

# Do Stimulants Reduce the Risk for Cigarette Smoking in Youth with Attention-Deficit Hyperactivity Disorder? A Prospective, Long-Term, Open-Label Study of Extended-Release Methylphenidate

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**Objective** Although attention-deficit hyperactivity disorder (ADHD) is a well-known risk factor for cigarette smoking, prospective studies aimed at reducing smoking risk in this population are critically needed.

**Study design** This was a 2-year, prospective, open-label clinical trial of extended-release methylphenidate for smoking prevention in adolescents with ADHD (n = 154). Smoking outcomes were assessed with the Fagerstrom Tolerance Questionnaire. Comparisons were made using data from a historical, naturalistic sample of ADHD (n = 103) and non-ADHD comparators (n = 188) of similar age and sex assessed with the same assessment battery as that used in subjects participating in the clinical trial.

**Results** The smoking rate at endpoint (mean, 10 months of methylphenidate treatment) was low in the clinical trial subjects and not significantly different from that in the non-ADHD comparators or the ADHD comparators receiving stimulants naturalistically (7.1% vs 8.0% vs 10.9%;  $P > .20$ ). In contrast, the smoking rate was significantly lower in the clinical trial subjects than in the naturalistic sample of ADHD comparators who were not receiving stimulant treatment (7.1% vs 19.6%;  $P = .009$  [not significant], adjusting for comorbid conduct disorder and alcohol and drug abuse).

**Conclusion** Although considered preliminary until replicated in future randomized clinical trials, the findings from this single-site, open-label study suggest that stimulant treatment may contribute to a decreased risk for smoking in adolescents with ADHD. If confirmed, this finding would have significant clinical and public health impacts. (*J Pediatr* 2013;162:22-7).

Because the majority of smokers begin in adolescence, cigarette smoking is considered a pediatric disease.<sup>1,2</sup> Approximately 4000 US youths try their first cigarette each day.<sup>3</sup> This rate is particularly concerning given contemporary models of nicotine dependence in youth that show symptoms of addiction within 1 month after first cigarette use, even in the context of nondaily use.<sup>4</sup>

One well-documented risk factor for cigarette smoking and nicotine dependence is attention-deficit hyperactivity disorder (ADHD). A disproportionately large number of individuals with ADHD smoke, and those that do have earlier initiation of smoking, a greater risk of rapid progression to regular smoking, and greater difficulty quitting smoking compared with their non-ADHD counterparts.<sup>5-7</sup> Consistent with these findings, the National Comorbidity Survey Replication study found that among psychiatric disorders, childhood externalizing disorders (principally ADHD) were most strongly predictive of nicotine use and dependence in young adulthood.<sup>8</sup> Estimated smoking rates in adolescents with ADHD are variable,<sup>7,9</sup> to an approximate doubling of the population rate.<sup>3</sup>

Drug treatment for ADHD may result in reduced impulsive experimentation with cigarettes or in unhealthy attempts at self-medication.<sup>9,10</sup> However, an alternate hypothesis is that stimulants may actually increase the risk of smoking owing to a putative sensitization of the dopamine system, leading to heightened reinforcing effects of nicotine.<sup>11,12</sup>

In a previous attempt to address smoking prevention in adolescents with ADHD, Monuteaux et al<sup>13</sup> conducted a double-blind randomized clinical trial of bupropion hydrochloride (an adult smoking cessation aid) in ADHD youth who were allowed to receive concomitant open-label treatment with stimulant medication, thereby not compromising the treatment of ADHD itself. Results of that study failed to support a role for bupropion in smoking prevention, but suggested instead that stimulants might have such an effect. Although patients treated with stimulants experienced a significant reduction in the risk for smoking initiation during the study relative to those who did

ADHD	Attention deficit hyperactivity disorder
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
FTQ	Fagerstrom Tolerance Questionnaire
OROS MPH	Extended-release methylphenidate

