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Treating nicotine dependence by targeting attention deficit hyperactivity disorder (ADHD): The role of ADHD severity and treatment response in a randomized controlled trial

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Abstract

Objective—To determine whether treatment of ADHD with osmotic-release oral system methylphenidate (OROS-MPH) promotes abstinence from smoking among ADHD-smokers with greater severity of ADHD symptoms at baseline, or greater improvement in ADHD during treatment.

Method—A randomized, double-blind, 11-week trial, was conducted between December 2005 and January 2008 at six clinical sites, sponsored by the National Drug Abuse Clinical Trials Network. Adult cigarette smokers, meeting DSM-IV criteria for ADHD, were randomly assigned to OROS-MPH (72 mg/day) (N = 127) or matching placebo (N = 128). All participants received nicotine patch (21 mg) 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 DSM-IV ADHD Rating Scale (ADHD-RS) score, change in ADHD-RS during treatment, and their interactions.

Results—Treatment interacted with both ADHD-RS at baseline ($p=0.01$), and with change in ADHD-RS during treatment ($p=0.008$). Among patients with higher ADHD-RS scores (>36) at baseline and the most improvement in ADHD during treatment (ADHD-RS change score ≥ 24), 70% achieved abstinence on OROS-MPH, compared to 37% on placebo ($p=.02$). In contrast, among patients with the lowest ADHD-RS baseline scores (≤ 30), 30% achieved abstinence on OROS-MPH, compared to 61% on placebo ($p=.02$).

Conclusions—OROS-MPH, in combination with nicotine patch, may be an effective treatment for nicotine dependence among smokers with more severe ADHD, and more robust response of

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ADHD symptoms to the medication. OROS-MPH may be counterproductive among smokers with lower severity of ADHD.

Introduction

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 examining treatment of co-occurring mood or anxiety with substance use disorders have yielded a mixture of positive and null results (7, 8, 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 pharmacological treatments (nicotine replacement products, bupropion, varenicline) (11), often runs a chronic, relapsing course (12,13). ADHD 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 (16,17,18). Early treatment of ADHD may reduce the risk of developing nicotine dependence (19). Nicotine and stimulant medications 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 (CTN) therefore conducted a placebo-controlled trial of osmotic-release oral system methylphenidate (OROS-MPH; Concerta) for treatment of co-occurring nicotine dependence and ADHD. Disappointingly, the primary outcome analysis, while showing the expected beneficial effect of OROS-MPH 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 likely 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 re-analyzed the OROS-MPH-smoking trial to evaluate the hypotheses that OROS-MPH would promote smoking abstinence, compared to placebo, among those patients with greater ADHD severity at baseline, or greater response of ADHD symptoms to treatment.

Methods

Participants

The trial was conducted by the National Drug Abuse Clinical Trials Network at six sites (Cambridge, Massachusetts; Columbus, Ohio; New York City (2 sites); Portland, Oregon; and Rochester, Minnesota). 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 Clinical Trials.gov (<http://www.clinicaltrials.gov>; Identifier: NCT00253747).

Eligible participants (N = 255) were smokers seeking to quit; aged 18 to 55 years; in good physical health; smoking 10 cigarettes daily with an expired carbon monoxide level 8 ppm; meeting DSM-IV criteria for ADHD as assessed by structured diagnostic interview with the Adult Clinical Diagnostic Scale version 1.2 (28); and DSM-IV ADHD Rating Scale (29) score 22. Prospective participants were excluded for current DSM-IV abuse or dependence on any substance other than nicotine; positive urine screen for any illicit drug; other current psychiatric disorders; medical contraindications to OROS-MPH; or a history of non-response to methylphenidate.

Procedures

This was an 11-week, double-blind, placebo-controlled trial of OROS-MPH (N = 127) vs matching placebo (N = 128) with stratification by site. OROS-MPH was titrated to a target dose of 72 mg/day during the first two 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 time-line follow-back method (31), verified by CO < 8 parts per million (32). The primary outcome measure was 'prolonged abstinence,' defined as tobacco abstinence during study weeks 7-10 without treatment failure, where failure is defined as any seven consecutive days of smoking on at least one day in two or more consecutive weeks. This outcome is consistent with FDA standards for approving smoking cessation medications (33).

