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Methylphenidate Transdermal System in Adults with Past Stimulant Misuse: an Open-Label Trial

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Abstract

Objective—This 8-week, open-label trial assessed the efficacy of methylphenidate transdermal system (MTS) in 14 adult individuals diagnosed with ADHD and with a history of stimulant misuse, abuse, or dependence.

Method—The primary efficacy endpoint was the Wender-Reimherr Adult ADHD Scale (WRAADS), and secondary efficacy endpoints included the Clinical Global Impression (CGI) ratings and substance abuse as quantified by urine drug screens and self-reported use.

Results—Significant improvements from baseline were found on both the WRAADS and CGI measurements. No abuse of the study medication was observed.

Conclusion—The findings suggested that MTS may improve ADHD symptoms in adults with a history of stimulant misuse; however, there were limitations. The study data showed the need for subsequent randomized studies that further explore findings made in this study.

Keywords

attention deficit hyperactivity disorder; transdermal methylphenidate; stimulant misuse

ADHD is now recognized not only as a disease of childhood but also a condition that may have symptoms that persist into adulthood in as many as 65% of cases (Barkley, 2006). The prevalence rate of current adult ADHD is estimated to be 4.4% (Kessler et al., 2006). Adults with ADHD have an approximately twofold higher lifetime risk of developing a substance use disorder (SUD) compared to adults without ADHD (Biederman et al., 1993). Individuals with ADHD may use substances for a variety of reasons, including impulsivity, impaired social and occupational functioning, and self-medication (Sullivan & Rudnik-Levin, 2001). ADHD has been shown to predict earlier age of onset of SUDs (Wilens, Biederman, Mick, Faraone, & Spencer, 1997). Also, individuals with ADHD have been noted to have a shorter transition time from drug abuse to drug dependence, a longer duration of SUD, and a slower rate of remission (Biederman, Wilens, Mick, Faraone, & Spencer, 1998; Wilens, Biederman, & Mick, 1998). Treatment seeking cocaine abusers with comorbid ADHD have been shown to have a more chronic course of addiction and a higher relapse rate following treatment than cocaine abusers without ADHD (Carroll & Rounsaville, 1995). Methylphenidate and amphetamines are considered to be among the first line of treatment for ADHD in children

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(Greenhill et al., 2002). Although treating children and adolescents with stimulants does not appear to increase the risk of SUDs (Wilens et al., 2008), little is known about the abuse of prescription stimulants in adults with ADHD. An analysis of data from the National Survey on Drug Use and Health reported that 1.3% of adults aged between 18 and 25 years and 0.9% of adults aged 26 years or older reported nonmedical use of stimulants indicated for the treatment of ADHD (Kroutil et al., 2006). Significant concern regarding stimulant misuse exists; therefore, regulatory mandates are enforced to control distribution, and some physicians may be reluctant to use stimulants in patients with drug abuse histories. A transdermal formulation of methylphenidate was approved in 2006 by the Food and Drug Administration for the treatment of ADHD in children. Because the transdermal formulation may increase compliance when minimizing abuse potential, it may be an attractive treatment option in the large population of individuals who have a history of previous drug use. The primary aim of this study is to assess the efficacy of methylphenidate transdermal system (MTS) in adults diagnosed with ADHD who have misused stimulants in the past. It was hypothesized that MTS would improve ADHD symptoms in this population with minimal substance abuse.

Method

The study was an 8-week, open-label trial of MTS (up to 3.3 mg/hr) in individuals with ADHD and a history of stimulant misuse, abuse, or dependence. Participants were primarily recruited through newspaper advertisements and flyers. All procedures were conducted in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki and received approval from the Medical University of South Carolina Institutional Review Board. All participants gave written, informed consent before study participation. The study was conducted between May 2007 and December 2008.

To be eligible for participation, participants had to be between 18 and 65 years of age and meet *Diagnostic and Statistical Manual of Mental Disorders* (4th ed; DSM-IV; criteria for ADHD. Participants also had to meet criteria for past stimulant abuse or dependence (with a minimum of 3 months since meeting *DSM-IV* criteria) or have a history of repeated stimulant misuse (defined as using someone else's stimulant ADHD medication for a minimum of 4 times in a 1-month period, and this misuse must have occurred for at least 3 months). Exclusion criteria included current dependence on any other substance (with the exception of caffeine or nicotine), history of psychotic disorder, current major depression or eating disorder, current treatment with a psychoactive medication, major medical illnesses, having a body mass index (BMI) greater than or equal to 30, and pregnancy, nursing, or inadequate birth control. All potential participants received a medical history and an evaluation for medical exclusions. The medical workup included a routine physical exam, blood chemistries, electrocardiogram, pregnancy test as indicated, and urine drug screen.