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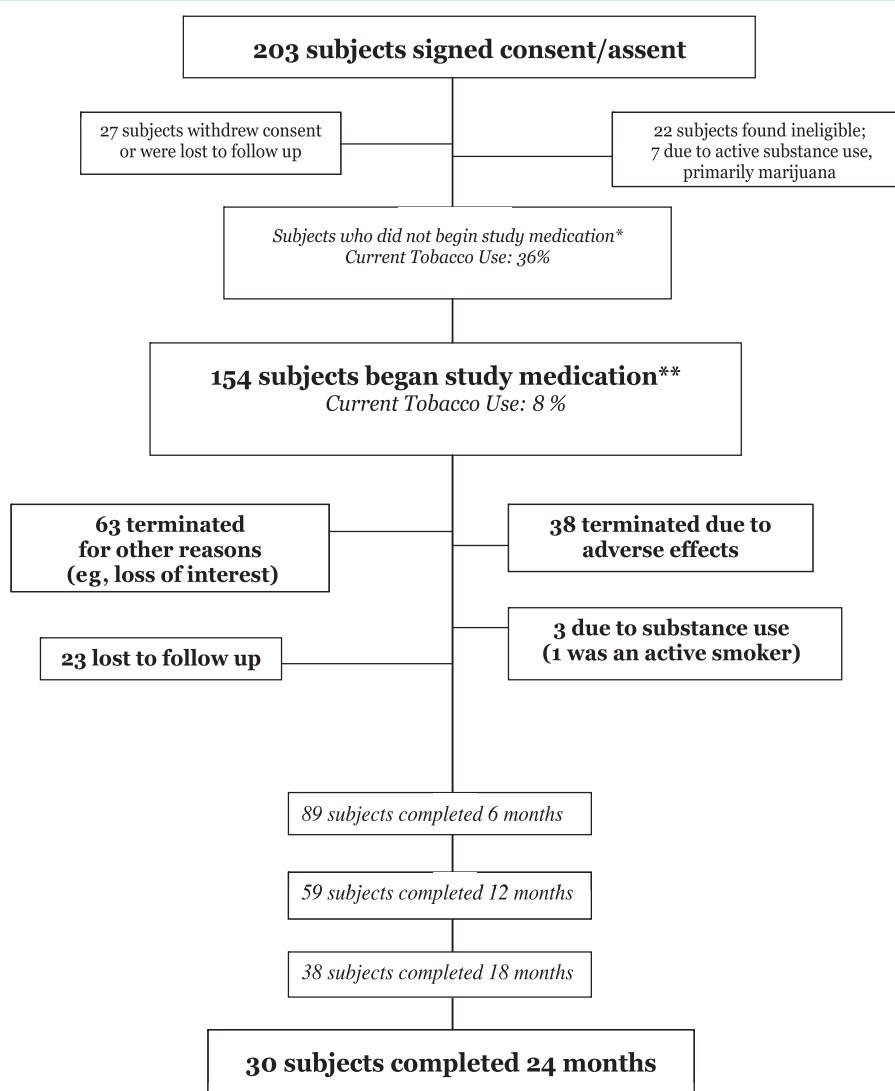
not receive stimulants, the effect of nonpharmacologic factors (ie, positive psychosocial and familial factors) could not be ruled out.

The main aim of the present study was to assess the effects of rigorous, long-term stimulant treatment on smoking rates in adolescents with ADHD. Although a long-term randomized, double-blind, placebo-controlled study would be ideal for evaluating this issue, such a study might not be feasible or ethical because it would deprive ADHD youth of effective treatment for a highly morbid disorder during a critical developmental period. Therefore, we conducted a long-term (2 years) open-label clinical trial of extended-release methylphenidate (OROS MPH) in a large sample of adolescents with ADHD (as defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* [DSM-IV]), and compared smoking outcomes with those derived from an opportunistic, naturalistic

sample of youth of similar age and sex with and without ADHD who received the same assessment measures. Our primary hypothesis was that long-term OROS MPH treatment would be associated with lower rates of cigarette smoking in ADHD youth participating in the clinical trial compared with untreated ADHD comparators and non-ADHD controls.

## Methods

Clinical trial subjects were ascertained from clinical referrals and advertisements in the local media (**Figure 1**). Eligible subjects, aged 12-17 years, met the diagnostic criteria for DSM-IV ADHD as determined by a clinical interview with a child and adolescent psychiatrist with expertise in ADHD. Subjects with clinically significant or unstable medical or psychiatric comorbidities based on this clinical



**Figure 1.** Clinical trial flowchart. \*Based upon N = 14 completed evaluation and laboratories before ending participation. \*\*Mean length of OROS MPH treatment for the sample = 10 months.

evaluation were excluded. We decided a priori to not exclude current cigarette smokers, feeling that excluding these cases would limit the generalizability of our findings in part by selecting a sample with less severe ADHD at lower risk for smoking.

