, and adult ADHD and conduct disorder symptoms, however, the above finding was not significant. Lifetime conduct disorder symptoms were significantly associated with cocaine use ($\beta = .819$, OR = 2.27, $p < .001$).
- Treated and untreated subjects were compared with regard to the presence of DSM-III-R psychoactive substance use disorder; no significant difference was found.
- When treated subjects were differentiated into subgroups of those treated with stimulant medication > 1 year ($N = 66$) and those treated < 1 year ($N = 53$), and the subgroups compared on all frequency and categorical measures, including DSM-III-R psychoactive substance use disorder, significant differences were found on 2 measures:
- Those subjects treated < 1 year were more likely to have cocaine abuse (6% vs. 0%) or to have hallucinogen abuse (9% vs. 2%, $p = .05$); this finding supports other research that has found that stimulant treatment for ADHD has a protective effect against the development of psychoactive substance use disorders.[8,15]
- When these findings were reanalyzed after controlling for childhood and adult ADHD and conduct disorder symptoms, the difference for hallucinogen abuse remained significant.

Analysis of Relationship of Continued Stimulant Therapy Through High School and Substance Use

The frequency of substance use and categorical use of the 10 identified substances was correlated with the duration of stimulant treatment for ADHD and was compared between subjects who had been treated with stimulants through the high school years and those who had not. Findings were as follows:

- When the frequency of use of each of the 10 substances was correlated with the duration of high school stimulant therapy, no results were significant.
- When subjects who had been treated in high school ($N = 32$) were compared with untreated subjects ($N = 115$), only cocaine use was higher in treated subjects ($p = .043$).
- After controlling for severity of childhood, adolescent, and adult ADHD and conduct disorder symptoms, that finding was no longer significant—conduct disorder symptoms again mediated the relationship. The same result occurred when cocaine use was defined categorically ("Have you ever used cocaine?").
- Stimulant therapy through high school was not significantly associated with any DSM substance use disorder.

CONCLUSIONS

The data accumulated in the follow-up study[10] indicate that stimulant therapy for ADHD in childhood is not associated with increased risk of adolescent experimentation with substance use, frequency of such use, or the risk of developing psychoactive substance use disorders by young adulthood. Early in the analyses, treatment for ADHD with stimulants did appear to be associated with an increased risk of ever trying cocaine, though not of an increased frequency of its use. However, when the severity of symptoms of childhood, adolescent, and adult ADHD and conduct disorder among the subjects was controlled for, the relationship between stimulant medication therapy and substance use was no longer significant. Among those mediators, lifetime conduct disorder severity was most strongly associated with ever having used cocaine or the frequency of use.

The duration of stimulant therapy for ADHD was not associated with a risk for any form of substance use in adolescence or adulthood. To the contrary, the analyses suggest that stimulant therapy in high school may well have provided a protective effect against hallucinogen abuse disorder by adulthood. These results run counter to those published by Lambert and Hartsough,[11] who identified a possible association between stimulant therapy in childhood and cocaine use and dependence in adulthood. The follow-up study[10] provides a possible explanation for the marked disparity between the Lambert and Hartsough[11] study and others on the topic by identifying a number of potentially confounding variables besides

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stimulant therapy that could well contribute to the higher risk that Lambert and Hartsough found for psychoactive substance use disorders in ADHD individuals.

It is our belief that the failure to control for adolescent or adult ADHD and conduct disorder symptoms provided Lambert and Hartsough[11] with potentially confounding variables in their comparison of children who had been treated with stimulants and those who had not. Study results[10] agree with those of other studies of this issue in disavowing any substantial link between stimulant therapy for ADHD and risk for subsequent psychoactive substance use disorders.

The 13-year longitudinal study[10] identified a "protective effect" of stimulant therapy for ADHD against the risk of developing only hallucinogen abuse. It is possible that the failure to find greater evidence of the protective effect among subjects treated with stimulants described by other researchers[8,15] resulted from the high percentage of comorbid conduct disorder present in the study population (44%–60% at the adolescent follow-up).[9]

Drug names: dextroamphetamine (Adderall), methylphenidate (Ritalin, Concerta, and others), pemoline (Cylert 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.

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