

Adolescent Substance Use in the Multimodal Treatment Study of Attention-Deficit/Hyperactivity Disorder (ADHD) (MTA) as a Function of Childhood ADHD, Random Assignment to Childhood Treatments, and Subsequent Medication

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Objective: To determine long-term effects on substance use and substance use disorder (SUD), up to 8 years after childhood enrollment, of the randomly assigned 14-month treatments in the multisite Multimodal Treatment Study of Children with Attention-Deficit/Hyperactivity Disorder (MTA; $n = 436$); to test whether medication at follow-up, cumulative psychostimulant treatment over time, or both relate to substance use/SUD; and to compare substance use/SUD in the ADHD sample to the non-ADHD childhood classmate comparison group ($n = 261$). **Method:** Mixed-effects regression models with planned contrasts were used for all tests except the important cumulative stimulant treatment question, for which propensity score matching analysis was used. **Results:** The originally randomized treatment groups did not differ significantly on substance use/SUD by the 8-year follow-up or earlier (mean age = 17 years). Neither medication at follow-up (mostly stimulants) nor cumulative stimulant treatment was associated with adolescent substance use/SUD. Substance use at all time points, including use of two or more substances and SUD, were each greater in the ADHD than in the non-ADHD samples, regardless of sex. **Conclusions:** Medication for ADHD did not protect from, or contribute to, visible risk of substance use or SUD by adolescence, whether analyzed as randomized treatment assignment in childhood, as medication at follow-up, or as cumulative stimulant treatment over an 8-year follow-up from childhood. These results suggest the need to identify alternative or adjunctive adolescent-focused approaches to substance abuse prevention and treatment for boys and girls with ADHD, especially given their increased risk for use and abuse of multiple substances that is not improved with stimulant medication. Clinical trial registration information—Multimodal Treatment Study of Children With Attention Deficit and Hyperactivity Disorder (MTA); <http://clinicaltrials.gov/>; NCT00000388. *J. Am. Acad. Child Adolesc. Psychiatry*; 2013;52(3):250-263. **Key Words:** attention-deficit/hyperactivity disorder (ADHD), substance use

Risk of substance use or substance abuse or dependence disorders for children with attention-deficit/hyperactivity disorder (ADHD) is a topic of substantial interest for

researchers, practitioners, and parents. Recent meta-analytic reviews of pertinent longitudinal studies have reported moderately higher rates of substance abuse and dependence by early adulthood for children with the disorder in relation to non-ADHD comparison groups.^{1,2} For example, although results across studies are heterogeneous, children with ADHD are more than twice as likely



This article is discussed in an editorial by Dr. Benjamin I. Goldstein on page 225.

as comparison peers to meet diagnostic criteria for marijuana abuse or dependence by early adulthood.² The included studies do not, however, provide data about the developmental course of substance use, and they tend to emphasize diagnosis of substance abuse or substance dependence even for adolescents whose addiction risk is often better measured by more developmentally sensitive, continuous variables (e.g., frequency of alcohol use).^{3,4} Nevertheless, the results raise important questions about factors, such as treatment history, that might affect ADHD-related addiction vulnerability.

Although not the only evidence-based treatment for ADHD,⁵ stimulants (e.g., methylphenidate, amphetamine) are the most commonly used and widely accessible treatment, and prescription rates have increased markedly in recent years.⁶ These medications reliably decrease ADHD symptoms for more than 80% of diagnosed children, sometimes dramatically.^{7,8} To the extent that symptoms of ADHD contribute to addiction vulnerability, treatment with stimulant medication should theoretically decrease risk. Indeed, a growing number of studies have shown that ADHD symptom persistence correlates with substance use.⁹⁻¹² In other accounts, however, risk of substance abuse has been hypothesized to *increase* for children medicated with stimulants.¹³ This possibility, potentially linked to the overlap in brain-based mechanisms for both addictive behaviors and stimulant medication efficacy,¹⁴ has been supported, with mixed results, in animal studies, showing an enhanced response to drugs of abuse following methylphenidate exposure.¹⁵ However, route of administration, relative dosages, developmental timing of medication receipt, and limits of cross-species parallels (or lack thereof) complicate interpretation.

An early, small meta-analytic review of stimulant treatment and risk of substance abuse reported a protective effect of medication use in adolescence and, to a lesser extent, in early adulthood.¹⁶ However, considering recently published studies, the accumulated data appear to be mixed. Some studies have found protective associations;¹⁷⁻²⁰ one reported predisposing associations (i.e., more medication treatment, more substance use),^{13,21,22} and three reported no association.²³⁻²⁵ Barkley *et al.*²⁵ reported one positive association for adulthood cocaine use, which fell to nonsignificance after controlling for conduct disorder. A retrospective chart review of a birth

cohort in Rochester, MN, reported protection from substance abuse by age 18 years.²⁶ Two other prospective longitudinal studies recently reported no association between years of stimulant treatment and substance use severity or disorder for 16- to 22-year-olds,²⁷ and no association between childhood treatment with stimulant medication (including course of medication) and SUD or tobacco use to age 24 years²⁸.

