A Controlled Trial of the Methylphenidate Transdermal System on Before-School Functioning in Children With Attention-Deficit/Hyperactivity Disorder

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Objective: Children with attention-deficit/hyperactivity disorder (ADHD) frequently manifest behavioral difficulties in the morning prior to school. Our aim was to examine the effects of the methylphenidate transdermal system (MTS) on before-school ADHD symptoms and functioning in children with ADHD.

Method: In this randomized crossover study, conducted from May 2007 until December 2008, 6- to 12-year-old subjects with *DSM-IV*–defined ADHD received either MTS or a placebo transdermal system (PTS) at 10 mg for 1 week and then 20 mg for 1 week. Subjects were then crossed over directly to the other treatment for the remaining 2 weeks. The primary efficacy measure was the ADHD Rating Scale. All analyses were intent to treat, with the last observation carried forward.

Results: Thirty subjects completed at least 1 week of treatment, and 26 subjects completed the entire protocol. The sample was primarily male, with a mean ± SD age of 9.17 ± 1.84 years. Compared to PTS, there were significant reductions with MTS in the ADHD Rating Scale score ($P < .001$). Adverse effects of MTS during the active (versus PTS) phase were similar to those seen in other controlled trials of MTS.

Conclusions: These results show that MTS is effective not only for morning ADHD symptoms, but also in improving associated activities and functioning that occur before school in children with ADHD.

Trial Registration: clinicaltrials.gov Identifier: NCT00586157

J Clin Psychiatry 2010;71(5):548–556

Submitted: *October 16, 2009; accepted February 1, 2010 (doi:10.4088/JCP.09m05779pur).*
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Attention-deficit/hyperactivity disorder (ADHD) is a common neurobehavioral disorder that affects an estimated 4 million children aged 3 to 17 years in the United States.[1] ADHD is characterized by developmentally inappropriate symptoms of inattention, hyperactivity, and impulsivity.[2] Clinically, many of the home-based difficulties for children with ADHD occur during the before-school time.[3] Deficits are observed during tasks of early-morning organization, self care, and preparing for the school day, as well as transportation to school.[4]

Despite an extensive literature on stimulants in school-age youth,[5,6] there is a paucity of literature on the naturalistic effects of stimulants and nonstimulants on before-school activities.[4,7–9]

Analog (laboratory) classroom studies have been very helpful in demonstrating the time course of treatment effects of stimulants on ADHD symptoms and productivity, generally showing effects by 1 to 2 hours after administration.[10,11] These studies however, do not routinely capture the naturalistic functioning of children prior to school.[3] Whalen et al,[3] for instance, using novel electronic diaries of maternal and child self report, showed in stimulant-treated children a number of important differences of before- and after-school ADHD symptoms, as well as differences in behaviors and negative mood states relative to non-ADHD controls.

Other studies involving atomoxetine have also shown improvement in morning ADHD symptoms. Whalen et al[12] also showed with electronic diaries that children taking atomoxetine received less negative ratings on morning inattention and hyperactivity/impulsivity than did those in the stimulant group. Their mothers reported higher levels of parent efficacy and satisfaction. Further, Wehmeier et al[13] showed in 2 open-label studies that behavior and ADHD-related difficulties in the morning and evening improved with daily atomoxetine. Given that the before-school time represents an important 2 to 3 hours, or 20% of the day, for children with ADHD and their families, studies capturing treatment efficacy naturalistically in this period of time will shed important light on both the nature of the dysfunction as well as potential treatment.

One delivery system that may provide a therapeutic option for treating before-school dysfunction in children with ADHD is the methylphenidate transdermal system (MTS). Transdermal delivery of methylphenidate is an option for children with ADHD who have difficulty tolerating or swallowing oral medications, or who would benefit from tailoring the duration of effect.[14,15] The efficacy of MTS at doses of 10 to 30 mg at a wear time of 9 hours has been demonstrated in multiple randomized, double-blind, placebo-controlled studies of children with ADHD.[11,14–17] In laboratory studies using MTS, improvement in ADHD symptoms and performance was demonstrated by the first time point of 2 hours after administration[11,15] and persisted between 2 and 4 hours after patch removal[15]; however, nothing is known about the naturalistic effect of this agent on before-school functioning. For instance, it remains to be seen if very early application of methylphenidate (eg, 6 AM) will assist in the early morning/before-school symptoms and associated impairment of ADHD or if such administration will be related to a different set of adverse events.

