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Title
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Permalink
https://escholarship.org/uc/item/6jj6k554

Journal
Pediatrics, 117(6)

ISSN
0031-4005

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Publication Date
2006-06-01

Peer reviewed

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ARTICLE

Behavioral Predictors of Substance-Use Initiation in Adolescents With and Without Attention-Deficit/Hyperactivity Disorder

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ABSTRACT

OBJECTIVE. Our goal was to examine substance-use initiation in healthy adolescents and in adolescents who have been diagnosed with attention-deficit/hyperactivity disorder.

METHODS. Seventy-eight adolescents (28 healthy and 50 with attention-deficit/hyperactivity disorder) participated in an ongoing longitudinal study of predictors of substance use. The substances most commonly reported were tobacco, alcohol, and marijuana. Aggression, conduct problems, hyperactivity, impulsivity, inattention, anxiety/depression, social difficulties, and somatic complaints were assessed at study entry and tested as predictors for later substance use.

RESULTS. With an average of 4 years into the study, 37 adolescents had not used any substances, 41 had experimented with at least 1 substance, and 29 experimented with >1 substance. Psychiatric diagnoses (attention-deficit/hyperactivity disorder, attention-deficit/hyperactivity disorder and conduct disorder, and attention-deficit/hyperactivity disorder and depression/anxiety) did not influence reports of substance use. Distinct behavioral measures collected at study entry predicted use of different substances. In a multivariate analysis, aggression had the greatest association with tobacco smoking and marijuana use. Impulsivity was associated with alcohol use. Severity of drug exposure, indexed by the number of substances used, was predicted by aggression.

CONCLUSIONS. This 4-year longitudinal study captured the onset of substance use, not abuse. Behavioral predictors differed with the type of substance used. These behavioral characteristics may raise suspicion among pediatricians for enhanced risk for substance-use initiation.

SUBSTANCE USE BEGINS for most individuals in adolescence. As experimentation with tobacco, alcohol, and marijuana (the 3 most commonly used substances by adolescents) commences between the ages of 13 and 15 years,[1] substance-use disorders develop as well, with a cumulative prevalence of such disorders estimated at 6% to 12% by age 16.[2,3] Furthermore, the earlier the onset of substance use, the more negative the evolution of behavior. For example, tobacco smoking in adolescence predicts a more severe and protracted course of tobacco dependence in adulthood.[4–6] In addition, early-onset substance users are at greater risk for later abuse, aggression, and delinquency,[7,8] as well as subsequent drug problems.[9,10] Currently, nearly 1 in 5 high school seniors smokes every day,[11] whereas >90% of 17-year-olds have experimented at least once with tobacco (68%), alcohol (88%), marijuana (53%), or other drugs (31%).[12]

A growing body of literature has identified a variety of psychiatric symptoms that are associated with adolescent substance use either as comorbid diagnoses or risk factors. It should be noted that psychiatric symptoms may be the manifestation of the chronic exposure to drugs of abuse and resolve once exposure is discontinued. Therefore, the assessment of psychiatric comorbidity usually requires several weeks of abstinence. Three of the major areas of inquiry with respect to psychiatric comorbidity have been depression, anxiety, and attention-deficit/hyperactivity disorder (ADHD) with or without conduct disorder (CD). Studies have long shown that adolescent substance users often present with comorbid depressive symptoms.[13,14] It has also been reported that depression is a risk factor for later substance use[15] and, conversely, that substance use can predict the development of depressive symptoms.[16,17] Findings such as these have led some researchers to posit a bidirectional relationship between depression and substance use: each behavior can initiate the other.[18]

Anxiety is another condition frequently comorbid with substance use, but the causal relationship between anxiety and substance use is less certain.[19] Although some studies have found that early anxiety increases the risk for later substance abuse, particularly in girls,[2] others have observed a weaker connection[18] or one that largely reflects other concurrent factors.[20] Recently, several studies have tested different types of anxiety separately in an attempt to better characterize the anxiety/substance-use connection. For example, Kaplow et al[15] found that overall anxiety at 9 years of age did not increase the risk for initiation of alcohol use, but only because the protective effect of separation anxiety disorder offset the increased risk induced by generalized anxiety disorder. Similarly, Zimmerman et al[21] found that adolescent anxiety predicted subsequent alcohol use, abuse, and dependence, but the only significant factors in this prediction were social phobia and panic disorder. As for the opposite causal direction, studies have shown that tobacco use can predispose adolescents to develop anxiety disorders.[22] Thus, as for depression, researchers have argued that anxiety and substance use may have a bidirectional association.[19]