Substantial and important variability in the methodologic features of these studies makes it difficult to synthesize the findings. Samples vary considerably in age both within and across studies, and age is a potentially confounding variable that is strongly related to both treatment and substance use (W. Pelham, unpublished conference presentation, 2004 October). Compounding this problem is that most relevant research is based on sample sizes of about 100, which can be insufficient for examining the association between stimulant treatment and a variable that has a low to moderate frequency occurrence even in high-risk samples (i.e., substance abuse). For example, marijuana abuse and dependence peak at 5.6% of 18- to 25-year-olds nationally and are even less frequent at younger ages.²⁹ A few of the relevant studies measured actual substance use,^{21,24,25,27} whereas others relied on diagnostic assessments of abuse or dependence (which, as mentioned earlier, may not identify teens on a developmental trajectory toward abuse/dependence in adulthood). Studies also vary in their operationalization of psychoactive treatment history, which has resulted in fundamentally different questions being addressed across studies comprising a relatively small body of literature.

The longitudinal follow-up of the children in the Multimodal Treatment Study of ADHD (MTA) provides an opportunity to examine the association between ADHD treatment and substance abuse with a large, diverse, narrow age-band sample recruited in childhood, treated for 14 months in a randomized clinical trial, and followed prospectively with substance use assessments through adolescence.¹⁴ The randomized trial design of the MTA in childhood (see below) provided partial protection from the influences of self-selection into treatment at an age when medication treatment is at its peak.^{30,31} In the first published MTA report of substance use²⁴ at 3 years after study baseline, no protective or predisposing associations were found between

substance use and early medication exposure, measured as either randomly assigned treatment or proportion of days medicated in the year leading up to the substance use assessment. However, substance use was nascent in the first follow-up report, with limited opportunity to detect treatment effects because ages ranged from 10 to 13 years. We now turn to the 8-year follow-up (mean age, 16.8 years), when substance use is more prevalent.³²

Hence, one aim of the current study was to test the association between medication treatment (both as randomly assigned during childhood and naturalistically used following the clinical trial) and adolescent substance use/SUD by mean age 17 years. We opted for a three-pronged approach to examine substance use/SUD as a function of treatment: random assignment to medication in childhood (at a mean age of 8.5 years); concurrent medication use across the multiple follow-up assessments; and, most importantly, duration of medication (specifically psychostimulant treatment) from study entry to the 8-year follow-up. Thus, we expanded our analyses to consider putative long-term exposure effects of stimulant medication that have been hypothesized to either protect children with ADHD from or increase risk for substance use/SUD.¹⁴ Although the initial randomization affected subsequent parental choices about medication and therefore provided only partial protection against the effects of confounding variables underlying natural selection into medication over time, initial group differences in medication use were lost by the 3-year follow-up.³³ To control for these and other individual differences in propensity to medicate over time, we selected an analytic approach—propensity score matching—favored for managing the effects of confounding variables.³⁴ A similar propensity analysis was conducted at the 3-year follow-up for effects of medication on ADHD symptoms, without significant results.³⁵

A second aim was to compare substance use/SUD at the 8-year follow-up between the children with ADHD and an MTA-recruited and followed comparison group without ADHD. This analysis tested an extension of our prior findings²⁴ of ADHD-related risk for substance use experimentation to heavier levels of use/SUD for the high school age range. Polysubstance use is highly prevalent among teen substance users, but questions have arisen about ADHD-related drug

specialization, especially for tobacco because of its distinct pharmacologic (stimulant) properties.³⁶ Thus, we examined use of other drugs by tobacco users. We also tested whether our failure to find sex differences in early adolescent substance use²⁴ would extend to this older age range. Because of the larger research literature on ADHD for boys than for girls, it is not surprising that little research has been conducted on use/SUD in girls with ADHD histories (for exceptions, see Babinski *et al.*,³⁷ Biederman, *et al.*³⁸ and Hinshaw *et al.*^{39,40}).

METHOD

Participants

The participants with ADHD in the MTA were 579 children with *DSM-IV* ADHD combined type. Each of the six participating sites randomized 95 to 98 children to one of four treatment groups: Medication Management (MedMgt), Behavior Therapy (Beh), Combined MedMgt plus Beh (Comb), and Community Comparison (CC). At baseline (pretreatment), participants were 7.0 to 9.9 years of age (mean = 8.5 years, SD = 0.8 years). The MTA recruitment strategy, procedures for diagnosing ADHD, treatment specifics, and sample demographics have been described elsewhere.^{41–46}

The children were reassessed at 3 and 9 months, at completion of the 14-month treatment phase, at 24 and 36 months after randomization, and again at 6 and 8 years after randomization. Participation rates dating from 14 months were 97%, 93%, 84%, 78%, and 75% of the original 579 enrolled, respectively. There were no significant differences in any baseline characteristics between participants and non-participants for the 36-month assessment.³³ However, children lost to the 8-year follow-up assessment, compared with those retained, were more often male and had younger mothers, less-educated parents, lower parent income, and parents more likely to have antisocial personality disorder at baseline ($p < .025$ corrected for experiment-wise error). There were no significant differences on the remaining sociodemographic or adversity variables (e.g., age, grade, ethnicity/race, parent marital status, stable residency, on welfare, parent job loss, child health, birthweight) or on baseline measures of intellect and achievement, parent and teacher report of ADHD and oppositional defiant disorder (ODD) symptoms, parent-reported aggression and conduct problems, parental diagnoses of mood, anxiety, alcohol, or other drug use disorders, or randomized treatment group assignment. Mean ages at the 6- and 8-year follow-up assessments were 14.9 (SD = 1.0) and 16.8 (SD = 1.0) years, respectively.

