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Exploring longitudinal course and treatment-baseline severity interactions in secondary outcomes of smoking cessation treatment in individuals with attention-deficit hyperactivity disorder

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Abstract

Background—A double blind, placebo-controlled randomized trial (NCT00253747) evaluating osmotic-release oral system methylphenidate (OROS-MPH) for smoking-cessation revealed a significant interaction effect in which participants with higher baseline ADHD severity had better abstinence outcomes with OROS-MPH while participants with lower baseline ADHD severity had worse outcomes.

Objectives—This current report examines secondary outcomes that might bear on the mechanism for this differential treatment effect.

Methods—Longitudinal analyses were conducted to evaluate the effect of OROS-MPH on three secondary outcomes (ADHD symptom severity, nicotine craving, and withdrawal) in the total sample ($N = 255$, 56% Male), and in the high ($N = 134$) and low ($N = 121$) baseline ADHD severity groups.

Results—OROS-MPH significantly improved ADHD symptoms and nicotine withdrawal symptoms in the total sample, and exploratory analyses showed that in both higher and lower baseline severity groups, OROS-MPH statistically significantly improved these two outcomes. No effect on craving overall was detected, though exploratory analyses showed statistically significantly decreased craving in the high ADHD severity participants on OROS-MPH. No treatment by ADHD baseline severity interaction was detected for the outcomes.

Conclusions—Methylphenidate improved secondary outcomes during smoking cessation independent of baseline ADHD severity, with no evident treatment-baseline severity interaction. Our results suggest divergent responses to smoking cessation treatment in the higher and lower

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Declaration of interest

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severity groups cannot be explained by concordant divergence in craving, withdrawal and ADHD symptom severity, and alternative hypotheses may need to be identified.

Keywords

Smoking; nicotine; longitudinal; withdrawal; craving; ADHD

Introduction

Cigarette smoking remains a significant public health challenge worldwide. Smoking is often associated with psychiatric co-morbidities, and a commonly co-occurring condition is attention-deficit/hyperactivity disorder (ADHD). Approximately 40% of patients who have ADHD also smoke cigarettes (1,2). The prevalence of smoking increases with severity of ADHD symptoms, and even patients with sub-threshold symptoms appear to be at an increased risk (3,4). Adolescents with more severe ADHD symptoms are more likely to be smokers (5). Presence of ADHD symptoms may make smoking cessation more difficult (2), and nicotine treatment may reduce ADHD symptoms both acutely and chronically (6,7). Given that ADHD is often undertreated (8), better treatment of co-morbid ADHD may be a pathway to better smoking-cessation treatment outcomes.

Methylphenidate is a commonly prescribed centrally acting psychostimulant (9). It acts primarily as a nor-epinephrine-dopamine reuptake inhibitor, binds to and blocks dopamine transporters and norepinephrine transporter, and increases the concentration of dopamine and norepinephrine in the striatum and the pre-frontal cortex at therapeutic doses (10). Osmotic-release oral systems methylphenidate (OROS-MPH) has a longer half-life and is an FDA approved once daily medication for the treatment of ADHD (11). A multi-center, randomized controlled trial was conducted in the National Drug Abuse Treatment Clinical Trials Network (NIDA-CTN-0029) to evaluate whether OROS-MPH, relative to placebo, would increase smoking-cessation rates in smokers with ADHD (12). Prolonged abstinence, the primary outcome, did not differ between placebo and OROS-MPH groups. Subsequent subgroup analyses showed that there was a substantial degree of treatment-response heterogeneity, with significant predictors such as ethnicity (13), baseline motivation (14), history of previous diagnosis of substance use disorders (15), and ADHD subtype (in a three-way interaction with baseline smoking severity and treatment) (16). Baseline ADHD severity emerged as a unique moderator that showed an interaction effect (17): patients with higher baseline ADHD, defined as a score ≥ 36 on the ADHD Symptoms Rating Scale (ADHD-RS), had better smoking abstinence outcomes with OROS-MPH than placebo; in contrast, participants with lower severity baseline ADHD (<36 on the ADHD-RS) had worse smoking-abstinence outcomes with OROS-MPH than with placebo. This interaction effect was also detected using unbiased subgroup analysis methods such as Best Approximating Model (15).

This finding suggests that stimulant treatment for nicotine dependence may indeed be an effective strategy, particularly in the presence of high severity ADHD. Clinical trial simulation and prediction modeling demonstrate treatment stratification using baseline ADHD severity alone may improve treatment outcome (18). However, the question remains

why the differential treatment effect existed, and in particular why smoking outcome was made worse by OROS-MPH among smokers with ADHD of lower severity.

