Impact of Attention-Deficit/Hyperactivity Disorder (ADHD) Treatment on Smoking Cessation Intervention in ADHD Smokers: A Randomized, Double-Blind, Placebo-Controlled Trial

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Objective: High smoking rates in adults with attention-deficit/hyperactivity disorder (ADHD) and nicotine's amelioration of ADHD suggest that effective ADHD treatment might facilitate abstinence in smokers with ADHD. The present study evaluated if using osmotic-release oral system methylphenidate (OROS-MPH) to treat ADHD enhances response to smoking cessation treatment in smokers with ADHD.

Method: A randomized, double-blind, placebo-controlled, 11-week trial with a 1-month follow-up was conducted at 6 clinical sites between December 2005 and January 2008. Adults (aged 18–55 years) meeting *DSM-IV* criteria for ADHD and interested in quitting smoking were randomly assigned to OROS-MPH titrated to 72 mg/d (n = 127) or placebo (n = 128). All participants received brief weekly individual smoking cessation counseling for 11 weeks and 21 mg/d nicotine patches starting on the smoking quit day (day 27) through study week 11. Outcome measures included prolonged smoking abstinence and *DSM-IV* ADHD Rating Scale (ADHD-RS) score.

Results: Of 255 randomly assigned participants, 204 (80%) completed the trial. Prolonged abstinence rates, 43.3% and 42.2%, for the OROS-MPH and placebo groups, respectively, did not differ significantly (OR = 1.1; 95% CI, 0.63–1.79; $P = .81$). Relative to placebo, OROS-MPH evidenced a greater reduction in *DSM-IV* ADHD-RS score ($P < .0001$) and in cigarettes per day during the post-quit phase ($P = .016$). Relative to placebo, OROS-MPH increased blood pressure and heart rate to a statistically, but not clinically, significant degree ($P < .05$); medication discontinuation did not differ significantly between treatments.

Conclusions: Treatment for ADHD did not improve smoking cessation success; OROS-MPH, relative to placebo, effectively treated ADHD and was safe and generally well tolerated in this healthy sample of adult ADHD smokers.

Trial Registration: clinical trials.gov Identifier: NCT00253747

J Clin Psychiatry 2010;71(12):1680–1688

Submitted: *January 30, 2009; accepted July 10, 2009.*
Online ahead of print: *May 18, 2010 (doi:10.4088/JCP.09m05089gry).*
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Each year, cigarette smoking accounts for an estimated 438,000 deaths and $92 billion in productivity losses in the United States.[1] Recent efforts to combat cigarette smoking have included not only the direct treatment of nicotine dependence but also co-occurring conditions that may make individuals vulnerable to the persistence of cigarette smoking.[2] Research suggests that cigarette smoking is significantly more common in children[3] and adults with attention-deficit/hyperactivity disorder (ADHD) compared to the general population and/or controls.[4,5] Moreover, ADHD is associated with earlier onset of cigarette smoking,[3] more severe nicotine dependence,[6] and more difficulty quitting smoking.[4] It has been suggested that this greater incidence of smoking might reflect an attempt at self-medication of ADHD symptoms.[7]

Adult ADHD, which has a prevalence rate of approximately 4.4%,[8] is characterized by symptoms of inattention, impulsivity, and hyperactivity and is associated with significant impairment in nearly every area of functioning, including poorer performance in educational and occupational settings, higher rates of divorce/separation, and higher rates of other psychiatric and substance use disorders.[9] While adult ADHD is one of the most common mental health disorders of adulthood,[10] treatment rates remain low.[11] Research indicates that nicotine is effective in decreasing ADHD symptoms,[7,12,13] and, in fact, several nicotinergic agents are currently being evaluated as ADHD treatments.[14] Some data also suggest that treating ADHD with stimulants protects against the development of later cigarette smoking.[15] If smokers with ADHD are, in fact, using nicotine in an attempt to ameliorate their symptoms, then successfully treating their ADHD should facilitate successful smoking cessation.

Psychostimulants are the mainstay pharmacologic treatment for ADHD. More than 200 randomized controlled trials,[16,17] along with decades of clinical experience, have established the safety and efficacy of methylphenidate (MPH) in treating ADHD.[18] In recent years, a long-acting formulation of MPH, osmotic-release oral system MPH (OROS-MPH), has been developed. Osmotic-release oral system MPH appears to be as effective as thrice-daily immediate-release MPH (IR-MPH),[19] with the benefits of requiring just once-a-day dosing and a lower abuse liability.[20] While OROS-MPH is effective in treating ADHD in adolescents[21] and adults,[22,23] there is no compelling evidence to suggest that it would be useful in managing nicotine

withdrawal, which includes changes in mood, appetite, and increased cigarette craving, and typically accompanies the early stages of smoking abstinence. In contrast, while nicotine has been found to increase attention, it may be less effective in increasing response inhibition.[24] Response inhibition, a core component of ADHD,[24] appears to be more difficult during early smoking abstinence for individuals with ADHD compared to those without ADHD.[25] This suggests that the use of nicotine replacement therapy alone may be insufficient for managing the re-emergence of ADHD symptoms following smoking cessation. On the basis of the available literature, we hypothesized that using OROS-MPH to treat ADHD in conjunction with smoking cessation treatment would facilitate successful smoking cessation in smokers with ADHD.

The present trial was an initial evaluation of the efficacy and safety of OROS-MPH with smoking cessation treatment, specifically nicotine patch and counseling, relative to placebo with smoking cessation treatment, in initiating and maintaining abstinence in adult smokers with ADHD. The safety evaluation focused on 2 primary areas of concern. The first involved possible increases in cardiovascular side effects associated with providing a stimulant to individuals already using a stimulant (ie, nicotine); this evaluation is timely given concerns about the degree to which stimulants may be associated with adverse cardiovascular events in both children and adults.[26] The second concern involved the possibility that OROS-MPH might actually increase, rather than decrease, smoking, a concern raised by laboratory studies finding that IR-MPH significantly increases smoking in adult non-ADHD smokers who were not trying to quit smoking[27,28]; on the basis of these findings, the investigators suggested that clinicians consider using nonstimulants to treat ADHD in smokers.[28] In the present trial, it was predicted that OROS-MPH with smoking cessation treatment, relative to placebo with smoking cessation treatment, would be safe and would significantly increase smoking abstinence in smokers with ADHD.