A local normative comparison group (LNCG, $N = 289$) was recruited at 24 months to reflect the local populations from which the ADHD sample was drawn.

The LNCG children were randomly selected from the same schools and grades and in the same sex proportions as the children with ADHD. LNCG children were not excluded from recruitment because of symptoms of ADHD, but those found to have diagnosable ADHD ($n = 31$) were excluded from the present analyses as we have done previously.⁴⁷ The assessment battery included the Diagnostic Interview Schedule for Children—Version IV (DISC-IV⁴⁸) and teacher-reported ratings of ADHD symptoms, which afforded examination of *DSM-IV* diagnoses and ADHD symptom severity. The LNCG had the same entry criteria as the children with ADHD except for ADHD diagnosis and age; they were matched to the age of the ADHD sample at 24 months after randomization. Thus, data for the LNCG are available starting at the 24-month assessment. At that time, average age of the LNCG (mean = 10.4 years, SD = 1.08 years) did not differ significantly from that of the ADHD sample ($t_{811} = 1.04, p = .36$) at that time point. The percentage of female subjects was similar in the LNCG (18.7%, $n = 54/289$) and the ADHD samples (19.7%, $n = 114/579, \chi^2_1 = 0.13, NS$). The percentage of retained LNCG participants by 6 and 8 years was 87% (252/289) and 90% (261/289), respectively. The LNCG participants lost to the 8-year assessment had less stable residency and younger mothers than those retained, but all other baseline variables were nondiscriminating. LNCG mean ages at the 6- and 8-year assessments were 14.5 (SD = 1.2) and 16.6 years (SD = 1.2), respectively.

Measures

The substance use outcomes were measured at all interviews beginning with the 24-month assessment. Use (e.g., consumption) of substances was measured separately from *DSM* symptoms of abuse or dependence.⁴⁹ The primary analyses made use of two variables: a single substance use variable and a single abuse/dependence variable, each composited across substances. Secondary analyses explored substance-specific associations.

Substance Use. Substance use was assessed with a child/adolescent-reported questionnaire⁵⁰ adapted for the MTA. The measure included items for lifetime and current (past 6 months) use of alcohol, cigarettes, chewing tobacco, marijuana, and other street drugs. Also included were items for nonprescribed use or other misuse of psychoactive medications, including stimulants. The measure was modeled after similar substance use measures in longitudinal or national survey studies of alcohol and other drug use^{51–53} that also rely on confidential youth self-report as the best source of data.⁵⁴ A National Institutes of Health (NIH) Certificate of Confidentiality further strengthened the assurance of privacy.

Our primary substance use variable was a binary composite that allowed consideration of multiple substance use classes simultaneously. Analysis of

substance use as an ordinal variable is a common approach—particularly for studying adolescents.⁵⁵ Substance use was coded positive if any of the following behaviors, selected after examining distributions, were endorsed as occurring in the participant's lifetime: drank alcohol (more than just a sip) more than five times or drunk at least once; smoked cigarettes or tried chewing tobacco more than a few times; used marijuana more than once; or used inhalants, hallucinogens, cocaine, or any of amphetamines/stimulants, barbiturates/sedatives, opioids/narcotics without a prescription or misused a prescription (used more in quantity or more often than prescribed). Each of the four types of substances, as well as daily use of tobacco and the number of substance use classes endorsed (0, 1, 2 or more), were explored in secondary analyses.

For the analysis of stimulant treatment duration in relation to substance use at the 8-year follow-up, the primary outcome was number of substances used in the past 6 months, to ensure that most stimulant treatment received would have preceded substance use. Component variables included the following: "drunk" once or more or drank alcohol three to four times or more; one or more cigarettes/day in the past month (time frame exception specific to tobacco); marijuana two or more times; and any other illicit drug use or prescription medication misuse. Secondary analyses explored each class of substances separately.

Substance Abuse or Dependence (SUD). *DSM-IV* abuse or dependence was based on a positive parent or child report with the Diagnostic Interview Schedule for Children Version 2.3/3.0 (DISC⁴⁸) at the 6- and 8-year follow-up assessments. The DISC includes both lifetime and past-year diagnoses. The Diagnostic Interview Schedule-IV⁵⁶ was used at the 8-year follow-up for participants 18 years or older ($n = 111$). SUD was defined as presence or absence of any abuse or dependence in the lifetime (excluding tobacco dependence, due to differences in the meaning of abuse/dependence for tobacco versus other substances). Additional analyses explored SUD for alcohol, tobacco, and marijuana/other drugs (illicit or misuse of prescription medications) separately.

For the analysis of stimulant treatment exposure over time in relation to substance use at the 8-year follow-up, the primary outcome variable was SUD in the past year for any substance (excluding tobacco). Secondary analyses explored alcohol and marijuana/other drug use disorders separately.

Psychoactive Medication Treatment. In addition to original randomized assignment to treatment, two medication treatment variables were calculated from responses to the Services for Children and Adolescents—Parent Interview,^{57,58} administered at all assessments to collect a cumulative history of medication treatment since enrollment into the study. Detailed information about the children's psychoactive

medication over the follow-up period has been previously reported.⁴⁷ One variable was the proportion of days medicated with psychoactive medications in the past year at each follow-up assessment. These medications were predominantly stimulants but occasionally included others (atomoxetine, guanfacine, and typical alternative medications such as clonidine and amitriptyline). A second medication variable was calculated for the current study to reflect the cumulative number of days stimulant-treated since enrollment into the study.