Previous research in smoking cessation in this co-morbid group suggests that baseline ADHD symptom severity (12), improvement in nicotine withdrawal (19), and nicotine craving during treatment (20) are predictive of abstinence. Previous analysis showed that withdrawal and craving had some correlation with baseline ADHD severity throughout the trial, that OROS-MPH reduced ADHD symptoms, and that craving was associated with abstinence during the trial (21). However, differences in secondary outcomes, if any, between lower vs. higher baseline ADHD severity subgroups were never analyzed or reported. We reasoned that if one or more of these outcomes is mechanistically related to the differential smoking outcome, there should be a significant treatment by covariate interaction effect between OROS-MPH (vs. placebo) and baseline ADHD severity. For example, if nicotine withdrawal were driving the differential effect, then we would expect to find that nicotine withdrawal was improved by OROS-MPH among those with higher baseline ADHD severity, but worsened by OROS-MPH among those with lower ADHD severity. In this secondary analysis, we therefore modeled each of these secondary outcomes, as a function of treatment (OROS-MPH vs. placebo), baseline ADHD severity (lower vs. higher), and time. We also explored the effects of treatment over time separately for the lower and higher ADHD groups. Our hypothesis was that for one or more of these outcomes, there would be a significant interaction of treatment by baseline ADHD severity, with outcome better on OROS-MPH compared to placebo among smokers with higher ADHD severity, and worse on OROS-MPH compared to placebo among smokers with lower ADHD severity.

Methods

Design of the parent trial

Details of the parent trial were described elsewhere (12). Briefly, the trial was a randomized, 11-week, double-blind, placebo-controlled trial conducted at six sites assessing the efficacy of OROS-MPH (fixed dose 72 mg/day) compared to placebo for increasing smoking cessation among adult smokers with ADHD when added to nicotine patch and counseling. Detailed inclusion and exclusion criteria were presented elsewhere (12). Potential individuals were screened and the study was explained face to face, and candidate was given an opportunity to review, discuss, and sign the informed consent form. The study was approved by the Institutional Review Board at each of the study sites across the United States.

Outcomes and measures

We examined changes in the secondary outcomes over time from week 0 (baseline) to week 11. ADHD symptom severity was assessed by trained raters using the DSM-IV ADHD Rating Scale (ADHD-RS) (22) with prompts for the interviewer (23). Tobacco withdrawal symptoms and craving were assessed with the Minnesota Nicotine Withdrawal Symptom Scale (MNWS) (24). Craving was measured by the “desire to smoke” item of the MNWS. Withdrawal was measured by the seven other MNWS items (anger/irritability, anxiety/

nervousness, difficulty concentrating, impatience/restlessness, hunger, awakening at night, and depression), without craving, consistent with other published studies (21). There were no measured secondary outcomes between week 1 and 4, as the target quit day was between week 4 and week 5 visits. In the first 4 weeks of the treatment trial, patient's OROS-MPH was gradually escalated to 72 mg/day.

Data analysis

Longitudinal mixed effects models were used to assess differences in the three outcomes over time and by baseline ADHD severity as a function of treatment and time. Predictors included the treatment, time (weeks 1, 2, 3, 4, 7, 9, and 11 for ADHD, and 5–11 for withdrawal and craving), baseline ADHD as low/high (dichotomized at ADHD-RS 36 as in a prior analysis (18)), all two-way interactions (treatment with week, treatment with baseline ADHD, and week with baseline ADHD), and the 3-way interaction. Fitted means from the models for each outcome with 95% confidence intervals were plotted across weeks. Patient drop-out occurred throughout the study: for ADHD-RS, the proportion of missing data varied between 9% (week 2) and 21% (week 9); for withdrawal and craving, the proportion of missing data varied between 16.9% (week 5) and 23.5% (week 10). The longitudinal mixed effect model used a missing at random assumption and analyzed all available data. Effect sizes for all treatment effects were calculated as Cohen's *d* by scaling the mean difference in treatment groups by the baseline standard deviation of the respective outcome. All models were additionally run controlling for gender, age, education and ethnicity, which did not affect the results from either parts of the analyses and so are not shown. All analyses were performed in SAS 9.4 in 2016.

Results

Sample characteristics

Participant characteristics as a function of baseline ADHD severity are provided in Table 1.