METHOD

Study Design

This randomized, intent-to-treat, double-blind, placebo-controlled trial included an 11-week treatment phase during which efficacy outcomes were measured and a 1-month follow-up assessment to collect additional safety data. Typically, smoking cessation trials include 6- and 12-month assessments of smoking abstinence. However, this trial was the first to assess the effect of OROS-MPH on smoking outcomes in adults with ADHD and, thus, was focused on more immediate effects. To evaluate whether ADHD treatment enhanced smoking cessation success, the present trial included an extended pre-quit phase to allow OROS-MPH to effectively ameliorate ADHD symptoms prior to the quit-smoking day. Specifically, the treatment period consisted of 2 phases: the pre-quit phase, which comprised the first 26 days of treatment, and the post-quit phase, starting on day 27 (the designated quit-smoking day) and continuing through the end of the treatment period. This trial was conducted by the National Institute on Drug Abuse Clinical Trials Network (CTN) between December 2005 and January 2008. Six study sites, located in Cambridge, Massachusetts; Columbus, Ohio; New York, New York (2 sites); Portland, Oregon; and Rochester, Minnesota, recruited participants. Two study sites were substance abuse community treatment programs that had participated in previous CTN trials; 4 additional sites were recruited for the present trial—2 ADHD clinics and 2 smoking cessation clinics. All participants were given a thorough explanation of the study, including possible side effects, and signed an informed consent form that was approved by the institutional review boards of the participating sites.

Participants

Recruitment methods included advertising, letters to clinic patients, and direct community promotions, such as networking with community professionals. Eligible participants were interested in quitting smoking and were between 18 and 55 years of age and in good physical health as determined by a medical history, electrocardiogram, and vital signs. The vital signs criterion cut-off was 135/85 mm Hg for blood pressure and 90 bpm for heart rate for the first 143 participants randomly assigned into the trial. However, based on Data and Safety Monitoring Board recommendations following the 2006 OROS-MPH labeling changes,[29] the criterion was made more restrictive for participants aged 40 years or older, with cut-off values being 130/80 mm Hg and/or a heart rate > 88 bpm for the remainder of the trial. Participants were required to meet *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*) criteria for ADHD as assessed by the Adult Clinical Diagnostic Scale, version 1.2[30]; to have a *DSM-IV* ADHD Rating Scale (ADHD-RS)[31] total score > 22; to smoke at least 10 cigarettes per day; to have a carbon monoxide (CO) level ≥ 8 ppm; and to have smoked cigarettes for at least 3 months. Candidates were excluded if they were a significant suicidal/homicidal risk; had used tobacco products other than cigarettes in the past week; had a positive urine screen for an illicit drug; or met *DSM-IV* criteria for current abuse or dependence for any psychoactive substance other than nicotine, current major depression, any current anxiety disorder except specific phobias, antisocial personality disorder, or a lifetime diagnosis of bipolar disorder or psychosis. Other exclusion criteria included a history of narrow angle glaucoma or seizure disorder, tics, or a family history of Tourette syndrome. Individuals were also excluded if they had been treated for ADHD with psychomotor stimulants or had used smoking cessation counseling programs or medications within the last 30 days, if they were currently taking a medication that could adversely interact with OROS-MPH, if they had a known allergy to OROS-MPH, or if they had been nonresponders to a reasonable course of MPH treatment. Women were ineligible if they were pregnant or breastfeeding or unwilling to use an adequate method of birth control.

Procedures

An overview of study procedures is provided in Figure 1. Randomization of participants to OROS-MPH or matching

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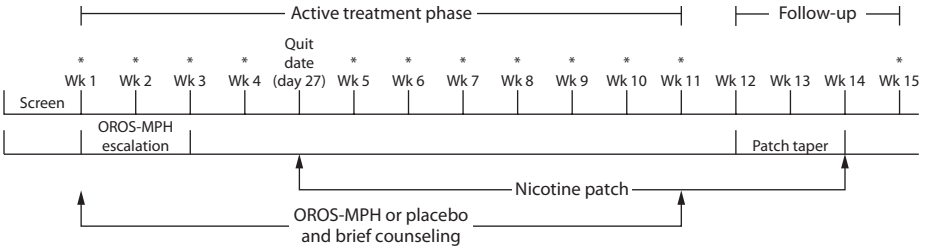
Figure 1. Study Schema



Abbreviation: OROS-MPH = osmotic-release oral system methylphenidate.
Symbol: * = scheduled research visit.

placebo was in a 1:1 ratio, stratified by site, and completed by computer at a centralized location. For OROS-MPH, the starting dose of 18 mg/d was escalated during the first 2 study weeks to a maximum of 72 mg/d or to the highest dose tolerated; OROS-MPH/placebo was taken through the week 11 visit.

A trained interventionist provided each participant with a weekly 10-minute smoking cessation counseling session during study weeks 1–11. The manual used was an unpublished manual, Smoke Free and Living It, developed by the Mayo Clinic Nicotine Research Program for use in clinical trials (Rochester, Minnesota). Interventionists received training on the manual and were certified after a review of a successful mock session. All therapy sessions were videotaped to monitor adherence; of the 163 sessions rated, 156 (95.7%) were rated as adherent.

All participants received transdermal nicotine patches (Habitrol, Novartis, Parsippany, New Jersey) and were instructed to wear a patch daily for 24 hours beginning on the target quit date (study day 27). Participants were provided with 21 mg/d patches for use through week 11; for tapering, participants were provided with 14 mg/d patches for study weeks 12 and 13, and 7 mg/d patches for study week 14. During the 11-week active trial, participants were scheduled to attend 1 research visit per week. Study participants received $25 per research visit; at the week 11 visit, participants received an additional $25 because of the larger assessment burden associated with the visit.

