Brief Report

Osmotic Release Oral System Methylphenidate Prevents Weight Gain During a Smoking-Cessation Attempt in Adults With ADHD

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Abstract

Background: Adults with attention-deficit/hyperactivity disorder (ADHD) are at increased risk for both cigarette smoking and being overweight or obese. Although smoking cessation tends to result in weight increase, potentially initiating or exacerbating weight problems, adults with ADHD who are treated with osmotic release oral system methylphenidate (OROS-MPH) tend to lose weight. It is unclear how the use of OROS-MPH during a smoking-cessation attempt might affect the typical weight gain that accompanies cessation.

Method: We examined changes in weight and hunger during a smoking-cessation attempt in 215 adults with ADHD who completed a multisite, randomized, controlled trial and were randomized to either OROS-MPH (n = 107) or placebo (n = 108) (NCT #00253747). Both groups also received open-label transdermal nicotine replacement and counseling.

Results: Participants who received OROS-MPH lost an average of 1.6% of their body weight during the 11-week study, whereas those who received placebo gained an average of 1.3% of their weight ($p < .001$). Hunger ratings were lower in the OROS-MPH group (M = 1.1, SD = 0.8) than in the placebo group (M = 1.6, SD = 0.9; $p < .001$).

Conclusions: The use of OROS-MPH during a smoking-cessation attempt prevents weight gain in adults with ADHD who substantially reduce or quit smoking. The potential utility of OROS-MPH in individuals with ADHD who are attempting to quit smoking and for whom weight gain would be problematic warrants further research.

Introduction

Adults with attention-deficit/hyperactivity disorder (ADHD) are roughly twice as likely to smoke cigarettes as individuals without ADHD (McClave, McKnight-Eily, Davis, & Dube, 2010) and may be less likely to quit smoking with conventional treatments (Covey, Manubay, Jiang, Nortick, & Palumbo, 2008; Humfleet et al., 2005). Only a few studies to date have focused on targeted smoking-cessation interventions for individuals with ADHD, and results of our recent trial revealed that osmotic release oral system methylphenidate (OROS-MPH), relative to placebo, did not enhance smoking-cessation treatment outcomes for individuals with ADHD receiving transdermal nicotine replacement therapy (NRT) and brief counseling (Winhusen et al., 2010). However, OROS-MPH was found to be safe when used in combination with transdermal NRT and was effective in reducing ADHD symptoms (Winhusen et al., 2010).

Another potential benefit from OROS-MPH, which we did not examine previously, is its potential to ameliorate the weight gain that typically accompanies smoking cessation. The majority of smokers who quit smoking will gain weight, averaging 3–6 kg within the first year (Klesges et al., 1997; Pisinger & Jorgensen, 2007). In addition, a sizable minority gain significantly greater amounts. In the Lung Health Study, for example, 11.9% of men and 13.5% of women who sustained smoking abstinence for 5 years gained 15 kg or more, whereas only 1.3% of male continuing smokers and 1.4% of female continuing smokers gained that amount over the same time period (O'Hara et al., 1998). Concerns about postcessation weight gain, which are more common among women than men (Clark et al., 2006), have been found to interfere with the success of efforts to quit smoking (Jeffery, Hennrikus, Lando, Murray, & Liu, 2000). Despite a multitude of attempts to identify effective behavioral or pharmacological interventions to prevent postcessation weight gain, these efforts have been largely unsuccessful (see review by Heffner, Winders-Barrett, & Anthenelli, 2006), and there is a considerable need to identify more effective methods of preventing or ameliorating postcessation weight gain in order to address this barrier to smoking cessation.

