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An exploration of site effects in a multisite trial of OROS-methylphenidate for smokers with Attention Deficit/Hyperactivity Disorder

Lirio S. Covey, Ph.D.,

New York State Psychiatric Institute, Columbia University Medical Center

Mei-Chen Hu, Ph.D.,

Department of Psychiatry, Columbia University

Carla A. Green, Ph.D., M.P.H.,

Center for Health Research, Kaiser Permanente Northwest

Gregory Brigham, Ph.D.,

Maryhaven, University of Cincinnati

Richard D. Hurt, M.D.,

Nicotine Dependence Center, Mayo Clinic

Lenard Adler, M.D., and

New York University Medical School, Veterans Affairs New York Harbor Healthcare System

Theresa Winhusen, Ph.D.

College of Medicine, University of Cincinnati

Abstract

Background—Multi-site trials, the gold standard for conducting studies in community-based settings, can mask variability across sites resulting in misrepresentation of effects in specific sites. In a placebo-controlled trial of osmotic-release oral system methylphenidate (OROS-MPH) as augmentation treatment for smokers with ADHD, three types of sites were selected according to their clinical research specialty (ADHD, smoking cessation, and general mental health).

Objective—Analysis was conducted to determine if clinical outcomes, i.e., reduction in ADHD symptoms and smoking cessation rates, and the effect of treatment on these outcomes would differ by type of site.

Method—255 adult smokers diagnosed with ADHD were enrolled in three clinic types: 72 in ADHD, 79 in tobacco dependence, 104 in the mental health clinics.

Results—The three site-types were similar in demographic characteristics, smoking history, baseline level of ADHD symptoms, and history of psychiatric illness. Site-type but not a site-type by treatment interaction predicted prolonged smoking abstinence. A significant three-way interaction of site-type, treatment, and time predicted improvement in ADHD symptoms. Moderate to strong effects of OROS-MPH relative to placebo were observed in the mental health and the ADHD clinics; a weak effect was observed in the tobacco dependence clinics.

Conclusion—OROS-MPH benefit varied by site for reducing ADHD symptoms but not for improving smoking abstinence.

Scientific Significance—Assessment of site-type effects can indicate the generalizability of findings from multisite trials and should be routinely incorporated in the design of multisite trials.

Introduction

The multisite trial is the gold-standard for conducting research concerned with the effectiveness and efficacy of community-oriented treatments. The multisite method can accelerate the pace of recruitment, increase enrollment, and achieve better variability in the characteristics of study participants. These procedures enhance the validity and generalizability of research findings (1). However, variations among sites can occur in ways that could obscure outcomes, for example, masking specific effects in particular subgroups when only aggregate results are assessed. Examination of site differences and the effects of those differences on the impact of the experimental treatment as a means for ascertaining validity and avoiding misrepresentation of findings has been advocated (2–5) but rarely done. In the present analysis, we investigated the effects of site and site-related variables measured at baseline as determinants of treatment outcome in a randomized clinical trial.

Multiple sites were selected for a trial of osmotic-release oral system methylphenidate (OROS-MPH) as augmentation treatment for smokers with Attention Deficit Hyperactivity/Impulsivity Disorder (ADHD) (6). The main trial objective was to determine the efficacy of OROS-MPH versus placebo treatment for improving smoking abstinence and reducing ADHD symptoms. Analysis of this primary aim observed a treatment effect of OROS-MPH on ADHD symptoms but not on smoking abstinence (6). An auxiliary purpose of the trial was to determine generalizability of findings across different types of patient samples. To that end, three types of participating research sites were selected based on their specialization in treating the disorders that characterized the patient sample: ADHD, tobacco dependence, or mental health (neither one of the two disorders). Accordingly, the objectives of this secondary analysis were to determine: a) site-type differences on smoking abstinence rates and on improvement in ADHD at the end of treatment, and b) variation by type of site in the relative effects of OROS-MPH versus placebo on the target clinical outcomes.

Method

Study design and procedures

Institutional Review Boards at the individual sites approved the parent trial. The study design was randomized, double-blind, comparing OROS-MPH versus placebo as adjunctive medication to standard smoking cessation treatment. The protocol included a four-week pre-quit phase and a seven-week planned smoking abstinence phase. The study protocol has been reported in detail elsewhere (6). The main inclusion criteria were: current use of 10 cigarettes daily, wish to quit smoking, age 18 to 55 years, good physical health, and DSM-IV diagnosis of ADHD assessed by the Adult Clinical Diagnostic Scale version 1.2 (7). Primary exclusion criteria included a positive urine drug screen for drugs of abuse, current psychiatric illness, current alcohol or drug abuse/dependence, current or past treatment contraindicating methylphenidate use, current treatment for ADHD or tobacco dependence, and for women, pregnancy, breastfeeding, or unwillingness to use adequate birth control.