Severity of ADHD symptoms was measured at baseline, and 2, 4, and 6 weeks after the target quit date (trial weeks 7, 9, and 11) with the DSM-IV ADHD Rating Scale (ADHD-RS) (29), an interviewer-rated scale (28), 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 Fagerstrom 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 chi-square tests and ANOVA. Logistic regression models were fit, modeling prolonged smoking abstinence as a function of medication treatment assignment, baseline ADHD-RS score, ADHD-RS change scores, and their interactions, controlling for baseline cigarettes per day and clinical sites. Interactions of baseline cigarettes per day with the other terms in these models were not found significant, and not included in the final models. The above analyses used the sample of all 255 patients randomized. To examine interaction effects, the observed proportions of patients achieving prolonged abstinence on OROS-MPH and placebo were calculated within the subsamples represented by the quartiles of baseline ADHD-RS and ADHD change; pair-wise contrasts between treatments within quartiles were tested with Chi-squares. Of the 255 patients 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 non-abstinent, and missing ADHD-RS scores as the most recent previous ADHD-RS score available.

Results

Sample Characteristics

Of 3865 prospective participants pre-screened, 255 (7%) met eligibility criteria, consented and were randomized. Overall, the sample was 56% male, predominantly Caucasian (80%), with an average age of 38 years. The mean Fagerström score was 5.54 (SD=2.21), reflecting a medium level of nicotine dependence. Patients smoked, on average, a pack of cigarettes a day. As previously reported, baseline features 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 during the trial. As can be seen, there was substantial variation in baseline ADHD 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 (more females among the higher quartiles of baseline ADHD-RS), major depression, and education level. Baseline ADHD-RS score was strongly associated with improvement in ADHD during the trial, with the top two 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 no change in the bottom quartile to a mean improvement of 30.5 points, or 76.4% 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 severity scores at baseline.

Smoking Outcome as a Function of Treatment and ADHD Symptoms

Logistic regression, modeling prolonged abstinence as a function of treatment alone plus covariates (clinical site, cigarettes per day at baseline), confirmed the prior finding (22) of no significant main effect of treatment on smoking outcome (Adjusted odds ratio (AOR)=1.06 (95% confidence interval: 0.63 to 1.79); $X^2(1)=0.05$, $p=0.82$).

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 is significant ($X^2(1)=6.58$, $p=0.01$). Figure 1 displays the raw proportions of patients achieving 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 two quartiles), OROS-MPH produces higher abstinence rates than placebo, consistent with what was hypothesized. Combining the top two quartiles of baseline ADHD severity, the abstinence rate is 55% (35/64) on OROS-MPH, compared to 34% (21/62) on placebo ($X^2(1)=5.53$, $p=0.02$). In contrast, in the lowest quartile of ADHD severity, the opposite is observed, namely OROS-MPH produces lower abstinence rates than placebo.

When abstinence is modeled as a function of treatment, change in ADHD severity during treatment, and covariates, the interaction of treatment by ADHD change score is also significant ($X^2(1)=7.05$, $p=.008$). As can be seen in Figure 2, the interaction again follows a crisscross pattern, with more abstinence on OROS-MPH than 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 during treatment, smoking abstinence rates across quartiles of ADHD change were examined in the half of the sample with higher baseline ADHD severity (Figure 3), where, as shown above, there OROS-MPH significantly increases the likelihood of smoking abstinence. Inspection of the Figure shows higher rates of abstinence on OROS-MPH, 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-MPH: 70% (21/30); Placebo: 36.8% (7/19), $X^2(1)=5.22$, $p=.02$). This pattern suggests that the subgroup of ADHD-smokers that responds to OROS-MPH is 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 being treated with nicotine patch and counseling, a beneficial effect of OROS-MPH on smoking outcome was observed among those patients with 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 the ADHD symptoms. This resembles findings from studies of treatment targeting co-occurring mood or anxiety disorders among drug or alcohol dependent patients, which have shown improvement in depression or anxiety in response to treatment to be associated with better substance use outcome (7,9,35,36,37). The primary outcome analysis on this study did examine patients with at least a 30% reduction in ADHD symptoms but did not find an effect of OROS-MPH 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 level of symptoms at baseline may be needed for OROS-MPH 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 interfering 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 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 OROS-MPH is a two-edged sword, reducing the likelihood of quitting among smokers with lower severity of ADHD at baseline. This finding was a surprise, but is consistent with human laboratory studies showing that methylphenidate or d-amphetamine administration increase nicotine self-administration in volunteers not seeking treatment for smoking, nor selected for ADHD (40-45). Several features of this phenomenon are of interest, including: 1) There is individual variability--some smokers demonstrate increased