Decreased hunger and weight loss are common side effects of psychostimulant medications used in the treatment

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of ADHD, which could potentially help to reduce or prevent postcessation weight gain. It is unclear, however, to what extent this effect might offset the seemingly intractable increases in weight that occur with discontinuation or reduction in smoking. In this post-hoc analysis of data from a larger clinical trial (Winhusen et al., 2010), we examined the effects of OROS-MPH on weight gain in adult smokers with ADHD who were enrolled in a smoking-cessation study. We hypothesized that relative to placebo plus NRT and counseling, OROS-MPH plus NRT and counseling would be associated with less weight gain, as well as attenuation of the increased hunger that commonly accompanies efforts to quit smoking.

Methods

Participants

Participants were 215 treatment-seeking adult smokers with ADHD who completed a multisite study examining the effects of OROS-MPH for smoking cessation (NCT #00253747), as an adjunct to transdermal nicotine replacement and brief counseling. Participants were between 18 and 55 years of age; in good physical health; smoking at least 10 cigarettes per day, with an expired carbon monoxide level ≥ 8 ppm; smoked for at least 3 months; and had a DSM-IV ADHD Rating Scale score > 22. Exclusion criteria were current non-nicotine substance abuse or dependence; current mood or anxiety disorders (except specific phobia); lifetime antisocial personality disorder or psychosis; personal history of narrow angle glaucoma, tics, or a seizure disorder; family history of Tourette syndrome; positive screen for illicit drug use; having received pharmacotherapy or behavioral treatment for smoking cessation in the prior 30 days; current use of tobacco products other than cigarettes; having received pharmacotherapy for ADHD in the prior 30 days; prior unsuccessful treatment with methylphenidate for ADHD; significant suicidal/homicidal risk; for women, pregnancy, breastfeeding, or refusal to use an approved means of contraception; allergies to OROS-MPH; and use of a monoamine oxidase inhibitor in the prior 14 days. For safety reasons, blood pressure readings greater than 130/80 and/or a heart rate more than 88 beats per minute on two clinic visits were exclusionary for individuals of age 40–55. If less than 40 years old, blood pressure readings greater than 135/85 and/or heart rate more than 90 beats per minute on two clinic visits were exclusionary.

Assessments

ADHD diagnosis and severity were determined using the Adult ADHD Clinical Diagnostic Scale (Adler & Spencer, 2004) and the DSM-IV ADHD Rating Scale (DuPaul et al., 1998), respectively. The Composite International Diagnostic Interview (CIDI; Robins et al., 1988) was also administered at screening by a trained rater to determine whether psychiatric inclusion/exclusion criteria were met. Medical history and physical examination were performed by a certified clinician, and demographic and smoking history information were obtained by a trained research assistant. Participants completed the Fagerström Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991) at baseline as a measure of severity of nicotine dependence. Body weight was assessed at three points during the study: baseline (1–4 weeks prior to randomization), postrandomization Week 6 (2 weeks after the target quit date), and postrandomization Week 11 (end of treatment). Self-reported abstinence from smoking was assessed using the Timeline Followback (Fals-Stewart et al., 2000) method at each weekly visit and verified with CO measurements of <8 ppm. The Withdrawal Scale for Tobacco (WST), a modification of the Minnesota Nicotine Withdrawal Scale (Hughes and Hatsukami, 1986), was used to assess severity of nicotine withdrawal symptoms. The WST lists each withdrawal symptom and asks participants to rate their experience over 24 hr prior to each weekly study visit on a 5-point scale from 0 (*none*) to 4 (*Severe*). For the purpose of this study, we used only the Hunger item from the WST.

