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# Stimulant Treatment as a Risk Factor for Nicotine Use and Substance Abuse*

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Children who have been diagnosed with attention deficit hyperactivity disorder (ADHD) are often treated with the central nervous system (CNS) stimulant methylphenidate. Although the therapeutic efficacy of methylphenidate has been established (Greenhill, 1992; Klein, 1993), very few studies have examined the long-term effects of treatment with the drug. In longitudinal research (Barkley, Fischer, Edelbrock, et al., 1990; Gittelman, Mannuzza, Shenker, et al., 1985; Lambert, 1988; Weiss, Hechtman, Milroy, et al., 1985), ADHD and childhood use of CNS stimulants have been shown to predispose children to early tobacco use and to adult use and dependence on tobacco and substances with stimulating properties (Hartsough, Lambert, 1987; Lambert, Hartsough, in press).

This investigation explores the predisposing properties of CNS stimulant medication in childhood in the uptake of regular smoking during the developmental period, daily smoking in adulthood, adult DSM-III-R psychoactive dependence diagnoses, and lifetime use of cocaine and stimulants. In addition to childhood CNS use, other independent variables in the analyses are a research diagnostic proxy for the severity of DSM-IV ADHD symptoms, severity of childhood conduct problems, gender, the age of initiation into tobacco, and birth year cohort.

There are four major, most likely complementary, explanations regarding the relationship of ADHD and CNS use to adolescent and adult use of substances.

The first hypothesis predicts that general behavior dysfunction in childhood and adolescence, characterized by psychosocial unconventionality or the presence of antisocial behavior (all of which are also prevalent among ADHD groups in adolescence), leads to both more smoking and more intensive substance use (Jessor, Jessor, 1980; Loney, 1980; Robins, 1980).

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Another perspective targets tobacco as a gateway drug and predicts that early tobacco use is likely to be common among all who use other substances (Fleming, Leventhal, Glynn, et al., 1989; Henningfield, Clayton, Pollin, 1990; Kandel, Yamaguchi, Chen, 1992). Tobacco dependence is an important addiction on its own merits, and tobacco also appears to be involved in the development of a variety of other drug dependencies.

Another hypothesis proposes that tobacco serves a self-medicating role for ADHD subjects and that initiation into and continued use of nicotine are sought because of its beneficial behavioral effects. Research with human subjects has suggested that both tobacco and cocaine may be used for self-medication, depending on the particular type of presenting symptomatology (Cocores, Davies, Mueller, et al., 1987; Rounsaville, Anton, Carroll, et al. 1991; Weiss, Mirin, 1986). Methylphenidate has pharmacological properties that closely resemble those of other stimulant drugs including cocaine and amphetamine (Robinson, Jurson, Bennett, et al., 1988; Volkow, Wang, Gatley, et al., 1996); therefore, repeated exposure to methylphenidate may be expected to produce effects similar to those engendered by repeated exposure to these other psychostimulants.

The fourth hypothesis is the methylphenidate/amphetamine sensitization hypothesis, founded primarily on animal studies. Pursuing a tobacco-cocaine sensitization hypothesis, animal research has shown that preexposure to nicotine predisposes rats to the reinforcing impact of cocaine (Horger, Shelton, Schenk, 1991). Likewise, evidence from the animal studies implicates the use of amphetamines as predisposing to the rewarding impact of cocaine (Schenk, Snow, Horger, 1991; Schenk, Valadez, McNamara, et al., 1993). The sensitization hypothesis posits that early exposure to either nicotine or amphetamines predisposes to adult stimulant and cocaine use because the increased neurochemical sensitization enhances responsiveness to cocaine's reinforcing properties. Thus, although subjects with ADHD may have more risk factors predisposing to adult tobacco and cocaine abuse, the fundamental processes involved in the sensitization hypothesis are thought to hold regardless of psychiatric symptomatology.