The psychiatrist evaluation was supplemented with a structured diagnostic interview (Schedule for Affective Disorders and Schizophrenia for School-Aged Children) that included a DSM-IV-based module inquiring about frequency of cigarette use and problems associated with smoking. Previous pharmacotherapy for ADHD was discontinued during the evaluation process, before starting study medication at baseline. A group of subjects ( $n = 25$ ) judged by the evaluating psychiatrist to be responders to OROS MPH, as defined by a Clinical Global Impression Improvement score of 1 or 2 (ie, much or very much improved), entered the study already on OROS MPH. Informed consent was ascertained from a parent/guardian, and assent was obtained from each subject. Subjects were compensated for study visits completed. The study was approved by Massachusetts General Hospital's Institutional Review Board and registered with [ClinicalTrials.gov](https://www.clinicaltrials.gov) (NCT00181714). Subjects were active between 2004 and 2011.

After evaluation and baseline assessments, study physicians prescribed OROS MPH under open-label conditions. Subjects were followed on a weekly basis for 6 weeks, then monthly thereafter for up to 24 months. Daily doses were clinically adjusted during the 6-week acute phase in increments of 9-18 mg/day (maximum, 1.5 mg/kg/day, or 126 mg/day), according to tolerability and efficacy, based on physician interview of subject and parent/guardian. Mean OROS MPH exposure for the sample was 10 months (endpoint), with a mean OROS MPH daily dose at study endpoint of  $61 \pm 25$  mg ( $0.97 \pm 0.36$  mg/kg/day). The mean clinician-rated ADHD rating scale score of  $27 \pm 10$  at baseline decreased significantly, to  $11 \pm 9.0$  at endpoint ( $t = 18$ ;  $P < .01$ ). There were no serious adverse effects related to the study medication; observed adverse effects were consistent with the well-documented safety profile of OROS-MPH. (Detailed information on adverse effects is available on request.) Early dropouts (ie, before the mean follow-up time of 10 months) were significantly more likely to be female (34% vs 15%;  $P = .01$ ) and older (14.9 years vs 13.6 years at baseline;  $P < .001$ ). However, early dropout was not associated with baseline multiple anxiety disorders, major depression, bipolar disorder, oppositional defiant disorder, conduct disorder, or any substance use disorder (all  $P > .20$ ).

### Comparator Subjects

The comparator samples consisted of opportunistic samples of youth of similar age and sex with and without ADHD, from naturalistic longitudinal studies of youth with and without ADHD.<sup>14-16</sup> As for the clinical trial subjects, diagnosis was based on structured diagnostic psychiatric interviews (using the Schedule for Affective Disorders and Schizophrenia for School-Aged Children), including a DSM-IV-based

module inquiring about frequency of cigarette use, and problems associated with its use. ADHD comparators were either currently on medication ( $n = 46$ ) or not on medication ( $n = 57$ ) at time of assessment. One-half (49%) of the ADHD comparator group not currently on medication did have a previous history of ADHD pharmacotherapy; the average time elapsed since last dose of medication for ADHD was 2.6 years.

### Smoking Assessment

Cigarette smoking was assessed by subject self-report using a modified version of the Fagerstrom Tolerance Questionnaire (FTQ).<sup>17</sup> The FTQ and modifications thereof offer short, reliable, valid self-report measures of smoking behaviors (eg, cigarettes per day) and physiological dependence to nicotine (eg, time to first cigarette after awakening), with application in adolescent psychiatric samples.<sup>18</sup> Rates of smoking were determined from the initial question from the modified FTQ; "Do you currently smoke (since the last visit)?" (yes/no). For the few ( $n = 5$ ) clinical trial subjects who did not complete the FTQ at baseline, information on smoking obtained at the same time point from the DSM-IV-based smoking module was used. In addition, subjects in the clinical trial also underwent urine assays for cotinine, the major metabolite of nicotine.