Procedures

For a complete description of procedures for the randomized controlled trial, see Winhusen et al. (2010). Briefly, the study was an 11-week, double-blind, placebo-controlled, parallel-group, multisite trial of OROS-MPH versus placebo (assigned in a 1:1 ratio, using computer-generated, site-stratified randomization), both of which were offered in combination with transdermal NRT and counseling, as a treatment for smoking cessation in adults with ADHD (N = 255). OROS-MPH was titrated to a maximum of 72 mg/day over the first 2 weeks of the study and continued at the maximum tolerated dose until the end of the active treatment period (Week 11). All participants received brief weekly individual smoking-cessation counseling for 11 weeks and 21 mg/day nicotine patch starting on the smoking quit day (Day 27) through study week 11. The primary efficacy endpoint for smoking cessation was prolonged abstinence during study weeks 7–10 of the trial, which allowed a 2-week grace period after the target quit date. Prolonged abstinence was defined as a self-report of not smoking either (a) once per day for seven consecutive days or (b) at least once per week for two consecutive weeks (Hughes, 2003) during study weeks 7–10. As noted previously, the main outcome of the trial suggested no effect of OROS-MPH on prolonged abstinence (Winhusen et al., 2010).

The two dependent variables in our analyses were percent weight change and hunger. Because assessments of weight were conducted only at three points during the trial (i.e., baseline, Week 6, and Week 11), only the study participants (n = 215) who completed the active treatment phase of the study were included in this analysis, as we determined that the time from baseline to the Week 6 study visit (i.e., less than 2 weeks after the target quit date) was not a sufficient period over which to capture OROS-MPH's effects on weight gain during a quit attempt. Thus, our primary measure of weight change was the percent change in body weight between baseline and Week 11 (i.e., end of active treatment phase). Eleven (5%) of the participants had missing data on weight, with no significant differences by treatment group (n = 3 in the OROS-MPH group, n = 8 in the placebo group, p = .21). These individuals were excluded from the analysis of percent weight change (n = 204) but were included in the analyses testing OROS-MPH's effects on Hunger (n = 215).

Statistical Analyses

First, we tested for treatment group differences in percent weight change from baseline to Week 11 using linear regression, with percent change in weight as the response variable and

treatment (OROS-MPH vs. placebo) as the primary predictor variable. Any demographic or clinical variables that either differed by treatment group or were significantly correlated with percent weight change were entered into the model as covariates. As exploratory analyses, we also considered interactions of treatment group with gender, baseline body mass index (BMI), and smoking status (i.e., prolonged abstinence and Week 10 point prevalence abstinence) in these models. Correlation with percent weight change was tested using ordinary least-squares regression. Correlation with treatment group was tested using Pearson's chi square, Fisher's exact, Wilcoxon, or Student's *t* as appropriate for the given baseline measure. Based on these preliminary analyses, only baseline BMI was selected as a covariate. Second, we tested OROS-MPH's effects on hunger by conducting a proportional odds logistic mixed-model regression, with WST-Hunger as the response variable and treatment as the primary predictor variable. In that analysis, baseline WST-Hunger scores and time were included as covariates (based on the corrected Akaike Information Criterion statistic, the treatment–time interaction term was not included as a covariate). Primary tests of the hypotheses were conducted using the full treatment completer sample (n = 215), with confirmatory results also reported for the subsample of participants who achieved prolonged abstinence (n = 108) and the subsample that decreased their number of cigarettes per day by at least 50% between baseline and Week 11 (n = 192). An alpha level of p = .05 was used for all tests. All analyses were conducted using SAS Version 9.1.3 (SAS Institute, Cary, NC).

Results

Among the treatment completers, there were no significant differences in demographic or clinical characteristics at baseline between the OROS-MPH and the placebo group (see Table 1). As shown in Table 2, treatment completers who received OROS-MPH lost an average of 1.6% of their body weight (M = 1.4 kg weight loss), whereas those who received placebo gained an average of 1.3% of their weight (M = 1.0 kg weight gain), a difference that was statistically significant (p < .001). In the percent weight change analyses, there were no statistically significant interactions between treatment group and gender, baseline BMI, or smoking status, suggesting that the effects of OROS-MPH on weight were independent of these factors. Treatment completers who received OROS-MPH also recorded lower severity of hunger on the WST (M = 1.1, SD = 0.8) than those who received placebo (M = 1.6, SD = 0.9), p < .001. These results held when we repeated the analyses in the subsample of participants who achieved prolonged abstinence, as well as in those who reduced their smoking by at least 50% compared with their baseline level of smoking.