Perhaps the most researched adolescent psychiatric condition associated with substance use is ADHD. Children and adolescents with ADHD are prone to initiate tobacco use (as well as other illicit substances) at an earlier age[23] and more frequently than healthy subjects.[24] They are also more likely to develop substance-use disorders than children and adolescents without ADHD.[25–27] Indeed, one third to one half of patients (adults and adolescents) seeking treatment for substance-use disorders have a history of ADHD.[28–30] However, there is some controversy as to whether the risk of developing substance-use disorder in adolescents with ADHD is actually mediated through CD, a common comorbid disorder in these adolescents.[4,31–36] For example, in the absence of CD, some studies have shown no association between ADHD and an increased risk of substance-use problems.[37,38] As a result, several researchers have posited a developmental sequence from ADHD to CD and only then to alcohol, tobacco, marijuana, and other drug use.[39] Recent reviews have attempted to resolve the controversy, arguing that adolescents with comorbid ADHD and CD have the highest risk of developing substance use but that ADHD alone confers an intermediate risk.[40,41]

Researchers recently tested the predictive power of specific symptoms of ADHD rather than the diagnosis. For example, Aytaclar et al[42] found that the cognitive component of ADHD (ie, vigilance, distractibility, planning) was a better predictor of early adolescent tobacco and marijuana use than its motoric component (ie, hyperactivity). Similarly, others have found that poor attention, but not necessarily an ADHD diagnosis, put subjects at risk for developing substance use 8 years later[43] and that both externalizing[31] and internalizing[44] problems were better markers of subsequent drug use than an ADHD diagnosis.

The goal of this preliminary prospective study was to identify clinical psychiatric predictors of substance-use initiation in adolescents (12–14 years of age at study enrollment) separately for tobacco, alcohol, and marijuana substances. Although other environmental (eg, peer relationships) and genetic factors also interact to confer vulnerability for substance use,[45] identification of psychiatric risk factors is critical in the search for effective measures to prevent adolescent substance use. On the basis of the literature reviewed above, we hypothesized that more severe externalizing problems (ie, aggression, hyperactivity, conduct problems, and impulsivity) would be associated with greater risk for substance-use initiation. Although the focus was directed onto externalizing disorders (ADHD and CD), we also pre-

dicted a contributory role of internalizing problems (ie, anxious, depressive symptoms and related somatic complaints) to the risk for substance use.

Given the recent work on symptoms rather than syndromes, we hypothesized that psychiatric diagnoses per se would be less relevant as predictors than symptoms as listed above. In addition, we tested the relevance of social problems in predicting substance use. Given the mixed findings in the literature (similar social impairments have been associated with both decreased[15,35] and increased[21,46] risks for substance use and initiation), we made no prediction on the direction of a potential association.

METHODS

Subjects

Adolescents between 12 and 14 years of age and without a history of substance (including tobacco) use were recruited to participate in an ongoing longitudinal study of risk factors for substance use. Participants were recruited from the metropolitan Baltimore, Maryland/Washington, DC, area by advertisements in regional newspapers and psychiatric clinics. Healthy adolescents and adolescents with ADHD and/or CD were recruited for this study. After receiving a detailed description of the research protocol, parents gave written informed consent, and adolescents gave written informed assent. Information provided by the adolescents was not shared with parents as long as it was not life threatening and did not involve history of sexual/physical abuse; this was discussed in much detail during the consent/assent process. Subjects who missed >2 consecutive follow-up visits were excluded from the study. Participants were compensated for their time and inconvenience. The study was approved by the National Institute on Drug Abuse Intramural Research Program Institutional Review Board.

Participants had a comprehensive initial assessment consisting of four 1- to 3-hour visits and a 1-hour follow-up visit every 4 months. Exclusion criteria were an IQ of <70, chronic medical illness, treatment with psychoactive medications (except for psychostimulants), and axis I psychiatric disorders except for CD, oppositional defiant disorder, and ADHD with or without comorbid mood disorders. Any history of substance use prevented adolescents from entering the study.