Given the well-documented efficacy of methylphenidate in ADHD,[5,6] we undertook a study to examine more specifically before-school efficacy and tolerability of transdermal methylphenidate for ADHD symptoms and related dysfunction. Based on the literature,[11,15] we hypothesized that MTS compared to a placebo transdermal system (PTS) would be associated with improved overall ADHD symptoms. Secondarily, we hypothesized that MTS would be associated with improvement in early morning ADHD symptoms, improvement in before-school functioning, and improvement in interactive behaviors with parents both clinically and statistically, compared to placebo. We also hypothesized that very early MTS administration would be associated with adverse events similar to those seen in other controlled trials of methylphenidate.

METHOD

Subjects

Eligible subjects, aged 6 to 12 years, had a diagnosis of ADHD by a clinical interview supplemented by a structured psychiatric interview. Excluded from the study were potential subjects with a medical condition, or treatment of a medical condition, that would either jeopardize subject safety or affect the scientific merit of the study. Also excluded from the study were potential subjects who had moderate to severe dermatologic atopy, were pregnant or nursing, or had identified structural cardiac abnormalities, mental retardation (IQ < 70), organic brain disorders, or seizure disorders. Likewise, youth with a history of psychosis or bipolar disorder and youth with current clinically significant comorbid psychopathology such as anxiety disorders, major depressive disorder, or Tourette's syndrome were not enrolled. Due to the age limits of this study, the diagnoses of substance use, abuse, and dependence were not a part of the exclusion criteria. Subjects with a history of no response or intolerable adverse effects to methylphenidate were excluded for ethical reasons. From November 2006 through November 2008, subjects were recruited from advertisements in local and regional media as well as from clinical referrals, including new and existing patients, from the outpatient psychiatric clinic. The Partners Human Research Committee approved the study. Parents of subjects completed an informed consent statement, and all subjects 7 and older gave assent prior to study entry.

Clinical Trial

This study was a randomized, controlled, 4-week crossover study. After being screened for ADHD, youth underwent a comprehensive clinical interview, supplemented by a structured psychiatric assessment. Eligible ADHD youth were washed out for a minimum of 1 week from their previous treatment (if applicable) before they started the medication protocol.

Subjects were randomly assigned to either MTS or PTS. Subjects began the trial by receiving either MTS or PTS at 10 mg for week 1 and then received 20 mg for week 2. Subjects were then crossed over directly to the other treatment for the remaining 2 weeks, again initiated at 10 mg for week 1 and 20 mg for week 2. There was no washout period before the subjects crossed over to the corresponding treatment.

Dosing. All prescriptions were filled at the Massachusetts General Hospital (MGH) Pharmacy. The MTS and the PTS were both provided by Shire Pharmaceuticals. The 10-mg patch provided a delivered dose of 10 mg over 9 hours (12.5 cm^2; 1.1 mg/h delivery rate). The 20-mg patch provided a delivered dose of 20 mg over 9 hours (25 cm^2; 2.2 mg/h delivery rate).[18] Subjects' parents were instructed on how to apply the patch and to alternate left and right hip placement each day. Parents were instructed to apply the patch to their child's hip between 6 and 7 AM and remove the patch between 3 and 4 PM every day. Diary data showed that families applied the patch between 6 and 7 AM 79% of the time. Medical compliance was assessed by counting both used and unused patches at each follow-up visit and was > 80% for all subjects.

Assessments

At screening/baseline and each week thereafter, all subjects had efficacy measures (eg, ADHD) and safety measures assessed. On average, each patient was assessed by the same clinician rater throughout the course of the study. All diagnostic assessments were made using the *DSM-IV*–based structured interviews by blinded raters with bachelor's or master's degrees in psychology who had been extensively trained and supervised by senior investigators. Psychiatric assessments relied on the *DSM-IV* Kiddie Schedule for Affective Disorders-Epidemiologic Version (KSADS-E)[19] and were based on independent interviews with the primary caregivers. No direct interviews were given to the children.

For every diagnosis, information was gathered regarding the ages at onset and offset of full syndromatic criteria and treatment history.

To assess the reliability of our diagnostic procedures, we computed κ coefficients of agreement by having 3 experienced, blinded, board-certified child and adult psychiatrists listen to audiotaped interviews of assessment staff administering the structured diagnostic interview to the subjects. While listening, the psychiatrists conducted their own assessment of the subject. The κ coefficient was than calculated to measure the diagnostic interrater reliability between the assessment staff and the psychiatrist. Thus, both raters had access to the same information to calculate their diagnosis for each subject. Based on 500 assessments from interviews of children and adults, the median κ coefficient was 0.98. Kappa coefficients for individual diagnoses included major depressive disorder, 1.0; mania, 0.95; ADHD, 0.88; conduct disorder, 1.0; oppositional defiant disorder, 0.90; antisocial personality disorder, 0.80; and substance use disorder, 1.0.

