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Does Childhood Treatment of ADHD With Stimulant Medication Affect Substance Abuse in Adulthood?

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One of the most controversial issues in childhood psychiatry is whether the wide-spread use of stimulant medications to treat children with attention deficit hyperactivity disorder (ADHD) increases the risk of substance abuse in adulthood. Part of the rationale for this concern is that stimulant medications (methylphenidate and amphetamine) share with drugs of abuse the ability to increase dopamine concentration in the nucleus accumbens, which is the neural mechanism considered crucial for their reinforcing effects (1). Indeed, methylphenidate and amphetamine are sometimes abused in some settings (2). This misuse can produce dependence. Another reason for concern is the timing of exposure. Human epidemiological studies have shown that the earlier an individual is exposed to substances with abuse potential, such as alcohol and nicotine, the greater the risk of drug abuse and dependence in adulthood (3). However, the opposite perspective has also been proposed—that stimulant treatment of children and adolescents with ADHD may reduce the risk of later substance abuse (4). Considering that individuals with ADHD are at higher-than-normal risk for substance abuse (5), it is urgent that these two perspectives be addressed properly, yet relatively few clinical studies have done so.

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Two articles in this issue of the *Journal* provide new clinical evidence pertaining to these viewpoints, based on findings from prospective observational studies. One study, conducted by Biederman et al. (6), compares subgroups of children with ADHD who received treatment with stimulants in childhood or adolescence with those who did not. Another study, conducted by Mannuzza et al. (7), evaluates the age when stimulant treatment was initiated in childhood and its relationship to drug abuse in adulthood. The study also compares the prevalence of substance abuse in persons with ADHD with a comparison group. Both studies document high rates (up to 45%) of substance use disorders in their adult cohorts, but both conclude that the long-established clinical practice of the use of stimulant medication to treat young children with ADHD does not affect—neither increasing nor decreasing—the risk for substance abuse in adulthood.

Because of the relevance of these findings to clinical practice, it is important to identify potential sources of uncertainty. These two studies evaluated clinically referred samples, and medication status was not randomized, making the findings vulnerable to referral bias. The samples were also small, especially for the subgroup untreated with stimulants. Also, treatment with stimulants was initiated (as usual) at an average age between 8 and 9 years, with most

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children discontinuing treatment after an average of 2 (7) to 6 years (6). Thus, most individuals were probably exposed to stimulants only a short time during childhood, and only a few were likely exposed to stimulants because of treatment during adolescence. Since preclinical studies revealed that exposure to stimulant drugs during the period corresponding with adolescence, but not in the period corresponding with childhood, increased sensitivity to the rewarding effects of cocaine (8), prospective studies of larger samples of adolescents treated with stimulant medications are necessary in order to more carefully evaluate the consequences of stimulant exposure during this developmental period. Studies in progress, such as the Multimodal Treatment Study of ADHD, which have larger samples of ADHD individuals and larger subgroups with extended or no treatment with stimulants throughout childhood and adolescence (9), will provide additional data on adult substance abuse outcomes.

An interesting finding of the Biederman et al. study is the failure to confirm the prior claim that treatment with stimulants markedly reduced the risk for substance abuse (4). They suggest that the prior finding was because of a temporary benefit that delayed the initiation of drug abuse. This merits further investigation, since reduction of drug exposure during this developmental stage would be expected to result in an improvement in outcomes, including less risk for dependence. However, others have proposed a parsimonious explanation that the untreated ADHD group was an average of 2 years older than the treated group and that an uncontrolled age difference accounted for the difference in substance use that increased with age during adolescence (10).

An interesting finding from the study by Mannuzza et al. is their observation that subjects with late initiation of stimulant medication (ages 8 to 12) had greater substance abuse that was mediated by an increase in antisocial personality disorder in adulthood. Remarkably, the subgroup with early treatment (before the age of 8) did not differ from comparison subjects in lifetime rates of non-alcohol substance use (27% versus 29%, respectively). The authors discuss the possibility that early stimulant treatment of ADHD may have a protective effect toward the emergence of conduct disorder, which usually precedes antisocial personality disorder and increases the risk for drug abuse. However, this hypothesis is not supported by early findings from the Multimodal Treatment Study of ADHD, in which treatment with stimulants in this prospective follow-up study did not selectively reduce conduct disorder (9), or by national trends over the past decade, when there has been a dramatic fivefold increase in the treatment of ADHD children in the United States with stimulants but no change in the prevalence of conduct disorder (11).

The two articles in this issue highlight the need to develop a better understanding of the natural history of ADHD over time. It was once assumed that ADHD was a childhood disorder and that most children with childhood diagnoses of ADHD would outgrow their symptoms after puberty. Later, this idea was rejected, and it was proposed that ADHD will persist in a large number of individuals, ranging from 35%-60% of cases, depending on the diagnostic criteria used for the original sample (12). Thus, an important question is whether these two trajectories—symptoms completely outgrown by adulthood versus a continued subset of symptoms—have a different neurobiology and whether they have different vulnerabilities for substance abuse disorders and long-term effects of treatment with stimulant medications.

A fundamental question is why there is such a high comorbidity between ADHD and substance abuse. There is evidence of impaired brain dopamine activity in individuals with ADHD (13), which could explain why individuals with ADHD are at greater risk of abusing drugs, since drugs of abuse acutely but temporarily raise the concentration of dopamine in the brain and could temporarily improve ADHD symptoms. In contrast, chronic drug abuse decreases dopamine brain activity (13). Inasmuch as dopamine modulates the activity of brain regions (including the prefrontal cortex, striatum, hippocampus, and amygdala) implicated in the

symptoms observed in ADHD, i.e., attention, executive function, and impulsivity (14), chronic drug exposure in ADHD individuals could exacerbate the symptoms of the disorder.

In these studies of the long-term outcomes of individuals with ADHD, the evidence that current clinical practice does not increase later substance use or abuse is comforting, but the failure to document that childhood treatment with stimulant medication decreases the high risk of substance abuse in adulthood is distressing. This highlights the need for the development of integrated treatments that target both ADHD and substance abuse in order to go beyond standard treatment and find a way to reduce or prevent substance abuse and provide better treatment if these disabling outcomes emerge.

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