Statistical Analysis

The analyses addressed the following aims: first, ADHD versus LNCG group differences in substance use and SUD; second, prediction of substance use and SUD from original randomized treatment assignment, including covariation with concurrent (past-year) medication at each assessment; and third, prediction of substance use and SUD from cumulative days stimulant treated since study entry (using propensity score-matching analysis).

The main analytic approach for the first and second items above was generalized estimating equation (GEE) analyses. As one method for mixed-effects regression with repeated measures, the GEE analysis is an extension of the general linear model (for a relevant overview, see Hedeker and Gibbons,⁵⁹ especially pp. 131–146). These analyses tested whether groups (subject group; assigned treatment group) differed as a function of time. In contrast to traditional repeated measures analysis of variance, mixed-effects regression allows inclusion of subjects with complete data on covariates but partial data on the outcome variable. Thus, all subjects with substance use data from at least one follow-up assessment between 24 months and the 8-year follow-up were included in tests of group \times time and treatment \times time effects ($n = 520$ ADHD; $n = 258$ LNCG). For the second aim, the ADHD sample size was reduced to $n = 515$ because of missing data for medication use. We tested individual point-in-time contrasts, treating group and time as fixed effects and the intercept as a random effect, to test the significance of group differences overall and at each follow-up assessment. Because of some variability in age at each assessment, age was controlled as a time-varying covariate (as expected, it was always a statistically significant correlate). Power was sufficient (≥ 0.80) to detect small treatment group differences (effect size of ≥ 0.28) at $p < .05$ or less. We used binary logit models for dichotomous outcomes and multinomial cumulative logit models for secondary analyses with ordinal count variable outcomes. We explored whether participant sex moderated results.

For the ADHD group only, effects of treatment were tested with three orthogonal contrasts following statistically significant treatment \times time interactions (or

for endpoint-only analyses, following statistically significant main effects of treatment): Comb+MedMgt versus Beh+CC, termed the MTA Medication Algorithm effect; Comb versus MedMgt, the Multimodality effect; and Beh versus CC, the Behavioral Substitution effect.⁶⁰ Consistent with prior analyses,^{24,47} we also tested an alternate set of planned contrasts in which behavioral treatment rather than medication algorithm was the primary divider: Comb+Beh versus MedMgt+CC (Intensive Behavioral effect); Comb versus Beh (Medication Addition effect); and MedMgt versus CC (Intensity of Medication effect). Covariates were site, age at each assessment and proportion of days medicated in the past year (time varying for repeated-measures analyses); and p values greater than .025 are not reported as significant to adjust for alpha inflation.

For the third aim (i.e., prediction of substance use and SUD from cumulative days stimulant treated since study entry), to test prediction of substance use and SUD from the number of days stimulant treated since study entry, we used propensity score matching analyses for ordinal treatment variables.³⁴ Propensity scores are calculated to represent each subject's propensity (e.g., probability) to be stimulant medicated over time as a function of baseline characteristics (e.g., original randomly assigned treatment, ADHD symptom severity, parent education, and family income). Participants with higher versus lower stimulant medication exposure are matched on the basis of these scores to statistically control for observed characteristics that may influence the likelihood of natural selection into treatment over time. We used matched pair analyses to compare the substance use and SUD variables between subjects with higher versus lower stimulant medication exposure.

RESULTS

Medication Use Over Time

To explicate the medication variable, we first examined medication use over time. As previously reported, proportion of days medicated in the past year declined over time to mean = 0.31 (SD = 0.42) by the 8-year follow-up. In contrast, at 14 months, when study-delivered treatment ended, the mean (SD) was 0.71 (0.22) for Comb; 0.71 (0.24) for MedMgt; 0.54 (0.41) for CC; and 0.16 (0.28) for Beh. At the 8-year follow-up, only 32.5% (132/406 with complete medication data) were medicated more than 50% of days in the past year (versus 63.3% or 257/406 at 14 months). Treatment was still predominantly with stimulants (83%) or stimulants plus nonstimulant treatment (8%). Cumulative number of days stimulant treated since enrollment into the study,

with mean (SD) = 1,402 (985) days (mean [SD] = 3.84 [2.70] years), was correlated 0.91 with cumulative dose ($p < .01$).

ADHD Versus LNCG

Substance Use. There was a main effect of ADHD versus LNCG group between the 24-month and 8-year follow-ups ($\chi^2 = 20.59, p < .0001$). Figure 1 depicts this finding as well as the expected increase in substance use with time. There was a barely significant group \times time interaction ($p = .05$), indicating variable group effects with time. Group differences were significant at each follow-up: 24 months ($\chi^2[1] = 12.54, p < .01$; 36 months, $\chi^2[1] = 6.65, p = .01$; 6 years, $\chi^2[1] = 11.11; p < .01$, 8 years, $\chi^2 = 4.24, p = .04$). However, the largest group difference was at the 6-year follow-up, when 35% (n = 155/443) of ADHD and 19.5% (n = 44/226) of LNCG participants reported substance use. Results were similar for number of substances used, with the ADHD versus LNCG group difference greatest at the 6-year follow-

up, with 17.8% (n = 79/443) of ADHD and 8% (n = 18/226) of LNCG participants reporting use of two or more substances (Figure 1).