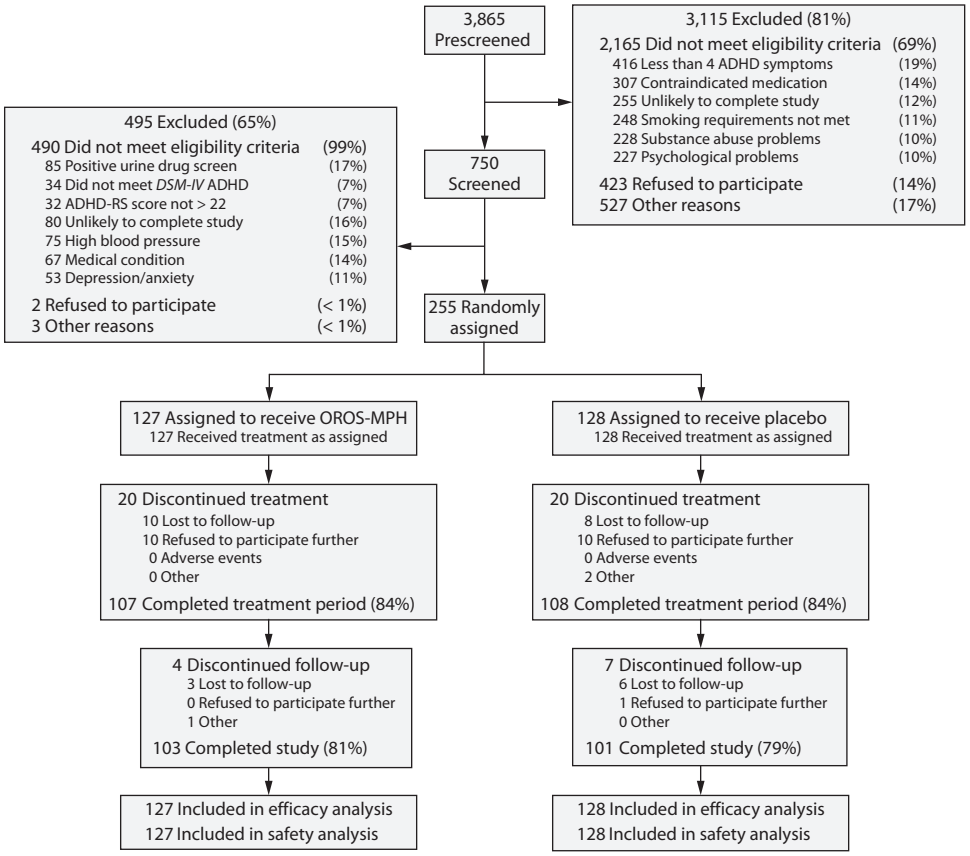
Measures

Self-report of cigarette use, assessed using time-line follow-back assessment,[32,33] and CO measurement were obtained weekly. Consistent with the recommendations of the Society for Research on Nicotine and Tobacco,[34] the primary outcome measure was prolonged abstinence defined as a self-report of tobacco abstinence without treatment failure (defined as smoking each day for 7 consecutive days or having smoked at least 1 day of each week in 2 consecutive weeks) during study weeks 7–10; the selection of a 4-week period is consistent with US Food and Drug Administration (FDA) standards for approving smoking cessation medications.[34] Secondary smoking outcome measures included point-prevalence abstinence at week 10, defined as self-report of not smoking in the previous 7 days, confirmed by a CO level < 8 ppm,[35] and self-reported cigarettes per day. Attention-deficit/hyperactivity disorder outcome measures included *DSM-IV* ADHD-RS total score,[31] assessed with prompts for the interviewer,[36] and ADHD severity assessed by the Clinical Global Impressions-Severity of Illness scale (CGI-S).[37] Rater training in ADHD measures was conducted according to accepted methodology[38] prior to study initiation. Both ADHD assessments were obtained weekly during the pre-quit phase and every 2 weeks during study weeks 7–11. Safety measures included weekly vital signs and adverse event assessments. Medication adherence was assessed weekly via self-report and pill count; nicotine patch adherence was assessed weekly via self-report and patch count (weeks 5–11 only).

Data Analysis

All analyses were completed on the intent-to-treat sample using SAS, Version 9.1.3 (SAS Institute, Cary, North Carolina).[39] Statistical tests were conducted at a 5% Type I error rate (2-sided) for all measures. Outcomes measured at multiple time points were analyzed using Generalized Estimating Equation models. Dichotomous efficacy measures were analyzed using logistic regression. Given the smoking quit date's substantial impact on cigarettes per day, analyses for cigarettes per day evaluated treatment effects for the pre-quit and post-quit phases as well as for the entire treatment phase. Analyses for cardiovascular effects included baseline as a covariate. All modeling included treatment, week, a treatment × week interaction effect, and site effects. Site effects were evaluated for statistical significance and dropped from the model if nonsignificant ($P > .10$). A significant treatment × week interaction effect suggests a significant difference in slope over time between the OROS-MPH and placebo groups, and, in the absence of a treatment × week interaction effect, a significant treatment effect suggests an absolute difference between the 2 groups; thus, both effects are of interest. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) and tabulated by body system and preferred term, seriousness, and relationship to study medication. Fisher mid–*P* value was used to examine differences between treatments in adverse event frequency. For the smoking abstinence measures, days for which data were missing were coded as smoking days; missing data for other measures were not imputed.

Figure 2. Participant Disposition



Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ADHD-RS = Attention-Deficit/Hyperactivity Disorder Rating Scale; *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; OROS-MPH = osmotic-release oral system methylphenidate.