### Data Analysis

Our primary hypothesis was that OROS MPH treatment would be associated with a lower rate of cigarette smoking in clinical trial subjects compared with untreated ADHD comparators. The clinical trial subjects included in this analysis included those adolescents who took at least one dose of OROS MPH after baseline assessment ( $n = 154$ ), with the last observation carried forward for subjects who did not complete the full study schedule of 24 months (**Figure 1**). The prevalence of current smoking at endpoint in the clinical trial sample was compared with the prevalence of current smoking in the comparator youth with and without ADHD using the Pearson  $\chi^2$  test. Potential confounders, such as IQ and psychiatric comorbidities, were controlled for using multivariate logistic regression. The McNemar  $\chi^2$  test and a Kaplan-Meier failure function were used to estimate the rate of smoking initiation in clinical trial subjects who were not smoking at baseline. Although the Kaplan-Meier failure function accounts for the censored data (ie, subjects who dropped out of the study early), it assumes that early dropout is not related to smoking outcome; thus, we conducted an analysis of early dropouts (ie, before the mean follow-up time of 10 months).

## Results

The majority of clinical trial and comparator subjects were male and in mid-adolescence; mean age and sex frequency did not differ meaningfully among the 3 groups (**Table I**).

IQ was significantly higher in the historical comparators compared with the clinical trial subjects. Although there were no significant differences in rates of psychiatric comorbidity between the clinical trial subjects and ADHD comparators currently on medication, rates of comorbidity with major depression, conduct disorder, and alcohol and drug abuse were significantly lower in the clinical trial subjects (Table I).

### Smoking Outcomes: Clinical Trial Subjects versus Comparators

The rate of current smoking (as assessed by the FTQ) in clinical trial subjects was similar to the rate observed in non-ADHD comparators and in ADHD comparators currently on medication (7.1% vs 8.0% vs 10.9%;  $P > .20$ ) (Figure 2). In contrast, the rate of smoking in clinical trial subjects was significantly lower than that in the ADHD comparators currently not on medication (7.1% vs 19.6%;  $P < .01$ ). This latter finding remained significant when controlling for IQ, anxiety disorders, major depression, bipolar disorder, oppositional defiant disorder, alcohol dependence, and drug dependence (all  $P < .05$ ), but not when controlling for conduct disorder and alcohol and drug abuse (all  $P > .05$ ). For the ADHD comparators currently not on medication, past history of any ADHD medication (vs never treated) did not significantly affect the age of onset of first-time smoking or smoking rates.

**Smoking Initiation.** The rate of new onset of smoking was low in clinical trial subjects as assessed by the FTQ self-report (Table II) and urine cotinine measurements (Table III; available at [www.jpeds.com](http://www.jpeds.com)) at endpoint. There was no single temporal pattern of smoking initiation in these subjects throughout the study period. Owing to the variable follow-up times, we used a Kaplan-Meier failure function. At endpoint we found a smoking rate of 2.8% in the 141 nonsmoking subjects entering the study; this rate

was estimated to be 7.5% if all subjects completed the 2-year study.

**Smoking Persistence.** Of self-reported smokers (with a positive FTQ at baseline and at endpoint), no quantitative changes in patterns of smoking (ie, cigarettes per day, days smoking per week) or symptoms of nicotine dependence (eg, difficulty controlling use) were seen throughout the study period. These subjects included intermittent smokers as well as regular daily users, generally smoking less than one-half of a pack per use.

## Discussion

Results from this prospective, open-label, long-term clinical trial of OROS MPH in adolescents with ADHD found that treatment with OROS MPH (mean duration, 10 months) was associated with a low rate of cigarette smoking, similar to the rates seen in non-ADHD and treated ADHD comparators and significantly lower than the rate seen in non-treated ADHD comparators. Although this study is limited by its open-label design, preliminary findings suggest that long-term treatment with OROS MPH may contribute to a decrease in the risk for smoking in adolescents with ADHD. If confirmed, this finding would have significant clinical and public health relevance.

