Treating Nicotine Dependence by Targeting Attention-Deficit/Hyperactivity Disorder (ADHD) With OROS Methylphenidate: The Role of Baseline ADHD Severity and Treatment Response

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ABSTRACT

Objective: To determine whether treatment of attention-deficit/hyperactivity disorder (ADHD) with osmotic-release oral system (OROS) methylphenidate promotes abstinence from smoking among smokers with ADHD who have greater severity of ADHD symptoms at baseline or greater improvement in ADHD during treatment.

Method: This is a secondary analysis of data from a randomized, double-blind, 11-week trial conducted between December 2005 and January 2008 at 6 clinical sites; the original trial was sponsored by the National Drug Abuse Clinical Trials Network. Adult cigarette smokers (aged 18–55 years) who met *DSM-IV* criteria for ADHD were randomly assigned to OROS methylphenidate (72 mg/d) (n = 127) or matching placebo (n = 128). All participants received nicotine patches (21 mg/d) and weekly individual smoking cessation counseling. Logistic regression was used to model prolonged abstinence from smoking (ascertained by self-report and breath carbon monoxide testing) as a function of treatment, baseline ADHD Rating Scale-IV (ADHD-RS) score, change in ADHD-RS score during treatment, and their interactions.

Results: Treatment interacted with both ADHD-RS score at baseline ($P = .01$) and change in ADHD-RS score during treatment ($P = .008$). Among patients with higher ADHD-RS scores (> 36) at baseline and the most improvement in ADHD during treatment (ADHD-RS change score ≥ 24), 70.0% of those who took OROS methylphenidate achieved abstinence from smoking compared to 36.8% of those who took placebo ($P = .02$). In contrast, among patients with the lowest ADHD-RS baseline scores (≤ 30), 30.3% of those who took OROS methylphenidate achieved abstinence from smoking compared to 60.7% of those who took placebo ($P = .02$).

Conclusions: OROS methylphenidate, in combination with nicotine patch, may be an effective treatment for nicotine dependence among smokers with more severe ADHD and more robust response of ADHD symptoms to medication. OROS methylphenidate may be counterproductive among smokers with lower severity of ADHD.

Trial Registration: ClinicalTrials.gov identifier: NCT00253747

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Substance use disorders are common, debilitating, and costly.[1,2] Effective treatments exist,[3] but treatment failure remains common, and alternative strategies are needed. One such strategy is to identify and treat co-occurring mental disorders,[1,2] which may be linked to substance abuse through "self-medication"[4,5] or shared neurobiological substrates.[6] Studies that have examined treatment of mood or anxiety disorders co-occurring with substance use disorders have yielded a mixture of positive and null results.[7–9]

In this context, the co-occurrence of nicotine dependence and attention-deficit/hyperactivity disorder (ADHD) seems a particularly promising therapeutic target. Nicotine dependence is the most common addictive disorder[10] and, despite effective pharmacologic treatments (nicotine replacement products, bupropion, varenicline),[11] often runs a chronic, relapsing course.[12,13] Attention-deficit/hyperactivity disorder is prevalent among people with nicotine dependence, has its onset in childhood, increases the chances of developing nicotine dependence,[14,15] and reduces the likelihood of achieving remission.[16–18] Early treatment of ADHD may reduce the risk of developing nicotine dependence.[19] Nicotine and stimulant medications that are used to treat ADHD both increase dopamine release, improving measures of attention.[20,21] These observations suggest the hypothesis that ADHD may be a causal risk factor for nicotine dependence and that effective treatment of ADHD may promote abstinence.