Assessment Procedures

Adolescents were assessed for lifetime and current psychiatric diagnoses by using a semistructured *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* diagnostic psychiatric interview, administered separately to the parents and to the adolescents (Diagnostic Interview for Children and Adolescents [DICA]).[47] Master's- and bachelor's-level research assistants were trained to administer the DICA, all behavioral rating scales, and the cognitive testing. Results were reviewed in weekly team meetings. Psychiatric diagnoses were determined by 2 child and adolescent psychiatrists (M.E. and M.K.L.) on the basis of all information obtained from adolescents, their parents, and their teachers (when available).

Initial screening consisted of psychiatric interviews, behavioral rating scales, cognitive testing, urine drug screen, physical examination (including sexual maturation staging using the Tanner classification),[48] and review of medical and school reports when available (<20% of the teachers returned completed forms). Parents, adolescents, and teachers were asked to complete behavioral-assessment instruments. Follow-up evaluations, consisting of questionnaires for updating family, school, social functioning, pharmacological treatment, and substance-use status, occurred every 4 months. These were performed either in person during visits to the National Institute on Drug Abuse Adolescent Research Program (4-, 12-, 16-, 24-, 32-, 40-, 44-, and 48-month visits) or by telephone interview (8-, 20-, 28-, and 36-month follow-ups). Information from parents as well as adolescents was gathered at in-person follow-up visits, but only the youths were asked to respond to follow-up questions over the telephone. The average follow-up for the whole sample was 3.8 ± 1.3 years: 6 [8%] had a 6-year follow-up, 23 [32%] participants had a 5-year follow-up, 15 [22%] had a 4-year follow-up, 18 [24%] had a 3-year follow-up, and 16 [22%] had a 2-year follow-up.

Assessment Instruments

The following instruments were used: (1) subtests of the Wechsler Intelligence Scale for Children, 3rd edition[49] (to assess intellectual function); (2) Child Behavior Checklist (CBCL),[50] Youth Self-Report (YSR),[51] Life History of Aggression (LHA),[52] Conners' 48-item rating scale,[53] and the Barratt impulsiveness rating scale[54] (to assess behavior); and (3) Drug Use Screening Inventory[55] (to assess drug use). These instruments provided measures for the 8 clinical domains of aggression, hyperactivity, conduct problems, somatic complaints, inattention, impulsivity, anxiety/depression, and social problems.

Substance-use initiation, the main outcome variable for this study, was recorded at each follow-up visit with the adolescents and parents using the Drug Use Screening Inventory and a semistructured interview that probed for tobacco, alcohol, and marijuana use in the past 4 months (ie, since the last interview). On the basis of these reports, substance-use status was stratified into 2 levels: nonusers (tobacco: smoked less than twice a month; marijuana: never used; alcohol: never drank alcohol when not under the supervision of parents or responsible caretakers) and users. Because the level of use was generally low with little variance (see "Results"), only dichotomous groups (users and nonusers)

were created. Substance-use severity was defined as the number of substances used by the participants (4-point scale: 0, none; 3, all 3 substances).

Statistical Analysis

Both self-rated (YSR, LHA, Barratt impulsiveness rating scale) and parentally rated (CBCL, Conners' rating scale) variables were used because of the different sensitivities of these scales.[56,57] Three categories of symptoms were sampled: externalizing symptoms, including overall measures of externalizing problems (CBCL, YSR), impulsivity (Barratt impulsiveness rating scale), aggression (LHA), conduct problems (Conners' rating scale), and hyperactivity (Conners' rating scale); internalizing symptoms, including overall measures of internalizing problems (CBCL, YSR), anxiety (Conners' rating scale), and somatic complaints (YSR, CBCL); and social adjustment (YSR, CBCL). Somatic complaints were included within the internalizing domain because they are interpreted as a manifestation of anxiety or depression.[58,59]

As mentioned above, subjects were classified into 3 substance-use groups (tobacco, alcohol, and marijuana) and characterized as a function of substance-use severity along a 4-point severity scale based on the number of substances used (0–3 substances) at last follow-up. Substance-use groups were compared separately on demographic factors using Fisher's exact test for dichotomous variables and t tests for continuous variables. Demographic factors that differed significantly between groups were used as covariates in the symptom analysis to avoid confounding.

A 2-step analytic approach was used and included an initial screen of the contribution of each variable to use status for each substance, followed by binary logistic regressions to determine which of the significant variables had the greatest independent relationship with group membership. The factors that were found to predict individual substance use were examined further for their predictive value of substance-use severity in a linear regression analysis.