Table 1. Baseline Demographic and Clinical Characteristics of the Sample by Treatment Group

	Placebo (n = 108)	OROS-MPH (n = 107)	p value
Age	38.0 (9.5)	38.4 (10.3)	.65
Sex, male	59 (54.6%)	65 (60.7%)	.36
Race			.77
Asian	2 (1.9%)	2 (1.9%)	
Black	6 (5.6%)	5 (4.7%)	
Native American	0 (0.0%)	1 (0.9%)	
Mixed	7 (6.5%)	3 (2.8%)	
Other	5 (4.6%)	4 (3.8%)	
White	88 (81.5%)	91 (85.8%)	
Hispanic	8 (7.4%)	8 (7.5%)	.98
Married	26 (24.3%)	41 (38.7%)	.12
Years of education	14.5 (2.5)	14.4 (2.5)	.46
Employed full time	76 (71.0%)	79 (74.5%)	.77
BMI	27.3 (6.3)	28.0 (5.8)	.09
Lifetime major depression	38 (35.2%)	33 (30.8%)	.50
Lifetime anxiety disorder	30 (27.8%)	34 (31.8%)	.52
Lifetime substance use disorder	75 (69.4%)	83 (77.6%)	.18
ADHD Rating Scale score	36.3 (7.5)	36.3 (7.2)	.91
ADHD Subtype			.51
Combined	68 (63.6%)	64 (59.8%)	
Hyperactive-impulsive	2 (1.9%)	5 (4.7%)	
Inattentive	37 (34.6%)	38 (35.5%)	
FTND	5.6 (2.3)	5.8 (2.2)	.42
Years of smoking	24.0 (10.2)	24.5 (10.3)	.81

Note. *BMI* = body mass index; *FTND* = Fagerström Test for Nicotine Dependence; *OROS-MPH* = osmotic release oral system methylphenidate.
Values in table are mean (*SD*) or *n* (%).

Table 2. Effects of OROS-MPH on Weight and Hunger

	% Weight change			WST-Hunger		
	OROS-MPH	Placebo	*p* value	OROS-MPH	Placebo	*p* value
Treatment completers[a]	−1.6% (3.7) [−1.4 kg (3.1)]	+1.3% (4.6) [+1.0 kg (3.9)]	<.001	1.1 (0.8)	1.6 (0.9)	<.001
Prolonged abstainers[b]	−1.7% (4.0) [−1.4 kg (3.0)]	+1.3% (6.1) [+1.0 kg (5.3)]	.003	1.0 (0.8)	1.5 (0.9)	.002
Reducers[c]	−1.7% (3.7) [−1.5 kg (3.1)]	+1.5% (4.9) [+1.1 kg (4.1)]	<.001	1.1 (0.8)	1.6 (0.9)	<.001

Note. *WST* = Withdrawal Scale for Tobacco; *OROS-MPH* = osmotic release oral system methylphenidate.

Where not specifically indicated, numbers represent means (standard deviations). Weight change, in kilograms, is shown for descriptive purposes only. All tests of the hypothesis that OROS-MPH reduces weight gain used % weight change as the dependent variable.

[a]Treatment completers were those who completed that 11-week treatment phase of the study (n = 204 for % Weight Change analysis, n = 215 for WST Hunger analysis).

[b]Prolonged abstainers were those with self-reported abstinence with no evidence of treatment failure (i.e., smoking once per day for seven consecutive days, or smoking at least once per week for two consecutive weeks) during the final 4 weeks of the treatment phase (n = 102 for % Weight Change analysis, n = 108 for WST Hunger analysis).

[c]Reducers were those who decreased their self-reported number of cigarettes per day by at least 50% between baseline and Week 11 (end of treatment) (n = 182 for % Weight Change analysis, n = 192 for WST Hunger analysis).

