Pharmacotherapy for Attention-Deficit/Hyperactivity Disorder (ADHD) Decreases the Risk for Substance Abuse: Findings From a Longitudinal Follow-Up of Youths With and Without ADHD

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Findings from a previously published longitudinal follow-up of adolescents with and without attention-deficit/hyperactivity disorder (ADHD) were reanalyzed to determine the extent to which pharmacotherapy for ADHD is associated with substance use disorders, including abuse and dependence. Using naturalistic data from 140 people with ADHD and 120 controls, researchers returned to previously accumulated data to determine whether exposure to stimulant therapy had increased rates of substance use disorder among ADHD patients. Findings included confirmation that, in fact, stimulant therapy protected medicated ADHD patients against substance use disorder, which occurred at rates that were 3 to 4 times greater among people with untreated ADHD.

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Attention-deficit/hyperactivity disorder (ADHD) is a common neuropsychiatric disorder associated with impaired academic performance and emotional distress for both child and parent that typically becomes apparent during the early school years. The etiology of the disorder, which affects an estimated 6% to 9% of school-aged children, is unknown.[1] Although for many years it was assumed that the disorder remitted during adolescence, it has been firmly established that many patients can expect to experience the disorder well into adulthood. Treatment of ADHD generally involves pharmacotherapy with stimulants, although behavior therapy and parent training are often used as well. ADHD is associated with a number of comorbid psychiatric disorders, including both conduct disorders and substance abuse.

Despite the well-documented fact that ADHD, in general, and the role of stimulants to treat it, in particular, have been studied almost constantly since 1937 (by 1996, 161 randomized controlled trials had been published[2]), controversy has surrounded both the disorder and the class of drugs proven to treat it effectively.[3,4] As a general rule, the controversial aspects of ADHD tend to fall into 3 broad categories: the belief that chemical treatment of behavioral symptoms is inherently political rather than truly therapeutic[5,6]; the conviction that the use of habit-forming stimulant medications to treat it inevitably creates a risk of future drug addiction[2,7–9]; and the suspicion that the disorder does not exist at all but was invented to justify the medical treatment of deviant behavior.[10] While much of the literature intended to discredit ADHD and its treatment is polemical and alarmist in nature,[10] genuine attempts to untangle the controversies surrounding the disorder have been and continue to be made.[8–10]

STIMULANT THERAPY AND SUBSTANCE ABUSE

One persistent myth attached to ADHD is the allegation that stimulant therapy can lead to drug addiction later in life.[11] This alarmist view is unfortunately rendered credible by the fact that the experimental use of both licit and illicit substances is extremely common among adolescents in general, most of whom engage in occasional experimentation with drugs such as alcohol and marijuana without becoming addicted.[12] In the case of stimulants, a class that includes cocaine and amphetamines, the alarmist mes-

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sage is further compounded by the fact that these are drugs that can be abused because, taken in large doses by injection or inhalation, they can provide a drug "high."

Yet, the language used to describe drug dependence and addiction is typically vague and confusing. True addiction is defined by a triad of characteristics, including psychological dependence or craving and the behavior involved in satisfying that craving; physiologic dependence, characterized by withdrawal symptoms upon discontinuation of the drug; and tolerance, or the need to increase the dosage to obtain desired effects.[13] The fact that the amphetamines are widely available drugs associated with abuse has been used carelessly by critics to suggest that taking stimulants to treat ADHD is somehow related to addiction, or at least to psychological dependence on the drug simply in order to perform normal life tasks.[6] In fact, it has been noted that there is no evidence that long-term treatment with stimulants or other psychoactive drugs prescribed for the treatment of ADHD is associated with high rates of substance abuse in either adolescence or adulthood,[8] a point acknowledged even by some critics.[6]

ADHD AND COMORBIDITY

The relationship between ADHD and substance abuse has been studied in various ways, evaluating a variety of possible relationships between the two. Unfortunately, many of these studies omitted any attempt to control for the confounding presence of conduct disorder among their subjects, despite the established fact that conduct disorder is extremely likely to place individuals at risk for developing substance use disorder.[8,14–17] In addition, our understanding of ADHD is complicated by the fact that it is unquestionably a heterogeneous disorder. As we have previously reported, that ADHD presents both alone and concurrent with certain disorders suggests that the disorder may well prove to be a group of disorders with different etiologies, risk factors, and outcomes, rather than a single entity.[1] ADHD has been associated with high levels of comorbidity with conduct and antisocial disorders, anxiety disorders, major depressive disorder, bipolar disorder, and learning disabilities.[1,12,15,18–25]