Type of Substance. ADHD/LNCG group differences were apparent for all substances. There was a main effect of ADHD versus LNCG group for alcohol use between the 24-month and 8-year follow-ups ($\chi^2[1] = 5.99, p = .01$), but no group \times time interaction. There was a main effect of ADHD versus LNCG group for tobacco use ($\chi^2[1] = 23.98, p < .01$ [group \times time interaction not tested because no LNCG subjects reported smoking at 24 or 36 months]). Few participants were sole tobacco users (i.e., did not also report other substance use), comprising 3.6% of participants with ADHD (n = 15/420) versus 0% of those with LNCG. There were more daily smokers at 8 years for ADHD (16.7%) than for LNCG (7.9%, $\chi^2[1] = 10.58, p < .01$). There was a main effect of ADHD versus LNCG group for marijuana and other drug use ($\chi^2[1] = 16.47, p < .01$), but no group \times time interaction. Figure 2

FIGURE 1 Proportion of participants using substances (by number of substances) from the 24-month through 8-year follow-up assessments. ADHD = attention-deficit/hyperactivity disorder; LNCG = local normative comparison group.

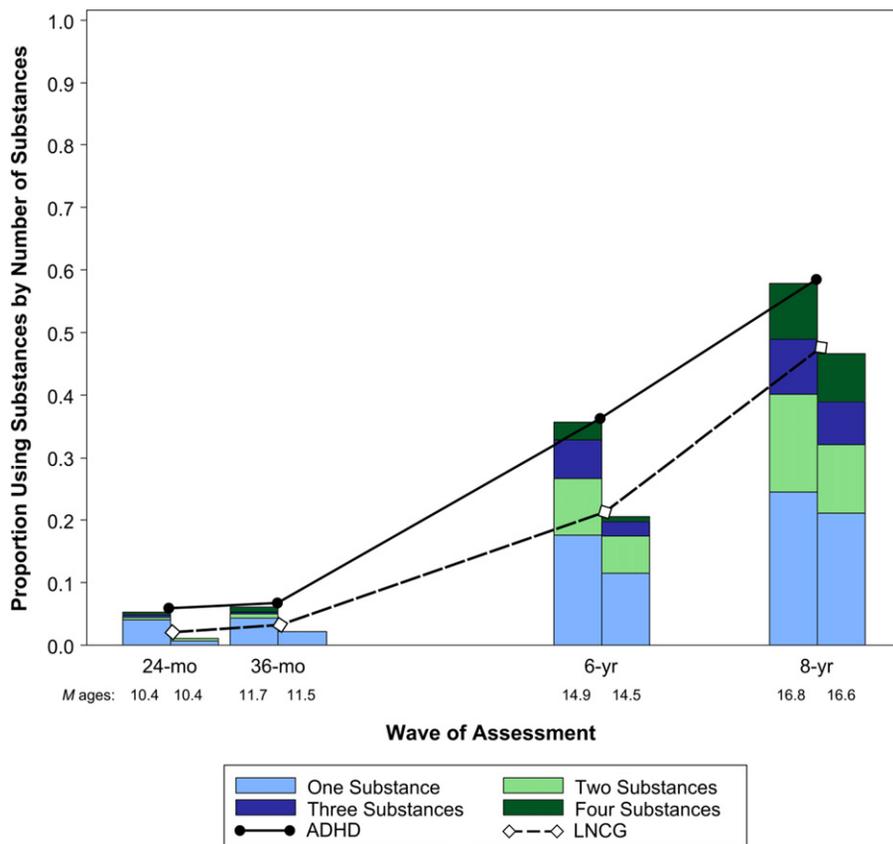
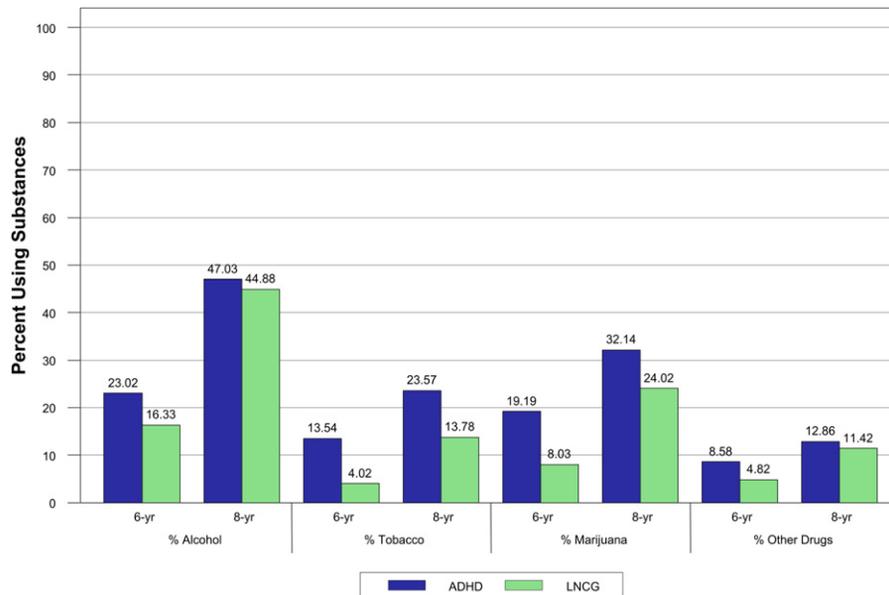


FIGURE 2 Percentage of participants reporting alcohol, tobacco, marijuana, and other drug use at each of the 6- and 8-year follow-up assessments. ADHD = attention-deficit/hyperactivity disorder; LNCG = local normative comparison group.



shows the expected age-related increases in substance use and the high prevalence of alcohol and marijuana use for both groups at a mean age of 17 years. The bar graphs also illustrate the relatively stronger contribution of tobacco and marijuana use to the ADHD versus LNCG group differences.