The initial screening of the variables was conducted with liberal interpretation of significance without correction for multiple comparisons ($P = .10$). In this initial screening, 14 behavioral variables were analyzed by using separate analyses of covariance (ANCOVAs), for which the fixed factor was the individual substance-use status, and the covariates were the demographic variables that differed among groups. Separate analyses were performed for tobacco, alcohol, and marijuana users. The normality assumption was examined for each behavior scale by using the Shapiro-Wilk's test. Homogeneity of variance was examined by using Levene's test. Variables that violated these assumptions were to be transformed by using square-root and base-10 log transformations. Because neither transformations nor nonparametric tests showed significant differences from the

outcome of the ANCOVAs, the original data are reported. All P values are 2-tailed.

As the second analytic step, we used logistic-regression models to examine whether the behaviors identified in the initial screening were independent predictors. Because a relatively large number of participants ($n = 20$ [26%]) had missing data on the Conners' rating scales, those scales were not entered into the multivariate analyses. Similarly, the externalizing scales of the YSR/CBCL were not used in these analyses because they cover a number of symptoms (ie, aggressive and delinquent behavior) that overlap with other individual scales of externalizing problems and, thus, could mask the effects of more specific symptoms. The variables with ANCOVA P values of $<.10$ were included in binary logistic regressions specific to each substance. To deal with multicollinearity, tolerance statistics and correlations among the significant behaviors from the first phase were examined. Variables with tolerance <0.6 and correlations with other variables >0.5 were eliminated. When ≥ 2 variables were correlated, the variable remaining in the model was selected on the basis of its clinical relevance. Wald's test was used to evaluate significance in the logistic regressions.

Finally, a linear regression was used to evaluate behavioral predictors of substance-use severity. In this analysis, we included only the behavioral variables that were used in the previous logistic regressions to determine whether those factors remained important within a broader substance-use context. Tolerance was evaluated in the same manner as for the logistic regressions. R^2 and adjusted R^2 are reported to depict the total variance explained by the model.

RESULTS

Sample Characteristics

Demographics for the full sample, by substance use and by substance-use severity, are presented in Table 1. Seventy-eight adolescents (28 healthy and 50 with an externalizing psychiatric diagnosis) were included in the study. Mean age was 12.7 ± 0.7 years at study entry and 16.0 ± 1.8 years at last follow-up. Sample characteristics are presented according to substance-use group in Tables 1 and 2. The last follow-up assessment showed that 37 (47%) adolescents had not initiated any use. By type of substance, 41 (53%), 27 (35%), 36 (46%), and 22 (28%) had initiated use of any substance, tobacco, alcohol, or marijuana, respectively. By number of substances used, 12 (15%) used 1, 12 (15%) used 2, and 17 (22%) used all 3 substances. As mentioned earlier, the level of use was generally low: only 4 nicotine users smoked ~1 pack per day, and 1 participant smoked >1 pack per day. Most nicotine users smoked between 2 and 5 cigarettes per day. Only 2 adolescents drank regularly during weekdays, and only half of the alcohol users reported

TABLE 1 Demographics by Substance Use and Severity of Substance Use

	All, N	Tobacco, n (%)a	Alcohol, n (%)	Marijuana, n (%)	No. of Substances Used, n (%)			
					0	1	2	3
Diagnosis								
Healthy	28	8 (29)	13 (46)	9 (32)	14 (50)	4 (14)	4 (14)	6 (21)
ADHD, CD, or depression	50	19 (38)	23 (46)	13 (29)	23 (46)	8 (16)	8 (16)	11 (22)
ADHD	27	10 (37)	11 (41)	5 (19)	13 (48)	6 (22)	4 (15)	4 (15)
CD	7	2 (29)	4 (57)	3 (43)	3 (43)	1 (14)	1 (14)	2 (29)
ADHD/CD	1	1 (100)	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)	1 (100)
ADHD/depression	15	6 (40)	7 (47)	6 (40)	7 (47)	1 (7)	3 (20)	4 (27)
Gender								
Male	54	21 (39)	26 (48)	18 (33)	24 (44)	8 (15)	9 (17)	13 (24)
Female	24	6 (25)	10 (42)	6 (25)	13 (54)	4 (17)	3 (13)	4 (17)
Medicationb								
Adrenergic	6	4 (67)	4 (67)	1 (17)	1 (17)	2 (33)	2 (33)	1 (17)
Antidepressant	22	10 (46)	11 (50)	8 (36)	8 (36)	5 (23)	3 (14)	6 (27)
Mood stabilizer	6	2 (33)	3 (50)	2 (33)	2 (33)	2 (33)	1 (17)	1 (17)
Neuroleptic	3	1 (33)	1 (33)	0 (0)	1 (33)	2 (67)	0 (0)	0 (0)
Stimulant	30	16 (53)	16 (53)	11 (37)	10 (33)	6 (20)	5 (17)	9 (30)

a Row percentages. Raw percentages add up to 100% only for the number of substances used, not for individual substances used (because of overlap in usage).
b Lifetime medications.