ADHD AND COMORBID SUBSTANCE ABUSE

Among the most persistent problems associated with the treatment of ADHD, particularly in adolescent and adult patients, has been the co-occurrence of the disorder with psychoactive substance use disorder. A higher than normal risk for substance use disorder has been well-documented in adults with histories of ADHD—an association that appears to be mediated by the presence of conduct and antisocial disorders.[14]

In a study of adults with childhood-onset ADHD persisting into adulthood, it was determined that not only did comorbid antisocial disorders significantly increase the risk for substance use disorder, but ADHD itself increased the risk for substance use disorder, independent of any comorbid psychiatric disorders.[14] An intricate relationship among ADHD, substance use disorder, and comorbid psychiatric disorders, especially conduct disorders, was confirmed in a sample of siblings of ADHD and non-ADHD probands, which showed that ADHD is associated with higher rates and earlier onset of substance use disorder.[26] These findings were validated by a controlled study of adults with childhood-onset and persistent ADHD, in which it was found that ADHD was associated with a longer duration of substance use disorder and significantly slower remission rates, compared with controls[15]; in fact, ADHD of childhood onset that persisted into adulthood was associated with a 2-fold increased risk for substance use disorder.[16]

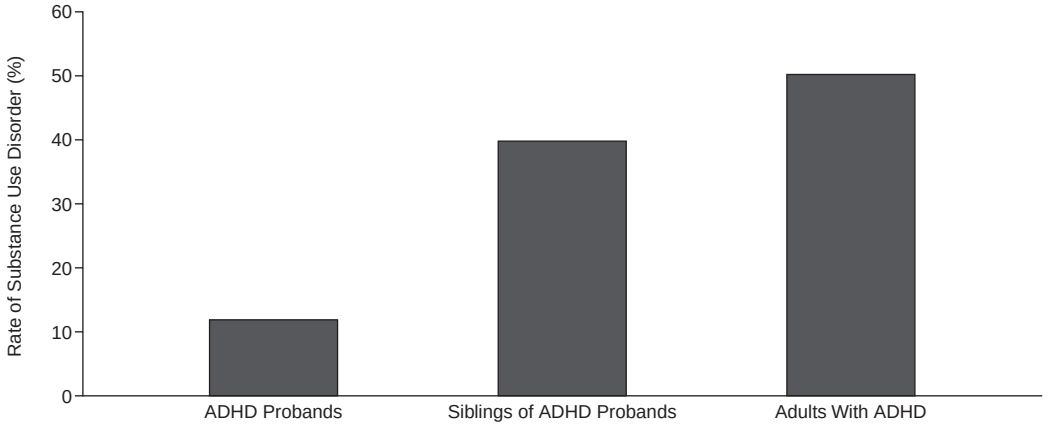
STIMULANT THERAPY AND SUBSTANCE USE DISORDERS

The identification of ADHD as a risk factor for substance use disorder has led to an attempt to elucidate the complex interrelationships among ADHD, substance use disorder, and psychiatric comorbidities such as conduct and antisocial disorders. To assess the extent to which stimulant therapy is associated with substance use disorder, we used data previously accumulated in a 4-year longitudinal study of children and adolescents with ADHD. This trial, which has been reported elsewhere,[17] was designed to examine prospectively the antecedents and correlates of substance use disorder at a 4-year follow-up, focusing on issues of familiality, psychosocial adversity, and comorbidity, all of which were hypothesized to be risk factors for substance use disorder in children with ADHD.

Data from this study[17] were obtained from an original sample of 260 children, of whom 140 were white boys aged 6 to 17 who had been diagnosed with ADHD and 120 were normal controls, all referred from both psychiatric and nonpsychiatric pediatric settings. At the time of follow-up, 91% of both the index and control group were available for interviews,[17] comprising in all 128 ADHD families and 109 non-ADHD families or 280 subjects and 226 controls, including siblings.