Total sample

Analysis of ADHD symptom severity ($n = 255$) revealed significant treatment ($b = -5.06$, effect size $ES = -0.69$, $p < .0001$), time ($F_{6, 1282} = 150.47$, $p < .0001$), and treatment-by-time interaction ($F_{6, 1282} = 7.04$, $p < .0001$) effects. Analysis of withdrawal symptoms revealed significant treatment ($b = -2.76$, $ES = -0.50$, $p < .0001$) and time ($F_{6, 1173} = 37.34$, $p < .0001$) effects, and a nonsignificant treatment-by-time interaction ($F_{6, 1173} = 0.83$, $p = 0.55$). Analysis of craving found a significant time effect ($F_{6, 1173} = 24.29$, $p < .0001$) and nonsignificant treatment ($b = -0.22$, $ES = -0.33$, $p = 0.09$) and treatment-by-time interaction ($F_{6, 1173} = 0.84$, $p = 0.54$) effects. None of the baseline ADHD severity by treatment interactions were significant (for ADHD symptoms: $F_{1, 1173} = 1.42$, $p = 0.23$); withdrawal symptoms: $F_{1, 1173} = 0.30$, $p = 0.59$); craving: $F_{1, 1173} = 1.69$, $p = 0.19$), nor were any of the baseline ADHD severity by treatment by time interactions significant (for ADHD symptoms: $F_{6, 1282} = 1.03$, $p = 0.40$; withdrawal symptoms: $F_{6, 1173} = 1.38$, $p = 0.22$; craving: $F_{6, 1173} = 1.10$, $p = 0.36$). Analysis of three-way-interactions (time by baseline ADHD symptom by treatment) also did not detect a significant effect for any of the

outcomes: ADHD symptom ($F_{6, 1282} = 1.03, p = 0.40$), withdrawal symptoms ($F_{6, 1173} = 1.38, p = 0.22$), and craving ($F_{6, 1173} = 1.10, p = 0.36$).

By baseline ADHD subgroup

Several possible scenarios can explain the lack of an interaction effect: OROS-MPH may exhibit no significant effect in either higher or lower severity groups alone, and pooling them together enhanced the power to detect a main effect but not interaction; OROS-MPH may have a significant effect in one group but not the other, and pooling the subgroups increased noise in the analysis of interactions; finally, OROS-MPH may have significant effect in both subgroups, but in the same direction, and hence no interaction was detected. To explore which of these scenarios may be more likely for each of the secondary outcomes, we additionally tested for an OROS-MPH effect for each outcome within the higher ($n = 134$) and lower ($n = 121$) baseline ADHD severity groups. Table 2 provides the treatment effect sizes for the ADHD severity subgroup analyses. As can be seen, in both the higher and lower baseline severity groups, ADHD severity and withdrawal symptoms improved. However, craving only improved in the higher baseline ADHD severity group.

Figure 1 displays the model-estimated means for outcome trajectories over time stratified by higher or lower baseline ADHD severity. For the higher baseline ADHD severity group, OROS-MPH treatment significantly improved all three outcomes (Figure 1). In the lower baseline severity ADHD group, OROS-MPH treatment significantly improved ADHD symptom severity and withdrawal symptoms but not craving, where the observed effect size is close to zero.

Discussion

This secondary analysis of the NIDA CTN Adult Smokers with ADHD Trial (CTN-0029) evaluated the potential mechanisms behind the differential treatment effect depending on baseline ADHD severity, wherein stimulant treatment (OROS-MPH) improved smoking outcome compared to placebo among smokers with higher severity of baseline ADHD symptoms but worsened smoking outcome among those with lower baseline ADHD severity (18). We sought to understand whether any of the three measured outcomes (ADHD symptom severity, nicotine withdrawal symptoms, cigarette craving) might explain the divergent smoking outcomes for patients with higher vs. lower baseline ADHD severity (17). We hypothesized that one of these outcomes would be improved by OROS-MPH for those with higher baseline ADHD severity, but worsened for those with lower baseline ADHD severity, suggesting a potential mechanism. We examined baseline ADHD severity by treatment interactions for each of the outcomes. Our results showed that there was no significant baseline ADHD severity by treatment interactions for any of the outcomes. Thus, our findings do not support our hypothesis that at least one of these outcomes can explain the worsened smoking outcome on OROS-MPH in the lower ADHD severity group.

For exploratory purposes, we also evaluated for a treatment effect on the outcomes within the higher and lower baseline ADHD severity groups. OROS-MPH, relative to placebo, significantly improved ADHD severity and nicotine withdrawal in both the higher and lower baseline ADHD severity subgroups. In contrast, OROS-MPH, relative to placebo,

significantly improved nicotine craving in the higher ADHD severity group but not in the lower ADHD severity group. However, in the absence of a significant baseline ADHD severity by treatment interaction, we cannot conclude that these findings represent a true difference between the higher and lower severity groups. Further, if craving accounted for the worsened smoking outcome in the lower ADHD severity group on OROS-MPH, we would expect to find that OROS-MPH significantly increased craving as opposed to the observed null effect.