TABLE 2 Behaviors by Substance Use

	Tobacco Use			Alcohol Use			Marijuana Use		
	No, Mean (SD)	Yes, Mean (SD)	t, P	No, Mean (SD)	Yes, Mean (SD)	t, P	No, Mean (SD)	Yes, Mean (SD)	t, P
Age at study entry	12.6 (0.7)	12.9 (0.7)	1.35, .18	12.6 (0.6)	12.9 (0.8)	2.18, .03	12.6 (0.6)	13.0 (0.8)	2.55, .01
Age at last follow-up	15.6 (1.7)	16.8 (1.7)	2.98, .004	15.4 (1.7)	16.8 (1.6)	3.76, .000	15.6 (1.7)	17.0 (1.6)	3.27, .002
IQ	101.3 (18.1)	99.3 (15.3)	0.49, .63	102.0 (19.2)	98.9 (14.3)	0.77, .44	101.5 (17.9)	98.6 (15.5)	0.69, .49
Socioeconomic status	50.4 (23.3)	59.2 (27.3)	1.51, .14	53.9 (24.7)	52.9 (25.6)	0.17, .87	52.1 (23.7)	56.5 (27.8)	0.71, .48
Tanner stage	3.3 (1.3)	3.4 (1.1)	0.59, .56	3.0 (1.2)	3.7 (1.1)	2.74, .01	3.0 (1.2)	4.0 (1.0)	3.68, .000
	Mean (SE)	Mean (SE)	F, P	Mean (SE)	Mean (SE)	F, P	Mean (SE)	Mean (SE)	F, P
Barratt impulsivity	73.4 (1.6)	77.3 (2.2)	1.99, .16	71.4 (1.7)	78.5 (1.9)	7.35, .01	74.4 (1.6)	75.4 (2.4)	0.13, .72
CBCL									
Externalizing	13.9 (2.0)	19.8 (2.7)	2.95, .09	14.9 (2.3)	17.3 (2.4)	0.49, .49	13.6 (1.9)	21.4 (2.9)	4.88, .03
Internalizing	9.5 (1.2)	11.0 (1.6)	0.49, .49	10.4 (1.3)	9.7 (1.4)	0.14, .71	9.5 (1.1)	11.2 (1.7)	0.61, .44
LHA									
Adolescent	7.8 (1.0)	12.8 (1.5)	7.51, .01	8.5 (1.2)	10.6 (1.3)	1.21, .28	8.0 (1.0)	12.8 (1.5)	6.56, .01
Parent	9.6 (1.7)	14.3 (2.3)	2.60, .11	10.7 (2.0)	12.0 (2.0)	0.20, .66	9.8 (1.7)	14.4 (2.4)	2.34, .13
YSR									
Attention	4.8 (0.5)	7.1 (0.7)	7.17, .01	4.9 (0.6)	6.4 (0.6)	2.88, .09	5.3 (0.5)	6.1 (0.8)	0.72, .40
Externalizing	11.5 (1.1)	17.6 (1.5)	10.11, .002	11.6 (1.3)	15.9 (1.4)	4.71, .03	12.2 (1.1)	16.9 (1.7)	5.20, .03
Internalizing	10.2 (1.2)	13.8 (1.6)	3.10, .08	10.7 (1.4)	12.4 (1.4)	0.70, .41	11.1 (1.2)	12.4 (1.8)	0.34, .56
Somatic complaints	2.5 (0.4)	3.7 (0.6)	2.75, .10	2.4 (0.5)	3.6 (0.5)	2.59, .11	2.7 (0.4)	3.6 (0.6)	1.65, .20
Social problems	3.0 (0.4)	4.1 (0.5)	3.24, .08	3.4 (0.4)	3.3 (0.4)	0.02, .89	3.5 (0.4)	3.1 (0.5)	0.27, .61
Conners' scale									
Anxiety	1.2 (0.3)	1.6 (0.3)	0.75, .39	1.5 (0.3)	1.2 (0.3)	0.56, .46	1.5 (0.3)	1.1 (0.3)	0.67, .42
Conduct problems	5.9 (1.1)	8.3 (1.3)	1.97, .17	6.7 (1.3)	7.0 (1.2)	0.03, .87	5.9 (1.0)	8.5 (1.4)	2.05, .16
Hyperactivity	10.2 (1.3)	16.1 (1.6)	7.99, .01	12.3 (1.6)	12.9 (1.5)	0.08, .77	12.1 (1.4)	13.5 (1.8)	0.38, .54
Learning	4.6 (0.6)	7.0 (0.8)	5.97, .02	5.5 (0.8)	5.7 (0.7)	0.02, .88	5.7 (0.7)	5.4 (0.9)	0.06, .81