RESULTS

Participants and Disposition

As shown in Figure 2, 3,865 candidates were prescreened, 750 gave informed consent and were screened, and 255 were randomly assigned to OROS-MPH or placebo. Approximately 84% of participants completed the 11-week active treatment period, with no treatment group differences on completion rate or reasons for noncompletion. Of noncompleters, 46% were lost to follow-up, 30% reported practical problems (eg, work schedule, transportation, etc), 13% reported not needing further treatment, 10% withdrew consent, and 1 participant was administratively discharged. No participant discontinued the study due to an adverse event. Demographic and baseline characteristics did not differ significantly between the groups. As can be seen in Table 1, the sample was approximately 56% male and 82% white, and participants were a mean age of 38 years. The sample had moderately severe ADHD, as assessed by the *DSM-IV* ADHD-RS total score, had a medium level of nicotine dependence as assessed by the Fagerström score, and, on average, smoked a pack of cigarettes per day. Medication adherence was high and did not differ significantly between treatment groups (Table 2).

Smoking Outcomes

The treatment groups did not differ significantly on the primary outcome measure of prolonged abstinence, with rates of 43.3% in the OROS-MPH and 42.2% in the placebo group ($\chi^2_1 = 0.06$; OR = 1.1; 95% CI, 0.63–1.79; $P = .81$). There was a similar lack of treatment effect on point-prevalence abstinence, with rates of 39.4% in the OROS-MPH and 38.3% in the placebo group ($\chi^2_1 = 0.08$, $P = .78$). Cigarettes per day analyses revealed one statistically significant effect, a treatment × week interaction effect for the post-quit phase ($\chi^2_1 = 5.85$, $P = .016$), which reflected fewer cigarettes per day in the OROS-MPH group, relative to the placebo group (Figure 3). It should be noted that this difference in cigarettes per day was quite small, equating to approximately 1 cigarette per day.

ADHD Outcomes

Relative to placebo, OROS-MPH participants had a significantly greater decrease in ADHD symptom severity as assessed by both the *DSM-IV* ADHD-RS total score ($\chi^2_1 = 15.93$, $P < .0001$; Figure 4) and the CGI-S ($\chi^2_1 = 6.97$, $P = .008$). Prior clinical trials for adult ADHD have reported treatment response rates defined as a 30% or greater decrease on the primary ADHD assessment and a change on the CGI-Improvement scale. The CGI-Improvement scale was not

Table 1. Participant Demographic and Baseline Characteristics (N = 255)[a]

Characteristic	OROS-MPH (n = 127)	Placebo (n = 128)
Age, y	38.1 (10.4)	37.5 (9.6)
Sex, male, %	60.6	52.3
Race/ethnicity, %		
African American	4.8	7.0
White	86.4	78.9
Asian	1.6	1.6
Native American/Alaskan	0.8	0.0
Other	3.2	4.7
Mixed race	3.2	7.8
Hispanic	7.9	6.3
Marital status, %		
Married	40.5	27.8
Separated/divorced/widowed	17.4	25.4
Never married	42.1	46.8
Education, y	14.4 (2.4)	14.5 (2.4)
Employed full-/part-time, %	94.4	89.7
Lifetime psychiatric comorbidity, %		
Major depression	32.3	35.9
Bipolar disorder	0.0	0.0
Anxiety disorder	34.6	32.8
Substance use disorder	63.0	58.6
DSM-IV ADHD Rating Scale total score	36.0 (7.1)	36.7 (7.5)
Adult ADHD subtype, %		
Inattentive	35.4	33.1
Hyperactive-impulsive	5.5	2.4
Combined	59.1	64.6
Smoking history		
Fagerström score	5.6 (2.1)	5.4 (2.3)
No. of smoking years	19.9 (10.0)	19.5 (9.3)
No. of cigarettes/d	19.8 (8.1)	19.8 (7.5)
No. of past quit attempts	7.5 (10.3)	6.4 (9.8)

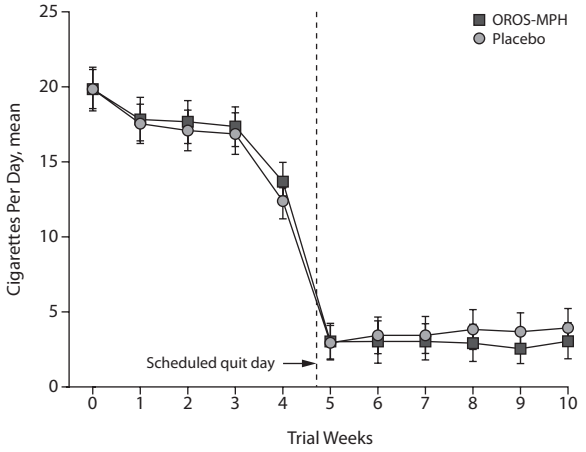
[a]Where not specifically indicated, numbers represent mean (SD).
Abbreviations: ADHD = attention-deficit/hyperactivity disorder; *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; OROS-MPH = osmotic-release oral system methylphenidate.

Table 2. Summary of Medication Adherence and Tolerability[a]

	OROS-MPH (n = 127)	Placebo (n = 128)	*P* Value
Medication adherence			
Percentage of OROS-MPH/placebo pills taken			
Self-report[b]	93.1 (13.5)	93.1 (13.3)	.41
Pill count[c]	95.8 (14.6)	95.2 (20.0)	.77
Percentage of nicotine patches taken			
Self-report[b]	84.6 (26.5)	78.9 (32.9)	.60
Patch count[c]	74.8 (29.6)	77.1 (27.4)	.79
Medication tolerability			
Tolerability of maximum OROS-MPH/placebo dose			
Reached maximum, n (%)	109 (85.8)	111 (86.7)	.84
Sustained dose at maximum, n (%)	80 (63.0)	88 (68.8)	.33
Sustained dose 21 mg/d for nicotine patch, n (%)	96 (75.6)	88 (68.8)	.22

