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

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ABSTRACT[*]

This investigation explored the roles of ADHD and histories of childhood CNS stimulant treatment as risk factors for adult tobacco and substance use for 399 of 492 participants in a prospective longitudinal investigation since childhood. The participants and their CNS stimulant treatment status were as follows: 104 Severe ADHD (42% treated with stimulants), 72 (57% treated) Moderate ADHD, 51 (12% treated) Mild ADHD, and 192 (5% treated) participants who did not satisfy DSMIV ADHD research criteria. Other independent variables included severity (pervasiveness) of ratings of conduct problems in childhood, age of initiation into tobacco; gender; and birth year cohort groups.

The dependent variables in the analyses were the uptake of regular smoking during the developmental period, daily smoking in adulthood and adult DSMIIIR Psychoactive Substance Use Disorders, and heavy lifetime use (abuse) of cocaine, stimulants, marijuana, and alcohol.

Severity of ADHD was significantly related to age of becoming a regular smoker, daily smoking in adulthood and DSMIIIR diagnoses of tobacco, cocaine, and stimulant dependence, but not marijuana and alcohol dependence. Stimulant treatment in childhood was significantly related to age of regular smoking, adult daily smoking, and DSMIIIR substance dependence diagnoses of tobacco and cocaine.

The results were discussed in terms of support both for a self-medicating process for those with severe ADHD symptoms. and a sensitization hypothesis for those who were treated with CNS stimulants. Evidence for the tobacco gateway theory and problem behavior theory as competing explanations for adult involvement with tobacco and substances were also explored.

BACKGROUND

The investigator's longitudinal research with the ADHD participants and age mate controls has shown that ADHDs smoke at an earlier age (1), and in early adulthood have higher rates of daily smoking, nicotine dependence, cocaine and stimulant dependence (2), but not marijuana and alcohol dependence .A significant relationship between stimulant treatment in childhood and daily smoking in adulthood and between tobacco and cocaine dependence also has been reported (2). This investigation explores the role of severity of DSMIV ADHD and the length of childhood stimulant medication as risk factors for tobacco smoking and DSMIIIR substance dependency and heavy use (abuse).

Perspectives on ADHD as a Risk Factor for Tobacco Smoking and Substance Use

Longitudinal studies have reported a pattern of excessive tobacco use among ADHDs (3) with higher rates of cigarette smoking among the ADHD at mid-adolescence and an earlier onset of smoking for ADHDs compared with age mate controls (4,5) Conduct disorders have also been implicated in these studies and raise questions about the relative strength of ADHD as the primary risk factor . One recent study reported (3) that even with controls for adolescent conduct disorders, ADHD was still a significant predictor.

A four year follow-up study of children age 6 - 17 (6) showed no differences between ADHDs and normal controls for Psychoactive Substance Use Disorder (PSUD), but these participants were not at the age where one could expect maximum use of substances. Several longitudinal studies have reported elevated rates of illegal drug use by ADHD subjects as adults (7, 8, 9), but these studies did not differentiate among types of psychoactive substances used and provided no information about adult smoking status. Higher rates of drug abuse and dependency among adult ADHDs (10) were reported when co-morbid DSMIIIR diagnoses of psychiatric disorders were accounted for. Conduct Disorders was also an independent predictor of substance use disorders, and there were different patterns of co-morbidity among ADHDs and controls related to substance use outcomes. (11). Persistent ADHD, with and without psychiatric disorders, was associated with age of onset of PSUD (12, 13). Further exploration of ADHD and PSUD by these authors (14) concluded that the duration of PSUD was longer (12 years versus 5 years) and the rates of remission were lower for ADHDs.

Hypotheses pertaining to higher rates of smoking and substance use by ADHDs.

The Self Medication Hypothesis. Self medication is often cited as the most reasonable hypothesis to explain the higher rates of substance use among ADHDs. Particular drugs are selected because of the interplay between the psychopharmacologic action of the drug and the dominant emotional feeling of the individual (15, 16, 17). A survey of adult patients seeking treatment for cocaine abuse reported that 35% of them had been diagnosed with ADHD (18). Cocaine abusers have been reported (16) to include those who were depressed and those with bi-polar disorders who used cocaine for its self-medicating effects, and adults with ADHD who used cocaine to increase attention span and reduce motor restlessness. Others suggest (16) that ADHD has an etiological and self mediating role in cocaine abuse. Treatment of adult cocaine abusers with and without an ADHD diagnosis with methylphenidate (20, 21) showed that the methylphenidate treatment effected reduced cocaine use in the ADHD subjects, but not those without ADHD.

The anecdotal reports and small sample sizes of some of the studies on which the self-medication proposition is based, and the lack of control over the contributions of other competing factors (22) weakens the proposition that individuals with ADHD may be self-medicating with cocaine or stimulants. On the other hand, clinical reports (23) suggest that substance dependent persons self-medicate because they cannot regulate their self esteem, relationships, or self-care. Their addictive vulnerability results from exposure to drugs combined with the inability to tolerate or to know one's feelings and one's deficits in self-care. Such conditions derive from developmental deficiencies in the individual's failure to consider at the cognitive level cause-consequence relationships involving harmful or dangerous conditions and the inability to anticipate harm and

danger (24). The self-medicating hypothesis for ADHDs, therefore, can be considered to be a cognitively compromised capacity to control or self-regulate the impulse to use substances and to become dependent on them.

The self medicating hypothesis in this study predicts that the more severe the ADHD symptoms, the greater the use of stimulants because stimulants work to reduce the distress and compromising conditions presented by the ADHD symptoms.

The stimulant treatment sensitization hypothesis. Behavioral sensitization is a process whereby intermittent stimulant exposure produces a time-dependent, enduring and progressively greater or more rapid behavioral response. It has been demonstrated in every mammalian species in which it has been examined, but it has been little studied in humans.(25) The results of a carefully controlled, randomized, double-blind study of increased doses of d-Amphetamine administered alternately with matched placebo, supported a sensitization effect for some amphetamine-induced behaviors, such as faster rates of eye blinks and increased motor activity/energy. (25) Sensitization may underlie the development of drug craving in humans, thereby contributing to substance dependence (26).