Means and SDs for behavior scales are least-squares values after controlling for age at last follow-up.

having been drunk. Only 3 marijuana users smoked regularly during weekdays. Overall, only 3 adolescents reported a level of use of alcohol or marijuana consistent with a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* diagnosis of substance abuse.

Gender, IQ, socioeconomic status, and psychiatric diagnostic membership did not differentiate the substance-use or substance-use severity groups. Furthermore, history of pharmacologic treatment up to last follow-up was not different among the groups (see Table 1). However,

TABLE 3 Logistic Regressions by Substance Use

	Tobacco Use[a]			Alcohol Use[b]			Marijuana Use[c]		
	Wald	P	OR (95% CI)	Wald	P	OR (95% CI)	Wald	P	OR (95% CI)
Barratt impulsivity	—	—	—	4.29	.04	1.06 (1.00–1.12)	—	—	—
LHA: adolescent	3.95	.05	1.09 (1.00–1.20)	—	—	—	5.53	.02	1.11 (1.02–1.20)
YSR: attention	1.47	.23	1.15 (0.92–1.45)	0.16	.69	1.03 (0.88–1.22)	—	—	—
YSR: social problems	0.03	.86	0.97 (0.71–1.33)	—	—	—	—	—	—

— indicates variable was not included in analysis.

[a] Age at last follow-up: Wald $\chi^2 = 7.31$; $P = .01$.

[b] Age at last follow-up: Wald $\chi^2 = 11.28$; $P = .001$.

[c] Age at last follow-up: Wald $\chi^2 = 7.49$; $P = .01$.

Tanner stage at study entry was higher in alcohol and marijuana users, but not tobacco users, compared with nonusers. Age at study entry was higher in each of the user groups, but this age difference was only significant for alcohol and marijuana. The age at last follow-up was greater in users of each substance than nonusers. Because age at last follow-up was higher for users of all of the substances and it was significantly related to age at study entry ($r = 0.56$; $P < .001$) and Tanner stage ($r = 0.29$; $P < .001$), age at last follow-up was used as a covariate in the ANCOVAs.

Behavioral Predictors
All test statistics are presented in Tables 2–4.

Tobacco Users Versus Tobacco Nonusers
ANCOVAs were used to compare tobacco users and nonusers on each of the behavioral variables controlling for age at last follow-up. Tobacco users had more externalizing symptoms, were more aggressive and hyperactive, and had more difficulty with learning and attention than tobacco nonusers. These findings were based on significantly higher scores on the YSR externalizing scale, LHA (self-report), Conner's hyperactivity scale, Conner's learning scale, and the YSR attention scale in users than nonusers. If a Bonferroni correction were used, only the YSR externalizing scale would remain significant (Table 2).

As a second analytic step, a logistic-regression model was run to examine whether apparent predictors from the univariate analysis remained significant when other factors were entered into the model. The final logistic-

regression model showed that aggression independently predicted smoking status (Table 3).

Alcohol Users Versus Alcohol Nonusers
ANCOVAs were used to compare alcohol users and nonusers on each of the behavioral variables controlling for age at last follow-up. The ANCOVAs showed significantly more YSR externalizing symptoms and impulsivity in alcohol users. No other behavioral variables differed significantly between alcohol users and nonusers. These findings would not be significant after Bonferroni correction (Table 2).

A logistic-regression model confirmed the significance of impulsivity as an independent predictor of alcohol use (Table 3).

Marijuana Users Versus Marijuana Nonusers
ANCOVAs were used to compare marijuana users and nonusers on each of the behavioral variables when controlling for age at last follow-up. Marijuana users showed significantly more self-reported aggression and externalizing symptoms from the YSR and CBCL than did marijuana nonusers. These univariate tests would not be significant after Bonferroni correction. No other behavioral variable differed between user and nonuser groups (Table 2).