responding for 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 dose dependent--among those who are sensitive to it, responding for nicotine increases with increasing dose of amphetamine. Perhaps the ADHD-smokers with lower baseline ADHD severity, 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 non-stimulant 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. Strengths 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 clearcut ADHD and without other current drug or alcohol use disorders. While this restricts generalizability to a small fraction of all smokers, it avoids heterogeneity that could have obscured 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 defining the responsive subgroup, are of limited precision and call for replication. ADHD change scores were chosen as a simple summary outcome for purposes of relating ADHD outcome to smoking outcome; change scores have weaknesses psychometrically, 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 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 suggested greater effect of OROS-MPH in the small subgroup of ethnic minorities (46). Minority status was not associated with either baseline ADHD severity or change during treatment. There is little evidence to suggest the impact of stimulant treatment on ADHD symptoms depends on ethnicity. A previous secondary analysis suggested OROS-MPH was effective among smokers with both the combined (hyperactive and inattentive) subtype of ADHD and greater nicotine dependence severity (47). This 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 to ethnicity, and to nicotine dependence severity.

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, 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 dose, that best treats their ADHD and/or smoking. For example, the Multimodal Treatment of ADHD (MTA) study showed the superiority of an adaptive algorithm of frequent assessment and treatment adjustment, compared to community care among children with ADHD (48). The maximum dose in the present study, 72 mg per day of OROS-MPH, is the maximum dose approved by the FDA. 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 have methodological implications for studies testing the strategy of identifying and treating a co-occurring psychiatric disorder (ADHD in this case) 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 sub-optimal, 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 holds out the promise of a treatment strategy complementary to existing medication and behavioral approaches.

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Clinical Points

1. Attention deficit hyperactivity disorder (ADHD) is prevalent among individuals with nicotine dependence, and reduces the likelihood of successfully quitting smoking.
2. Treatment of ADHD with stimulant medication may help nicotine dependent patients quit smoking, particularly if the ADHD is more severe, and if the ADHD symptoms are substantially improved by treatment.
3. Clinicians can help patients 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.

Abbreviations: ADHD = Attention deficit hyperactivity disorder; ADHD-RS = ADHD Rating Scale; OROS-MPH = Osmotic-release oral system methylphenidate.

^a Range of baseline ADHD-RS scores that defined each quartile (number of patients in each quartile)

^b Tests for pair-wise contrasts between treatment groups within each quartile

Figure 1.

Baseline ADHD symptoms and the observed percentages of patients with co-occurring ADHD and nicotine dependence (N = 255) achieving prolonged abstinence from cigarette smoking by treatment groups.

Abbreviations: ADHD = Attention deficit hyperactivity disorder; ADHD-RS = ADHD Rating Scale; OROS-MPH = Osmotic-release oral system methylphenidate.

^a ADHD change scores were calculated as the ADHD-RS score at baseline, minus the score at end of study; values shown are the range of change scores within each quartile (number of patients per quartile).

^b Tests for pair-wise contrasts between treatment groups within each quartile

Figure 2.

Improvement in ADHD symptoms during treatment^a and the observed percentages of patients with co-occurring ADHD and nicotine dependence (N = 255) achieving prolonged abstinence from cigarette smoking.

Abbreviations: ADHD = Attention deficit hyperactivity disorder; ADHD-RS = ADHD Rating Scale; OROS-MPH = Osmotic-release oral system methylphenidate.

^a ADHD change scores were calculated as the ADHD-RS score at baseline, minus the score at end of study; values shown are the range of change scores within each quartile (number of patients per quartile).

^b Tests for pair-wise contrasts between treatment groups within each quartile

Figure 3.

Among the half of patients (N = 126) who had higher ADHD severity at baseline (ADHD-RS score > 36), observed percentages achieving prolonged abstinence from smoking as a function of improvement in ADHD during treatment

Table 1

ADHD symptom severity (ADHD-Rating Scale scores) and associated factors among patients with co-occurring ADHD and nicotine dependence (N=255)