Animal models of sensitization are well-established. Methylphenidate, the most commonly used CNS stimulant treatment has pharmacological properties that closely resemble other stimulant drugs, including cocaine and amphetamine (27); therefore, repeated exposure to methylphenidate may be expected to produce effects similar to repeated exposure to other psychostimulants. Rats that are pre-exposed with amphetamine or cocaine learn to self-administer amphetamines and cocaine more rapidly than rats that are not exposed. (28, 29, 30, 31, 32, 33, 34).Schenk has shown in a recent study that rats pre-treated with methylphenidate more rapidly acquired cocaine self-administation (personal communication.) The motor activating effects of cocaine were more evident in rats that were exposed to methamphetamine (35) and amphetamine (36). Similarly, exposure to amphetamine (37) or nicotine (28) sensitized rats to the reinforcing effects of cocaine. The sensitizing effects of the preexposure regimen are persistent and have been demonstrated to effect stimulant responsiveness for months following the last exposure (38, 39).These studies suggest that a similar form of sensitization may be occurring in humans who are exposed to methylphenidate and other CNS stimulants, and that the propensity to self-administer cocaine and other stimulants may be, at least in part, determined by the individual's pharmacologic history.

Longitudinal studies of ADHDs (40) have reported that stimulant treatment in childhood is associated with elevated levels of substance use in childhood, age of initiation into and age of maximum use of cocaine. The age of first CNS treatment and the number of years of stimulant treatment was significantly related to tobacco smoking at age 16-18 (41)

The sensitization hypothesis predicts that CNS stimulant treatment is a risk factor for subsequent use of stimulants like tobacco and cocaine, but not for marijuana and alcohol. The prospective longitudinal research with community samples of both ADHD and age mate controls with different psychostimulant treatment histories and different presenting problems in childhood provides a natural laboratory for investigating this hypothesis. Documented histories of stimulant exposure are available in order to avoid problems associated with inaccurate adult reports of prescription drugs used in childhood. It should be noted at the outset, however, that the rationale for the investigation does not argue for a decisive role for either an ADHD self-medicating hypothesis or a CNS stimulant sensitization hypothesis as these two risk factors appear to be jointly involved in the dynamics of substance abuse among ADHDs.

Other Risk Factors for Substance Use.

Tobacco as the gateway to substance use. Studies of the initiation into substance use consistently show that most people who had ever used illegal drugs had earlier used cigarettes or alcohol while those who had never smoked only infrequently abused illicit substances (42, 43). Tobacco dependence not only is an important addiction on its own merits (44), but the incidence and severity of various drug dependencies are related to tobacco use, and tobacco use, in turn, may be increased by dependence producing drugs. (45, 46, 47).

Problem behavior as a risk factor for substance use. Several investigators (48, 49) have suggested initiation to tobacco as well as other illicit drugs may have common determinants in

psychosocial unconventionality. General behavior dysfunction in childhood and adolescence, characterized by problem behavior in childhood and the presence of conduct disorders in adolescence, (both of which are also prevalent among ADHD groups), leads both to more intensive substance use as well as use of a variety of different substances.

ADHD symptoms can be considered to be a subset of behaviors within the domain of behavior problems and psychosocial unconventionality. Hinshaw (50) noted that there is sufficient evidence for considering the domains of hyperactivity/attention deficits and conduct problems/aggression as partially independent, and urged investigators to use measures of conduct problems/aggression as well as attention/hyperactivity-impulsivity in order to clarify the relationships of these problem behaviors to outcomes.

RESEARCH OBJECTIVES

This investigation explores the roles of ADHD and CNS stimulant treatment in the age of becoming a regular smoker, daily smoking in adulthood, DSMIIIR Psychoactive Substance Use Disorders of tobacco, cocaine, stimulant, marijuana, and alcohol dependence..

These hypotheses are:

1. Severity of ADHD symptoms will be reflected in a) earlier regular smoking and adult smoking status and b) significantly higher rates of dependence on substances with stimulating properties - tobacco, cocaine, and stimulants - but not with substances acting as depressants, such as marijuana and alcohol. If tenable, this hypothesis would support the self-medicating needs of ADHDs since it could be argued that aspects of behavioral inhibition reflected in the symptomatology of ADHD are risk factors for seeking out these substances.

2. The CNS stimulant treatment sensitization hypothesis proposes that early exposure to either methylphenidate or amphetamines predisposes to adult tobacco, stimulant, and cocaine use because the increased neurochemical sensitization enhances responsiveness to cocaine's reinforcing properties. The sensitization hypothesis predicts that participants treated with CNS stimulants in childhood will smoke regularly earlier, have higher rates of adult smoking, and be significantly related to dependence on tobacco, cocaine, and stimulants, but not to marijuana and alcohol.

3. In multivariate analysis both severity of ADHD and childhood CNS stimulant treatment will jointly affect the dependent variables of adult daily smoking and DSMIIIR dependence on substances with stimulating properties, namely tobacco, cocaine, and stimulants, but not to substances which act as depressants, such as marijuana or alcohol.

METHODS

Participants

The participants in this investigation are 399 adults who have been subjects since childhood in a prospective longitudinal investigation of the life histories of 492 subjects, approximately one third of whom were diagnosed and treated for ADHD symptoms. The ADHD subjects and age mate controls, born 1962 to 1968, were selected from a sample of 5212 kindergarten through fifth grade children attending the public, parochial, and private schools in the East Bay Region of the San Francisco Bay Area in the 1973-74 school year. These participants were evaluated prospectively through the end of high school and later as young adults. Of the initial 492 subjects, 22% were female and 23% were members of minority ethnic groups. The procedures for identifying the subjects have been explicated elsewhere, but are summarized below (51, 52).

Our diagnostic criteria for "hyperactivity" (ADHD) required agreement among the three social systems involved in the identification and treatment of the child - the physician, the parent, and the teacher. We asked parents and school teachers of all 5212 children in 191 K-5 classrooms to inform us if the child was being treated for hyperactivity or if they were planning to request a medical evaluation. We contacted every physician in the area who treated children to notify us, after receiving parent permission, with the names of children they were treating for hyperactivity or those for whom they were prescribing stimulant treatment. We developed a standard medical evaluation

and diagnostic system based on surveys of physicians (pediatricians, pediatric neurologists, child psychiatrists, and family practice physicians) who were treating children referred for evaluation (53) of "overactivity, restlessness, distractibility, and short attention span" (54, p. 50), the cardinal symptoms used for the diagnosis of hyperkinetic disorder of childhood. Of the 5212 children, 175 were classified as "primary hyperactive", 39 were "secondary hyperactive" (possible competing medical problems), 68 were untreated hyperactives (evidence from two, but not three of the diagnostic sources, or the parents did not seek medical assistance with the child's problem), 51 were behavior controls. children who had behavior problems, but did not meet the diagnostic criteria, and there were 159 age mate case controls attending the same classrooms with the hyperactive subjects.