The same design, procedures, and assessments were implemented across the sites. Study participants were randomized to OROS-MPH or placebo in a 1:1 ratio with stratification by site. All participants received OROS-MPH or placebo during weeks 1–11. Participants used 21 mg. nicotine patches daily beginning on the target quit date (i.e., the fifth day of Week 4) through week 11; nicotine patch dose was tapered thereafter through week 14.

Participants received 10-minute behavioral smoking cessation counseling during clinic visits from weeks 1–11. Each site assigned counselors to deliver the individual counseling interventions following the “Smoke Free and Living It” manual developed at the Mayo Clinic Nicotine Dependence Center. Counselors received two-day training at the Mayo

Clinic prior to initiating the study. All counseling sessions were videotaped throughout the study, and representative tapes were selected for monitoring and assessment by Mayo Clinic supervisors. Feedback and recommendations for improvement were made as needed.

Project Coordinators from each site attended a two-day protocol training conducted by the lead investigative team. Further staff training in clinical procedures and administering study instruments was provided by the same training team and conducted prior to study initiation at each site, and at interim points. Throughout the study, weekly telephone conferences were led by the lead investigative team and attended by principal investigators, project coordinators, and research assistants from each study site, as well as representatives from the data coordinating center. Progress and problems regarding recruitment, treatment delivery, and completion rates were discussed at these meetings.

Measures

The clinical outcomes examined were prolonged smoking abstinence and improvement in ADHD symptoms. Prolonged abstinence was defined as self-reported tobacco abstinence without treatment failure (smoking each day for seven consecutive days or smoking at least one day of each week in two consecutive weeks) during four weeks (weeks 7–10) at the end of treatment. This definition is consistent with the recommendations of the Society for Research on Nicotine and Tobacco (8). The timeline follow-back method (9) was used to assess participants' weekly use of tobacco during the study. Reports of abstinence were confirmed by expired carbon monoxide 8 parts per million (10). Change in ADHD symptoms was determined with the ADHD-Rating Scale (ADHD-RS) (11) assessed weekly by trained and certified study clinicians. The ADHD-RS uses adult prompts and is composed of 9 items denoting inattention symptoms and 9 items denoting hyperactive/impulsivity symptoms.

Our main predictor variable for this analysis was site-type: ADHD clinic, tobacco dependence clinic, or mental health clinic. Two sites were selected to represent each site-type; the assumption of similarity between the two sites representing each site-type was supported by data showing mostly similarities than differences on most of the sample characteristics measured. As seen in the Supplemental Data Table, of 17 pair-wise comparisons within site-types, three showed significant difference in the ADHD and in the smoking clinics, five in the mental health clinics. Covariates measured were participants' demographic, smoking background, ADHD symptom score at baseline, and psychiatric history recorded at baseline (as shown in Table 1). These were tested as potential moderators of site-type and treatment because of their putative relationships with the targeted clinical outcomes (smoking abstinence and ADHD symptoms). The demographic variables were: age, gender, ethnicity, marital status, and educational level. The smoking history variables were: number of cigarettes smoked daily prior to the study and nicotine dependence level as measured by the Fagerström Test for Nicotine Dependence (12). The psychiatric variables included disorders experienced at least one month prior to the screening visit (major depression, anxiety disorders, alcohol abuse/dependence, drug abuse/dependence). The Composite International Diagnosis Interview (CIDI). (<http://www.crufad.unsw.edu.au/cidi/cidi.htm>) was used to measure psychiatric history.

Statistical Analysis

We used χ^2 -tests for categorical variables and F-tests or t-tests for continuous variables to compare the site-types on the prevalence of or mean scores on the covariates. To assess site-type effects on treatment outcomes, without adjustment for covariates, we calculated odds ratios and 95% confidence intervals (CI) for prolonged abstinence and the effect size (Cohen's *d*) for improvement in ADHD symptoms. To observe independent effects of our

hypothesized predictors of treatment outcome, we tested multiple logistic regression models on the prolonged smoking abstinence rate at the end of treatment and mixed effects models using PROC Glimmix (SAS 9.2) (13) on ADHD symptoms at Weeks 1–4, 7, 9, and 11 (with identity link function for normal data). The main effects of site-type, treatment, and other covariates and their interactions remained in the final models if statistically significant ($p < 0.05$). Site-type was entered as a fixed effect since the three site-types were selected to represent specific site expertise and settings. All other covariates were modeled as exerting fixed effects. Time in weeks was log-transformed because the weekly decrease in ADHD symptoms during the first phase (before quit day) was steeper than in the second phase (after quit day). The log-transformed time variable produced a better fit than the original model. Missing values for prolonged abstinence were coded conservatively (that those individuals had smoked) following convention in the published literature (8).