The Structured Clinical Interview for *DSM-IV* (SCIDIV; First, Spitzer, Gibbon, & Williams, 1994) was used to assess for psychiatric exclusions, and the Mini Mental Status Exam (Folstein, Folstein, & McHugh, 1975) was administered to assess absence of cognitive impairment. The Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID; Conners, Erhardt, & Sparrow, 1999) was used to determine ADHD diagnosis. ADHD symptom ratings were also obtained from someone who knew the participant well, such as a spouse or partner, parent, sibling, or close friend, through completion of the Conners' Adult ADHD Rating Scale-Observer (CAARS-O; Conners et al., 1999). The *DSM-IV* criteria were amended such that the criterion for age of onset was set at 12 rather than 7 years of age. This adjustment was made on the basis of the fact that no evidence exists to show that the *DSM-IV* criterion of age 7 years distinguishes valid from invalid cases (Barkley & Biederman, 1997). Also, the *DSM-IV* field trial found that the use of this criterion diminished the

reliability of clinical diagnosis (Applegate et al., 1997). Substance use for the 90 days before study entry was estimated using the Time-Line Follow-Back (TLFB; Sobell & Sobell, 1978), and TLFB data were collected weekly throughout the study. The Clinical Global Impression of Severity and Improvement Scales (CGI-I and CGI-S; Guy, 1976) to rate ADHD symptoms were assessed weekly. The Wender-Reimherr Adult ADHD Scale (WRAADS; Wender, Reimherr, Wood, & Ward, 1985) was administered at baseline and Weeks 1, 2, 4, 6, and 8. Qualitative urine drug screens (detecting presence of methamphetamine, cocaine, marijuana, benzodiazepines and opioids) were performed at baseline and at each weekly visit.

Medication was provided by the manufacturer of transdermal methylphenidate (Shire Pharmaceuticals). Medication dosage was started at 1.1 mg/hr methylphenidate daily, for a cumulative dose of approximately 10-mg methylphenidate over the 9-hour wear period. Participants were counseled to place the patch on alternate hips daily. The dose was increased to 1.6 mg/hr daily during the second week, and to 2.2 mg/hr during the third week based on tolerability and response. During the fourth week, the dose could be increased to 3.3 mg/hr daily; however, none of the participant required this dose. Medication side effects were evaluated weekly using a standard medication side effects checklist; pulse and blood pressure were also assessed at each weekly visit. Compliance was assessed by a patient completed diary and returned patch count. Participants received nominal monetary reimbursement for completion of study assessments.

Statistical Considerations

Primary hypothesis and endpoints—The primary hypothesis was that MTS would lead to improvement in ADHD symptoms with no increase in illicit stimulant use or stimulant medication misuse. The primary efficacy endpoint was the WRAADS scale measured longitudinally over the course of 8 weeks. Secondary efficacy endpoints included the CGI ratings and substance abuse as quantified by urine drug screens and self-reported use. This study was designed as a pilot study; therefore, no formal power calculations were performed.

Analytical methods—To test the primary hypothesis, a linear growth curve, a special case of a mixed-effects regression model, was fit to the longitudinal WRAADS measurements (Singer, 1998). Candidate regression models examined the longitudinal trajectories of Study Week I through Week 8, with a covariate adjustment for baseline (Study Week 0) and simpler models that allowed the linear trajectory to be estimated over all assessments of the WRAADS, namely, Study Weeks 0 through 8. A combination of graphical displays, residual analysis, and Akaike's Information Criterion suggested that the latter model with a random intercept fit the data best. Accordingly, the primary efficacy results were derived from this model. A similar set of models were fit for the longitudinal assessments of the CGI-S. The final CGI-S model consisted of random effects for the slope and intercept using all CGI-S ratings over Study Weeks 0 through 8. For both models, the primary regression parameters of interest were the estimated regression coefficients for study week; these values quantified the amount of decline in ADHD symptoms over each study week, with study week taking on the integer values 0 to 8.

Secondary analyses of ADHD symptoms were conducted using change from baseline measures, with last observation carried forward if the participant failed to complete the study. Safety data were summarized using frequencies and percentages. All analyses were conducted using the SAS System (v9.2, Cary, NC); *p* values less than .05 were taken as statistically significant, and no correction for multiple testing has been applied to the reported *p* values.