Development of Research Diagnostic Proxies for ADHD.

Concomitant with our identification of all of the children in the representative sample who met our social system definition for hyperactivity, we prepared parent and teacher rating scales composed of items from the research literature that had shown to be sensitive to CNS treatment effects or that differentiated between hyperactive and normal children. We did not use the results of these ratings to identify participants for the prevalence phase of our work.

Four sub-scales on the *Children's Attention and Adjustment Survey* (CAAS) (55, 56), reflecting "Inattention", "Hyperactivity", "Impulsivity", and "Conduct Problems" were defined by factor analytic studies. The items composing each scale were consistent with the DSM criteria for these symptoms permitting us to develop research diagnostic criteria for DSMIII Attention Deficit Disorder With and Without Hyperactivity, (57, 42), DSMIIIR Attention Deficit Hyperactivity Disorder (58, 2), and DSMIV ADHD (59). The alphas for the school and home form scales were respectively: .89 and .85 (Inattention), .85 and .89 (Hyperactivity), 78 and .78 (Impulsivity), and .92 and .91 (Conduct Problems).

The research diagnostic criteria for DSMIV ADHD include pervasive (both home and school) and situational (either home or school) ratings on the CAAS on Inattention and Hyperactivity-Impulsivity, and evidence for early onset of symptoms. The alpha reliabilities for the scale combining hyperactivity and impulsivity were .89 for the school form and .83 for the home form.

<u>DSMIV ADHD research diagnostic proxies: inattentive and hyperactive-impulsive symptoms and onset of symptom criteria</u>. Reclassifications of our participants according to DSMIV research diagnostic criteria are not retrospective; they are based on parent and teacher ratings on the CAAS at the time a subject entered the study. An average rating of 2.5 (on a scale from 1 to 4) identified subjects who would have met the DSMIV symptom criteria.

<u>DSMIV criteria of onset of symptoms.</u> Our proxy for onset of symptoms was the presence of one of the following: a) a parent report that the symptoms first were noted before age 8; b) medical assistance was sought before 8; or, c) parent rating of the child's temperament during infancy and early childhood of high "activity level" (hyperactivity), or low "attention span and persistence" (inattention) based on analysis of temperament questions from the Berkeley parent interview (60).

<u>Criteria for severity of ADHD</u>. We followed the lead of other investigators (61, 62, 63, 64) who have shown the importance of distinguishing between subjects whose symptoms are situational or characteristic of behavior in one setting and those whose symptoms are pervasive or characteristic of behavior in more than one setting, as necessary prerequisites to clarifying the behavioral antecedents of cognitive and social outcomes.

Four levels of severity of ADHD were established.

• CAAS DSMIV ADHD - <u>Severe</u>. A subject was classified as <u>pervasive and severe ADHD</u> if one of the following research criteria was met on <u>both</u> the home and school forms of the CAAS: 1) Combined type - both inattentive and hyperactive-impulsive; 2) Primarily Inattentive and 3) Primarily Hyperactive-Impulsive.

• CAAS DSMIV ADHD - <u>Moderate</u>. These participants were situationally ADHD with ratings on either the home form or the school form that met the research criteria for Inattention and Hyperactive-Impulsive or there was a mixed patterns of symptoms - Inattention on one form and Hyperactive-Impulsive on another.

• CAAS DSMIV ADHD - <u>Mild</u> . Only one of the symptoms in one setting was present.

• CAAS DSMIV ADHD - <u>No Symptoms Present.</u> None of the research diagnostic criteria was met.

<u>CAAS conduct problem criteria.</u> An average rating of 2.5 or higher on the Conduct Problem scales of either the Home or School Form of the CAAS was to used to classify a participant as "severe" (pervasive) if both parent and teacher ratings were in the criterion range and "moderate" (situational) if only one rating was in the criterion range.

<u>DSMIV ADHD classification compared with original classification of subjects.</u> Evaluation of the diagnostic efficiency of these criteria (65) comparing the social system criteria with the DSMIV ADHD research criteria for the total original sample of 492 produced sensitivity and specificity estimates of 93% and 86% with a 90% positive predictive power. The false negative rate was 7% and the false positive rate 14% with a kappa of .79[1].

Table 1 presents the distribution of the 399 participants in this investigation by DSMIVADHD by the original classification. Table 2 provides data on the numbers of participants who were treated with CNS stimulants by the original classification and the DSMIV research diagnostic criteria.

Procedures

The tobacco and substance use data for this research were obtained as part of an adult interview containing eight major sections, portions of which were selected for this study. The first section provided information on ADHD symptoms and treatment history. A second section replicated our child and adolescent interview questions of life history reports of tobacco use and current smoking status, use of cocaine, stimulants, marijuana, beer and wine, alcohol, heroin/opiates, glue/inhalants, and psychedelics. The QDISIIIR (66) was administered to provide DSMIIIR diagnoses of psychoactive substance use disorders and diagnoses of the major psychiatric disorders.

Interview protocols with were obtained for 399 (81%) of the original 492 subjects (77% of the ADHD and 86% of the controls), and analyses of differential loss (67) showed no significant differences in the interviewed group compared to rates in the total sample for ADHD, gender, family configuration, social class, and ethnic status and indicated that there was no appreciable impact on reported rates of tobacco and substance use that could be attributed to attrition at follow-up.

Variables in the Statistical Analyses

<u>Dependent Variables.</u>

<u>Age of regular smoking</u> Our life history records compared with the adult interview provided a record of the age when regular smoking began for all of those who had tried a cigarette.

<u>Adult smoking status.</u> An adult smoker was defined as having smoked 100 cigarettes lifetime and being a current smoker (68). Participants were grouped as daily smoking, smoker, but not a daily smoker; not a smoker, and initiated or never smoked.

<u>DMSIIIR diagnoses of psychoactive substance use disorders.</u> The QDISIIIR provided dependency diagnoses of nicotine, cocaine, stimulants, marijuana, and alcohol

<u>Independent Variables.</u>

<u>Severity of ADHD.</u> Levels of severity - Severe, Moderate, Mild, and Not ADHD. <u>Severity of conduct problems.</u> Levels of severity - Severe or pervasive. Moderate or situational or No Conduct Problems

.   <u>Childhood CNS stimulant treatment.</u> Prospective histories of treatment interventions for ADHD participants included age CNS stimulants were first prescribed, the number of years the stimulant treatment was used, and the age treatment stopped. Among those subjects who used CNS stimulants, 69% used only methylphenidate, 16% used combinations of methylphenidate with other CNS stimulants and 15% used other CNS stimulants (Dexedrine, Benzedrine, Cylert, or Deaner).