The participants in this investigation are adults who have been subjects since childhood in a prospective longitudinal investigation of the life histories of ADHD subjects and their age-mate controls. DSM-IV ADHD research diagnostic criteria based on 1974 parent and teacher ratings on the Children's Attention and Adjustment Survey (CAAS) (Lambert, Hartsough, Sandoval, 1990) of inattention and hyperactive-impulsive symptoms and age of onset of symptoms classified all 492 subjects on the presence and severity of ADHD in childhood. Of the 492 subjects, 22 percent were female and 23 percent were members of minority ethnic groups. Of the 492, 132 were classified as severe DSM-IV ADHD, 99 were moderate ADHD, 61 were mild ADHD, and 200 subjects did not satisfy DSM-IV ADHD research criteria. Of those originally receiving medical diagnoses of hyperactivity with no competing explanations for their condition (Lambert, Sandoval, Sassone, 1978), only 4 percent failed to satisfy the DSM-IV ADHD diagnostic proxy. On the other hand, 3 percent of the age-mate controls met the criteria for

DSM-IV ADHD and might have been identified as ADHD in 1974, when they entered the study, had the 1994 DSM-IV diagnostic criteria been used (American Psychiatric Association, 1994).

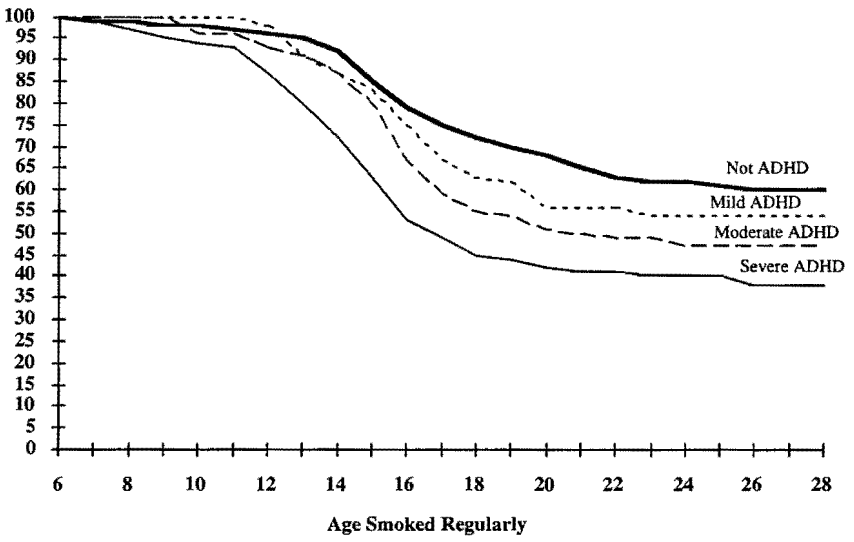
Histories of treatment interventions in childhood, derived from parent and subject reports, included the age at which CNS stimulants were first prescribed and duration of use. Among those subjects who used CNS stimulants, 69 percent used only methylphenidate, 16 percent used combinations of methylphenidate and other CNS stimulants, and 15 percent used other CNS stimulants (Dexedrine, Benzedrine, Cylert, or Deaner). CNS stimulants were used by 45 percent of the severe ADHD, 51 percent of the moderate ADHD, 15 percent of the mild ADHD, and 5 percent who were not classified as ADHD.

Other independent variables included severity (pervasiveness) of early ratings of conduct problems on the CAAS; age of initiation into tobacco; gender; and birth-year cohort groups. Social status and cognitive ability measures were explored as well.

Research goals were realized through use of an adult interview comprising eight major sections, among which were adult ADHD symptoms and treatment history, lifetime reports of tobacco use and current smoking status, and the Quick Diagnostic Interview Schedule, III-R (QDIS III-R) (Marcus, Robins, Bucholz, 1990). Adult interview protocols were obtained for 81 percent of the original 492 subjects (77 percent of those with ADHD and 86 percent of the controls), and analyses of differential loss indicated no appreciable impact on reported rates of tobacco and substance use that could be attributed to loss at followup (Hartsough, Babinski, Lambert, 1996).