Rates of illicit drug use other than marijuana, including misuse of prescription medications, were low and not significantly different by group. At the 8-year follow-up, the following categories of substance use had base rates below 5%: amphetamines/ stimulants, barbiturates/sedatives, opioids/narcotics, inhalants, hallucinogens/ psychedelics, and cocaine. These rates included misuse (more use than prescribed or use without a prescription) of amphetamine/ stimulant medications for the ADHD (8/422, 1.9%) and LNCG (4/230, 1.7%) groups.

SUD. There was a main effect of group (ADHD versus LNCG) on SUD, but no main effect of time or group \times time interaction. The group effect was statistically significant at 6 years [$\chi^2(1) = 11.01, p < .01$] but not at 8 years [$\chi^2(1) = 1.45, p = .23$] (for rates, see Table 1).

Type of SUD. For alcohol abuse or dependence, there was no main effect of group, no main effect of time, and no group \times time interaction (for all rates, see Table 1). For marijuana/other

drug abuse or dependence, there was a main effect of group, but no main effect of time and no group \times time interaction. For nicotine dependence, there was a main effect of group, but no main effect of time. In each case, the ADHD group had greater use. There were too few nicotine dependence diagnoses among LNCG subjects to evaluate a group \times time interaction.

Sex. There was no main effect of sex ($\chi^2[1] = .49, p = .49$), and no sex \times ADHD group interaction ($\chi^2[1] = 0.30, p = .59$) for substance use. Results were parallel for number of substances used ($\chi^2[1] = 0.82, p = .37$, and $\chi^2[1] = .19, p = .66$, respectively). There was a main effect of sex for SUD ($\chi^2[1] = 4.21, p = .04$), with more boys (17.9%) than girls (11.5%) meeting diagnostic criteria. There was no group \times sex interaction ($\chi^2[1] = 0.02, p = .89$).

Associations With Treatment: Randomly Assigned in Childhood and Naturalistic Medication Use at Each Follow-up Assessment

Substance Use. Neither treatment assignment at baseline nor proportion of days medicated in the past year was significantly associated with substance use at any follow-up assessment. For the orthogonal treatment contrasts, p values ranged

TABLE 1 Percentage (n) of Participants Reporting Substance Use Disorders at Each of the 6- and 8-year Follow-Up Assessments

	6-Year				8-Year				GEE Model Results, χ^2 (df), p					
	ADHD		LNCG		ADHD		LNCG		Group (ADHD vs. LNCG)		Time	Group \times Time		
	n	%	n	%	n	%	n	%	χ^2	df	p	χ^2	df	p
Any SUD	9.93	(44)	3.14	(7)	15.06	(64)	10.76	(24)	8.66	(1), p < .01	.04	(1), p = .84	3.79	(1), p = .05
Alcohol	5.19	(23)	2.69	(6)	8.24	(35)	7.17	(16)	1.05	(1), p = .31	.12	(1), p = .73	1.16	(1), p = .28
Marijuana/other drug	7.22	(32)	1.79	(4)	12.50	(53)	6.73	(15)	12.66	(1), p < .01	.07	(1), p = .80	1.69	(1), p = .19
Nicotine dependence	3.39	(15)	0	(0)	4.47	(19)	1.79	(4)	11.55	(1), p < .01	1.33	(1), p = .25	—	—

Note: Nicotine dependence diagnoses are not included in the proportions reported for diagnosis with any substance use disorder (SUD). Attention-deficit/hyperactivity disorder (ADHD) sample sizes are n = 443 (6 years) and n = 425 (8 years). Local normative comparison group (LNCG) sample size is n = 223 (6 and 8 years). GEE = generalized estimating equations.

from .03 to .96 (with an average $p = .52$). The overall effect of the proportion of days medicated was not significant ($p = .68$), and there were no statistically significant medication \times time interactions. Removal of the treatment group assignment variables (because of their correlation with medication treatment at the earlier assessments) did not change the pattern of results ($p = .59$). Results were similar for number of substances used.

Type of Substance. There were no statistically significant associations between original randomized treatment assignment and alcohol use (average $p = .60$), tobacco use (average $p = .26$), or marijuana/drug use (average $p = .58$; p values ranged from .07 to .99). There were also no associations between these variables and ADHD medication use at each assessment for alcohol use (average $p = .55$), for tobacco use (average $p = .25$), or for marijuana/drug use (average $p = .46$; p values ranged from .22 to .82).

SUD. Neither randomized treatment assignment nor proportion of days medicated in the past year was a statistically significant predictor (correlate) of SUD at the 6- and 8-year assessments. Across all orthogonal treatment contrasts and across assessments, the average p value for the treatment group comparisons was $p = .51$ (range = 0.03 to 0.89). The association between proportion of days medicated and SUD was also not statistically significant ($p = .37$), and did not interact with assessment point ($p = .48$). There were no statistically significant associations for any specific type of SUD (alcohol, marijuana/drug) or for nicotine dependence.