CNS stimulants were used by 46% of the Severe DSMIV ADHD, 57% of the Moderate DSMIV ADHD, 12% of the Mild DSMIV ADHD, and 5% who were not classified as DSMIV ADHD. Subjects were categorized for the analysis as: no CNS stimulant treatment; up to 1 year (32% of those treated); 2 or more years (68% of those treated).

Age of initiation into smoking. This variable was categorized as: Initiated before Age 11, Initiated between 11 and 15, Initiated after Age 15 or Not yet Initiated.

Gender and Birth-year Cohort. Other independent variables included gender and birth year cohort groups. Birth-year cohorts were grouped into three categories: participants born before 1964, those born in 1964 through 1966, and those born in 1967 or later.

Statistical Analysis

Effects of ADHD and childhood CNS stimulant treatment with age of regular smoking and adult smoking status.

We used survival analyses (69) to ascertain the nature of the relationships of ADHD and CNS stimulant treatment with age of becoming a regular smoker. Subjects who, at the time of the adult interview, had not become a regular smoker were assigned an age of regular smoking that occurred after the interview and a status variable was computed that indicated this age was "censored" or had not yet occurred and those cases were censored in the survival analysis. The method produces a survival function displaying the cumulative proportions of subjects in each group who have not yet become regular smokers at each age.

Chi-square statistics provided evidence of the association of ADHD and CNS stimulant treatment with adult smoking status.

Effects of independent variables in prediction of DSMIIIR substance dependence diagnoses.

Logistic regressions were conducted to provide evidence for the effects of the independent variables on adult daily smoking and the DSMIIIR diagnoses of Tobacco, Cocaine, Stimulants, Marijuana, and Alcohol Dependence for all subjects classified as dependent or not dependent.

The DSMIIIR dependency criteria do not require a high lifetime use rate or current rate of use. If a participant reports using the substance 5 or more times "to get high," the follow-up questions focus on use of more than intended, difficulty in cutting down despite problems, and development of a tolerance to the drug. Of these participants, the proportion of heavy users who were also dependent were: 77% (80 of 104) of the daily smokers, 51% (47 out of 93) of heavy users of cocaine (20+ times), 60% (55 out of 91) of heavy users of stimulants (20+ times), 55% (94 out of 170) of heavy users of marijuana (40+ times), and 51% (56 out of 98) of heavy users of alcohol (40+ times).

Results

Survival Analysis of Delay in Onset of Regular Smoking by Severity of ADHD..

The survival analysis for severity of ADHD (Figure 1) was significant ($p \le .01$). Pairwise comparisons showed that the survival curve for Severe ADHDs ($p \le .001$) and the survival curve for the Moderate ADHDs ($p \le .05$) were significantly different from the Not ADHDs. The survival curves for the Mild ADHD compared with the Not ADHDs and for the Severe ADHDs compared with the Moderate ADHDs were marginally significant ($p \le .10$).

Survival Analysis of Delay in Onset of Regular Smoking by Use of CNS Stimulant Treatment in Childhood.

Figure 2 shows that the percentage of participants who have not yet become regular smokers is significantly different ($p \le .05$) for those who used CNS stimulant treatment versus those who were not treated.

To examine a possible protective effect where using stimulant treatment might delay onset of regular smoking, we grouped subjects by the age at which stimulant treatment ended and conducted a survival analysis (Figure 3) The result was significant ($P \le .01$) Pairwise comparisons showed

that the proportion of participants who stopped taking CNS stimulants by age 10 were more likely to become regular smokers at an earlier age than those who never used stimulant treatment (p≤.001) or those (p≤ .10) who stopped treatment after age 14. Stimulant treatment appears to "protect" against becoming a young regular smoker in childhood. The three groups also differed with respect to the number of years they had been treated (1.72 years for the terminated treatment by age 10 group, 3.79 years for the terminated treatment between 11 and 13, and 6.66 for the terminated treatment after age 14).

This "protective" effect is short-lived. When the data for daily smoking in adulthood were examined, there was no significant difference by length of treatment in rates of daily smoking - 46% for the terminated treatment by age 10 group, 40% for the group that terminated between ages 11 and 13, 44% for the participants who terminated after age 14 compared with 19% for those who were never received stimulant treatment.

The Relationship of Severity of ADHD and Childhood Stimulant Treatment to Adult Smoking

Among the participants 57% who reported that they had been regular smokers in childhood smoked daily in adulthood. We next examined the relationship of ADHD and childhood CNS Stimulant Treatment to rates of smoking in adulthood. The participants were grouped as ADHD (Severe or Moderate DSMIV ADHD) versus Not ADHD (Mild and Not ADHD) (Figure 4). The Chi-square for this comparison was significant (p≤.001); childhood ADHD is significantly associated with adult daily smoking.

The Chi-square analysis of rates of adult smoking for groups defined by CNS stimulant treatment for 6 months or more versus never using CNS stimulants in childhood (Figure 5) was also significant (p≤.001). The relative effects of ADHD and CNS stimulant treatment will be explored in the multivariate analysis.

Multivariate prediction of adult daily smoking DSMIIIR psychoactive substance use disorders (PSUD).

There were significant differences between the ADHD (Severe and Moderate) and Not ADHD (Mild and Not) groups on adult daily smoking (38% vs 18%) and the DSMIIIR dependency diagnoses of tobacco (45% vs 22%), cocaine (23% vs 11%), and stimulant dependence (25% vs 13%), but not marijuana (29% vs 28%) and alcohol dependence (40% vs 31%.). There were significant differences in use of stimulant treatment for 6 months or more and adult daily smoking (43% vs 19%), tobacco dependence (48% vs 26%), and cocaine dependence (24% vs 13%).

Logistic regressions were used to estimate the joint effects of the independent variables. Other potentially relevant independent variables, such as socio-economic status, cognitive ability, and ethnic status were examined in preliminary analyses but were not were found to be associated with these dependent variables.

Table 3 displays the adjusted odds ratios for adult daily smoking and for each of the DSMIIIR dependence diagnoses. Childhood conduct problems was not included in the summary table since it did not contribute significantly to any of the dependent variables. Although ADHDs smoked daily significantly more than not ADHDs, the adjusted odds ratio for ADHD in the prediction of daily smoking was not significant; however, the adjusted odds ratios for any use of CNS stimulants in childhood was significant.