The National Drug Abuse Clinical Trials Network therefore conducted a placebo-controlled trial[22] of osmotic-release oral system (OROS) methylphenidate for treatment of co-occurring nicotine dependence and ADHD. Disappointingly, the primary outcome analysis, while showing the expected beneficial effect of OROS methylphenidate on ADHD symptoms, failed to show an effect on smoking.[22] However, since the underlying hypothesis is that the ADHD is driving the smoking, the smoking might be expected to respond only among those patients with greater improvement in ADHD during treatment. Relatedly, response of smoking to stimulant treatment might depend upon greater severity of ADHD. Patients with more ADHD symptoms have more room to improve. Response of psychiatric disorders to treatment often depends on baseline severity,[23] as with antidepressant treatment.[24,25] Greater severity may indicate a more homogeneous form of the disorder, more in need of specific medication treatment. Patients with more severe ADHD are likely to experience greater functional impairment.[26,27] For them, smoking may be a particularly important coping mechanism, and improvement in ADHD due to treatment correspondingly more valuable in reducing the drive to smoke. We therefore reanalyzed data from the OROS methylphenidate smoking trial[22] to evaluate

Clinical Points

- Attention-deficit/hyperactivity disorder (ADHD) is prevalent among individuals with nicotine dependence and reduces the likelihood of successfully quitting smoking.
- Treatment of ADHD with stimulant medication may help nicotine-dependent patients quit smoking, particularly if the ADHD is more severe initially and if the ADHD symptoms are substantially improved by treatment.
- Clinicians can help patients who are seeking to quit smoking by screening for and treating ADHD and optimizing ADHD treatment response (adjusting doses or changing medications if needed) before initiating a quit attempt with nicotine replacement.

the hypotheses that OROS methylphenidate would promote smoking abstinence, compared to placebo, among those patients with greater ADHD severity at baseline or greater response of ADHD symptoms to treatment.

METHOD

Participants

The original randomized, double-blind, 11-week trial[22] was conducted by the National Drug Abuse Clinical Trials Network at 6 sites (Cambridge, Massachusetts; Columbus, Ohio; New York, New York [2 sites]; Portland, Oregon; and Rochester, Minnesota) between December 2005 and January 2008. Institutional review boards at each site approved the study, and all participants gave written informed consent. The study methods are described in detail elsewhere.[22] The trial was registered with ClinicalTrials.gov (identifier: NCT00253747).

For the current secondary analysis, eligible participants (N = 255) were smokers seeking to quit smoking; were 18–55 years of age; were in good physical health; smoked ≥ 10 cigarettes daily, with an expired carbon monoxide level ≥ 8 ppm; met *DSM-IV* criteria for ADHD, as assessed by structured diagnostic interview with the Adult ADHD Clinical Diagnostic Scale, version 1.2[28]; and had an ADHD Rating Scale-IV[29] score ≥ 22. Prospective participants were excluded for current *DSM-IV* diagnoses of abuse of or dependence on any substance other than nicotine; positive urine screen for any illicit drug; other current psychiatric disorders; medical contraindications to OROS methylphenidate; or a history of nonresponse to methylphenidate.

Procedures

The original study[22] was an 11-week, double-blind, placebo-controlled trial of OROS methylphenidate (n = 127) versus matching placebo (n = 128), with stratification by site. OROS methylphenidate was titrated to a target dose of 72 mg/d during the first 2 study weeks. Participants were asked to set a quit date during the fourth week of the trial and to use 21-mg nicotine patches daily through the remainder of the trial. Brief, individual weekly counseling was provided according to the Mayo Clinic Nicotine Research Program's *Smoke Free and Living It* manual.[30]

Assessment

Daily abstinence from cigarettes during the study was assessed weekly using the timeline follow-back method,[31] verified by carbon monoxide levels < 8 ppm.[32] The primary outcome measure was *prolonged abstinence*, defined as tobacco abstinence during study weeks 7–10 without treatment failure, with *failure* defined as any 7 consecutive days of smoking on at least 1 day in 2 or more consecutive weeks. This outcome is consistent with US Food and Drug Administration standards for approving smoking cessation medications.[33]

Severity of ADHD symptoms was measured at baseline and at 2, 4, and 6 weeks after the target quit date (trial weeks 7, 9, and 11) with the ADHD Rating Scale-IV (ADHD-RS),[29] an interviewer-rated scale,[28] with scores ranging from 0 to 54. Change in ADHD symptoms during the trial was calculated as the difference in ADHD-RS scores between baseline and end of treatment. Severity of nicotine dependence was measured with the Fagerström test.[34]