	Quartile 1 Baseline ADHD 30 (N=61)	Quartile 2 Baseline ADHD 31 - 36 (N=68)	Quartile 3 Baseline ADHD 37 - 41 (N=58)	Quartile 4 Baseline ADHD 42 (n=68)	<i>X² or F-test</i>	P
ADHD Rating Scale Scores at baseline:	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 Rating Scale scores between baseline and end of study	10.56 (9.69)	9.93 (12.88)	19.70 (11.80)	20.20 (13.48)	11.82	< .0001
<u>Other Baseline Features</u>						
<u>Demographics:</u>						
Male (vs. Female)	60.66	66.18	56.90	42.65	8.33	< .05
Age (years)	38.36 (9.79)	39.14 (9.98)	36.75 (10.69)	36.86 (9.58)	0.87	0.46
Caucasian (vs. not)	77.05	85.07	77.19	79.41	1.69	0.64
Education (years)	13.93 (2.33)	15.07 (2.24)	14.71 (2.43)	13.97 (2.46)	3.65	< .05
Marital Status					11.09	0.09
Married	47.54	35.29	29.31	23.53		
Divorced/separated	13.11	22.06	22.41	30.88		
Never married	39.34	42.65	48.28	45.59		
<u>Nicotine Dependence:</u>						
Cigarettes smoked daily	20.46 (8.02)	20.68 (7.27)	18.86 (7.20)	20.51 (8.23)	0.73	0.54
Nicotine dependence (FTND score)	5.49 (2.27)	5.57 (2.15)	5.16 (2.17)	5.87 (2.25)	1.10	0.35
<u>Psychiatric Comorbidity:</u>						
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	0.25
Alcohol dependence	26.23	30.88	29.31	27.94	0.37	0.95
Drug dependence	21.31	16.18	31.03	20.59	4.20	0.24

Values in the table are means (standard deviation), or percents.

Abbreviations: ADHD = Attention deficit hyperactivity disorder; FTND = Fagerstrom Test for Nicotine Dependence; OROS-MPH = Osmotic-release oral system methylphenidate.

Table 2

Improvement in ADHD symptoms^a during treatment with OROS-MPH and associated factors among patients with co-occurring ADHD and nicotine dependence (N=255).

	Quartile 1 No Improvement change: 4 (N=62)	Quartile 2 Small Improvement change: 5 - 13 (N=66)	Quartile 3 Moderate Improvement change: 14 - 23 (N=63)	Quartile 4 Large Improvement change: 24 (n=64)	χ^2 or F-test	P
ADHD Rating Scale scores at end of study	37.53(8.04)	26.14(8.26)	16.65(7.03)	10.02(6.62)		
Change in ADHD Rating Scale scores between baseline and end of study	-2.77(5.98)	9.03(2.78)	18.27(2.89)	30.53(5.64)		
Percent improvement in ADHD Rating Scale scores	-8.81 (19.33)	26.92(10.12)	54.06(12.14)	76.36(14.07)		
<u>Baseline Features:</u>						
ADHD Rating Scale Scores at baseline:	34.76(6.50)	35.17(7.72)	34.92(7.04)	40.55(6.25)	10.51	<.001
<u>Demographics:</u>						
Male (vs. Female)	50.00	71.21	49.21	54.69	8.33	0.04
Age (years)	36.54(10.35)	36.28(10.74)	38.93(9.99)	39.48(8.53)	0.89	0.45
Caucasian (vs. not)	78.69	81.82	80.65	78.13	0.35	0.95
Education (years)	14.94(2.36)	14.21(2.30)	13.90(1.72)	14.66(2.99)	2.32	0.08
Marital Status					7.75	0.26
Married	33.87	33.33	34.92	32.81		
Divorced/separated	24.19	16.67	15.87	32.81		
Never married	41.94	50.00	49.21	34.38		
<u>Nicotine Dependence:</u>						
Cigarettes smoked daily	19.87(7.01)	20.55(7.38)	20.49(8.41)	19.75(8.01)	0.18	0.91
Nicotine dependence (FTND score)	5.52(2.12)	5.44(2.27)	5.75(2.33)	5.44(2.15)	0.27	0.85
<u>Psychiatric Comorbidity:</u>						
Major depression	37.10	31.82	34.92	31.25	0.64	0.89
Anxiety disorders	27.42	39.39	41.27	26.56	5.13	0.16
Alcohol dependence	24.19	28.79	25.40	35.94	2.59	0.46
Drug dependence	16.13	18.18	28.57	25.00	3.73	0.29

Values in the table are means (standard deviation), or percents.

Abbreviations: ADHD = Attention deficit hyperactivity disorder; FTND = Fagerstrom Test for Nicotine Dependence; OROS-MPH = Osmotic-release oral system methylphenidate.

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