The adjusted odds ratio for severe ADHD was significantly associated with dependence on all of the substances with stimulating properties - tobacco, cocaine, stimulants, and either cocaine or stimulant dependence - but not for marijuana and alcohol. There was a significant adjusted odds ratio for CNS stimulant treatment for cocaine dependence; and marginally significant odds ratios for predictions of tobacco dependence and stimulant or cocaine dependence.

The adjusted odds ratios for early initiation into tobacco were significant for all substances. The adjusted odds ratio for gender was significant for tobacco dependence, marijuana dependence, and alcohol dependence indicating that more males were tobacco dependent, marijuana dependent and alcohol dependent.

DISCUSSION

This investigation used prospective longitudinal life history records from childhood to early adulthood of ADHD and Age Mate Control participants to explore two hypotheses relevant to age of becoming a regular smoker, daily smoking in adulthood, and DSMIIIR substance dependence diagnoses - an ADHD self medicating hypothesis and a CNS stimulant treatment sensitization hypothesis.

Support for the self-medicating hypothesis

The severity of ADHD symptoms was shown to be significantly related to the age of onset of regular smoking during the developmental period; the more severe the ADHD symptoms, the earlier the onset of regular smoking. Rates of adult smoking were significantly different for ADHD (Severe and Moderate) versus not ADHD (Mild and not) participants indicating that a greater number of ADHD adolescents who were regular smokers become daily smokers in adulthood. The results of the survival analysis and the Chi-square analysis of adult smoking support a self-medicating hypothesis. Support for a self-medicating process is reflected as well in significant differences between severe and moderate ADHDs and Mild and Not ADHDs on rates of DSMIIIR dependence diagnoses of tobacco, cocaine, and stimulants.

The more severe the DSMIV ADHD symptoms the more likely individuals were to become dependent on tobacco, cocaine, stimulants, and either cocaine or stimulants, but not marijuana or alcohol. A self-medicating hypothesis predicts the use of particular substances, not any substance. And the substances of interest for ADHDs are those that would be most likely to self-medicate the ADHD symptoms, namely stimulants.

When the severity of ADHD was entered into a logistic equation (with age of initiation into tobacco, gender, stimulant treatment, conduct problems, and birth-year cohort group) predicting adult daily smoking and DSMIIIR substance dependence diagnoses, Severe ADHDs were 2.5 times more likely to become tobacco dependent, 3.8 times more likely to become cocaine dependent, and 3.0 times more likely to become stimulant dependent. Such findings suggest that aspects of ADHD symptomatology cognitively compromise the capacity to control or self-regulate the impulse to use substances with stimulating properties and to become dependent on them.

The fact that severity of ADHD was not a significant predictor of adult daily smoking, but was a significant predictor for tobacco dependence suggests that ADHD may be more implicated in dependence on substances with stimulating properties (self medication) and stimulant treatment more implicated in heavy use of tobacco (sensitization). Further exploration of such differential effects for substance dependence versus substance abuse of stimulants is warranted.

In order to explore further the self-regulating processes involved in dependence on tobacco, cocaine, and stimulants, subsequent investigation should align itself with recent proposals (24) to distinguish between those individuals whose problems reside in the behavioral inhibition domain (hyperactive-impulsive) in contrast to those with primarily inattentive symptoms. The cognitive processes on which behavioral inhibition rely affect ability to anticipate outcomes and to regulate behavior to avoid harmful conditions such as involvement with substances.

Support for the sensitization hypothesis

The survival analysis comparing age of regular smoking for those who received stimulant treatment compared with those not receiving stimulant treatment provided support for a sensitization hypothesis in humans since stimulant treatment predisposed to regular smoking at an earlier age. Although there seemed to be a "protective effect" for the length of time stimulant treatment was used, and those being treated longer smoked regularly at a later age, this protective effect was short-lived since the rates of adult daily smoking did not differ by length of stimulant treatment.

Significant differences in rates of adult daily smoking for those using stimulant treatment and those not treated also supported the sensitization hypothesis.

The logistic regression of the childhood variables with adult daily smoking also supported a sensitization effect in that the odds ratio for severity of ADHD was not significant when the effects of CNS stimulant treatment and age of initiation into tobacco were accounted for. Children who used stimulant treatment for less than one year were 4 times more likely to become daily smokers in

adulthood, and those who used stimulant treatment for more than a year were 2.8 times more likely to become daily smokers.

The logistic regressions of childhood variables with DSMIIIR substance dependence diagnoses showed that children who used CNS stimulants for more than 1 year were 2.3 times more likely to become cocaine dependent. The odds ratios were marginally significant for tobacco and stimulant dependence. But there was no relationship between use of stimulant treatment and dependence on marijuana or alcohol.

The pattern of sensitization appears to follow the path of CNS stimulant treatment to early onset of regular smoking, to adult daily smoking, to adult tobacco, cocaine, and stimulant dependence. The investigation did not permit definitive conclusions, however, regarding the relative strength of either a sensitization or a self medicating explanation.

The tobacco gateway hypothesis.

There is increasing evidence that "tobacco use is involved, possibly more than by simple association, in the use of other substances containing psychoactive chemicals" (45 p. 279.) In this study there were earlier and higher rates of regular tobacco use among ADHD participants and those treated with stimulants. The inferences follow that in childhood ADHDs are more likely to self-medicate with nicotine and that stimulant treatment may sensitize to early tobacco use (28.) Early involvement with nicotine, in turn, predisposes to higher rates of dependence on cocaine and stimulants in adulthood. The significant role of tobacco in marijuana and alcohol dependence is not answered in this investigation.

Childhood Problem Behavior as a Factor in PSUD

This study provided no support for the childhood problem behavior hypothesis predicting higher rates of smoking and substance abuse. It is important to distinguish childhood evidence for conduct problems based on parent and teacher ratings as used in this study from subsequent adolescent diagnoses of Conduct Disorders and Oppositional Defiant Disorders (49, 50, 70, 71).

Some investigators (70) have provided evidence to refute the commonly held belief that individuals who have a history of early childhood problem behavior always persist in their aggressive behavior through adolescence. A developmental model of aggression is the more reasonable approach. Ratings of participants' behavior in this study occurred when they were at an average age of 9. There was a significant linear relationship between severity of childhood conduct problems and severity of ADHD, but among those rated as having childhood conduct problems are those who develop both Conduct Disorders and/or Oppositional Defiant Disorder in adolescence as well as those with transitory problem behavior in childhood whose problems will not persist past adolescence. Methods that group subjects into the life-course, transitional, and late onset types of aggressive behavior will be necessary to provide explanatory evidence on the relationship between types of childhood conduct problems, adolescent conduct disorders and oppositional defiant disorders and adult substance use for these participants.