Data Analysis

For descriptive purposes, the baseline ADHD-RS scores and the ADHD-RS change scores were split into quartiles, and the quartiles were compared on baseline demographic and clinical features using χ^2 tests and analyses of variance. Logistic regression models were fit, modeling prolonged smoking abstinence as a function of medication treatment assignment, baseline ADHD-RS score, ADHD-RS change score, and their interactions, controlling for number of cigarettes smoked per day at baseline and clinical sites. Interactions of cigarettes smoked per day at baseline with the other terms in these models were not found to be significant and were not included in the final models. The above analyses used the sample of all 255 randomized patients. To examine interaction effects, the observed proportions of patients who achieved prolonged abstinence with OROS methylphenidate and placebo were calculated within the subsamples represented by the quartiles of baseline ADHD-RS scores and ADHD-RS change scores; pairwise contrasts between treatments within quartiles were tested with χ^2. Of the 255 patients who were randomized, 36 (14%) did not complete the trial and were missing data at the end of the study. These missing data were imputed by coding missing study days as nonabstinent and by coding missing ADHD-RS scores as the most recent previous ADHD-RS score available.

RESULTS

Sample Characteristics

Of 3,865 prospective participants who were prescreened, 255 (7%) met eligibility criteria, gave informed consent, and were randomized. Overall, the sample was 56% male, was predominantly white (80%), and had a mean age of 38 years. The mean Fagerström score was 5.54 (standard deviation = 2.21), reflecting a medium level of nicotine dependence. Patients smoked, on average, a pack of cigarettes per day. As previously reported, baseline features

Table 1. ADHD Symptom Severity (ADHD-RS scores) and Associated Factors Among Patients With Co-Occurring ADHD and Nicotine Dependence (N = 255)

Variable	Quartile 1: Baseline ADHD-RS Score ≤ 30 (n = 61)	Quartile 2: Baseline ADHD-RS Score of 31–36 (n = 68)	Quartile 3: Baseline ADHD-RS Score of 37–41 (n = 58)	Quartile 4: Baseline ADHD-RS Score ≥ 42 (n = 68)	χ^2 (for categorical variables) or *F* (for continuous variables)	*P*
ADHD-RS score at baseline, mean (SD)	27.08 (2.49)	33.21 (1.65)	38.91 (1.32)	45.65 (3.15)		
ADHD combined subtype (hyperactive + inattentive), %	31.67	63.24	75.86	89.71	51.10	< .0001
Change in ADHD-RS score between baseline and end of study, mean (SD)	10.56 (9.69)	9.93 (12.88)	19.70 (11.80)	20.20 (13.48)	11.82	< .0001
Other baseline features						
Demographics						
Gender, male (vs female), %	60.66	66.18	56.90	42.65	8.33	< .05
Age, mean (SD), y	38.36 (9.79)	39.14 (9.98)	36.75 (10.69)	36.86 (9.58)	0.87	.46
Race, white (vs not), %	77.05	85.07	77.19	79.41	1.69	.64
Education, mean (SD), y	13.93 (2.33)	15.07 (2.24)	14.71 (2.43)	13.97 (2.46)	3.65	< .05
Marital status, %					11.09	.09
Married	47.54	35.29	29.31	23.53		
Divorced or separated	13.11	22.06	22.41	30.88		
Never married	39.34	42.65	48.28	45.59		
Nicotine dependence, mean (SD)						
Cigarettes smoked daily	20.46 (8.02)	20.68 (7.27)	18.86 (7.20)	20.51 (8.23)	0.73	.54
Nicotine dependence (Fagerström score)	5.49 (2.27)	5.57 (2.15)	5.16 (2.17)	5.87 (2.25)	1.10	.35
Psychiatric comorbidity, %						
Major depression	21.31	42.65	29.31	39.71	8.22	< .05
Anxiety disorders	26.23	29.41	39.66	39.71	4.10	.25
Alcohol dependence	26.23	30.88	29.31	27.94	0.37	.95
Drug dependence	21.31	16.18	31.03	20.59	4.20	.24

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ADHD-RS = ADHD Rating Scale-IV.

did not differ between treatment groups, and medication adherence was high.[22]