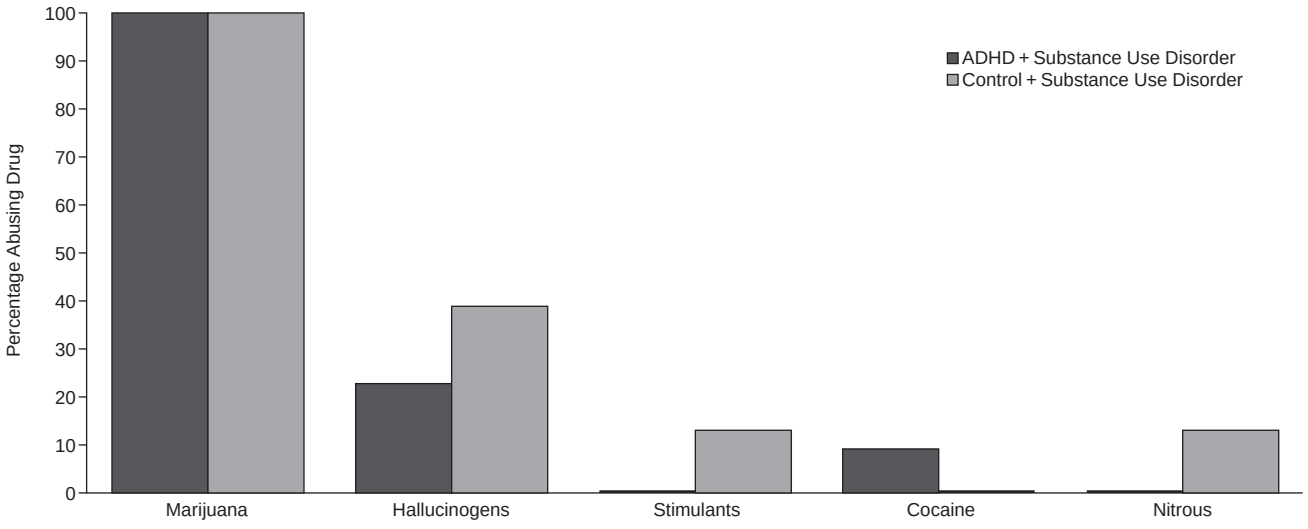
The data accumulated in this study[17] proved to be exceptionally rich and informative, extending well beyond the original study goals, thereby making it possible to debunk some of the myths that continue to surround ADHD and its treatment. To assess substance use among the original probands, reanalysis was confined to boys who were 15 years or older, in accordance with diagnostic criteria.[27] Three groups were involved: medicated subjects with ADHD (N = 56); unmedicated subjects with ADHD (N = 19); and non-ADHD controls (N = 137).

Figure 1. Rate of Substance Use Disorder in ADHD Probands, Their Siblings, and Adults With ADHD[a]



[a]Adapted with permission from Biederman et al.[17]
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

Figure 2. Preferred Drugs of Abuse by Attention-Deficit/Hyperactivity Disorder (ADHD) Probands Versus Controls[a]



[a]Data from Biederman et al.[17]
No pairwise comparisons were significant.