Results

Characteristics of the sample

A total of 255 adult smokers who met DSM-IV criteria for ADHD at screening were enrolled: 72 in two ADHD clinics, 79 in two tobacco dependence clinics, and 104 in two mental health programs. The sample included slightly more males (56%), had a mean age of 37.7 (s.d.=10.0) and was predominantly non-Hispanic white (80%). By marital status, the never-married comprised the largest group (44%); the average participant had completed schooling beyond high school; a majority (74%) was fully employed. Participants were moderate to heavy daily cigarette smokers (mean cigarettes per day=20.7, s.d.=7) who had begun smoking early in their lives (mean age = 13.9 years, s.d.=3.1). The rates of past psychiatric conditions were: major depression = 34%, anxiety disorders=34%, alcohol abuse/dependence=49%, and drug abuse/dependence= 41%.

Sample characteristics by site-type

Baseline characteristics generally did not differ across the site-types (Table 1). The few exceptions of significant site-type differences ($p < 0.05$) were: a greater proportion of males among the ADHD clinics (76% versus 49% and 48% in the tobacco and the mental health clinics, respectively), higher proportions of participants with past drug abuse/dependence in the ADHD clinics (54% versus 39% in the mental health clinics and 31% in tobacco dependence clinics); and slightly less school years among participants in the mental health clinics (13.9 years versus 14.9 and 14.6 in the ADHD and tobacco clinics, respectively).

Treatment outcomes by site-type

Table 2 shows prolonged smoking abstinence rates by site-type and treatment condition. Improvement in ADHD symptom scores by site-type and treatment condition are shown in Table 2 and Figure 1. Significant differences across the site-types were observed for both prolonged smoking abstinence and ADHD symptoms. However, as also shown in Table 2, treatment effect on prolonged abstinence for each site-type, measured by unadjusted odds ratios, was not significant. The treatment effect on the improvement of ADHD was large in the mental health clinics, medium in the ADHD clinics, and small in the tobacco dependence clinics.

The final regression model on prolonged smoking abstinence, adjusted for covariates (Table 3), showed a significant effect of site-type ($\chi^2(2) = 18.29, p < 0.0001$), reflecting the larger proportion of abstainers in the tobacco clinics than in the other two types of sites. The abstinence rate was higher in tobacco clinics than mental health sites (AOR = 2.63, 95% = 1.34–5.17, $\chi^2(1) = 7.90, p < .01$), and higher in mental health sites than ADHD sites (AOR = 2.15, 95% = 1.01–4.56, $\chi^2(1) = 3.97, p < .05$). The interaction of site-type and treatment

did not reach statistical significance ($\chi^2(2) = 2.90, p=0.24$), and no other interactions between site-type and covariates were significant. The differences in abstinence by site-type were not due to the differences in participants' characteristics, i.e., male, age, education, drug abuse/dependence, which were controlled in the model. Additionally, higher number of cigarettes smoked at baseline (AOR = 0.93, 95%CI = 0.88–0.98, $\chi^2(1) = 8.19, p < 0.01$), and a positive history of alcohol abuse/dependence (AOR = 0.40, 95%CI = 0.21–0.78, $\chi^2(1) = 7.37, p < 0.01$) predicted a lower abstinence rate. Male (AOR= 2.71, 95%CI = 1.38–5.33, $\chi^2(1) = 8.37, p < 0.01$), and older age (AOR= 1.04, 95%CI = 1.01–1.08, $\chi^2(1) = 5.34, p < 0.05$) exerted significant positive effects on prolonged abstinence.