Baseline Severity of ADHD Symptoms

Table 1 shows ADHD severity at baseline, divided into quartiles of ADHD-RS scores, and associations with other baseline demographic and clinical features and with change in ADHD-RS scores during the trial. As can be seen, there was substantial variation in baseline ADHD-RS scores, ranging from the 20s in the lowest quartile, representing mild to moderate ADHD, to scores in the 40s and above in the highest quartile, representing severe ADHD. Several associations are evident between baseline ADHD severity and gender (there were more women among the higher quartiles of baseline ADHD-RS scores), major depression, and education level. Baseline ADHD-RS score was strongly associated with improvement in ADHD during the trial, with the top 2 quartiles of baseline ADHD severity showing more improvement.

Change in ADHD Symptoms During Treatment

Table 2 shows the improvement in ADHD symptoms experienced during the trial, divided into quartiles of ADHD-RS change scores. As can be seen, the degree of improvement varied substantially, from little or no change in the bottom quartile to a mean improvement of 30.53 points, or a 76.36% reduction, in the top quartile. Again, the only baseline feature strongly associated with level of improvement in ADHD was the severity of ADHD (ADHD-RS score) at baseline. The top quartile (most ADHD improvement) had higher ADHD-RS severity scores at baseline.

Smoking Outcome as a Function of Treatment and ADHD Symptoms

Logistic regression, which modeled prolonged abstinence as a function of treatment alone plus covariates (clinical site, cigarettes smoked per day at baseline), confirmed the prior finding[22] of no significant main effect of treatment on smoking outcome (adjusted odds ratio = 1.06; 95% CI, 0.63–1.79; $\chi^2_1 = 0.05$; $P = .82$).

When abstinence was modeled as a function of treatment, baseline ADHD severity (ADHD-RS score), and covariates, the interaction of baseline ADHD severity with treatment was significant ($\chi^2_1 = 6.58$; $P = .01$). Figure 1 displays the raw proportions of patients who achieved prolonged abstinence by treatment group and quartile of baseline severity. As can be seen, the interaction follows a crisscross pattern. Among patients with higher baseline severity (the top 2 quartiles), OROS methylphenidate produced higher abstinence rates than placebo, consistent with what was hypothesized. Combining the top 2 quartiles of baseline ADHD severity, the abstinence rate was 55% (35/64) for treatment with OROS methylphenidate, compared to 34% (21/62) for placebo ($\chi^2_1 = 5.53$; $P = .02$). In contrast, in the lowest quartile of ADHD severity, the opposite was observed, namely that OROS methylphenidate produced lower abstinence rates than placebo.

Table 2. Improvement in ADHD Symptoms During Treatment With OROS Methylphenidate (n = 127) or Placebo (n = 128) and Associated Factors Among Patients With Co-Occurring ADHD and Nicotine Dependence (N = 255)[a]

Variable	Quartile 1: No Improvement, ADHD-RS Change Score ≤ 4 (n = 62)	Quartile 2: Small Improvement, ADHD-RS Change Score of 5–13 (n = 66)	Quartile 3: Moderate Improvement, ADHD-RS Change Score of 14–23 (n = 63)	Quartile 4: Large Improvement, ADHD-RS Change Score ≥ 24 (n = 64)	χ^2 (for categorical variables) or F (for continuous variables)	P
ADHD-RS score at end of study, mean (SD)	37.53 (8.04)	26.14 (8.26)	16.65 (7.03)	10.02 (6.62)		
Change in ADHD-RS score between baseline and end of study, mean (SD)	−2.77 (5.98)	9.03 (2.78)	18.27 (2.89)	30.53 (5.64)		
Percent improvement in ADHD-RS score, mean (SD)	−8.81 (19.33)	26.92 (10.12)	54.06 (12.14)	76.36 (14.07)		
Baseline features						
ADHD-RS score at baseline, mean (SD)	34.76 (6.50)	35.17 (7.72)	34.92 (7.04)	40.55 (6.25)	10.51	< .001
Demographics						
Gender, male (vs female), %	50.00	71.21	49.21	54.69	8.33	.04
Age, mean (SD), y	36.54 (10.35)	36.28 (10.74)	38.93 (9.99)	39.48 (8.53)	0.89	.45
Race, white (vs not), %	78.69	81.82	80.65	78.13	0.35	.95
Education, mean (SD), y	14.94 (2.36)	14.21 (2.30)	13.90 (1.72)	14.66 (2.99)	2.32	.08
Marital status, %					7.75	.26
Married	33.87	33.33	34.92	32.81		
Divorced or separated	24.19	16.67	15.87	32.81		
Never married	41.94	50.00	49.21	34.38		
Nicotine dependence, mean (SD)						
Cigarettes smoked daily	19.87 (7.01)	20.55 (7.38)	20.49 (8.41)	19.75 (8.01)	0.18	.91
Nicotine dependence (Fagerström score)	5.52 (2.12)	5.44 (2.27)	5.75 (2.33)	5.44 (2.15)	0.27	.85
Psychiatric comorbidity, %						
Major depression	37.10	31.82	34.92	31.25	0.64	.89
Anxiety disorders	27.42	39.39	41.27	26.56	5.13	.16
Alcohol dependence	24.19	28.79	25.40	35.94	2.59	.46
Drug dependence	16.13	18.18	28.57	25.00	3.73	.29