Our finding showing an association between treatment with OROS MPH monotherapy and a low rate of smoking is consistent with results from a previous prospective study conducted by our group to assess the efficacy of bupropion for smoking prevention in youth with ADHD receiving concomitant treatment with stimulants for ADHD.<sup>13</sup> Although results from that study failed to support a role for bupropion in preventing smoking initiation, youth who were prescribed a concomitant stimulant medication had a lower rate of smoking initiation (hazard ratio, 0.2; 95% CI, 0.08-0.89;  $z = -2.2$ ;  $P = .03$ ) and a lower rate of smoking continuation

**Table I.** Characteristics of clinical trial subjects and comparator subjects

	OROS MPH clinical trial subjects (n = 154)	ADHD comparators currently receiving medication (n = 46)	ADHD comparators currently not receiving medication (n = 57)	Non-ADHD comparators (n = 188)	Test, P value
Age, years, mean $\pm$ SD*	15.3 $\pm$ 1.8	15.1 $\pm$ 3.3	16.1 $\pm$ 3.2	15.4 $\pm$ 2.6	$F_{(3,441)} = 1.88$ ; $P = .13$
Male sex, n (%)	114 (74)	31 (67)	36 (63)	126 (67)	$\chi^2_{(3)} = 3.13$ ; $P = .37$
IQ score, mean $\pm$ SD	102.1 $\pm$ 11.8 <sup>†,‡</sup>	106.9 $\pm$ 16.1	105.7 $\pm$ 15.3 <sup>§</sup>	110.6 $\pm$ 13.4	$F_{(3,426)} = 10.74$ ; $P < .01$
Psychiatric comorbidity, n (%) <sup>§</sup>					Fisher exact test
Multiple ( $\geq 2$ ) anxiety	21 (14) <sup>†</sup>	3 (7)	6 (11) <sup>†</sup>	4 (2)	$P < .01$
Major depression	7 (5) <sup>¶</sup>	5 (11)	10 (18) <sup>†</sup>	7 (4)	$P < .01$
Bipolar disorder	5 (3) <sup>†</sup>	5 (11) <sup>†</sup>	4 (7) <sup>†</sup>	0 (0)	$P < .01$
Oppositional defiant disorder	40 (26) <sup>†</sup>	17 (40) <sup>†</sup>	17 (30) <sup>†</sup>	9 (5)	$P < .01$
Conduct disorder	2 (1) <sup>¶</sup>	0 (0) <sup>¶</sup>	6 (11) <sup>†</sup>	2 (1)	$P < .01$
Alcohol abuse	1 (1) <sup>¶</sup>	2 (4)	6 (11) <sup>†</sup>	6 (3)	$P < .01$
Alcohol dependence	0 (0)	0 (0)	1 (2)	2 (1)	$P = .38$
Drug abuse	1 (1) <sup>¶</sup>	1 (2)	5 (9) <sup>†</sup>	3 (2)	$P = .01$
Drug dependence	1 (1)	1 (2)	3 (5) <sup>†</sup>	0 (0)	$P < .01$

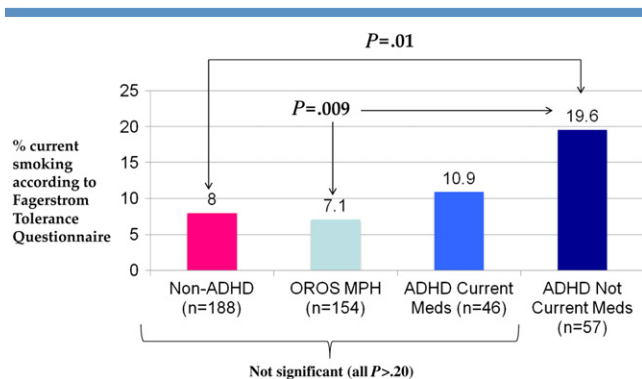
\*Age at endpoint (clinical trial subjects); age at assessment (comparators).

<sup>†</sup> $P < .05$  vs non-ADHD comparators.

<sup>‡</sup> $P < .05$  vs ADHD currently on medication comparators.

<sup>§</sup>Current, last month comorbidity according to structured diagnostic interview at baseline (clinical trial subjects); at assessment (comparators).

<sup>¶</sup> $P < .05$  vs ADHD currently not on medication comparators.



**Figure 2.** Rates of current smoking on OROS MPH compared with non-ADHD and ADHD comparators. Omnibus test,  $\chi^2(1) = 8.29$ ,  $P = .04$ .