The final model on ADHD symptoms (Table 3) showed a significant three-way interaction of site-type, treatment, and time ($F(2, 1279) = 3.99, p = 0.02$). The ADHD symptoms in the tobacco dependence clinics in the first week, for both placebo and OROS-MPH, were lower than in the mental health clinics ($t=2.71, p < .01$). The treatment effect on weekly change in ADHD symptoms was significantly strong at the mental health clinics ($t = 5.71, p < 0.001$) and the ADHD clinics ($t = 3.76, p < 0.001$), but not significant in the tobacco dependence clinics ($t = 1.33, p = 0.18$). The treatment effect over time was stronger at the mental health clinics than at the tobacco dependence programs ($t = 2.73, p < 0.01$), but was not significantly different when compared to the ADHD clinics. The Glimmix model also showed that ADHD symptoms during the trial were higher with higher ADHD symptom score at baseline ($t = 5.41, p < 0.0001$) and younger age ($t = 2.37, p = 0.02$).

Discussion

Site differences can emanate from patient or site characteristics. Different sites may draw patients of varying disease severity, treatment-readiness, treatment-resistance, or other individual characteristics that could impact treatment response (2, 4). The sites themselves may differ in their staffs' training, work history, or skill level, and overall program atmosphere (2, 4). This analysis examined differences by site-type in patient characteristics measured at baseline. We did not analyze the role of events or changes that occurred post-baseline. A further limitation is the non-randomization of participants by site. An additional consideration is the presence of shared characteristics because of the participants' common status as cigarette smokers who wished to stop. Thus, we acknowledge the tentative nature of our findings and interpretations.

The present analysis showed significant site-type differences in the rates of prolonged abstinence and improvement in ADHD symptoms. However, we did not observe a significant site-type by treatment interaction effect on prolonged abstinence, negating a moderating role of site in the effect of OROS-MPH relative to placebo. On the other hand, site-type moderated the reduction in ADHD symptoms, as shown by significant interactions between site-type, treatment, and time. As shown in Table 2 and illustrated in Figure 1, the treatment effect size on ADHD symptoms was large in the mental health clinics, medium in the ADHD clinics, and virtually nil in the tobacco dependence clinics. Although not the focus of our analysis, we observed differences by site in the frequencies of variables indicating treatment compliance (i.e., pills used, patches used, and number of clinic visits) (data not shown), nevertheless, site-type differences in the clinical outcomes were observed indicating that the basis for the differences among the site-types was not in the compliance measures.

The finding of significant site-type variability for both prolonged abstinence and ADHD symptoms among participants in the placebo arm, which represents the treatment-as-usual condition, is noteworthy. There were more abstainers who did not receive the active drug in the tobacco clinics than in either the ADHD or the mental health clinics. Treating smokers is

a principal focus of the tobacco dependence clinics but not of the two other site-types. Expectable differences in the work experience of staff and the overall program culture as well as particular qualities of the type of patient drawn to an established tobacco dependence treatment facility could explain this site variability in the placebo arm. Perplexing at first blush is the greater extent of ADHD symptom improvement among placebo treated participants in the tobacco clinics than in the non-tobacco clinics (see Table 2). The finding from an earlier smoking cessation trial that successful abstainers are more likely than continuing smokers to experience improvement in depressive mood, anxiety, and suicidal thoughts following a target quit day (14) may help to explain the counterintuitive finding. The larger proportion of placebo-treated abstainers in the tobacco clinics may have produced greater improvements in mood states, which extended to their reporting of greater improvements in ADHD symptoms, without benefit of OROS-MPH.

On the other hand, the analysis of treatment effects showed consistency across the site-types in the lack of treatment effect on prolonged abstinence, suggesting that the negative OROS-MPH effect previously reported for the entire sample (6) could be generalized to other smokers with ADHD. By contrast, site variability in treatment effect for improving ADHD symptom was observed. As portrayed in Figure 1, the decline in ADHD symptoms was virtually identical for OROS-MPH or placebo treatment in the tobacco clinics but markedly greater with the active drug than placebo in the ADHD clinics and the mental health clinics. To explain the anomalous lack of OROS-MPH efficacy in the tobacco clinics, we revert to the presumed positive effect of smoking abstinence on mood. The large decline in ADHD symptoms among placebo patients in the tobacco clinics (see Table 2) may have created a ceiling effect that prevented the detection of added benefit from the active drug.

Although cautious interpretation is warranted, the study findings have methodological implications and clinical relevance that include the following. First, the significant treatment benefit for improving ADHD symptoms observed across the trial (6), was apparent in only two of the three site-types; accordingly, had the study been conducted in the tobacco dependence clinics only, an erroneous null or, at best, weak effect of OROS-MPH on ADHD symptoms might have emerged. Second, the consistency of negative OROS-MPH efficacy for smoking abstinence despite differences in the sites' background specialties suggests that OROS-MPH is a poor candidate cessation aid for smokers with ADHD. The uneven presence of site-type effects, observed in this analysis, affirms the need for *a priori* consideration and measurement of potentially influential site-related factors in the design and analysis of multisite trials.