Conclusion.

This prospective longitudinal study of ADHD and age mate control subjects, reconfigured according to research diagnostic proxies for severity of DSMIV ADHD, has provided evidence that childhood use of CNS stimulant treatment is significantly and pervasively implicated in the uptake of regular smoking, in daily smoking in adulthood, as well as DSMIIIR diagnoses of tobacco and cocaine dependence. The severity of ADHD was a significant risk factor in adult dependence on substances with stimulating properties, namely tobacco, cocaine, and stimulants. The use of stimulant treatment in childhood was significantly related to the age of onset of regular smoking, daily smoking in adulthood, and to cocaine dependence. Early initiation into tobacco was generally related to predictions of PSUD. Further research to clarify the differential role of nicotine as a sensitizing agent in heavy lifetime use of substances with stimulating properties in contrast to its role in dependence on marijuana and alcohol would be desirable.

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Table 1 - Number and percent of adult participants initially identified by social system definers re-classified with DSMIV ADHD research diagnostic proxies. N=399.

| DSMIV ADHD Patterns & Severity | Original Classification Groups - N & % Satisfying DSMIV ADHD Research Diagnostic Criteria | | | | |
| | Hyperactives | | | Controls | |
	Primary N=136	Secondary N=31	Untreated N=50	Behavior N=41	Age Mates N=141
Severe - Pervasive Combined	37 (27%)	5 (16%)	5 (10%)	0	0
Pervasive Inattentive	21 (16%)	9 (29%)	11 (22%)	2 (5%)	3 (2%)
Pervasive Hyper-Impulsive	7 (5%)	1 (3%)	3 (6%)	0	0
Total Severe	**65 (48)%**	**15 (48%)**	**19 (38%)**	**2 (5%)**	**3 (2%)**
Moderate-Situational Mixed	3 (2%)	0	3 (6%)	0	0
Situational Combined	41 (30)%	9 (29%)	8 (16%)	3 (7%)	5 (4%)
Total Moderate	**44 (32%)**	**9 (29%)**	**11 (22%)**	**3 (7%)**	**5 (4%)**
Mild Situational Inattentive	12 (9%)	3 (10%)	12 (24%)	3 (7%)	7 (5%)
Situational Hyper-Impulsive	7 (5%)	0	4 (18%)	0	3 (2%)
Total Mild	**19 (14%)**	**3 (10%)**	**16 (32%)**	**3 (7%)**	**10 (7%)**
Symptom Criteria Not Met	**8 (6%)**	**4 (13%)**	**4 (8%)**	**33 (81%)**	**123 (87%)**
Symptom Criteria Met	**128 (94%)**	**27 (87%)**	**46 (92%)**	**8 (19%)**	**18 (13%)**

Table 2 - Rates of treatment with CNS stimulants for participants grouped by initial classification and by research diagnostic criteria for severity of DSMIV ADHD.

| Severity of DSMIV ADHD | N prescribed stimulant treatment and total N in each group | | | | | Total by Severity |
| | Hyperactives | | | Controls | | |
	Primary N=136	Secondary N=31	Untreated N=50	Behavior N=41	Age Mates N=141	of ADHD
Severe	51 of 64	11 of 15	0 of 19	0 of 2	0 of 3	62 of 103 (60%)
Moderate	40 of 44	7 of 10	0 of 11	1 of 3	0 of 5	48 of 73 (66%)
Mild	10 of 19	1 of 3	0 of 16	0 of 3	0 of 10	11 of 51 (22%)
Not ADHD	7 of 8	2 of 4	0 of 4	0 of 33	1 of 123	10 of 172 (6%)
Total by Original Classification	108 of 135(80%)	21 of 32 (66%)	0 of 50	1 of 41 (2%)	1 of 141 (<1%)	131 of 399 (33%)

