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

Paul Hammerness, MD[1], Gagan Joshi, MD[1], Robert Doyle, MD[1], Anna Georgiopoulos, MD[1], Daniel Geller, MD[1], Thomas Spencer, MD[1], Carter R. Petty, MA[1], Stephen V. Faraone, PhD[2], and Joseph Biederman, MD[1]

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.[1,2] Approximately 4000 US youths try their first cigarette each day.[3] 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.[4]

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.[5-7] 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.[8] Estimated smoking rates in adolescents with ADHD are variable,[7,9] to an approximate doubling of the population rate.[3]

Drug treatment for ADHD may result in reduced impulsive experimentation with cigarettes or in unhealthy attempts at self-medication.[9,10] 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.[11,12]

In a previous attempt to address smoking prevention in adolescents with ADHD, Monuteaux et al[13] 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

From the [1]Clinical and Research Program in Pediatric Psychopharmacology and Adult ADHD, Massachusetts General Hospital and Harvard Medical School, Boston, MA; and [2]Child and Adolescent Psychiatry Research, SUNY Upstate Medical University, Syracuse, NY

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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

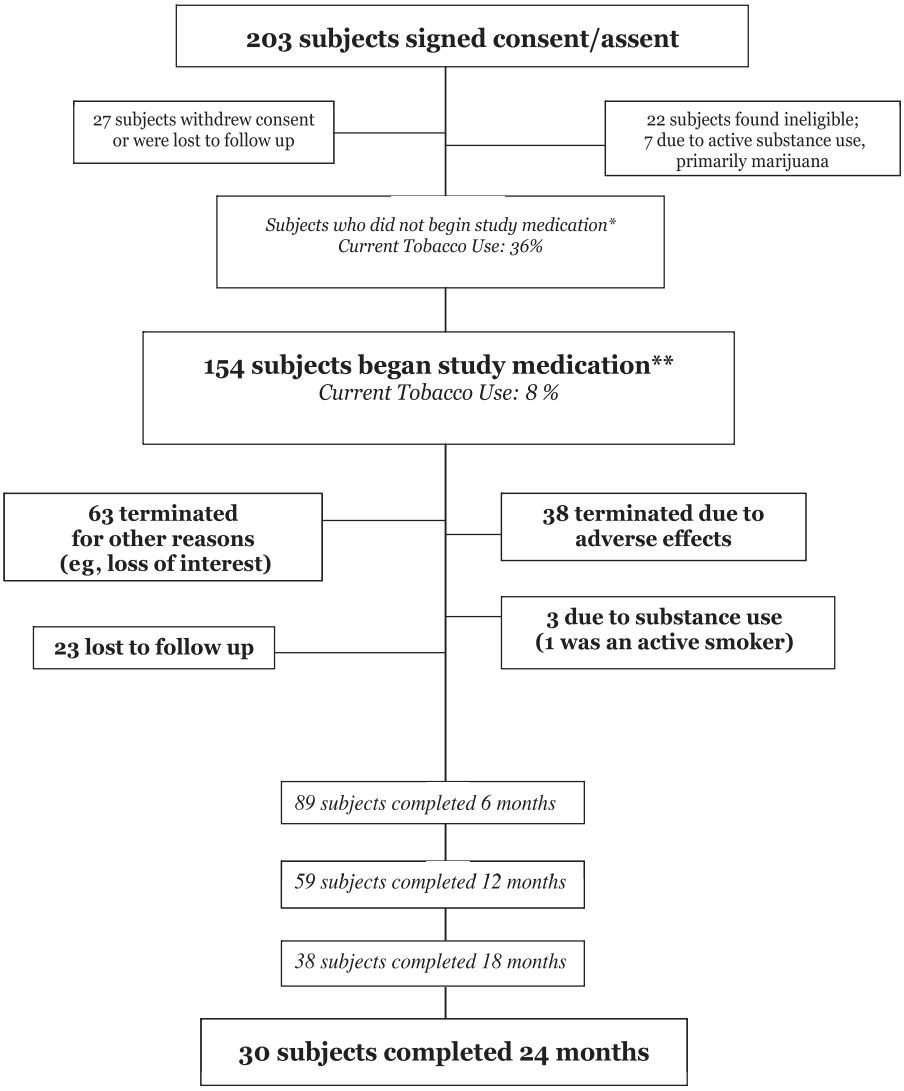

Figure 1. Clinical trial flowchart. *Based upon N = 14 completed evaluation and laboratories before ending participation. **Mean length of OROS MPH treatment for the sample = 10 months.