Brief Report

Divergence by ADHD Subtype in Smoking Cessation Response to OROS-Methylphenidate

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Abstract

Introduction: Attention deficit hyperactivity disorder (ADHD) is a neuropsychiatric condition subclassified in *DSM-IV* according to its core symptoms domains as (a) predominantly inattentive (ADHD-IN), (b) predominantly hyperactive/impulsive (ADHD-H), and (c) combined inattentive and hyperactive/impulsive (ADHD-C). Whether these subtypes represent distinct clinical entities or points on a severity continuum is controversial. Divergence in treatment response is a potential indicator of qualitative heterogeneity. This study examined smoking cessation response by ADHD subtype to osmotic-release oral system methylphenidate (OROS-MPH).

Methods: Male and female adult smokers (ADHD-C = 167 and ADHD-IN = 87) were randomized to receive OROS-MPH or placebo as augmentation treatment to nicotine patch and counseling. Logistic regression was conducted to test the effect of OROS-MPH versus placebo on prolonged smoking abstinence by ADHD subtype.

Results: The subtypes were similar in baseline demographic, smoking, and psychiatric history but differed in smoking cessation response to OROS-MPH or placebo as a function of nicotine dependence level. The 3-way interaction was significant; $\chi^2(1) = 8.22$, $p < .01$. Among highly dependent smokers, the prolonged abstinence rates were greater with OROS-MPH than with placebo in the ADHD-C group (60% vs. 31.3%, respectively, $p < .05$) but higher with placebo than with OROS-MPH in the ADHD-IN group (60% vs. 11.8%, respectively, $p < .01$). Abstinence rates did not differ by subtype or treatment among smokers who were less nicotine dependent.

Conclusion: Contrasting treatment response and divergence in the impact of nicotine dependence level support the hypothesis

of ADHD subtypes as distinct clinical entities and may indicate the need and directions for personalized targeted treatments of smokers with ADHD.

Introduction

Attention deficit hyperactivity disorder (ADHD) is a neuropsychiatric condition of childhood onset and, in about half of cases, persistence to adulthood (Kessler et al., 2010). The estimated worldwide prevalence of ADHD is 5.29% (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). ADHD is classified in *DSM-IV* according to its core symptom domains: (a) predominantly inattentive (ADHD-IN), (b) predominantly hyperactive/impulsive (ADHD-HI), and (c) combined inattentive and hyperactive/impulsive (ADHD-C). The validity of these diagnostic subtypes remains controversial (Coghill & Seth, 2011). Evidence exists for ADHD as a unitary diagnosis (Riley et al., 2008; Volk, Henderson, Neuman, & Todd, 2006), but evidence indicating clinical heterogeneity exists as well from epidemiological and clinical studies (Elkins, McGue, & Iacono, 2007; Wilens et al., 2009). Mixed evidence regarding heterogeneity in treatment response by ADHD subtype has been reported from trials of ADHD treatments conducted with children and adolescents, that is, no difference (Barbaresi et al., 2006; Biederman & Pliszka, 2008) as well as response heterogeneity (Chou et al., 2009; Gorman, Klorman, Thatcher, & Borgstedt, 2006; Grizenko, Paci, & Joobar, 2010).

Higher rates of smoking and lower rates of smoking cessation in the presence of ADHD symptoms or the diagnosis have been reported (Gray & Upadhyaya, 2009; Kollins, McClernon, & Fuemmeler, 2005). Several studies have found higher risk with hyperactivity/impulsivity than with inattention symptoms for smoking initiation, progression to regular smoking or nicotine dependence, and smoking relapse (Elkins et al., 2007;

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Fuemmeler, Kollins, & McClernon, 2007; Rukstalis, Jepson, Patterson, & Lerman, 2005). A smoking cessation trial observed lower abstinence rates among smokers with predominantly hyperactivity/impulsivity than with predominantly inattention symptoms (Covey, Manubay, Jiang, Nortick, & Palumbo, 2008). No evidence exists to date regarding distinctiveness by subtype in smokers with diagnosed ADHD.

The present analysis aimed to fill that knowledge gap by exploring difference by ADHD subtype in cessation response among adult smokers who met full *DSM-IV* criteria for ADHD. Data were obtained from a randomized placebo-controlled trial of osmotic-release oral system methylphenidate (OROS-MPH) as augmentation treatment to nicotine patch and counseling. The main outcome report for that study did not observe OROS-MPH benefit for improving the prolonged abstinence rate relative to standard treatment (Winhusen et al., 2010). Further analysis by race/ethnicity also did not find a differential treatment effect on prolonged abstinence but found significantly higher rates for non-White compared with Whites on complete abstinence (no slips or lapses during the last four weeks of treatment; Covey et al., 2010). The possibility that earlier findings of differential outcomes by type of ADHD symptoms (Covey et al., 2008) would extend to differences in prolonged abstinence rates by ADHD subtype provided the rationale for the present analysis. Because of the small number of non-White smokers (51/255 smokers), we did not attempt to further disaggregate the racial/ethnic groups by ADHD subtype.