The main implication of our results is that the significant effect of OROS-MPH on the outcomes measured—ADHD severity, nicotine withdrawal, and nicotine craving—cannot explain the divergent effect of OROS-MPH on prolonged abstinence from nicotine. There may be other explanatory mechanisms, such as that psychostimulant may directly increase the rewarding effect of cigarettes (“good drug effect”) without affecting craving or withdrawal, consistent with some human laboratory findings (25–28). This clinical trial we analyzed here did not measure “good drug effect” or any other subjective indicator of the rewarding effects of nicotine, and future studies should include such measures. Different types of craving and their temporal relationship with treatment may also be a factor that might be studied further in future studies (29).

The present study has several limitations. First, while we consider here the most obvious secondary outcomes, additional unmeasured factors as described above may be at work. Secondly, while the parent study had a relatively large sample size, power to detect interaction effects is limited. Using a single item as a craving measure may also decrease sensitivity (30). Thirdly, because prolonged abstinence was defined over a period of 4 weeks, conducting mediation analysis to this dataset would yield difficult to interpret results, as the outcome (prolonged abstinence) and mediators (secondary outcomes) may be correlated by definition. Future studies with more precise temporal measures of the outcomes may be better candidates for more definitive identification of mediation (31).

In conclusion, the mechanisms accounting for the differential effect of OROS-MPH on smoking-cessation outcomes as a function of baseline ADHD severity (17) remain unclear, and do not appear to be explained by differential effects of OROS-MPH on outcome of ADHD symptoms, or nicotine withdrawal symptoms or craving. Future work in this area might benefit from measuring the reinforcing effects of nicotine and from incorporating finer metrics of craving.

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Figure 1.

Secondary outcomes trajectories (model means) as a function of time in lower (left column) and higher (right column) baseline ADHD severity groups. (A) For ADHD severity, treatment was significantly associated with reduction in symptoms in both higher and lower baseline severity groups, with a significant treatment by time interaction. (B) There was a significant effect for both treatment and time for nicotine withdrawal symptom severity. (C) There was a significant effect for treatment only in the high severity group. Secondary outcome collection began in week 5, after the target smoking quit date.

Table 1

Participant demographic and baseline characteristics as a function of baseline ADHD symptom severity.

	Low baseline ADHD severity (<i>n</i> = 121)	High baseline ADHD severity (<i>n</i> = 134)	<i>X</i> ² or F-test	<i>p</i>
ADHD Rating Scale Scores at baseline:	29.93 (3.52)	42.16 (4.34)	F(1,253) = 602.46	<.0001
ADHD combined subtype (hyperactive + inattentive)	46.7%	82.8%	<i>X</i> ² (1) = 36.78	<.0001
Other baseline features				
Demographics:				
Male (vs. female)	62.0%	51.5%	<i>X</i> ² (1) = 2.85	0.09
Age (years)	38.77 (9.88)	36.91 (10.05)	F(1, 251) = 2.20	0.14
Caucasian (vs. not)	80.0%	79.7%	<i>X</i> ² (1) = 0.00	0.95
Education (years)	14.50 (2.35)	14.36 (2.45)	F(1, 250) = 0.23	0.64
Marital status			<i>X</i> ² (2) = 7.58	0.03
Married	42.2%	26.1%		
Divorced/separated	18.2%	26.1%		
Never married	39.6%	47.8%		
Nicotine dependence:				
Cigarettes smoked daily	20.64 (7.54)	19.75 (7.82)	F(1, 253) = 0.85	0.36
Nicotine dependence (FTND score)	5.57 (2.22)	5.51 (2.21)	F(1, 252) = 0.05	0.84
Psychiatric comorbidity:				
Major depression	31.4%	35.8%	<i>X</i> ² (1) = 0.55	0.46
Anxiety disorders	28.1%	38.8%	<i>X</i> ² (1) = 3.26	0.07
Alcohol dependence	28.1%	29.1%	<i>X</i> ² (1) = 0.03	0.86
Drug dependence	19.0%	24.6%	<i>X</i> ² (1) = 1.17	0.28

Where not otherwise indicated, numbers represent means (standard deviations).

OROS-MPH reduction of secondary outcomes as a function of baseline ADHD severity.

Table 2

Treatment effect	Low baseline ADHD severity (<i>n</i> = 121)			High baseline ADHD severity (<i>n</i> = 134)		
	ADHD severity	Withdrawal	Craving	ADHD severity	Withdrawal	Craving
Estimated decrease (SE)	3.68 (1.68)	3.09 (0.87)	0.054 (0.19)	6.45 (1.61)	2.43 (0.84)	0.39 (0.18)
Cohen's d	0.5	0.56	0.08	0.88	0.44	0.58
<i>p</i> -value	0.0291	0.0004	0.77	<0.0001	0.0037	0.03