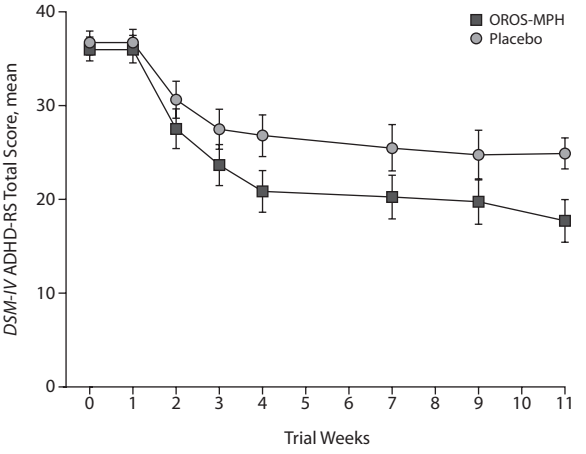
[a]Where not specifically indicated, numbers represent mean (SD).
[b]Self-reported adherence was calculated by dividing the number of pills/patches taken by the number prescribed and multiplying by 100.
[c]For pill/patch count, adherence was calculated by taking the number of pills/patches dispensed minus the number returned or reported lost divided by the number of pills/patches prescribed to be taken and multiplying by 100. In cases where participants failed to return their medication bottles/patches, those bottles/patches were excluded from the analysis.
Abbreviation: OROS-MPH = osmotic-release oral system methylphenidate.

Figure 3. Cigarettes Per Day as a Function of Treatment Group and Time



Abbreviation: OROS-MPH = osmotic-release oral system methylphenidate.

Figure 4. *DSM-IV* ADHD-RS Total Score as a Function of Treatment Group and Time



Abbreviations: ADHD-RS = Attention-Deficit/Hyperactivity Disorder Rating Scale; *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; OROS-MPH = osmotic-release oral system methylphenidate.

included in the present trial; thus, a treatment responder was defined as a participant whose week-11 *DSM-IV* ADHD-RS total score was reduced by 30% or more compared to baseline and who had a 1 point or greater reduction in week-11 CGI-S score relative to baseline. Of the 255 randomly assigned participants, 215 participants, 107 OROS-MPH and 108 placebo, had week-11 data and, thus, could be classified as responders or nonresponders. In these 215 participants, the treatment response rate was 71% in the OROS-MPH group and 44% in the placebo group, a statistically significant difference ($\chi^2_1 = 15.56$, $P < .001$).

Smoking Outcomes as a Function of Pre-Quit ADHD Treatment Response

As would be expected, not all OROS-MPH participants were treatment responders. If, as would be suggested by the

Table 3. Summary of Treatment-Emergent Adverse Events

TEAE, n (%)	OROS-MPH (n = 127)	Placebo (n = 128)	*P* Value
Any TEAEs[a]	122 (96.1)	112 (87.5)	.01
TEAEs related to study medication[b]	111 (87.4)	95 (74.2)	.01
Any serious TEAEs	2 (1.6)	0 (0.0)	.25
Discontinued medication due to TEAEs	7 (5.5)	2 (1.6)	.10
Most frequent TEAEs[c] by MedDRA[d]-preferred term			
Psychiatric disorders			
Nervousness	28 (22.0)	21 (16.4)	.24
Anxiety	24 (18.9)	18 (14.1)	.28
Insomnia	22 (17.3)	17 (13.3)	.34
Abnormal dreams	9 (7.1)	9 (7.0)	.90
Initial insomnia	9 (7.1)	5 (3.9)	.23
Depression	7 (5.5)	2 (1.6)	.07
Nervous system disorders			
Headache	35 (27.6)	28 (21.9)	.28
Dizziness	8 (6.3)	5 (3.9)	.33
Psychomotor hyperactivity	9 (7.1)	1 (0.8)	.01
Gastrointestinal disorders			
Nausea	18 (14.2)	10 (7.8)	.09
Dry mouth	15 (11.8)	7 (5.5)	.06
Dyspepsia	9 (7.1)	1 (0.8)	.01
Musculoskeletal/connective tissue disorders			
Back pain	7 (5.5)	6 (4.7)	.68
Musculoskeletal pain	7 (5.5)	2 (1.6)	.07
Nasopharyngitis	20 (15.7)	14 (10.9)	.24
Fatigue	15 (11.8)	12 (9.4)	.48
Cough	11 (8.7)	6 (4.7)	.18
Decreased appetite	23 (18.1)	7 (5.5)	.00
Rash	10 (7.9)	4 (3.1)	.08
Heart rate increase	9 (7.1)	1 (0.8)	.01
Palpitations	9 (7.1)	1 (0.8)	.01

[a]TEAEs are adverse events defined as a new illness, or an exacerbation of a preexisting condition, with onset date post-randomization.
[b]TEAE rated as possibly, probably, or definitely related to treatment.
[c]Reported by > 5% of OROS-MPH group and at a greater rate than by the placebo group.
[d]MedDRA terminology is the international medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. MedDRA is a registered trademark of the International Federation of Pharmaceutical Manufacturers and Associations.
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, OROS-MPH = osmotic-release oral system methylphenidate, TEAE = treatment-emergent adverse events.

self-medication hypothesis, smoking cessation would be more successful in individuals in whom ADHD has been effectively treated, then it would be expected that the smoking behavior of treatment responders will differ significantly from those of nonresponders. To determine whether ADHD treatment response during the pre-quit phase improved smoking outcomes, responder analyses were completed for which a responder was defined as a participant whose week-4 *DSM-IV* ADHD-RS total score was reduced by 30% or more compared to baseline and who had a 1 point or greater reduction in week-4 CGI-S score relative to baseline. Of the 255 randomly assigned participants, 229 participants, 114 OROS-MPH and 115 placebo, had week-4 data and, thus, could be classified as responders or nonresponders; the 26 participants with missing week-4 data were excluded from the responder analyses. The mean week 4 dose was 3.54 pills (SD = 0.95) per day for the OROS-MPH group (ie, a mean of 63.72 mg/d) and 3.72 pills (SD = 0.73) per day for the placebo group. Seventy-one (ie, 62%) and 39 (ie, 34%) of OROS-MPH and placebo participants, respectively, were treatment responders at week 4. To test the effect of responder status on smoking outcome, the models used in the intent-to-treat analyses were modified to include the responder and the responder × treatment interaction effects. The results revealed no significant responder × treatment interaction effects for prolonged abstinence ($\chi^2_1 = 0.15$, $P = .70$), point-prevalence abstinence ($\chi^2_1 = 0.15$, $P = .70$), and post-quit cigarettes per day ($\chi^2_1 = 2.28$, $P = .13$).