Methods

Participants

The trial was conducted at six U.S. research sites between December 2005 and September 2007. The institutional review board at each site approved the study. Participants were recruited through advertising media and networking with medical facilities. Eligible participants were smokers who fulfilled *DSM-IV* criteria for ADHD, smoked ≥ 10 cigarettes daily, wished to quit, were 18–55 years, and in good physical health as determined by medical history, electrocardiogram, and vital signs. Exclusion criteria included the use of tobacco products other than cigarettes in the past week and, at baseline, positive screen for an illicit drug, current drug abuse/dependence for any substance other than nicotine, current major depression or anxiety disorder (except specific phobias), antisocial personality disorder, lifetime diagnosis of bipolar disorder or psychosis, and significant suicidal/homicidal risk. Additional exclusions were current ADHD treatment with stimulants, nicotine dependence treatment within the last thirty days, any medical condition contraindicated by methylphenidate and, for women, pregnancy, breast feeding, or unwillingness to use an adequate method of birth control.

Procedures

Participants provided signed informed consent. Eligible participants were randomized double blind to OROS-MPH or placebo in a 1:1 ratio. Participants received OROS-MPH or placebo during Weeks 1–11; Weeks 1–4 were a prequit phase, and Weeks 5–11 were the planned abstinence period. The dosage schedule was fixed at a starting dose for OROS-MPH of 18 mg/day and increased during the first two weeks to a maximum of 72 mg/day for the duration of the trial. Dose reductions could be made according

to tolerability. All were instructed to use 21 mg nicotine patches daily for 24 hr beginning on the target quit date through the end of Week 11. Standardized smoking cessation counseling using the Mayo Clinic Nicotine Research Program's "Smoke Free and Living It" manual was provided in weekly 10-min sessions and monitored through assessments of videotaped sessions by supervisors from each site and the Mayo Clinic. Participants received \$25 compensation for each completed visit.

Measures and Instruments

The dependent variable was prolonged smoking abstinence during Weeks 7–10 without treatment failure, defined as use of cigarettes or any other tobacco product for seven consecutive days or at least one day of each week in two consecutive weeks (Hughes et al., 2003). Cigarette use during the study was assessed weekly using the timeline followback method (Sobell & Sobell, 1992); self-reports of abstinence were verified by expired CO ≤ 8 parts per million (Jarvis, Tunstall-Pedoe, Feyerabend, Vesey, & Saloojee, 1987). Dropouts were considered nonabstainers. The main predictor was ADHD diagnosis by subtype (i.e., ADHD-inattentive, ADHD-hyperactive/impulsive, and ADHD-combined) following the adult ADHD Clinical Diagnostic Scale (ACDS) version 1.2 (Adler & Cohen, 2004). The ability of the ACDS to establish ADHD diagnosis and subtype following *DSM-IV* criteria was demonstrated in community-based studies (Kessler et al., 2006, 2010). The ACDS raters had a minimum of M.A. degree and were trained and certified in the use of the ACDS (per Adler et al., 2005). Other covariates selected because of prior evidence of their potential effects on smoking abstinence were total ADHD symptoms at baseline, nicotine dependence level and other smoking history (number of cigarettes smoked daily at baseline and age began smoking), past psychiatric history (major depressive disorder, any anxiety disorder, alcohol abuse/dependence, and drug abuse/dependence), and demographic characteristics (age, gender, marital status, education, and employment status). For measuring ADHD symptom level, we used the ADHD-Rating Scale (DuPaul, Power, Anastapolous, & Reid, 1998). The presence of comorbid psychiatric diagnoses was assessed with the Composite International Diagnosis Interview (CIDI) version 2.1 (<http://www.cruafad.unsw.edu.au/cidi/cidi.htm>). Nicotine dependence level was measured with the Fagerström Test for Nicotine Dependence (FTND) using 7 as the cut score to distinguish participants according to low to medium (<7) or high (≥ 7) dependence level. This cut score produced maximum agreement with the presence of *DSM-III-R*-diagnosed nicotine dependence compared with cuts of 5, 6, or 8 (Moolchan et al., 2002). Evidence exist indicating the reliability and validity of the instruments used to measure the covariates, that is, ADHD-RS (Döpfner et al., 2006; Rösler, Retz, & Stieglitz, 2010), CIDI (Andrews & Peters, 1998), and FTND (de Meneses-Gaya, Zuardi, Loureiro, & de Souza Crippa, 2009).