Results

Table 1 presents the demographic and baseline summary of the 4 participants who received at least one dose of methylphenidate. All participants were White, and the majority (8/14) was women. The median age at enrollment was 28.5 years (interquartile range: 22-44 years). Most (12/14) of the sample had obtained at least high school degree when consented. Time since last stimulant use by participants ranged from 3 months to 35 years (mean 7.1 ± 11.5 years). As noted in the Method section, current abuse or dependence on substances other than caffeine or nicotine was not permitted; 2 participants met criteria for past alcohol dependence, 1 participant met criteria for past alcohol abuse, and 1 participant met criteria for past marijuana dependence. Half of the participants had a CGI-S rating of “Moderate Symptoms” at baseline; the remaining half had ratings of “marked symptoms” (11 = 4) or “severe symptoms” (11 = 3). The mean (*SD*) WRAADS score was 28.6 (4.6) at baseline.

ADHD Symptomatology

Table 2 presents the summary of ADHD symptomatology. Across all four measures of efficacy, ADHD symptomatology was found to decrease over the duration of the study in support of the primary hypothesis. In particular, the longitudinal growth curve fitted for the WRAADS total score with a random intercept estimated the WRAADS total score decreased 2.14 units every week ($P = -2.14, p < .001$). This model fit the data better than a more complex model that allowed for random slopes and intercepts, and the slope estimates of the two models were essentially identical (final model: - 2.1395, random slopes and intercepts model: -2.1265). The mean (*SD*) change from baseline in the WRAADS total score was - 17.93 (5.89), and this change was statistically different from 0 ($p < .001$).

When modeling the longitudinal CGI-S scores, the more complex random slopes and intercepts model was supported by the data. The CGI-S scores were estimated to decrease -0.24 units per study week ($\sim -0.24, p < .0001$) or approximately 2 units over the duration of the 8 week study. This estimate was supported by the change from baseline calculation on the CGI-S. In particular, the median change from baseline using last observation carried forward (LOCF) was - 2.0 units: $p < .0001$, range -4-0, $M(SD) = -1.7 (1.1)$. Likewise, the median final CGI-1 rating for this sample was “much improved,” and all but 1 participant (out of 14) improved on the study according to the CGI-1 rating.

Substance Abuse

Participants submitted between 4 and 9 ($M = 7.6, SD = 1.8$) urine drug screens over the course of the study including baseline. All submitted urines (107/107) were negative for stimulants, but 1 participant self-reported use of oral stimulants at Week 6 in the study. This was the only indication of stimulant use in the study. There were, however, positive (nonstimulant) urine drug screens observed during the study. A total of 4 participants (29%) tested positive for other substances including marijuana (3/14), opioids (1/14), and benzodiazepines (1/14). One participant contributed both the positive opioid screen (at Study Week 2) and the benzodiazepine screen (at Study Week 4).

Safety Summary

The mean (*SD*) final dose received by participants was 1.82 (0.36) mg/hr. The range of doses was from 1.1 mg/hr (11 = 1) to 2.2 mg/hr (11 = 6), with the remaining 7 participants receiving a dose of 1.6 mg/hr. The mean (*SD*) wear time reported by medication diary was 9.05 (1.43) hours per day.

The most frequent adverse events were associated with localized skin reactions at the site of patch application (Table 3). A total of 8 (57%) participants reported mild-to moderate

localized irritation, pruritis, or rash at some point in the study. One participant was removed from the study due to the severe localized skin irritation; symptoms resolved after discontinuation of the medication. No generalized skin reactions were noted. One participant with a history of major depression was removed from the study due to the reemergence of depression symptoms; therefore, the participant was referred to appropriate treatment. Point estimates on delta scores for changes in systolic blood pressure, diastolic blood pressure, and pulse were small (1.1, 0.7, and 2.6, respectively) and were not considered clinically significant.

Discussion

As hypothesized, improvements in ADHD symptomatology were found with MTS treatment. Although transdermal methylphenidate has not been widely studied for the treatment of adult ADHD, other formulations of methylphenidate have been shown to be effective in treating adult patients. Of note, no misuse of study medication was observed. In contrast, a recent report on predictors of medication diversion and misuse in adult patients prescribed methylphenidate found significant rates of diversion and inappropriate use, particularly among individuals with comorbid SUDs (Darredeau, Barrett, Jardin, & Pihl, 2007). Absence of misuse in the present investigation may have been attributable to the short duration of the study (8 weeks). Furthermore, Darredeau and colleagues (2007) were assessing individuals receiving oral methylphenidate therapy; therefore, it is not known whether similar diversion or misuse rates would be observed with use of the transdermal formulation.