Figure 1 - Survival Analysis - Percent Not Smoking Regularly During the Developmental Period by ADHD Classification
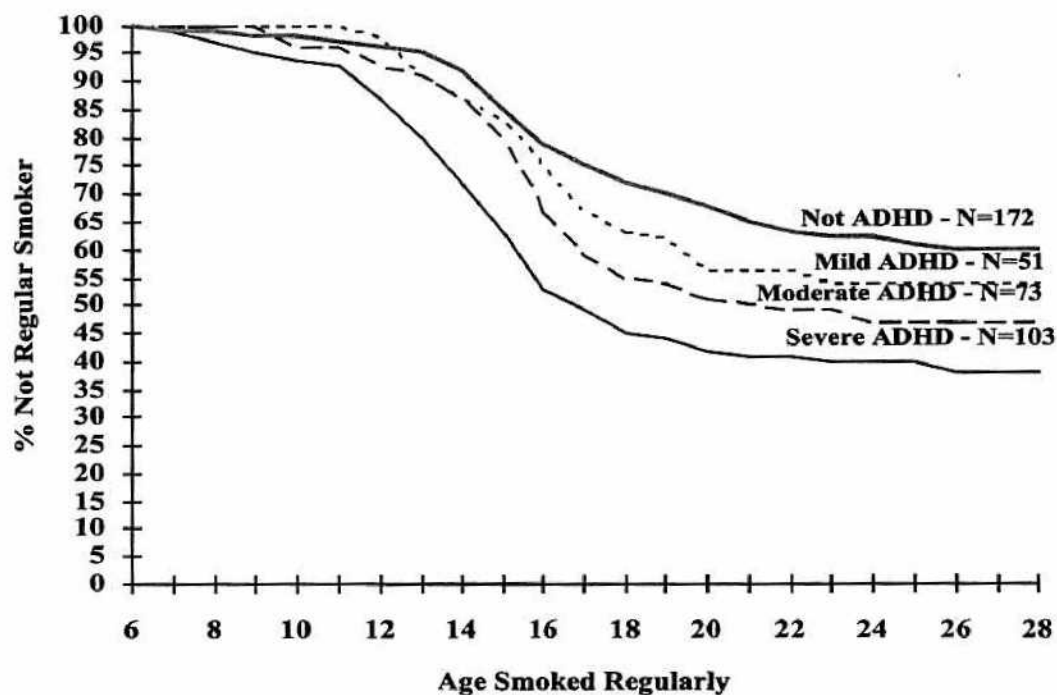
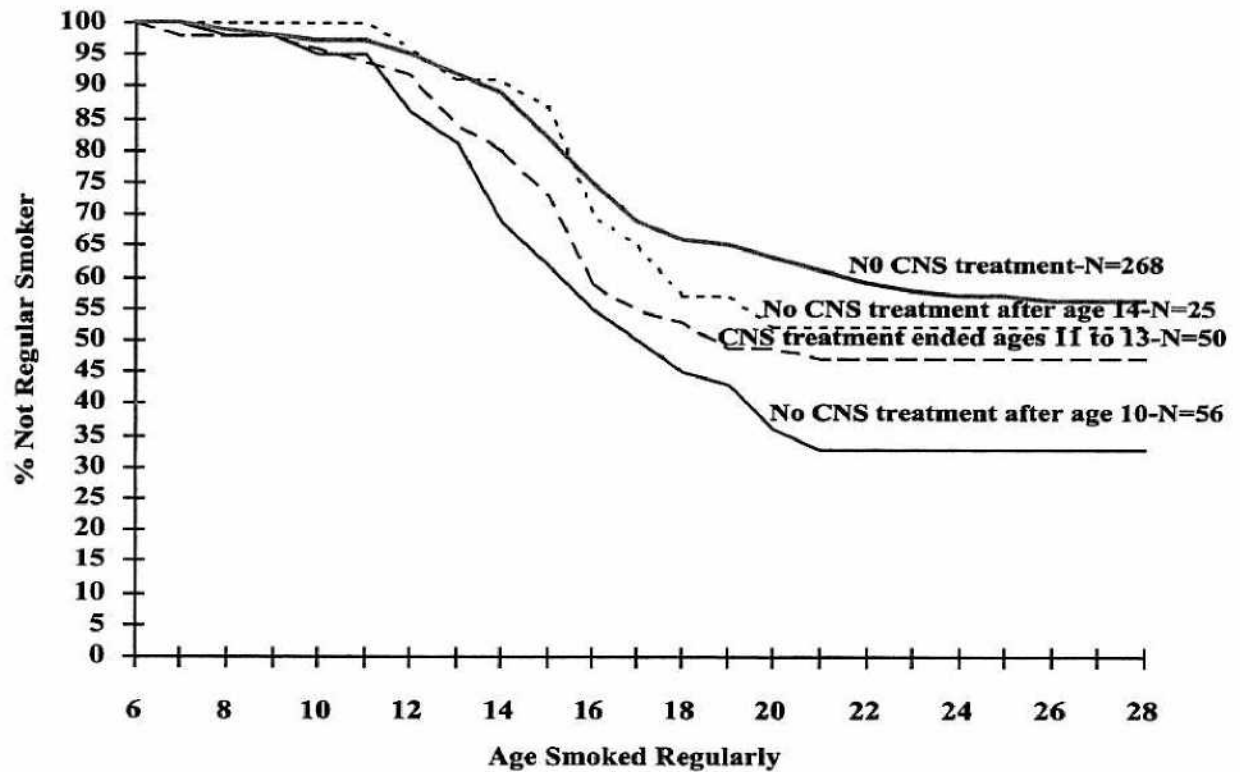Overall Comparison: Lee Desu Statistic 15.166, df=3, $p \leq .01$

Pairwise Comparisons: Severe vs Never $p \leq .000$; Severe vs Mild $p \leq .05$; Severe vs Moderate $p \leq .10$; Moderate vs Never $p \leq .10$

Stimulant Treatment as a Risk Factor

Figure 2 - Survival Analysis - Percent Not Smoking Regularly During Developmental Period for Subjects Who Used CNS Stimulant Treatment Before They Become Regular Smokers
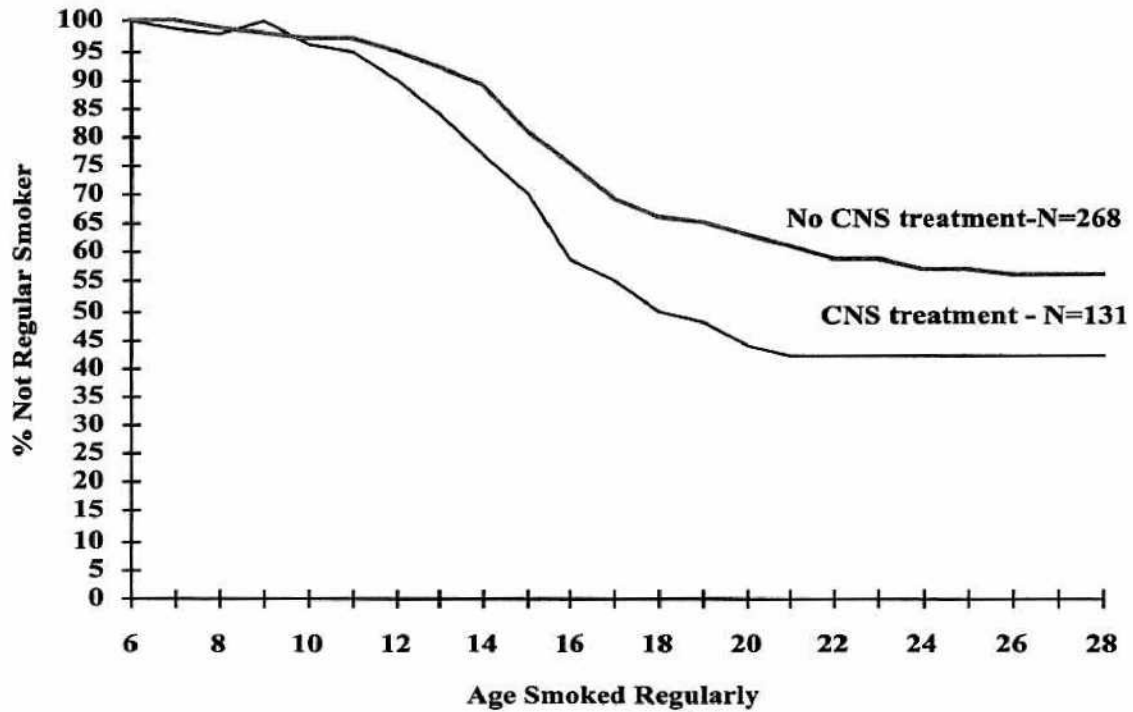
Overall Comparison: Lee Desu Statistic 5.825 df=1 $p \leq .05$