[a]ADHD-RS change scores were calculated as the ADHD-RS score at baseline minus the score at the end of the study, and the change scores were split into quartiles.

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ADHD-RS = ADHD Rating Scale-IV, OROS methylphenidate = osmotic-release oral system methylphenidate.

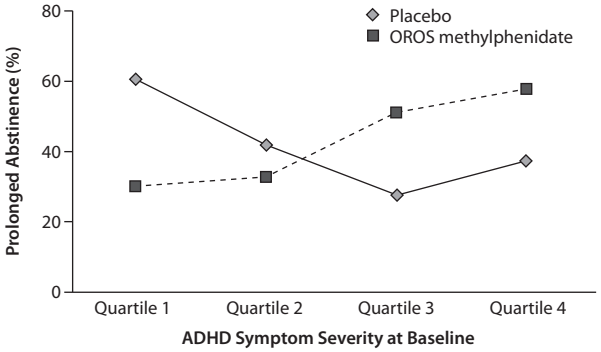
When abstinence was modeled as a function of treatment, change in ADHD severity during treatment, and covariates, the interaction of treatment by ADHD change score was also significant ($\chi^2_1 = 7.05$; $P = .008$). As can be seen in Figure 2, the interaction again followed a crisscross pattern, with more abstinence with OROS methylphenidate treatment than with placebo in the top quartile (most improvement) and the opposite trend in the lower quartiles.

In an effort to understand the relative contributions of baseline ADHD severity and change in ADHD severity during treatment, smoking abstinence rates across quartiles of ADHD change scores were examined in the half of the sample with higher baseline ADHD severity (Figure 3), for which, as shown above, OROS methylphenidate significantly increased the likelihood of smoking abstinence. Inspection of Figure 3 shows higher rates of abstinence on OROS methylphenidate treatment, compared to placebo, when there is more improvement in ADHD during treatment, and the difference reaches significance in the highest quartile of ADHD improvement (OROS methylphenidate: 70.0% (21/30); placebo: 36.8% (7/19); $\chi^2_1 = 5.22$; $P = .02$). This pattern suggests that the subgroup of smokers with ADHD who responded to OROS methylphenidate was characterized by a combination of both higher baseline ADHD severity and greater improvement of ADHD symptoms during treatment.

DISCUSSION

Among patients with nicotine dependence and ADHD who were being treated with a nicotine patch and counseling, a beneficial effect of OROS methylphenidate on smoking outcome was observed among those patients who had greater ADHD severity at baseline and the most improvement in ADHD symptoms during treatment. Thus, stimulant treatment of ADHD may be an effective adjunct to standard smoking cessation therapy in a subgroup of smokers with greater ADHD severity and robust response of ADHD symptoms. This result resembles findings from studies[7,9,35–37] of treatment that targeted co-occurring mood or anxiety disorders among drug- or alcohol-dependent patients, which showed that improvement in depression or anxiety in response to treatment was associated with better substance use outcomes. The primary outcome analysis of the trial[22] did examine patients with at least a 30% reduction in ADHD symptoms but did not find an effect of OROS methylphenidate on smoking within that subgroup.[22] The findings here suggest that at least a 60% reduction in ADHD symptoms during treatment, or a moderately severe