It has been postulated that methylphenidate may have less potential for abuse in patients diagnosed with ADHD than in non-ADHD-diagnosed individuals (Kollins, 2003). A review of the literature on the abuse potential of methylphenidate in animals and humans found that methylphenidate produced reinforcing, discriminative-stimulus, and subjective effects similar to amphetamines or cocaine (Kollins, MacDonald, & Rush, 2001). However, the majority of the studies supporting the abuse potential of methylphenidate did not include individuals with ADHD. Choice preference paradigms conducted in ADHD-diagnosed patients have found that methylphenidate is reliably chosen over placebo in a dose-dependent manner; however, these reports also found a lack of subjective effects that would be indicative of abuse liability (Fredericks & Kollins, 2004; MacDonald Fredericks & Kollins, 2005).

Little research has been conducted assessing the use of stimulants in individuals with histories of drug abuse and ADHD, although some limited data are available regarding the use of methylphenidate in current stimulant users. A laboratory study evaluating response to cocaine alone and in combination with methylphenidate in cocaine abusers with ADHD found that maintenance on methylphenidate decreased some of the positive and reinforcing effects of cocaine (Collins, Levin, Foltin, Kleber, & Evans, 2006). However, placebo-controlled trials evaluating the efficacy of oral methylphenidate treatment in adults with current cocaine dependence and ADHD have had mixed results in regards to improvement in ADHD symptoms and minimal to no effect on cocaine use outcomes (Levin, Evans, Brooks, & Garawi, 2007; Schubiner et al., 2002).

Interpretation of the current study results is limited by the small sample used and the open-label design, and the preliminary nature of this trial precludes the ability to make treatment recommendations based on its results. It would be important to replicate the findings in a larger controlled trial. Also, as stated previously, a longer follow-up period may be necessary to fully assess potential misuse of this form of methylphenidate in former

stimulant users with ADHD. Further research is needed to determine the role MTS fully may have in the treatment of this population.

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Table I
Demographics of Study Participants

	<i>N</i>	<i>%</i>
Sex		
Male	6	42.9
Race		
White	14	100.0
Education		
Did not graduate high school	2	14.3
High school graduate or some college	6	42.9
College graduate	5	35.7
Graduate studies	1	7.1
Past stimulant use criteria/pattern		
Misuse	6	42.9
Abuse	2	14.3
Dependence	6	42.9
Simulant used/misused		
Powder cocaine	5	35.7
Oral prescription stimulant	7	50.0
Oral non-prescription stimulant	2	14.3
	<i>M</i>	<i>SD</i>
Age	33.9	13.2
ADHD symptoms at baseline		
WRAADS total score	28.6	4.6
CAARS total score	44.0	12.9
CGI-S	3.6	1.0
General measures		
HAM-D	4.0	2.3
HAM-A	87	4.4

WRAADS = Wender-Reimherr AdultADHD Scale; CGI-S = Clinical Global impression for Severity; CAARS = Conners' AdultADHD Rating Scale; HAM-D = Hamilton Depression Scale; HAM-A = Hamilton Anxiety Scale (HAM-A).

Table 2
Summary of ADHD Outcome Measures

	Statistical summary	<i>p</i> value
WRAADS total score		
Unit change per study week		
β	-2.M	<.001
SE	0.27	
Change from baseline, LOCF		
<i>M</i>	-17.93	<.001
<i>SD</i>	5.89	
CGI-Severity		
Unit change per study week		
β	-0.24	<.001
SE	0.04	
Change from baseline, LOCF		
<i>M</i>	-1.71	<.001
<i>SD</i>	1.14	

WRAADS = Wender-Reimherr Adult ADHD Scale; CGI = Clinical Global Impression; LOCF = last observation carried forward.

Table 3**Summary of Adverse Events**

	Frequency	
	Reported	Participants (%)
Adverse event		
Dry mouth	2	2 (14.3)
Feeling dehydrated	1	1 (7.1)
Feeling depressed	1	1 (7.1)
Headache	5	4 (28.6)
Hot flash	1	1 (7.1)
Hyperactivity	1	1 (7.1)
Insomnia	1	1 (7.1)
Mouth sores	1	1 (7.1)
Muscle cramps	1	1 (7.1)
Paresthesia	2	1 (7.1)
Sinus/col d/allergies	1	1 (7.1)
Skin reaction	9	8 (57.1)
Other	2	1 (7.1)