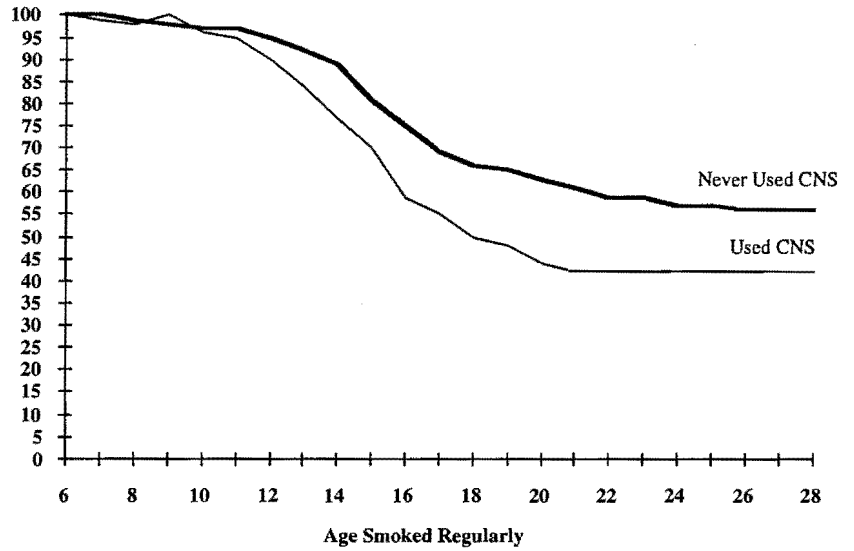
Three sets of statistical analyses were completed. The survival analyses (Cox, Oakes, 1984) of the age subjects became regular smokers during the child-adolescent-early adult developmental period used both ADHD and CNS use as independent variables. Next, chi-square statistics explicated the association between ADHD and CNS use and adult daily smoking. Logistic regressions were conducted with the QDIS III-R dependence measures of tobacco, cocaine, stimulants, marijuana, and alcohol. The dependency criteria do not assess high rates of use, but they do focus on using more than intended, difficulty in cutting down despite problems, and developing a tolerance to the drug. Logistic regressions were also conducted with lifetime use measures for tobacco, cocaine, stimulants, and use of cocaine and stimulants combined. For substances other than tobacco, lifetime use was divided into a low-use group (1 to 19 times) and a high-use group (20+ times). The results of the investigation were as follows:

1. Tobacco use in the survival analyses was measured as "age smoked on a regular basis." Subjects who had never smoked were given a later age, and those cases were censored in the analysis. The survival analyses for severity of ADHD and use of CNS in childhood (Figures 1 and 2) show that both severe ADHD symptoms and childhood CNS treatment are childhood risk factors that predispose to earlier onsets of regular smoking in childhood and adolescence.




Overall comparison: Lee Desu Statistic 15.166, df = 3, $p \leq .01$. Pairwise comparisons: Severe vs. Never, $p \leq .000$; Severe vs. Mild, $p \leq .05$; Severe vs. Moderate, $p \leq .10$; Moderate vs. Never, $p \leq .10$.

**Figure 1.** Survival analysis—percentage not smoking regularly during the developmental period by ADHD classification.




Overall comparison: Lee Desu Statistic 5.825, df = 1, $p \leq .05$.

**Figure 2.** Survival analysis—percentage not smoking regularly during developmental period for subjects who used CNS treatment before they became regular smokers and those who never used CNS.

2. There is evidence for a "protective" effect of CNS use. Survival analysis that groups subjects by the age CNS terminated (Figure 3) shows that the longer the CNS treatment was used, the longer the delay in the "age smoked on a regular basis." This suggests that subjects begin regular smoking when CNS treatment ends, implicating support for both the self-medicating and sensitization hypothesis. Even so, the adult rates of daily smoking for each of the three CNS treatment groups are comparable, indicating that this protective effect may be short-lived.

3. Childhood CNS treatment for more than 6 months is significantly related to rates of adult daily smoking (Figure 4). Rates of daily smoking (Figure 5) in adulthood are significantly higher for ADHD (Severe and Moderate groups combined) compared with Not ADHD (Mild and Not ADHD combined).

4. The logistic regressions of the independent variables with adult smoking and substance use variables produced the following results:

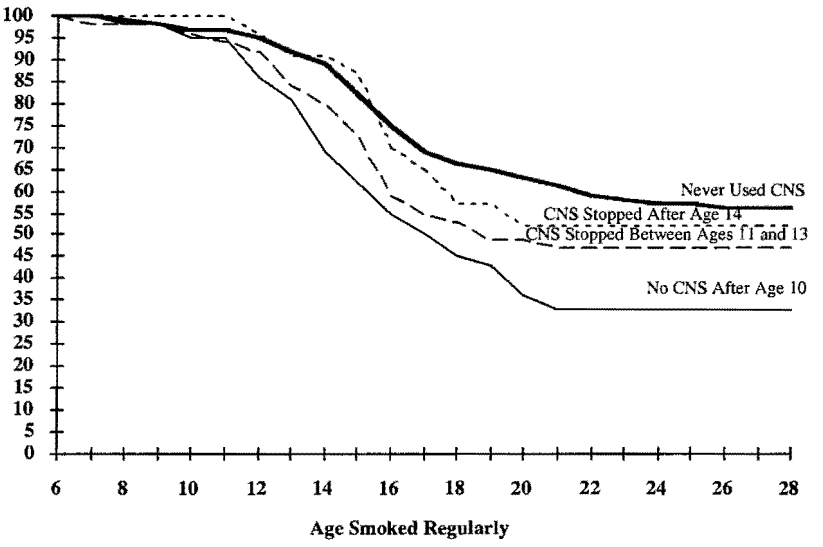
    a. There was a significant odds ratio for early initiation into tobacco in the regressions for all of the DSM-III-R dependence diagnoses. Severity of ADHD was significantly related to tobacco, cocaine, and stimulant dependence but not to marijuana and alcohol dependence. There was a significant odds ratio for CNS stimulants in the prediction of cocaine dependence. Although early initiation into smoking was prevalent for all substance dependencies, ADHD contributed significantly to the predictions for dependence on substances with stimulating properties, namely tobacco, cocaine, and stimulants. Subjects with severe ADHD symptoms are more likely to become involved with substances with stimulating properties and have greater difficulty reducing or eliminating their use.

    b. Adult daily smoking and lifetime use of cocaine and stimulants were predicted by early initiation into smoking and use of CNS stimulants for a year or more. This supports hypotheses on the early use of nicotine and CNS stimulants as sensitizing agents in greater lifetime use of tobacco, cocaine, and stimulants.

    c. There was a significant odds ratio for gender only for alcohol and marijuana dependence, with males more likely to be dependent. Severity of ADHD was not related to marijuana or alcohol dependence.

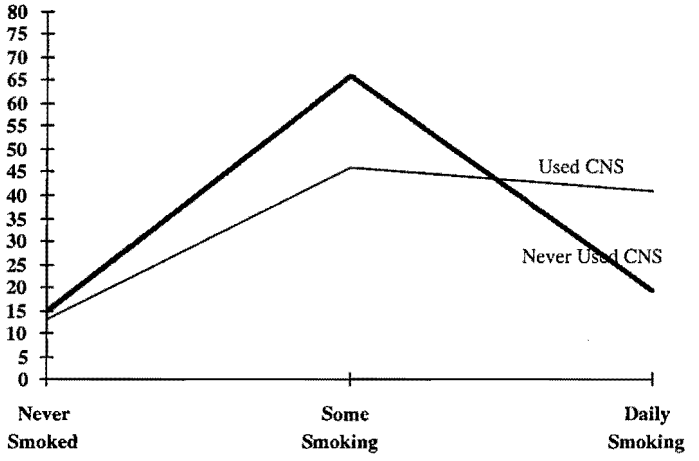
    d. Support for the stimulant sensitization hypothesis was shown by significant odds ratios for CNS treatment in the regressions for adult daily smoking, cocaine dependence, lifetime use of stimulants, and a combined measure of lifetime use of both cocaine and stimulants.

5. When subjects who became cocaine-dependent were grouped as (1) neither smoker nor CNS user, (2) CNS user only, (3) smoker only, and (4) smoker and CNS user, there was a significantly higher rate of cocaine dependence for subjects who were both smokers and CNS users (Figure 6).



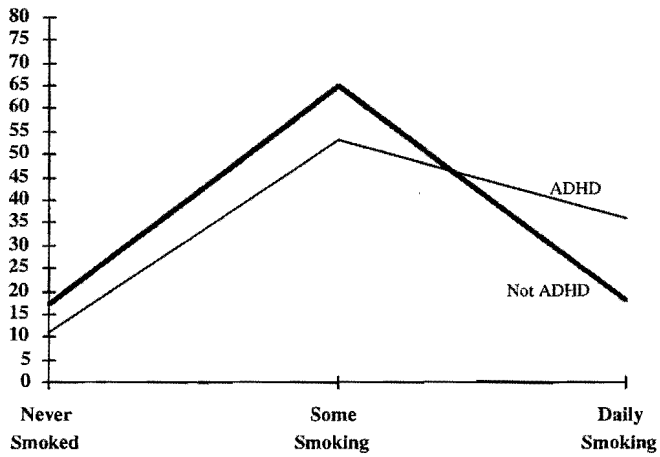

Overall comparison: Lee Desu Statistic 15.280, df = 3, $p \leq .01$. Pairwise comparisons: no CNS after age 10 vs. no CNS, $p \leq .001$; no CNS after age 10 vs. off CNS after age 14, $p \leq .10$.