Adverse Events

The occurrence of treatment-emergent adverse events was significantly higher in the OROS-MPH group, relative to placebo group, for both treatment-emergent adverse events in general as well as treatment-emergent adverse events rated as related to study medication (Table 3). Treatment-emergent adverse events reported at significantly higher rates in the OROS-MPH group included dyspepsia, decreased appetite, heart rate increase, and palpitations. Consistent with OROS-MPH participant report of decreased appetite, the OROS-MPH participants lost a mean of 2.2 pounds (SD = 11.1) between baseline and week 11 while the placebo participants gained a mean of 2.1 pounds (SD = 8.5) during the same time frame ($\chi^2_1 = 42.91$, $P < .0001$). The week-11 body mass index was comparable for the 2 groups, 27.67 kg/m^2 (SD = 5.81) for OROS-MPH and 27.57 kg/m^2 (SD = 6.81) for placebo, suggesting that the weight loss in the OROS-MPH group was not clinically significant.

The 2 serious adverse events reported during the trial were in the OROS-MPH group but were considered unrelated to the study medication. One entailed an accident-related hospitalization and the other an overnight hospitalization for worsening depression in a participant who had switched to a new antidepressant while in the trial; the dose of the new medication was "suboptimal" according to the emergency room staff, and the participant's antidepressant dose was consequently increased to a more optimal level.

The OROS-MPH and placebo groups did not differ significantly on the number of participants discontinued from study medication due to treatment-emergent adverse events. Tolerability for OROS-MPH/placebo and the nicotine patch did not differ significantly between treatments (Table 2).

Cardiovascular Effects

There was a significant treatment main effect for systolic blood pressure ($\chi^2_1 = 5.22$, $P < .05$), diastolic blood pressure ($\chi^2_1 = 12.13$, $P < .001$), and heart rate ($\chi^2_1 = 10.56$, $P < .01$), which reflected greater increases in the OROS-MPH group. While statistically significant, the mean change in blood pressure and heart rate was minimal for the OROS-MPH group as a whole (Table 4). Evaluation of clinically elevated systolic blood pressure, diastolic blood pressure, and heart rate post-randomization values revealed no significant treatment group differences. For systolic blood pressure, 21 OROS-MPH (16.7%) and 12 placebo (9.6%) participants experienced a maximum systolic blood pressure of 140 mm Hg

Table 4. Changes in Blood Pressure and Pulse as a Function of Treatment Group and Time

	Systolic Blood Pressure (mm Hg)				Diastolic Blood Pressure (mm Hg)				Heart Rate (bpm)			
	OROS-MPH		Placebo		OROS-MPH		Placebo		OROS-MPH		Placebo	
Time	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Baseline	127	119.1 (9.6)	128	115.4 (10.8)	127	74.5 (6.5)	128	72.8 (7.0)	127	76.0 (7.4)	128	75.2 (7.7)
Wk 2	114	0.6 (7.7)	118	−0.6 (8.5)	114	1.3 (5.5)	118	0.4 (6.9)	114	6.3 (9.0)	118	2.4 (8.8)
Wk 4	111	0.8 (8.8)	113	−1.8 (8.2)	111	1.5 (6.2)	113	−1.2 (5.1)	111	5.8 (10.8)	113	2.6 (8.1)
Wk 6	109	0.4 (9.7)	102	−1.2 (7.9)	109	0.1 (6.7)	102	−1.1 (6.0)	109	2.8 (10.2)	102	0.1 (8.0)
Wk 8	102	−0.7 (10.0)	94	−1.4 (8.8)	102	1.0 (7.1)	94	−1.3 (6.2)	102	3.6 (8.9)	94	0.6 (8.4)
Wk 11	107	1.8 (10.0)	109	0.1 (8.3)	107	1.4 (7.0)	109	−0.8 (6.2)	107	2.2 (10.2)	109	0.6 (8.4)
Wk 15[a]	104	1.6 (10.3)	101	0.4 (8.9)	104	0.6 (7.2)	101	0.1 (7.1)	104	1.8 (10.8)	101	2.4 (11.0)

[a]One-month follow-up.
Abbreviation: OROS-MPH = osmotic-release oral system methylphenidate.

or greater ($\chi^2_1 = 2.74$, $P = .10$). For diastolic blood pressure, 26 OROS-MPH (20.6%) and 15 placebo (12.0%) participants experienced a maximum diastolic blood pressure of 90 mm Hg or greater ($\chi^2_1 = 3.42$, $P = .06$). For heart rate, 26 OROS-MPH (20.6%) and 19 placebo (15.2%) participants experienced a maximum heart rate of 100 bpm or greater ($\chi^2_1 = 1.26$, $P = .26$).

DISCUSSION

The results from this 11-week randomized, double-blind, placebo-controlled trial suggest that using OROS-MPH, relative to placebo, to treat ADHD did not improve smoking outcomes in adult smokers with ADHD participating in smoking cessation treatment (ie, nicotine patch and counseling). There might be several reasons for this lack of significant effect. First, all participants were provided with the nicotine patch, which has been found to be effective for both smoking cessation[40] and for ameliorating inattention symptoms[7,12,13]; thus, the lack of OROS-MPH effect might reflect a ceiling effect. The abstinence rates—43% for prolonged abstinence and 39% for point-prevalence abstinence—would appear to be sufficiently low, however, to allow the demonstration of a treatment effect if one were present. Alternatively, the lack of effect might, in fact, reflect a true lack of medication effect. While the self-medication hypothesis might account for the observed differences between ADHD and non-ADHD individuals in smoking onset[3] as well as the potential protective effects of stimulant medication in preventing the onset of smoking in individuals with ADHD,[15] it might be that, once an individual becomes nicotine dependent, the dependence itself is the primary factor determining outcome as opposed to the factors that initially led to dependence.