Cumulative Psychostimulant Treatment and Substance Use/SUD at 8 years

For the propensity score–matching analyses, and following Lu *et al.*,³⁴ the distribution of days that participants had been stimulant treated since baseline was divided into five ordinal groups using quintile cut points. Using an ordinal logit model, quintile group membership was regressed on 36 variables selected for their potential to predict stimulant treatment. These included demographics (e.g., parent education and income; marital status; child sex), receipt of medication or school assistance before study enrollment, ADHD symptom severity (parent and teacher report), parent-reported impairment, other behavior

problems (e.g., parent and teacher ratings of oppositionality and aggression), social skills ratings by parent and teacher, achievement test scores and IQ estimate, parental psychopathology (mood, anxiety, alcohol, or drug use disorder), and original randomly assigned treatment group (references for these variables are reported elsewhere⁴⁵). A propensity score was produced for each participant, estimated from baseline characteristics, as an index of the likelihood of receiving more or fewer days of stimulant treatment between baseline and the 8-year follow-up. Participants were subsequently matched in pairs to minimize their differences in propensity scores and to maximize their differences in days of stimulant treatment. These matched pairs produced two groups distinguished by more versus fewer days treated. As planned, the groups differed significantly in days stimulant treated (mean = 2071.10, SD = 728.87, versus mean = 763.08, SD = 765.00; $p < .01$), but not in any of the 36 baseline variables (all p values $> .10$; average p value = .70).

Matched-pair analyses were performed for each of the primary (composited number of substances used; any SUD excluding nicotine dependence) and secondary (alcohol; marijuana; cigarettes; SUD for alcohol and SUD for marijuana/other drugs) variables. There were no statistically significant associations for any of these variables. For the primary outcomes, the Wilcoxon signed-rank test for number of substances used was $z = -0.34$ ($p = .73$); McNemar's χ^2 test for any SUD was $\chi^2(1) = .44$ ($p = .62$). For the exploratory analyses, the following values were observed: alcohol use, $z = 0.42$, $p = .68$; cigarettes, $z = -.54$, $p = .59$; marijuana, $z = .45$, $p = .65$; alcohol abuse or dependence, $\chi^2(1) = 0.00$, $p = 1.00$; marijuana or other drug abuse or dependence, $\chi^2(1) = 1.29$, $p = .35$.

DISCUSSION

The current study first tested the hypothesis that children with combined type ADHD have increased risk of substance use and SUD in adolescence. We found a significantly higher prevalence of substance use by adolescents with, versus former classmates without, ADHD histories. Overall group differences for any SUD (*DSM-IV* abuse or dependence) were also observed, but these occurred at comparatively lower rates and only at certain ages—for

marijuana and nicotine only—highlighting the importance of measuring levels of certain types of substance use in adolescence that may foreshadow later SUD in adulthood. The multi-site nature of the MTA sample, including demographic diversity (e.g., 20% female) and other unique sample features (discussed below), underscores for the first time the significance of the substance abuse risk for both boys and girls with childhood ADHD. This finding renders all the more important our examination of treatment effects on substance use/SUD risk. Across all analyses, we found no associations to suggest either harm or benefit from medication (mostly stimulant) treatment in regard to rates of adolescent substance use or SUD. As this is the first study to include a period of randomized assignment to treatment and the first to consider a large number of potential confounding variables, these findings are the strongest test to date of the association between medication for ADHD and adolescent substance abuse.

About one-third of the ADHD group was at high risk of adult substance abuse because of teenage substance use. At the 6-year follow-up (mean age = 15 years), group differences were greatest with 35% of the ADHD versus 20% of the LNCG (non-ADHD) groups reporting use of one or more substances. We also detected group differences in SUD at the 6-year follow-up, but for fewer participants, which may explain other smaller studies' failure to find statistically significant group differences in adolescent SUD.^{50,61} A large body of research has shown that substance use at a young age is prognostic of later abuse/dependence in adulthood.^{62,63}

Marijuana and tobacco use most clearly distinguished the ADHD from LNCG groups. Only a few longitudinal studies of children diagnosed with ADHD have examined marijuana use, as opposed to abuse/dependence, and the results have been mixed.^{50,64,65} In the current study, approximately one-third of the children with ADHD (32%) had used marijuana more than once by the 8-year follow-up (mean age = 17 years) versus 24% of the LNCG. These high rates for both groups reflect the increasing use of marijuana by teens in the United States,⁶⁶ but they also indicate a relatively higher risk of marijuana use for teens with ADHD histories. This risk was barely visible in early adolescence but was more pronounced by the 6-year follow-up assessment (mean age =

15 years). At this age, nearly one-fifth of our participants with ADHD histories reported marijuana use more than once, indicating that this outcome variable should be directly targeted for future research. Marijuana use at a young age has been associated with a host of negative cognitive sequelae such as neurocognitive decrements, decreased academic achievement, and poor physical health.^{67–72} Given the long-term impact of childhood ADHD on educational, occupational, and psychosocial outcomes of adulthood,⁹ early and chronic marijuana use has the potential to significantly undermine later adult accomplishments for this population.