Discussion

Our findings suggest that the effects of OROS-MPH on body weight during a smoking-cessation attempt in adults with ADHD go beyond merely preventing the weight gain that typically accompanies cessation—individuals who received OROS-MPH lost an average of 1.4 kg compared with an approximate 1 kg weight gain among those who were received placebo. These estimates were remarkably consistent across the treatment completer sample, the prolonged abstainer sample, and the reducer sample, and coupled with the previous finding that OROS-MPH was not more effective than placebo in promoting smoking cessation (Winhusen et al., 2010), suggest that the effect of OROS-MPH on weight is independent of smoking status. Our exploratory analyses also suggested that the effect of OROS-MPH was not moderated by gender or baseline BMI.

The weight loss observed with OROS-MPH in this study is slightly less than that observed in other short-term ADHD treatment studies. For example, Biederman et al. (2006) reported an average loss of 2.7 kg over a 6-week treatment period with OROS-MPH. Although its effects on hunger and weight did not translate into better overall efficacy for smoking cessation in this study (Winhusen et al., 2010), when coupled with OROS-MPH's previously established safety in smokers with ADHD and its efficacy in reducing ADHD symptoms, this clear indication of its effects on postcessation weight gain suggests that future research on the potential benefit of OROS-MPH among particular subgroups of smokers with ADHD—such as those who are deterred from making a quit attempt due to weight concerns or who are prone to relapse as a result of weight gain—may be in order. At the same time, the side-effect profile of OROS-MPH (particularly, in comparison to smoking-cessation medications that can attenuate weight gain, such as bupropion and nicotine gum; Heffner et al., 2006) should be taken into consideration. A complete analysis of treatment-emergent adverse effects of OROS-MPH versus placebo can be found in Winhusen et al. (2010), but, briefly, OROS-MPH was associated with higher rates of psychomotor hyperactivity, dyspepsia, heart rate increase, and heart palpitations, in addition to decreased appetite.

Several limitations of the study should be considered when interpreting the results. First, even participants in the prolonged smoking abstinence group were not completely abstinent from nicotine at the final assessment of weight, as they were still using the nicotine patch, but previous research does not provide strong evidence that the nicotine patch effectively reduces postcessation weight gain (Heffner et al., 2006). In addition, out of necessity (i.e., due to the timing of the assessments of weight), we used a treatment completer sample (n = 215) rather than the full intent-to-treat sample (N = 255), which introduces the possibility of bias; however, our prior work suggested that the two treatment groups did not differ on rates of completion or reasons for noncompletion (Winhusen et al., 2010). Finally, this was a proof-of-concept study to examine the effect of pharmacologic treatment for adult ADHD on short-term outcome of an assisted smoking-cessation attempt. As such, there are no long-term follow-up data available to determine the durability of its effects when used for longer than 11 weeks, the effects of medication discontinuation on weight, and the OROS-MPH's effects compared to those of the first-line medications for smoking cessation that have been shown to attenuate postcessation weight gain, such as buproprion or nicotine gum (Heffner et al., 2006). In spite of these limitations, this study has a number of strengths, including its use of a large, geographically diverse sample of treatment-seeking adult smokers with ADHD. It also provides compelling preliminary data suggesting that psychostimulant treatment of ADHD can prevent postcessation weight gain during a quit attempt and therefore may provide a dual benefit for smokers for whom postcessation weight gain could present real or perceived difficulties (e.g., individuals with weight-related medical comorbidity or concerns about effects of weight gain on physical health and/or appearance). However, because weight-related

medical problems and concerns were not assessed as part of this study, additional research is needed to test this hypothesis.

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Declaration of Interests

Dr. Heffner has served as a consultant for Pfizer, Inc. and has received research support from Nabi Biopharmaceuticals and Pfizer. Dr. Winhusen and Mr. Lewis have no financial disclosures to report.

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