Past research suggests that smokers with ADHD have more difficulty quitting smoking compared to smokers without ADHD.[4,41] The present trial did not include a non-ADHD comparison group, and, thus, we are unable to directly address the relative efficacy of the nicotine patch and counseling in our ADHD sample relative to a non-ADHD sample. However, to provide a context for our results, it is helpful to compare the present abstinence rates to those from nicotine patch trials completed in study samples not selected on ADHD status. A meta-analysis evaluating the efficacy of the nicotine patch revealed that the abstinence rate, generally defined as point-prevalence abstinence, for trials using the nicotine patch for 8 weeks or less was 37.9% on average.[42] This rate is comparable to the point-prevalence abstinence rate in the present trial, which was 39% after 6 weeks of nicotine patch treatment. It is thus possible that the ADHD participants in the present trial did not experience greater difficulty in quitting smoking when treated with nicotine patch and counseling relative to non-ADHD individuals.

From a public health perspective, the key finding from the present study was that OROS-MPH, relative to placebo, was effective and safe in treating ADHD in adult smokers. In the present trial, 71% of OROS-MPH participants had a clinically meaningful decrease in symptoms (ie, a decrease of at least 30%), a rate comparable to that reported for prior MPH trials conducted with samples not selected for smoking. The 44% treatment response rate in the placebo group was somewhat high but is consistent with the 39% placebo response rate reported by Biederman et al.[22] Thus, neither smoking nor smoking cessation treatment appeared to decrease the effectiveness of OROS-MPH in treating ADHD.

The safety profile of OROS-MPH in the present trial, in which it was used in combination with the nicotine patch in smokers, is similar to that observed in 2 large clinical trials of OROS-MPH in adults with ADHD.[22,23] Similar to the findings from these prior trials, OROS-MPH, relative to placebo, was associated with statistically significant, but relatively small, increases in blood pressure and heart rate. In the present study, there was no significant treatment group difference for the number of participants experiencing a clinically significant elevation of heart rate while there was a nonsignificant trend for more OROS-MPH participants to have clinically significant elevations in blood pressure; patients taking OROS-MPH should have their blood pressure and heart rate monitored as recommended in the prescribing information for OROS-MPH. The treatment-emergent adverse events occurring at a significantly greater rate with OROS-MPH (decreased appetite, dyspepsia, psychomotor hyperactivity, heart rate increase, and heart palpitations) have been associated with OROS-MPH in previous trials.[22,23] In the present trial, 5.5% of OROS-MPH and 1.5% of placebo participants were permanently discontinued from OROS-MPH/placebo, rates comparable to those of Medori et al[23] and lower than those of Biederman et al.[22] The latter difference is likely due to higher doses used by Biederman et al[22]

(1.3 mg/kg/d). The present findings also indicate that the 72 mg/d OROS-MPH dose was generally well tolerated and that OROS-MPH did not significantly affect tolerability of the 21 mg/d nicotine patch. In comparing the present safety results to those of prior trials,[22,23] it is important to note that the vital signs eligibility criterion utilized in the present trial was most likely more restrictive than the criterion used in prior trials and, thus, may underestimate risks that might arise if OROS-MPH were used in smokers with higher baseline blood pressure and heart rate.

Evaluation of the second key safety concern, that OROS-MPH might increase, rather than decrease, smoking, revealed that both OROS-MPH and placebo participants decreased their cigarettes per day during both the pre-quit and post-quit phases of the trial and that this decrease was to a statistically greater degree in the OROS-MPH group, relative to placebo group, during the post-quit phase. This finding is not consistent with laboratory findings that IR-MPH significantly increases smoking in adult smokers without ADHD who are not trying to quit smoking.[27,28] Several critical differences between the laboratory studies and the present study, including the MPH formulation and study population, might account for the discrepant findings. In addition, it should be noted that the effects of acute dosing observed in laboratory studies do not necessarily predict a medication's effects when used in on-going treatment. A prime example of the differing effects associated with acute and chronic dosing is bupropion, which was found to increase smoking in a laboratory study,[43] but which is an FDA-approved smoking cessation treatment.[44] The results of the present trial suggest that the clinical use of OROS-MPH will not increase the daily smoking rate in adult smokers with ADHD who are interested in quitting smoking.

The present study had several strengths. First, this trial utilized a randomized, double-blind, placebo-controlled design, the gold standard in clinical trials. Second, study retention was high, with 84.3% of participants completing the 11-week active study phase. Third, compliance with taking OROS-MPH/placebo was high, with an average of 94% of prescribed pills taken. A final strength is that the study was conducted at sites that were geographically diverse as well as diverse in expertise, with 2 sites having expertise in smoking cessation trials, 2 sites with expertise in ADHD trials, and 2 sites with expertise in neither area; this diversity helps to ensure the generalizability of the results. One weakness of the present study was the somewhat restrictive eligibility criteria utilized, including the restrictive vital signs criterion and the *DSM-IV* exclusions, including current abuse or dependence for a substance other than nicotine; thus, the present sample may not be representative of adult smokers with ADHD.

In conclusion, the use of OROS-MPH to treat ADHD did not significantly improve smoking outcomes in adult smokers with ADHD participating in smoking cessation treatment (ie, nicotine patch and counseling), counter to our hypothesis. It did not worsen smoking outcomes, however, as might be predicted from human laboratory findings that IR-MPH increases smoking in smokers without ADHD.[27,28] Results from the present trial suggest that OROS-MPH was safe and generally well tolerated by this sample of healthy adult ADHD smokers and effectively treated ADHD, a relatively common mental health condition, which left untreated, can result in significant impairment in nearly every area of functioning.