A logistic-regression model confirmed self-reported aggression as a significant independent predictor of marijuana use (Table 3).

Severity of Substance Use
Only the variables found to be strongly associated with use of individual substances were examined for their predictive value in severity of use. These variables (impulsivity and self-reported aggression) were entered into the linear-regression model simultaneously. Age at last follow-up was used as a nuisance covariate. No variables showed issues with tolerance, so none were removed. Aggression was the strongest independent predictor (standardized $\beta = .27$). More aggression predicted more severe substance use (Fig 1). Impulsivity was not a significant independent predictor (standardized $\beta = .11$). Thus, adolescents with more aggression initiated use of

TABLE 4 Linear Regression With Number of Substances Used (Tobacco, Alcohol, and Marijuana) as Outcome

	No. of Substances Used (0–3)[a]		
	Standardized β	t	P
Barratt impulsivity	.11	1.09	.28
LHA: adolescent	.27	2.57	.01

$R^2 = 0.28$; adjusted $R^2 = 0.25$.

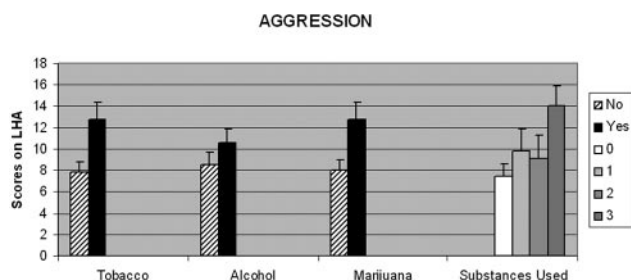[a] Age at last follow-up: standardized $\beta = .41$; $t = 4.07$; $P < .001$.

FIGURE 1
Mean (±SE) aggression scores on the LHA according to substance use and substance-use severity.

more substances. The final model explained 25% of the variance in the number of substances used.

DISCUSSION

This study offers a unique perspective on the behavioral predictors of substance-use initiation among adolescents. By focusing on initiation, we provide insights into a critical time period for early preventive interventions. At present, most studies that have examined substance use in adolescence focused on regular substance use, substance abuse, or dependence, and thus have not captured this very first stage.[25,28,44,60]

Tobacco, alcohol, and marijuana, the 3 most commonly used substances by adolescents, were targeted in this study. A few adolescents may have used hard drugs such as cocaine, PCP, or heroin, but urine drug screens did not detect stimulants outside therapeutic use. More than half of the sample (53%) started using at least 1 substance within the average 4-year follow-up, between the ages of 12 and 16 years. Alcohol (46%) was the most frequently used substance, followed by tobacco (35%) and marijuana (28%).

The proportion of users of any substance was similar in girls (users: 46% [11 of 24]) and boys (users: 56% [30 of 54]). Reports of greater vulnerability to substance use in boys[2,12] have usually been based on rates of substance abuse, not substance use, which could indicate that transition from use to abuse is more prevalent among boys than girls.

There was no effect of psychostimulant treatment on any substance use. These results are consistent with the literature; most longitudinal studies have found that stimulant therapy in childhood is not associated with increased adolescent or adult substance use[61,62] and may even protect against it.[63,64]

Our predictions fell into 3 major categories: (1) how externalizing and internalizing problems affect later substance use; (2) whether these symptoms are better predictors of substance use than overall psychiatric diagnoses; and (3) how social problems affect initiation of substance use.

Behavioral Predictors

Consistent with our predictions, we found associations of initiation of substance use with several externalizing factors measured at baseline (before any substance use). First, both attention problems and aggression were associated with greater tobacco use, and aggression was an independent predictor of tobacco use. Second, marijuana users were more aggressive than marijuana nonusers. Third, alcohol users showed more impulsivity than alcohol nonusers. However, in contrast to our predictions, none of the internalizing behavioral problems or social problems predicted substance-use initiation. Finally, aggression was the most important predictor for severity of substance-use initiation.