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Figure 1.
Weekly scores of ADHD symptoms by OROS-MPH and placebo groups for each site-type

Table 1

Baseline characteristics of participants by type of treatment/research sites (N=255)

	ADHD (N=72)	Tobacco Dependence (N=79)	Mental Health (N=104)		
	% or Means (s.d.)			χ^2 or <i>F</i>	p-value
Male (vs. female)	76.4 ^a	49.4 ^b	48.1 ^b	15.30	p<.001
Age	36.9(9.9)	37.1(10.3)	39.0(9.8)	1.21	p=.30
Caucasian (vs. not)	85.9	79.5	76.0	2.56	p=.28
Education (years)	14.9(2.6) ^a	14.6(2.7) ^a	13.9(1.9) ^b	8.18	p<.05
Marital Status				4.39	p=.34
Married	31.7	37.5	30.6		
Divorced/separated	24.1	25.0	16.7		
Never married	44.3	37.5	52.8		
ADHD Symptom Scores at baseline	36.2(6.7)	36.9(7.3)	36.0(7.7)	0.33	p=.72
Cigarettes smoked daily	20.3(7.4) ^{ab}	18.8(7.1) ^b	21.1(8.3) ^a	2.08	p=.13
Nicotine Dependence (Fagerstrom Test for Nicotine Dependence)	5.6(2.3)	5.3(2.2)	5.6(2.2)	0.91	p=.45
Psychiatric Comorbidity (past):					
Major depression	40.28	29.11	32.69	2.18	p=.34
Anxiety disorders	34.72	32.91	33.65	0.06	p=.97
Alcohol abuse/dependence	45.83	50.63	50.00	0.41	p=.81
Drug abuse/dependence	54.17 ^a	31.65 ^b	39.42 ^c	8.11	p=.02

Groups with same superscripts in the same row were not significantly different at p<.05.

Table 2

Prolonged smoking abstinence rates and improvement of ADHD symptoms by type of treatment/research site.

	ADHD (N=72)	Tobacco Dependence (N=79)	Mental Health (N=104)
% Prolonged smoking abstinence			
Total sample	27.8 ^a	62.0 ^b	38.5 ^a
By treatment group			
OROS-MPH	30.6 ^a	66.7 ^b	34.6 ^a
Placebo	25.0 ^a	57.5 ^b	42.3 ^{ab}
Odds Ratio	1.32 ^a	1.48 ^a	0.72 ^a
95% Confidence Interval	0.47–3.72	0.59–3.69	0.33–1.60
Improvement of ADHD symptom score from baseline Mean (s.d.)			
Total sample	9.9(10.9) ^a	18.8(13.3) ^b	12.8 (13.0) ^a
By treatment group			
OROS-MPH	13.1(10.8) ^a	20.3(14.5) ^b	18.0(11.3) ^{ab}
Placebo	6.7(10.1) ^a	17.4(12.1) ^b	7.6(12.6) ^a
Effect size	0.61	0.22	0.87
95% Confidence Interval	0.14–1.09	–0.23–0.66	0.47–1.27

Groups with different superscripts in the same row are significantly different at $p < .05$.

Table 3

Predictors of prolonged smoking abstinence in the logistic regression and weekly ADHD symptoms obtained from a mixed effects model

	Prolonged Smoking Abstinence		Weekly ADHD Symptoms		
	DF	χ^2	P	DF	P
Type of site	2	18.29	<0.001	2	3.73 0.024
Treatment	1	0.01	0.933	1	0.69 0.406
Number of cigarettes smoked per day at baseline	1	8.19	0.004	1	0.15 0.702
Alcohol abuse/dependence	1	7.37	0.007	1	0.67 0.412
ADHD symptoms at baseline	1	1.27	0.259	1	29.24 <0.001
Male (vs. Female)	1	8.37	0.004	1	3.57 0.059
Age	1	5.34	0.021	1	5.63 0.018
Time (logged week)				1	200.7 <0.001
Type of site*Treatment				2	0.20 0.823
Type of site*Time				2	11.28 <0.001
Treatment*Time				1	36.53 <0.001
Type of site*Treatment*Time				2	3.99 0.019

Caucasian, education, marital status, FTND nicotine dependence, major depression, anxiety disorder, and drug abuse/dependence were controlled in both models.