Drug names: bupropion (Zyban and others), methylphenidate (Ritalin and others).

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Potential conflicts of interest: **Dr Adler** is a consultant for Abbott Laboratories, Cortex Pharmaceuticals, Novartis Pharmaceuticals, Pfizer, Shire, Eli Lilly, Ortho McNeil/Janssen/Johnson and Johnson, New River Pharmaceuticals, Cephalon, Merck, Organon, Sanofi-Aventis Pharmaceuticals, Psychogenics, Mindsite, Major League Baseball, and Psychogenics; has received grant/research support from Abbott Laboratories, Cortex Pharmaceuticals, Bristol-Myers Squibb, Merck and Co, Novartis Pharmaceuticals, Pfizer, Shire, Eli Lilly, Ortho McNeil/Janssen/Johnson and Johnson, New River Pharmaceuticals, Cephalon, and the National Institute of Drug Abuse; is a member of the speakers/advisory boards for Abbott Laboratories, Cortex Pharmaceuticals, Novartis Pharmaceuticals, Pfizer, Shire, Eli Lilly, Ortho McNeil/Janssen/Johnson and Johnson, New River Pharmaceuticals, Cephalon, Merck, Organon, Sanofi-Aventis Pharmaceuticals, Eli Lilly, and Shire; and has received royalty payments (as inventor) from NYU for license of adult ADHD scales and training materials. **Dr Weiss** is a consultant for Titan Pharmaceuticals and has received grant/research support from Eli Lilly. **Drs Winhusen**, **Somoza**, **Brigham**, **Liu**, **Green**, **Covey**, **Croghan**, and **Leimberger** and **Mr Lewis** and **Ms Dorer** have no personal affiliations or financial relationships with any commercial interest to disclose relative to the article.

Funding/support: This study was supported by the following grants from the National Institute on Drug Abuse: U10-DA015831 and K24 DA022288 to Harvard University (Dr Weiss); U10-DA013035 to New York State Psychiatric Institute (Dr Nunes); U10-DA013046 to New York University (Dr Rotrosen); U10-DA013036 to Oregon Health and Science University (Dr McCarty); and U10-DA013732 to the University of Cincinnati (Dr Somoza). The study medication and matching placebo were provided by McNeil Consumer and Specialty Pharmaceuticals at no cost.

Acknowledgment: John Hughes, MD (University of Vermont), provided suggestions for the study design, including the outcome measures.

The following individuals provided additional medical support at their sites: Alvin Pelt, MD (Maryhaven); Darian Minkunas, MD, and Bentson McFarland, MD, PhD (Kaiser Permanente Northwest); Jane Fried, MD, Jeanne Manubay, MD, Alexander Glassman, MD, and Yvonne Singletary, RN, PhD (New York State Psychiatric Institute [NYSPI]); Richard Hurt, MD, Jon Ebbert, MD, Tim Lineberry, MD, J. Taylor Hays, MD, and Lowell Dale, MD (Mayo Clinic); Vatsal Thakkar, MD (New York University [NYU]/ VA New York Harbor Healthcare System [VANYHHS]); Craig Surman, MD, and Paul Hammerness, MD (MGH Pediatric Psychopharmacology).

The following individuals provided administrative support for study teams at their sites: Vivian Russell (Maryhaven); Dennis McCarty, PhD, and Lynn Kunkel, MS, CCRP (Oregon Health and Science University); Edward Nunes, MD, and Jennifer Lima, MPH (Columbia University and NYSPI); Richard Hurt, MD (Mayo Clinic); John Rotrosen, MD, Agatha Kulaga, MSW, and Patricia Novo, MPA (NYU/VANYHHS); and Jennifer Sharpe Potter, PhD, MPH (Harvard University).

The following individuals provided training or monitoring support at their sites: Frankie Kropp, MS, Peggy Somoza, MS, and Sharon Pickrel, BS (Maryhaven); Joanne Weidemann, BS, and Marie Shea, MS (Kaiser Permanente Northwest); Catherine LoDuca, BA (NYPSI); Michelle

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Cordner, BA, Karen Loncto, BSN, MS, and Karen Venuto, BA (NYU/VANYHHS and NYSPI); Judy Trautman, RN, and Richard Morris, BA (Mayo Clinic); David Sitt, PsyD (NYU/VANYHHS); Scott Provost, MM, MSW, and Amy Loree, BA, (MGH Pediatric Psychopharmacology).
The following individuals collected data at participating sites: Rebecca Shoemaker, RN, Jessica Rich, BA, Ann Whetzel Nevar, MPA, Stella M. Resko, MSW, PhD, Gwyn Stetler, Vicki Johnson, MS, LPCC, LICDC, and Theresa Smith (Maryhaven); Shannon Janoff, MPH, Marti Summer, RN, BSN, MPA, Michelle Roberts, RN FNP, MSN, Micah Yarborough, MA, Lynette Currie, MA, Nancy Siegel, PA-C, MPH, Catherine Briggs, BS, Monica Jo-Mueller, RPh (Kaiser Permanente Northwest); Catherine LoDuca, BA, Jenny Masmela, BA, Victoria Salzman, BA, Judith Weissman, PhD, Fay Stetner, MS, MPA (NYSPI); Judy Trautman, RN; Richard Morris, BA, Marianne Kosel, Kim Van Rooy, Donna Rasmussen, RN, and Sara Mason, RN (Mayo Clinic); David Shaw, BA, Alexis Brigge, BA, Lisa Reingold, BA, Erica Maya, BA, and Lauren Lynch, BA (NYU/VANYHHS); and Rob Sawtelle, Allison Santry, Julia Whitley, Linsey Utzinger, Meghan Hellieson, Jennifer Park, and Lynn Sahaida (MGH Pediatric Psychopharmacology).

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