Statistical Methods

Differences in demographic characteristics, smoking and psychiatric history, and ADHD symptom ratings were analyzed by the χ^2 test for categorical variables and the *t* test for continuous variables. Statistical significance was set at $p \geq .05$. Logistic regression modeling was applied to analyze prolonged smoking abstinence as a function of the independent variables. Clinical sites were entered as a fixed effect. Adjusted odds ratios (AORs)

and 95% *CI* associated with main effects and interaction terms were assessed. SAS PROC LOGISTIC (SAS 9.2, Cary, N.C.) was used to conduct the analyses.

Results

Sample Characteristics

Participants were classified into ADHD-IN ($n = 87$), ADHD-HI (10), and ADHD-C ($n = 157$); the ADHD-HI participants were grouped with the ADHD-C subtype. There was no difference in the proportions of randomized assignment to OROS-MPH (ADHD-IN = 51.7%; ADHD-C = 49.1%). As shown in Table 1, the sample included slightly more males (56%) and was predominantly non-Hispanic White (79%), with mean age of 37.8 years ($SD = 10.0$). The largest proportion by marital status had never married, the average participant completed 14 years of schooling, and the majority was fully employed. The rates of past major depression, anxiety disorders, alcohol abuse/dependence,

and drug abuse/dependence ranged from 34% to 49%. The participants were moderate to heavy smokers; the mean age of smoking onset was 13 years; more than a third scored ≥ 7 on the FTND. Comparison by subtype revealed broad similarity on these baseline characteristics with the exception of more males among the ADHD-IN and higher ratings on the total ADHD symptom score for the ADHD-C.

Prolonged Smoking Abstinence

The multiple logistic regression model on prolonged abstinence revealed a significant three-way interaction of subtype, treatment, and nicotine dependence level; $\chi^2(1) = 8.22$, $p < .01$. As shown in Figure 1, participants with low to medium nicotine dependence ($FTND < 7$) showed similar abstinence rates (42.9%–44.2%) when classified by ADHD subtype and treatment. Participants with high nicotine dependence ($FTND > 7$) showed divergence by subtype and treatment, that is, the prolonged abstinence rates were greater with OROS-MPH than with placebo in the ADHD-C group (60% vs. 31.3%, respectively, $\chi^2(1) = 5.17$, $p < .05$) but

Table 1. Patient Demographic and Baseline Characteristics by Subtype of ADHD ($N = 254^a$)

	(a) Total ($N = 254$)	(b) Inattentive ($N = 87$)	(c) Combined ^b ($N = 167$)	Subtype differences	
	<i>M</i> (<i>SD</i>) or %			<i>t</i> or χ^2	<i>p</i> Value
Age	37.8 (10.0)	38.6 (9.3)	37.4 (10.4)	0.89	.37
Sex (% male)	56.3	67.8	50.3	7.13	<.01
Race/ethnicity (%)				3.01	.39
Black	5.9	8.1	4.8		
Caucasian	79.1	79.3	79.0		
Hispanic	7.1	8.1	6.6		
Mixed/other	7.9	4.6	9.6		
Marital status (%)				1.19	.55
Married	33.9	37.9	31.7		
Separated/divorce/widowed	22.4	19.5	24.0		
Never married	43.7	42.5	44.3		
Education (years of school)	14.4 (2.4)	14.6 (2.3)	14.3 (2.5)	0.92	.36
Employment (%)				1.41	.49
Full time	74.4	73.6	74.9		
Part time	16.5	19.5	15.0		
No	9.1	6.9	10.2		
Total ADHD symptom rating score at baseline	36.4 (7.3)	31.9 (5.8)	38.8 (6.8)	8.00	<.001
Psychiatric comorbidity (%)					
Major depression	33.9	33.3	34.1	0.02	.90
Anxiety disorder	33.9	33.3	34.1	0.02	.90
Alcohol abuse/dependence	49.2	43.7	52.1	1.62	.21
Drug abuse/dependence	41.3	41.4	41.3	0.00	.99
Smoking history					
Fagerström Test for Nicotine Dependence ≥ 7 (%)	35.2	31.0	37.4	1.00	.32
Number of cigarettes per day	20.2 (7.7)	19.8 (8.0)	20.4 (7.5)	0.54	.59
Carbon monoxide level	23.2 (10.4)	23.0 (10.9)	23.3 (10.1)	0.22	.82
Age began smoking	13.9 (3.1)	13.6 (3.4)	14.0 (2.9)	0.77	.44

Note. ADHD = attention deficit hyperactivity disorder.

^aOne patient without six inattentive or six hyperactive/impulsive symptoms was excluded.

^bIncluded 10 cases with hyperactive/impulsive only.