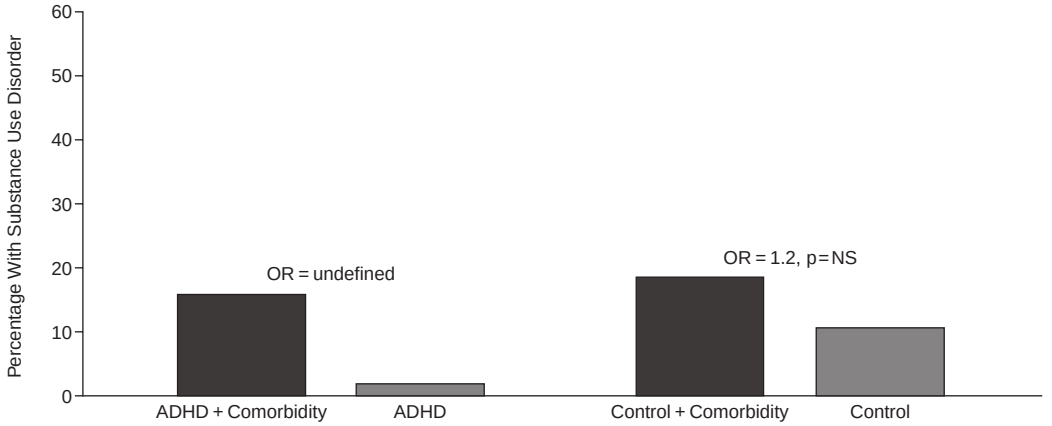
FINDINGS

As we have reported elsewhere,[27] the original data set was analyzed to determine whether exposure to stimulant therapy is associated with the development of substance use disorder. Among the ADHD subjects, about 75% received pharmacotherapy in childhood while 25% did not; treatment lasted an average of 4 years. Substance use disorder data were obtained by questioning both children and their parents, differentiating between alcohol and drugs. Diagnosis of substance use disorder was obtained by consensus; frequency and severity of use were assessed. Statistical analysis used ordinary regression for continuous variables and logistical regression for binary variables. Data were corrected by age, socioeconomic status, presence of conduct disorder, presence of baseline substance use disorder, and family history of substance use disorder.

The Nature of Substance Use Disorder Among ADHD Subjects

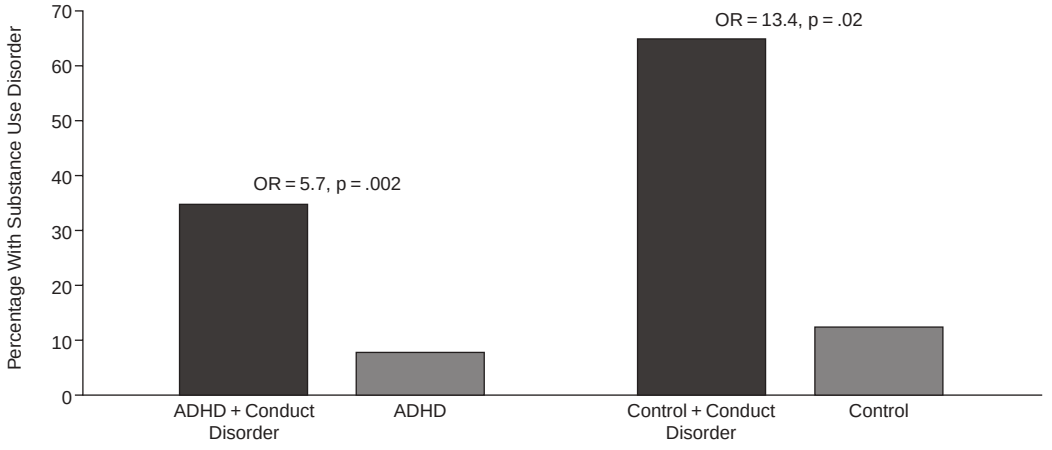
The chief findings of the original study[17] were several indications of the rate of substance use disorder among ADHD probands compared with their siblings and with adults with ADHD. Among the core sample of boys with ADHD, the rate of substance use disorder was about 10%,

Figure 3. Substance Use Disorder in ADHD and Control Probands With and Without Psychiatric Comorbidity[a]



[a]Reprinted with permission from Biederman et al.[17]
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, OR = odds ratio.

Figure 4. Substance Use Disorder in ADHD and Control Probands With and Without Conduct Disorder[a]



[a]Adapted with permission from Biederman et al.[17]
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, OR = odds ratio.

a percentage that was strikingly less than that reported by their siblings, who were only about 2 years older, on average, and who reported a rate of substance use disorder of about 40%. Adults with ADHD reported a rate of about 50% (Figure 1).