Figure 3 - Survival Analysis - Percent Not Smoking Regularly During Developmental Period for Subjects with Different CNS Stimulant Treatment Histories
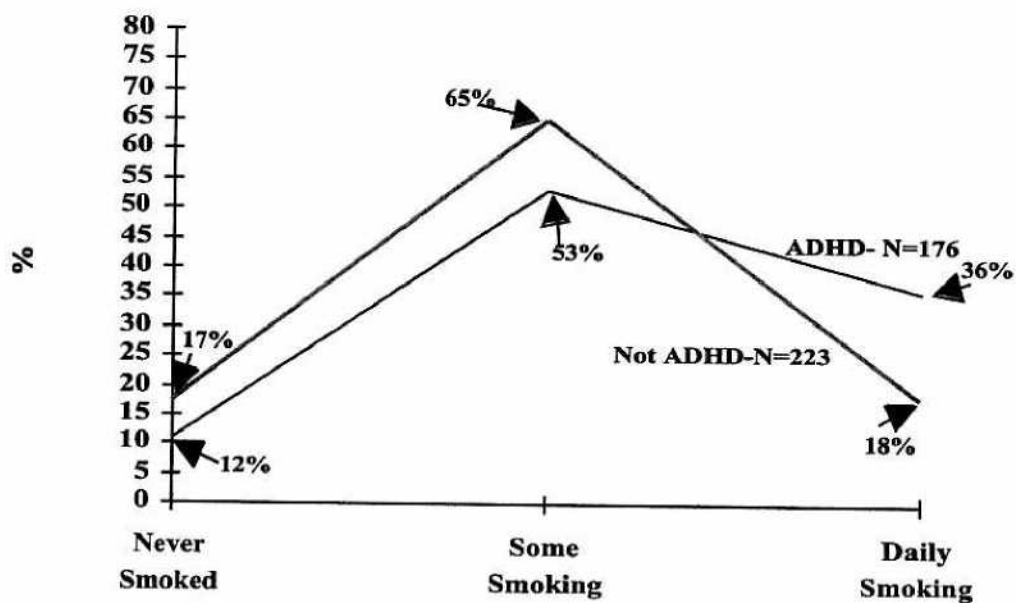

Overall Comparison: Lee Desu Statistic 15.280 df=3 $p \leq .01$

Pairwise Comparisons: No CNS after Age 10 vs no CNS $p \leq .001$;. No CNS after Age 10 vs Off CNS After Age 14 $p \leq .10$
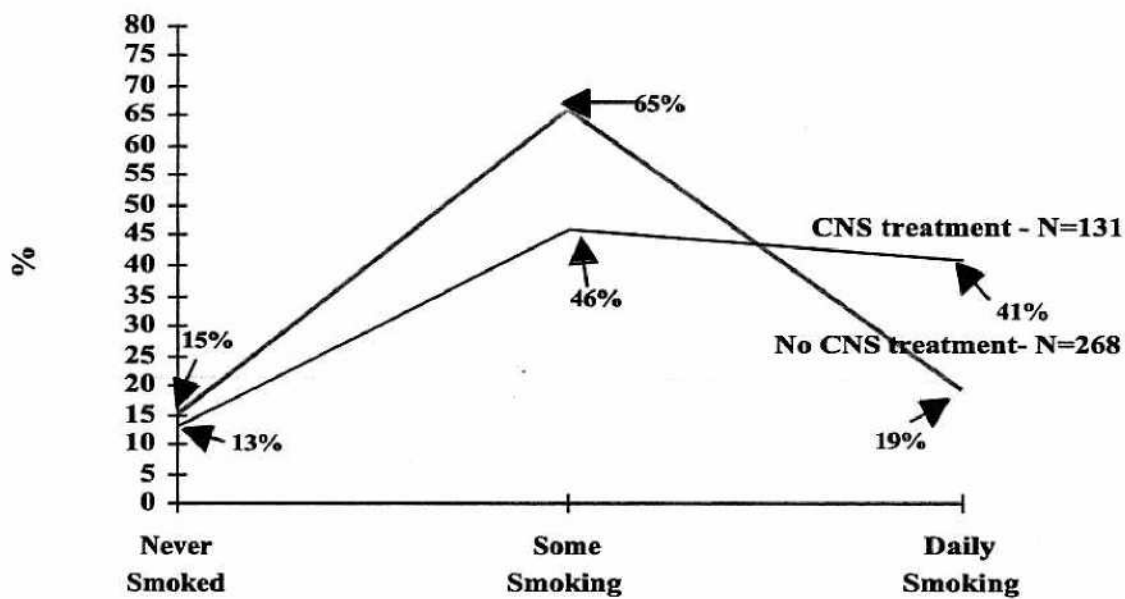
Figure 4 - Adult smoking status for ADHDs (Severe and Moderate) and not ADHDs (Mild and not ADHD)

Pearson

Chi-square $_{df=2}$ = 16.835, $p \le .001$

Figure 5 - Adult Smoking Status of Subjects Treated with CNS Stimulants in Childhood Compared with Those Who Were Not Treated with CNS Stimulants

Pear

Chi-square $_{df=2}$ = 23.156 $p \leq .000$

Table 3 - Adjusted Odds Ratios in Logistic Regressions Predicting Adult Daily Smoking and DSMIIIR Psychoactive Substance Use Disorders. N= 360.

Variables in the analysis	Adult Daily Smoking	DSIIIR Psychoactive Substance Use Dependence					
		Tobacco	Cocaine	Stimulant	Cocaine or Stimulant	Marijuana	Alcohol
	Adjusted Odds Ratio	Adjusted Odds Ratio	Adjusted Odds Ratio	Adjusted Odds Ratio	Adjusted Odds Ratio	Adjusted Odds Ratio	Adjusted Odds Ratio
DSMIVADHD							
Severe	1.600	2.465*	3.778**	2.965*	2.695*	.859	1.475
Moderate	1.516	1.671	1.763	2.560*	1.417	.660	.789
Gender	1.329	2.212*	1.806	1.619	1.378	2.499***	3.677***
Smoking Status							
Initiated Before Age 11	2.144+	4.818***	5.253**	3.751**	3.748**	4.550***	2.170*
Initiated by Age 11 - 13	3.128**	4.862***	4.666**	4.281**	4.117**	4.835***	2.294**
CNS Stimulant Treatment							
More than 1 yr.	2.817**	1.900+	2.251*	1.194	1.893+	1.280	1.520
Less than 1 yr.	3.951**	1.239	1.963	.767	.999	1.072	1.184
Age Group at Entry							
Oldest	1.098	1.095	2.436*	1.075	1.496	1.063	.806
Middle	.930	.887	1.794	1.093	1.401	1.038	.932

Note to Table: *** $p \leq .001$, ** $p \leq .01$; * $p \leq .05$; + $p \leq .10$ Logistic regressions also controlled for childhood Conduct Problems.

None of the interactions between independent variables and the dependent variables was significant.