Figure 1. Prolonged abstinence rates by low to medium (Fagerström Test for Nicotine Dependence [FTND] < 7) versus high to very high (FTND ≥ 7) nicotine dependence level, subtype (attention deficit hyperactivity disorder [ADHD]-inattention vs. ADHD-combined hyperactivity/impulsivity and inattention), and randomized treatment (OROS-MPH vs. placebo). After controlling for other covariates in the model, the three-way interaction among nicotine dependence level, ADHD subtype, and treatment was significant; $\chi^2(1) = 8.22, p < .01$. FTND score was missing from one participant.

higher with placebo than with OROS-MPH treatment in the ADHD-IN group (60% vs. 11.8%, respectively, $\chi^2(1) = 7.03, p < .01$). Male gender (AOR = 2.96, 95% CI = 1.45–6.07, $p < .01$) and older age (AOR = 1.04, 95% CI = 1.00–1.08, $p < .05$) increased abstinence, whereas the mean number of cigarettes smoked per day at baseline (AOR = 0.92, 95% CI = 0.87–0.97, $p < .01$) and alcohol abuse/dependence (AOR = 0.41, 95% CI = 0.21–0.82, $p < .05$) decreased abstinence. These latter variables did not show significant interaction with other covariates. The model did not indicate significant effects on prolonged abstinence of race/ethnicity, education, marital status, employment status, age of smoking onset, the total ADHD symptom score at baseline, and history of major depression, anxiety disorder, or drug abuse/dependence history (all p values > .1).

Discussion

The present analysis revealed three levels of smoking cessation response according to ADHD subtype and OROS-MPH versus placebo treatment: (a) significant benefit of the active drug over placebo for the ADHD-C subtype when nicotine dependence is high, (b) a worse outcome with OROS-MPH among smokers with ADHD-IN subtype when nicotine dependence is high, and (c) no added benefit of OROS-MPH regardless of ADHD subtype with lower nicotine dependence level.

A prior secondary analysis of data from the same parent trial had indicated the presence of a particular subgroup that could experience benefit from augmentation treatment with OROS-MPH, specifically, non-White smokers who showed higher rates of complete abstinence when treated with OROS-MPH than with placebo in contrast to their White counterparts who showed no superior effect of the active drug (Covey et al., 2010). The present analysis has suggested that ADHD-C smokers who are highly nicotine dependent comprise another subgroup likely to benefit from OROS-MPH treatment. The data also identified a subgroup for whom OROS-MPH is not a treatment of choice, that is, highly dependent ADHD-IN smokers

who were found to do poorly with OROS-MPH but responded well to nicotine patch (and counseling) alone. Neurobiological and other mechanisms underlying the contrasting clinical manifestations warrant further study.

One implication of the divergence in response by ADHD subtype, relevant to the ongoing debate regarding the structure of ADHD (Coghill & Seth, 2011), is that qualitatively distinct clinical entities comprise the diagnosis. The inability of the continuous measure of ADHD symptoms at baseline to predict smoking abstinence argues against the alternative possibility that the ADHD subtypes represent points on a severity continuum. A second implication, relevant to smoking cessation treatment research, is that OROS-MPH offers targeted benefit for smokers with high nicotine dependence and other features that delineate the symptom structure of ADHD.

The rigorous study design and careful assessment of ADHD diagnosis and cessation outcome in the parent trial are strengths of the study. Limitations that call for cautious interpretation of findings include the use of selection factors in participant recruitment (including the exclusion of smokers with current substance use or other psychiatric disorders) and the post hoc and subgroup nature of the present analysis. The moderating effect of the FTND, observed post hoc, requires more investigation. The small numbers of non-White participants ($n = 51$) prevented a valid investigation of a potential impact of race/ethnicity.

Smoking prevalence is higher and cessation lower among smokers with ADHD than among psychiatrically unaffected smokers, and smoking outcomes may differ according to the predominance of inattentive or hyperactive/impulsive symptoms. The present observations from a trial of OROS-MPH suggest that assessment of ADHD subtype and of nicotine dependence level comprise elements of a targeted personalized treatment approach for smokers with ADHD. More research to validate this implication and test its applicability to other nicotine-analog drugs is warranted.

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Declaration of Interests

LSC received an Investigator Initiated Research Award from Pfizer, Inc. in 2009. Since 2007, LA received support for research from and provided consultation activities to Abbott Laboratories, Bristol Myers Squibb, Merck, Novartis, Pfizer, Shire, Eli Lilly, OrthoMcNeill/Johnson & Johnson, New River Pharmaceuticals, Cephalon, Chelsea Therapeutics, and additional compensation for consultancy to Organon and provided consultation to Cortex Pharmaceutical, Sanofi-Aventis, Psychogenics, Astra Zeneca, Epi-Q, INC

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