(hazard ratio, 0.3; 95% CI, 0.11-0.85;  $z = -2.3$ ;  $P = .02$ ). As in the present study, the possible effect of nonpharmacologic factors (ie, positive psychosocial and familial factors) on smoking outcomes could not be ruled out.

The small number of smokers in the clinical trial limited our ability to detect associations between smoking and other variables. Nonetheless, we can speculate that stimulants might exert a protective effect in part by reducing core symptoms of ADHD and associated comorbid disorders.<sup>19</sup> Although in this study the statistically significantly lower rate of smoking in clinical trial subjects versus nontreated ADHD comparators remained significant when controlling for oppositional defiant disorder and alcohol and drug dependence, it was no longer statistically significant when controlling for conduct disorder and alcohol and drug abuse. Therefore, observed smoking outcomes might have been more related to between-group differences in these respective comorbidities than to a protective effect of stimulant treatment. More work is needed to further elucidate the contributions of comorbid disruptive disorders (ie, diagnoses and symptoms of oppositional defiant disorder, conduct disorder) and alcohol and drug abuse on smoking in youth with ADHD.<sup>9,10</sup> In addition, future prospective studies should examine whether stimulant dose, formulation (ie, short- or long-acting), response to treatment, or tolerability (eg, adverse effect profile, cardiovascular changes) may influence smoking outcomes in youth with ADHD.<sup>9,10,20</sup>

Given the open-label design of our trial, our results cannot refute a theoretical association between ADHD medication exposure and increased tobacco use.<sup>11,12</sup> However, studies testing this hypothesis have typically been conducted outside

the context of ADHD, examining the impact of nontherapeutic doses of immediate-release stimulants on smoking in adult smokers<sup>12</sup> and intravenous/intraperitoneal administration in animal models.<sup>21</sup> Laboratory studies of oral OROS MPH administration do not support behavioral sensitization or cross-sensitization to nicotine, consistent with the documented importance of the speed (ie, slow speed with oral administration vs high speed with nonoral) at which stimulants reach the brain for abuse liability risk.<sup>22</sup> Recent prospective studies<sup>23,24</sup> and retrospective reports<sup>25,26</sup> of adolescent and adult smokers with ADHD have shown no increase in cigarette use in the context of stimulant therapy. Yet, consistent with other reports,<sup>23,24</sup> examination of smoking trajectories in the few clinical trial subjects who smoked at baseline revealed no decrease in cigarette use.

Strengths of this study include the long-term systematic assessment of smoking outcomes in a large cohort of adolescents with ADHD rigorously treated with OROS MPH. Our results must be viewed in light of some methodological limitations, however. The main limitation stems from the study's uncontrolled, open-label design. Thus, we cannot assert a causal relationship between lower smoking rates and OROS MPH administration. Although a long-term, randomized, double-blind, placebo-controlled study of stimulant monotherapy would be ideal for evaluating this issue, such an approach would be unfeasible and perhaps unethical because it would deprive adolescents with ADHD of an effective treatment for a highly morbid disorder during a critical developmental period. The only previous attempt to address smoking prevention in adolescents with ADHD was the placebo-controlled study by Monuteaux et al<sup>13</sup> that tested the efficacy of bupropion in ADHD youth receiving open-label treatment with stimulants, thereby not compromising the treatment of ADHD itself. Our trial's open-label design also affected our analytic approach, because for ethical reasons, we required participants to be medication responders at 6 weeks to continue into the 2-year long-term treatment phase.

In addition, we cannot rule out the possibility that our findings reflect an atypical clinical trial subject pool with an unusually low baseline rate of smoking, rather than the effect of OROS MPH. Consistent with this notion is the higher rate of smoking (36%) in subjects screened for the clinical trial who chose not to participate or were ineligible to participate. Conversely, the relatively elevated smoking rates in nontreated comparator ADHD youth might be related to other factors than the lack of medication per se. Families who successfully participate in clinical trials or who successfully obtain and maintain medication treatment for their

**Table II.** Rates of current smoking before and after treatment with OROS MPH: FTQ results

Endpoint	Baseline		
	No current smoking	Current smoking	
No current smoking	137 (89%) remain nonsmoking	6 (4%) stop smoking	McNemar $\chi^2(1) = 0.40$ ; $P = .53$
Current smoking	4 (3%) start smoking	7 (5%) keep smoking	