Figure 1. Baseline ADHD Symptoms and the Observed Percentages of Patients With Co-Occurring ADHD and Nicotine Dependence (N = 255) Who Achieved Prolonged Abstinence From Cigarette Smoking by Treatment Group



Prolonged Abstinence by Treatment Group	Quartile 1: Low Severity, Score[a] ≤ 30 (n = 61)	Quartile 2: Moderate Severity, Score[a] of 31–36 (n = 68)	Quartile 3: Moderate to High Severity, Score[a] of 37–41 (n = 58)	Quartile 4: High Severity, Score[a] ≥ 42 (n = 68)
Placebo, % (n)	60.7 (28)	42.1 (38)	28.0 (25)	37.8 (37)
OROS methylphenidate, % (n)	30.3 (33)	33.3 (30)	51.5 (33)	58.1 (31)
Chi-square[b]	5.68	0.55	3.24	2.77
P	.02	.47	.07	.10

[a]Range of baseline ADHD-RS scores that defined each quartile (no. of patients in each quartile). [b]Tests for pairwise contrasts between treatment groups within each quartile.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ADHD-RS = ADHD Rating Scale-IV, OROS methylphenidate = osmotic-release oral system methylphenidate.

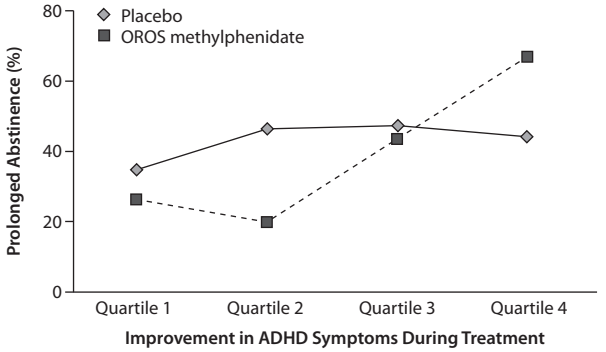
level of symptoms at baseline, may be needed for OROS methylphenidate to impact smoking outcome.

The observed pattern is consistent with either a shared diathesis model or a self-medication model of the co-occurrence of ADHD and smoking. A shared diathesis model would hold that both ADHD and nicotine dependence derive, in part, from a common underlying dysfunction in the dopamine system,[38] which might be addressed by stimulant medication. Consistent with a shared diathesis, we recently showed in the same dataset that ADHD severity and nicotine withdrawal severity are strongly associated during treatment.[39] The self-medication model would hold that those with ADHD are drawn to nicotine because it affords some temporary improvement in attention and functioning. Greater severity of ADHD might indicate a stronger influence of the diathesis on smoking (again, perhaps reflected in measures of smoking severity such as withdrawal), greater functional impairment that interferes with efforts to stop smoking, or a stronger drive to self-medicate, leading either way to a greater sensitivity of smoking to stimulant treatment. Improvement of ADHD symptoms with treatment could signal correction of the underlying diathesis, or a reduced drive to self-medicate, sufficient to support abstinence. Future research should examine temporal sequences of improvement in ADHD symptoms, quit attempts, nicotine withdrawal, and craving in an effort to disentangle the relationships between ADHD and smoking and their responses to treatment.

The data also suggest that OROS methylphenidate is a 2-edged sword, reducing the likelihood of quitting smoking among smokers with lower severity of ADHD at baseline. This finding was a surprise but is consistent with human laboratory studies[40–45] that have shown that methylphenidate or dextroamphetamine administration increased nicotine self-administration in volunteers who were not seeking treatment for smoking or who were not selected for ADHD. Several features of this phenomenon are of interest, including the following: (1) there is individual variability—some smokers demonstrate increased self-administration of nicotine in the presence of amphetamine, and others do not[41,45]; (2) those who increase smoking seem to experience more positive subjective effects from amphetamine[45]; and (3) the effect appears to be dose-dependent—self-administration of nicotine increases with an increasing dose of amphetamine. Perhaps the smokers with ADHD who have lower baseline ADHD severity and whose smoking responds poorly to stimulant pharmacotherapy are more sensitive to the effects of stimulants and might do better on lower stimulant doses or on a nonstimulant ADHD treatment. In any case, a stimulant trial for ADHD takes a matter of weeks to optimize, and, if ADHD and smoking have not responded, the medication can be discontinued and another treatment tried. Thus, from a clinical perspective, the risk of worsening smoking for a few weeks during a therapeutic trial of a stimulant may be worth taking in return for the chance of achieving abstinence from smoking should the response be good.