**Figure 3.** Survival analysis—percentage not smoking regularly during developmental period for subjects with different CNS stimulant medication histories.



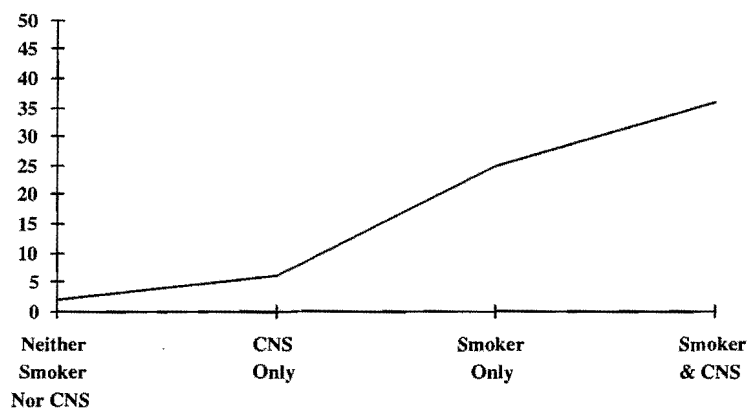

Pearson $X^2_{df=2} = 23.156$, $p \leq .000$; Mantel-Haenszel $X^2_{df=1} = 13.850$, $p \leq .000$.

**Figure 4.** Adult smoking status for subjects with CNS treatment in childhood compared with those who never used CNS treatment (percentage).




Pearson $X^2_{df=2} = 16.835$, $p \leq .001$; Mantel Haenszel $X^2_{df=1} = 13.818$, $p \leq .001$.

**Figure 5.** Adult smoking status for ADHD and not ADHD subjects (percentage).




Pearson $X^2_{df=3} = 52.61$, $p \leq .000$; Mantel-Haenszel $X^2_{df=1} = 50.689$, $p \leq .000$. Among those who were cocaine-dependent, 62 percent were ADHD and 39 percent were not ADHD.

**Figure 6.** Adult cocaine dependence as a function of childhood ADHD, CNS treatment, and smoking history.

No support was apparent for the problem behavior hypothesis of higher rates of smoking and substance abuse. It is important to distinguish between childhood evidence for conduct problems based on parent and teacher ratings and subsequent adolescent diagnoses of conduct disorders and oppositional defiant disorders. Other investigators (Hinshaw, 1987; Loeber, Stouthamer-Loeber, 1998; O'Donnell, Hawkins, Abbott, 1995) have summarized evidence to refute the commonly held belief that individuals who have a history of early aggression always persist in their aggressive behavior. A developmental model of aggression is the more reasonable approach. Ratings of subjects' behavior in this study occurred when they were on average 9 years old. Among those classified as having severe and moderate conduct problems will be those who develop both conduct disorders and/or oppositional defiant disorder in adolescence and those with transitory aggressive behavior in childhood whose problems will not persist past adolescence. Grouping subjects into the life-course, transitional, and late-onset types of aggressive behavior will be necessary to provide explanatory evidence for the relationship between types of childhood conduct problems and adult substance use.

This prospective longitudinal study of ADHD and age-mate control subjects, reconfigured according to research diagnostic proxies for severity of DSM-IV ADHD, has provided evidence that childhood use of CNS treatment is significantly and pervasively implicated in the uptake of regular smoking, in daily smoking in adulthood, in cocaine dependence, and in lifetime use of cocaine and stimulants. The severity of ADHD and early onset of tobacco use are significant risk factors for adult use and dependence on substances with stimulating properties, namely tobacco, cocaine, and stimulants. Implications for the self-medication and sensitization hypotheses are explored.

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