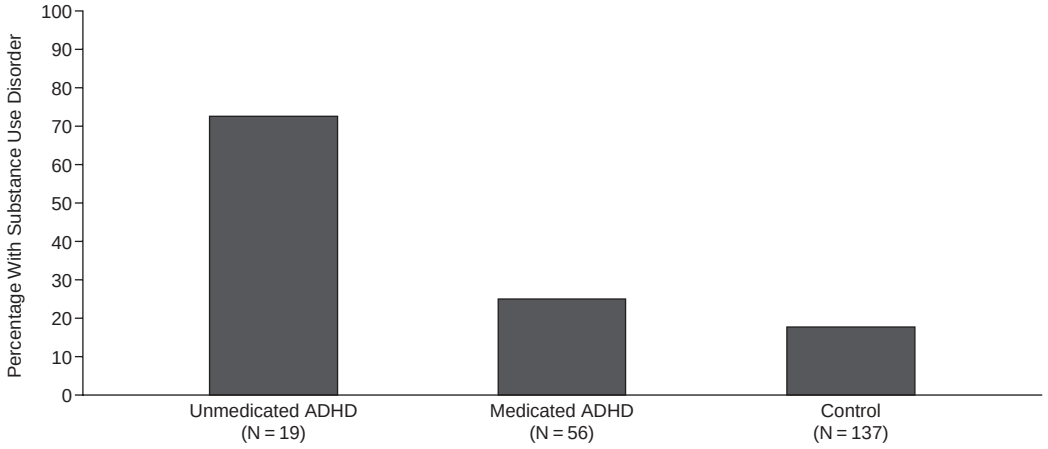
Among subjects who did engage in substance abuse, overwhelmingly the drug of choice for both ADHD probands and controls was marijuana (Figure 2). In response to critics who insist that stimulant therapy for ADHD inevitably causes patients to seek out illicit stimulants and cocaine, it is noteworthy that no substance-abusing ADHD proband used other illicit stimulants, and only 1 such proband acknowledged using cocaine.

The presence of psychiatric comorbidity in the profiles of substance-abusing probands with ADHD was striking. Virtually no probands with ADHD but without any comorbid psychiatric condition acknowledged substance use, compared with about 20% of those ADHD probands with comorbidities (Figure 3). Moreover, comorbid conduct disorder was overwhelmingly associated with substance use disorder in ADHD probands and controls (Figure 4).

Substance Use Disorder at 4-Year Follow-Up

When comparison was made between medicated and unmedicated substance-using adolescents with ADHD who were at least 15 years old,[27] the difference in rate of substance use disorder between the 2 groups was striking (Figure 5). Fully 75% of unmedicated ADHD adolescents were substance users, compared with 25% of medicated

Figure 5. Substance Use Disorder in Unmedicated and Medicated ADHD and Control Adolescents (≥ 15 years)[a]



[a]Adapted with permission from Biederman et al.[27]
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

ADHD youths and 20% of controls. As we have already pointed out, these are not adolescents engaged in typical experimental drug use, but adolescents whose substance use has already become abuse or dependence, suggesting that children with untreated ADHD represent a group at high risk for rapid escalation to substance use disorder.[17] It is clear that ADHD itself, even without psychiatric comorbidities, is a risk factor for substance use disorder, and that people with unmedicated ADHD are at 3 to 4 times the risk for developing substance use disorder as are those who are medicated.

Protective Effect of Medication for ADHD

That medicated ADHD patients developed substance use disorder at a rate similar to that found among controls suggests that, far from causing drug addiction, stimulant therapy actually has a beneficial protective effect against developing substance abuse. To verify this important finding, we compared the same subjects—medicated ADHD, unmedicated ADHD, and controls—according to specific drugs of abuse, including alcohol, marijuana, cocaine, other illicit stimulants, and hallucinogens. In all cases, unmedicated ADHD youths were at significantly increased risk for substance use disorder compared with medicated ADHD youths and controls.

Although stratification of the sample by specific categories of abuse or dependence reduced power, the direction of the protective effect of exposure to pharmacotherapy for each of the substance use disorder subtypes was similar to that seen for the larger category of substance use disorder. In each instance, medicated ADHD subjects at baseline were at reduced risk relative to unmedicated subjects for each type of substance use disorder.

CONCLUSIONS

This study had a number of potential limitations: the sample was naturalistic and treatment was not randomized; moreover, medication was measured as a function of overall exposure and information about compliance or dosage was not included. It is possible that by examining the substance use of mid-adolescents (15–21 years old) exclusively, we may have failed to capture the full risk of substance use disorder. Finally, our data about substance use came from self-reports and parental reports and were therefore not measured objectively. In spite of these potential limitations, we can draw the following conclusions:

1. Unmedicated ADHD youths in mid-adolescence were at highest risk for substance use disorder.
2. Medicated ADHD youths in mid-adolescence were at lower risk for substance use disorder compared with unmedicated ADHD youths.
3. Medicated status was found to be protective against substance use disorder in ADHD youths in mid-adolescence.
4. Pharmacotherapy for ADHD reduces the risk of substance use disorder in ADHD youths.
5. ADHD is a risk factor for substance use disorder, which is increased by psychiatric comorbidities.

Disclosure of off-label usage: Dr. Biederman has determined that, to the best of his 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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