The findings need to be considered in light of both the strengths and the limitations of the study. The strengths

Figure 2. Improvement in ADHD Symptoms During Treatment[a] and the Observed Percentages of Patients With Co-Occurring ADHD and Nicotine Dependence (N = 255) Who Achieved Prolonged Abstinence From Smoking



Prolonged Abstinence by Treatment Group	Quartile 1: No Improvement, Change Score[a] ≤ 4 (n = 62)	Quartile 2: Small Improvement, Change Score[a] of 5–13 (n = 66)	Quartile 3: Moderate Improvment, Change Score[a] of 14–23 (n = 63)	Quartile 4: Large Improvment, Change Score[a] ≥ 24 (n = 64)
Placebo, % (n)	34.9 (43)	46.3 (41)	47.4 (19)	44.0 (25)
OROS methylphenidate, % (n)	26.3 (19)	20.0 (25)	43.2 (44)	66.7 (39)
Chi-square[b]	0.44	4.66	0.09	3.21
P	.51	.03	.76	.07

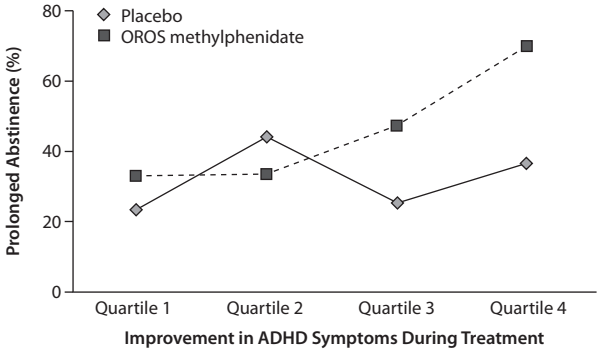
[a]ADHD-RS change scores were calculated as ADHD-RS score at baseline minus score at end of study; values shown are the range of change scores within each quartile (no. of patients per quartile). [b]Tests for pairwise contrasts between treatment groups within each quartile.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ADHD-RS = ADHD Rating Scale-IV, OROS methylphenidate = osmotic-release oral system methylphenidate.

include the placebo-controlled design, careful diagnostic assessment of ADHD, good treatment adherence, and a low dropout rate. The sample consisted of cigarette smokers with clear-cut ADHD and without other current drug or alcohol use disorders. While these eligibility criteria restrict generalizability to a small fraction of all smokers, they avoided heterogeneity that could have obscured the effects of treatment. The sample size was sufficient to have a chance of detecting interactions. However, the subsamples in which treatment effects were detected were smaller. Thus, the estimates of the size of the effects and of the thresholds that defined the responsive subgroup are of limited precision and call for replication. The ADHD change scores were chosen as a simple summary outcome for purposes of relating ADHD outcome to smoking outcome. Change scores have psychometric weaknesses, particularly dependence on baseline scores; however, the fact that the effect of ADHD improvement by treatment seems to reside among the patients with greater ADHD severity at baseline mitigates this concern. This study was a secondary analysis, although based upon the underlying hypothesis of the study. This trial examined abstinence from smoking at the end of an acute trial. Future trials should address whether ongoing treatment of ADHD helps sustain abstinence from smoking or reduce relapse over the long term.