The identification of different independent predictors of alcohol initiation (impulsivity) versus tobacco or marijuana initiation (aggression) suggests different biological vulnerability factors for initiation of use of these substances. The association of impulsivity with alcohol initiation in this study echoes a body of literature linking alcohol abuse with impulsivity in adolescents[65,66] and adults, particularly those with type II alcoholism.[67] This association has been proposed to reflect alterations in serotoninergic function,[68–70] although it remains unclear whether serotonin dysfunction is a direct mediator of risk for alcohol abuse or is indirectly related to this pathology through increased impulsivity. The present finding adds to these data by indicating that impulsivity and potentially associated serotoninergic dysfunction can also play a role in the earliest stages of alcohol use and precede chronic exposure to alcohol. It is important to note that aggression, which is also a feature of type II alcoholism, was not found to predict alcohol initiation in this study. This may suggest that the contribution of aggression to the risk of alcoholism becomes significant only after the initiation phase and may be a consequence of alcohol exposure.

In contrast, aggression was found to play a role in both tobacco and marijuana use initiation. This finding of a common predictor to both substances may reflect the fact that a high proportion of marijuana users were also tobacco smokers (79%). The size of our sample does not permit us to separate marijuana users without tobacco use from marijuana users with tobacco use. This common association remains an important question to examine in future studies.

Although impulsivity and aggression both implicate serotoninergic alterations[71,72] and co-occur in a number of pathologies (eg, suicidal behavior), they differ on the degree of affective processes' involvement. Aggression is commonly expressed in association with strong emotions, whereas impulsivity is typically externally driven, particularly in the context of ADHD. Our finding of distinct links of alcohol with impulsivity and tobacco/marijuana with aggression may indicate that emotional factors constitute a unique vulnerability for tobacco/

marijuana-use initiation. However, internalizing factors were not found to predict substance-use initiation. The failure to detect a predictive value of internalizing symptoms for substance-use initiation may reflect the underrepresentation of mood and anxiety disorders in this sample and the restricted range of severity of internalizing symptoms. Finally, impulsivity and aggression may share common genetic substrates that, after interacting with specific environmental and/or biological factors, are expressed behaviorally differently as impulsivity or aggression.

Symptoms Versus Syndromes

In addition to behavioral symptoms, we tested whether psychiatric diagnoses could predict substance initiation. We found that psychiatric diagnosis in general did not differentiate users from nonusers. This lack of association was unexpected given the large literature on psychiatric comorbidity with substance abuse, particularly with respect to externalizing disorders in adolescents.[60] However, it is important to emphasize that we did not examine substance abuse but rather initiation, for which the relevance of psychiatric diagnosis is less supported. In addition, our results were consistent with previous studies that reported that specific components of ADHD, such as attention[43] or externalizing[31] problems, were better predictors of later substance use than ADHD diagnosis per se. Overall, our findings seem to suggest that categorical syndromic classifications are not as helpful as selective behavioral measures in gauging vulnerability to initial substance use, although the sample size in the present study is too small to draw a definitive conclusion.

Social Problems

Finally, we found no relation of social problems (as measured by the YSR/CBCL social factor) to the initiation of substance use. This absence of significant association may reflect the lack of statistical power to detect such an effect. Alternatively, predisposing social factors may be less important for the initiation of substances than for the transition to regular use.

Limitations

The main limitation of this work is the relatively small sample size, which reduces the power to detect potential significant associations. In addition, because functional neuroimaging examinations had been planned for this study, we had elected to recruit older children starting at 12 years old to satisfy requirements of the neuroimaging protocol. This prevented us from examining children with earlier substance-use onset who are at greater risk for later substance abuse.

Clinical Implications

The pattern of behavioral associations found in this study is consistent with reports in the literature and confirms the importance of several vulnerability factors for substance-use initiation. More specifically, externalizing symptoms such as aggression and impulsivity may contribute to a behavioral phenotype in adolescents that could be more closely evaluated and subjected to genetic examination. Studying the interactions of genetic vulnerability with environmental factors could help design strategies aimed at modifying these environmental factors and decreasing drug experimentation. Indeed, a growing body of literature has identified a variety of psychosocial[73,74] and psychiatric symptoms that are associated with adolescent substance use, as either comorbid disorders or risk factors.

Furthermore, these findings suggest that a more effective approach to identifying adolescents who are at risk for substance use is a dimensional one, focused on symptom severity, rather than a categorical one, focused on psychiatric diagnosis. Such an approach may allow school personnel and primary care providers to identify adolescents who are vulnerable to substance use earlier and facilitating more successful, broadly based preventive interventions.

Experimentation with illicit substances is a common behavior among adolescents; >90% of 17-year-olds try some substance at least once.[12] However, substance-use initiation confers vulnerability for later substance abuse, and a better understanding of its behavioral predictors can help to shape preventive measures at both the individual and societal levels.

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