Tobacco use (mostly cigarette smoking) was strongly associated with childhood ADHD. Nearly one-quarter (24%) of the ADHD sample had smoked cigarettes or used other forms of tobacco more than a few times by the 8-year follow-up, and 17% were already daily smokers. These are high rates compared with both the LNCG (8% were daily cigarette users) and daily smoking rates for high school students nationally, (11.2%).⁷³ Combined with other reports of high rates of daily smoking from single-site samples,^{9,74} these findings suggest that the MTA children are headed toward a previously projected⁴ doubling of the 19.3% adulthood prevalence of smoking currently found in the United States.⁷⁵ Cigarette use that begins in adolescence is associated with an increased likelihood of nicotine addiction into adulthood and with a lower likelihood of successful quitting.^{76,77} Adolescent cigarette use is also associated with use and abuse of other drugs⁷⁸—a finding strongly supported by the current data for both the ADHD and non-ADHD groups. In fact, we found extremely few adolescents who reported using only cigarettes.

Assignment to study treatments in childhood did not predict any high school-aged substance-related outcomes. This result parallels our previously reported failure to find treatment group differences for any of the other 24 symptom, behavioral, and functioning (e.g., arrests, psychiatric hospitalizations) variables examined at the same age.⁴⁸ Many of these variables (e.g., impulsivity, conduct problems, academic achievement) are long-established predictors of substance use for teens in the general population,^{79–81} and in other studies they correlate with substance use for adolescents with ADHD histories.^{12,82,83} To the extent that these variables were not differentially

affected by assigned treatment group in childhood,⁴⁷ it follows that substance use/SUD in adolescence should not be differentially affected. Collectively, these findings are in stark contrast to the widely held belief that starting treatment early (here, mean age = 8 years) will, in and of itself, change long-term outcomes that also include SUD vulnerability. Instead, treatments found to be efficacious for adolescent substance abuse^{84,85} may hold some promise for this population because of their targeting of the same behavioral, academic, and familial/peer vulnerabilities known to accompany adolescent ADHD.

Our findings did not provide any evidence that ADHD medication protects from, or increases risk for, adolescent substance use or SUD. This finding held for recent medication and for days cumulatively treated with stimulants. Unmeasured confounders may have been operating because of the naturalistic follow-up study design, and we did not statistically control for psychopathology and functioning at the follow-up assessments. However, we conducted the most carefully controlled analysis to date using a statistical method (propensity score matching analysis) that allowed consideration of multiple baseline factors that might contribute to long-term medication treatment or termination. Moreover, our prior report that medication at high school age does not relate to multiple indicators of symptoms and daily functioning⁴⁷ revealed that addition of these covariates was not indicated. Our findings conflict with anecdotal clinical experience with long-term patients who appear to derive benefit from continued medication. We speculate that these experiences reflect a subset of well-monitored teens who, unlike the majority of our sample, continue to be accepting of medication recommendations and other concurrent protective strategies and/or may have a low risk profile for developing substance use.

The observed lack of associations between stimulant exposure over time and adolescent substance use/SUD do not discount the possibility that brain-based changes in neural mechanisms underlying addiction vulnerability are occurring as a function of prolonged stimulant treatment. Volkow *et al.* recently demonstrated, for stimulant-naïve adults with ADHD, an up-regulation of the dopamine transporter and decreased D2 receptor availability in the striatum after 1 year of methylphenidate treatment.^{86,87}

Although demonstrated with adults, these findings heighten concern about potential stimulant-related adjustments in dopaminergic mechanisms pertinent to drug abuse vulnerability. On the other hand, Castellanos *et al.* suggested neuroprotection from stimulant use in childhood and adolescence for youth with ADHD.⁸⁸ Studies of differential responsivity to drug challenges in adulthood as a function of prior stimulant treatment would be useful. In adolescence, as in the present study, other factors that increase substance abuse risk, such as parental and peer influences, may outweigh developing biological vulnerability.

The substance use/SUD outcomes for the MTA should be considered in the context of several unique study features and limitations. All of the children in the MTA were diagnosed with the combined type of *DSM-IV* ADHD, and generalization of study results should generally not extend beyond this subtype. It is interesting that conduct disorder, a common comorbidity for the combined subtype that is also a strong proximal mediator of ADHD-related substance use/SUD, was infrequent. Compared with other clinic-based longitudinal studies of ADHD, for which CD rates range from 25% to 30% for boys^{64,83} and 18% to 23% for girls,^{38,39} the MTA rate of 8% at the 8-year assessment,⁴⁷ and even the rate of 14% at baseline,⁴⁴ is low. The sample recruitment that included, in addition to psychiatric clinics, pediatrician offices and school settings⁴¹ may have contributed to this finding⁸⁹. Our follow-up assessments, which relied on self-report and often with 2-year windows, may have missed episodes of substance use, and rates may be underestimated. Similarly, the precision of our treatment data relies on the accuracy of parent recall at each assessment, which no doubt includes some degree of error.

Thus, children with ADHD have increased risk of substance use, in particular tobacco and marijuana, against a backdrop of high rates of alcohol use for all teens, and our standard treatments (short-term psychosocial, medication) for ADHD have not, to date, countered this risk. Given the ubiquity of medicinal treatment for ADHD and our failure to find relations between ADHD medication treatment and adolescent substance use/SUD, the findings argue for additional research on neurobiological and psychosocial factors that fuel the vulnerability and can inform the types of treatment so urgently needed. ☞

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