A previous exploratory analysis[46] suggested a greater effect of OROS methylphenidate in the small subgroup of ethnic minorities. Minority status was not associated with either baseline ADHD severity or change in ADHD severity during treatment. There is little evidence to suggest that the impact of stimulant treatment on ADHD symptoms depends on ethnicity. A previous secondary analysis[47] suggested that OROS methylphenidate was effective among smokers who had both the combined (hyperactive and inattentive) subtype of ADHD and greater severity of nicotine dependence. This finding is consistent with the present analysis in that the combined subtype was associated with greater ADHD severity (see Table 1). In future research on stimulant treatment of co-occurring ADHD and smoking, further attention is needed on ethnicity and on severity of nicotine dependence.

The immediate clinical significance of the present findings is that identification and treatment of ADHD should be considered among the treatment options for a smoker who wants to quit. Further, the emphasis should be on forging a substantial improvement in ADHD symptoms, exploring the dose range for medication, and trying alternative treatments should the initial treatment fail. It may also make sense to wait until treatment of ADHD is optimized before making the quit attempt. Patients may vary in regard to both the particular medication and the dose that best treats their ADHD and/or smoking. For example, the Multimodal Treatment Study of Children with ADHD[48] showed the superiority of an adaptive algorithm of frequent assessment and treatment adjustment as compared to community care among children with ADHD. The maximum dose in the present study, 72 mg/d of OROS

Figure 3. Among Patients (n = 126) Who Had Higher ADHD Severity at Baseline (ADHD-RS score > 36), Observed Percentages Are Shown of Those Who Achieved Prolonged Abstinence From Smoking as a Function of Improvement in ADHD During Treatment



Prolonged Abstinence by Treatment Group	Quartile 1: No Improvement, Change Score[a] ≤ 4 (n = 23)	Quartile 2: Small Improvement, Change Score[a] of 5–13 (n = 27)	Quartile 3: Moderate Improvment, Change Score[a] of 14–23 (n = 27)	Quartile 4: Large Improvment, Change Score[a] ≥ 24 (n = 49)
Placebo, % (n)	23.5 (17)	44.4 (18)	25.0 (8)	36.8 (19)
OROS methylphenidate, % (n)	33.3 (6)	33.3 (9)	47.4 (19)	70.0 (30)
Chi-square[b]	0.22	0.31	1.17	5.22
P	1.17	.58	.28	.02

[a]ADHD-RS change scores were calculated as ADHD-RS score at baseline minus score at end of study; values shown are the range of change scores within each quartile (no. of patients per quartile). [b]Tests for pairwise contrasts between treatment groups within each quartile.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ADHD-RS = ADHD Rating Scale-IV, OROS methylphenidate = osmotic-release oral system methylphenidate.

methylphenidate, is the maximum dose approved by the US Food and Drug Administration. However, the optimal dose for a given individual may vary. Some patients may require higher doses, while some may fare better on lower doses or alternative treatments.

The findings of this study have methodological implications for studies that test the strategy of identifying and treating a co-occurring psychiatric disorder (ADHD in this case) so as to impact a substance use disorder. Given the potential importance of baseline severity of the psychiatric disorder and its improvement during treatment, experimental designs and analytic plans are needed that incorporate severity and improvement a priori as moderator and/or mediator.[23,24,49] Further, rather than testing, for example, a single ADHD medication at a fixed target dose, future studies might test adaptive approaches that systematically evaluate response, optimizing the dose of medication and switching treatments if response is suboptimal in order to drive ADHD symptoms not just toward partial improvement but toward substantial improvement or remission. Nicotine and other substance dependencies can be difficult to treat. The identification and aggressive treatment of ADHD and other comorbidities hold out the promise of a treatment strategy complementary to existing medication and behavioral approaches.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), dextroamphetamine (Dexedrine and others), methylphenidate (Focalin, Daytrana, and others), OROS methylphenidate (Concerta), varenicline (Chantix).

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Author contributions: Dr Nunes had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The authors alone are responsible for the content and writing of the article.

Potential conflicts of interest: **Dr Nunes** has been a consultant for Eli Lilly and has received medication for research studies from Alkermes/Cephalon. **Dr Levin** has been a consultant for GW Pharmaceuticals and has received medication for a clinical trial from US WorldMeds. **Drs Covey**, **Brigham**, **Hu**, **Somoza**, and **Winhusen** report no competing interests.

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