ADHD-affected children may create a host of protective factors against smoking. Another limitation is the inclusion of only a small number of smokers at baseline. Ideally, future studies will be limited to smoking-naïve youth. Our conclusions are tempered by the high rate of attrition over the 24-month study duration. Early dropouts were more likely to be female and older, but they did not have a greater degree of baseline psychiatric comorbid illness than the remainder of the sample. Finally, given that the sample was referred and mostly Caucasian, our results might not generalize to nonclinical samples or other ethnic groups.

Further examination of the impact of stimulant treatment on smoking risk in youth with ADHD is clearly warranted. Given that youth who continue to smoke through adulthood may shorten their life expectancy by 5-10 years,<sup>27</sup> any reduction in smoking risk would have significant clinical and public health impacts. ■

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## Appendix

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Stephen Faraone, PhD, has received consulting fees and research support from and served on advisory boards for Shire Development within the past year. In previous years, he received consulting fees from, served on advisory boards for, or participated in continuing medical education programs sponsored by Shire, McNeil, Janssen, Novartis, Pfizer, and Eli Lilly. He receives royalties from a book published by Guilford Press.

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Joseph Biederman, MD, currently receives research support from Elminda, Janssen, McNeil, Next Wave Pharmaceuticals, and Shire. In 2011, he gave a single unpaid talk for Juste Pharmaceutical Spain and also received honoraria from the Massachusetts General Hospital's Psychiatry Academy for a tuition-funded CME course. He also received an honorarium from Cambridge University Press for a chapter publication, and departmental royalties from a copyrighted rating scale used for ADHD diagnoses, paid by Eli Lilly, Shire, and AstraZeneca to the Department of Psychiatry at Massachusetts General Hospital. In 2010, he received a speaker's fee from a single talk given at Fundación Dr Manuel Camelo AC in Monterrey Mexico. He provided consultation for Shionogi Pharma and Cipher Pharmaceuticals, with the honoraria for these consultations paid to the Department of Psychiatry at Massachusetts General Hospital. He received honoraria from the Massachusetts General Hospital' Psychiatry Academy for a tuition-funded CME course. In 2009, he received speaker's fees from Fundacion Areces (Spain), Medice Pharmaceuticals (Germany), and the Spanish Child Psychiatry Association. In previous years, he received research support, consultation fees, or speaker's fees from Abbott, Alza, AstraZeneca, Boston University, Bristol Myers Squibb, Celltech, Cephalon, Eli Lilly, Esai, Forest, Glaxo, Gliatech, Hastings Center, Janssen, McNeil, Merck, MMC Pediatric, Brain and Behavior Research Foundation, National Institute on Drug Abuse, New River, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institute of Mental Health, Novartis, Noven, Neurosearch, Organon, Otsuka, Pfizer, Pharmacia, Phase V Communications, Physicians Academy, the Prechter Foundation, Quantia Communications, Reed Exhibitions, Shire, the Stanley Foundation, UCB Pharma, Veritas, and Wyeth.

Thomas Spencer, MD, has received research support from, been a speaker for, served on a speaker bureau or an advisory board of, or served as an advisor to Shire Laboratories, Eli Lilly, Glaxo-Smith Kline, Janssen, McNeil, Novartis, Cephalon, Pfizer, and the National Institute of Mental Health. He receives research support from royalties and licensing fees on copyrighted ADHD scales through the Massachusetts General Hospital's Corporate-Sponsored Research and Licensing. He has a US Patent Application pending (provisional no. 61/233 686) through Massachusetts General Hospital corporate licensing, on a method to prevent stimulant abuse.

**Table III.** Rates of current smoking before and after treatment with OROS MPH: urine cotinine results\*

Endpoint	Baseline		
	No current smoking	Current smoking	
No current smoking	130 (84%) stay nonsmoking	2 (1%) stop smoking	McNemar $\chi^2$ (1) = 1.29; $P$ = .26
Current smoking	5 (3%) start smoking	4 (5%) keep smoking	

\*n = 132 at baseline and n = 135 at endpoint owing to missing cotinine levels in some subjects.