ADHD Rating Scale. Our primary outcome was the ADHD Rating Scale (ADHD-RS).[20] Physicians assessed each of the individual symptoms of ADHD in *DSM-IV* (0–3 on a scale of severity) across the day (total score ranged from 0–54).[21] Psychometric properties have been established in children, and the scale has been shown to be sensitive to stimulant drug effects.[20,22] The time frame of the ADHD-RS was the past week. In an exploratory manner, after capturing the primary outcome, we examined more specifically morning ADHD symptoms, using the ADHD-RS to assess symptoms for the time period of 6 AM to 9 AM only (ADHD-AM-RS).

Before-School Functioning Questionnaire. A secondary outcome was a before-school functioning questionnaire that was created by Drs Timothy E. Wilens and Paul Hammerness (available from the authors on request). This new clinician-rated and -completed 20-item questionnaire, generated from commonly reported areas of dysfunction in early morning activities associated with ADHD, assesses ADHD symptomatology and functioning on a severity scale of 0 to 3 (Likert scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe). It focuses primarily on early morning, before-school activities (breakfast, hygiene, time awareness, getting to school, etc). Before answering, parents were asked questions regarding the 6 AM to 9 AM period only.

The questionnaire also includes a self-report section that is completed collaboratively by the child and the parent and/or guardian. The self-report section assesses how the child felt, his/her relationship with parents and siblings, his/her success with morning activities or problems, and whether the child was proud of him/herself over the past week from 6 AM to 9 AM. The self-report questions range from 0 = no to 2 = a lot.

Conners' Global Index-Parent Version. We also assessed the Conners' Global Index-Parent Version: a brief, 10-item parent-rated questionnaire for children aged 5 to 18 that assesses activities on a scale from 0 = not true at all, to 3 = very much true.[23] The questionnaire is scaled into 2 categories: restless/impulsive and emotional lability. The questionnaire also has a scaled total score. When parents completed this index, they were blinded to the medication (or placebo) their child was taking and were asked to report answers based on the morning time period, but not specifically 6 AM to 9 AM.

Clinical Global Impressions-Improvement scale. We also collected ratings from the physician-rated Clinical Global Impressions scale,[24] a widely used scale to measure the overall severity and improvement. We used the subscale Global Improvement (1 = very much improved to 7 = very much worse). The treating physician completed this scale. Per the direction of the scale, to maintain its reliability and validity, information was collected about the entire day.

Behavioral Rating Inventory of Executive Functioning. The Behavioral Rating Inventory of Executive Functioning (BRIEF) was another outcome, and the subject's parents completed the parent form. The BRIEF has been to shown to be a reliable and valid behavior rating scale of executive functioning in children and adolescents, with a high internal consistency (Cronbach α: range = 0.80–0.98), a moderate interrater reliability, and a high test-retest reliability correlation coefficient (range = 0.72–0.85).[25–28] The BRIEF is an 86-item questionnaire for parents and teachers of children that assesses the everyday behavioral expressions of executive functions. Per the direction of the form, to maintain its reliability and validity, information was collected about the entire day.

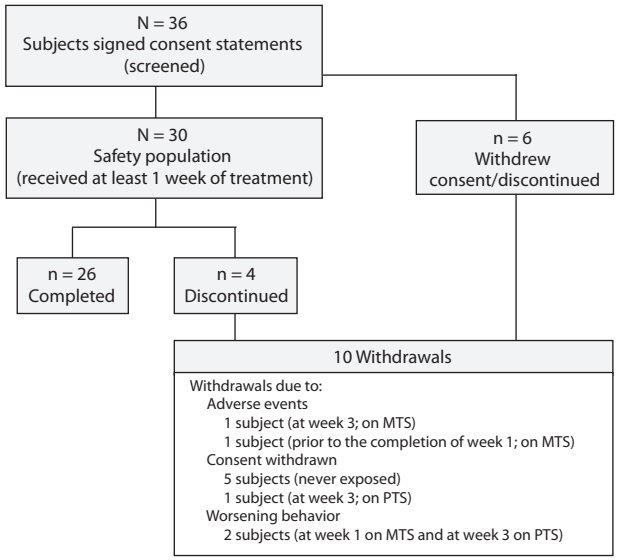
The *DSM-IV* Global Assessment of Functioning (GAF) scale was also collected at each weekly visit. The GAF scale is a composite rating of an individual's overall level of psychological, social, and occupational functioning (1 = worst to 100 = best).

Safety. Adverse events and vital signs were assessed at each clinic visit. Adverse events were assessed through the evaluation of spontaneously reported, treatment-emergent adverse effects. Additionally, all subjects had an electrocardiogram (ECG) at baseline and at the end of study.

Data Analysis

To examine the before-school efficacy and tolerability of MTS, we included in our analysis all subjects who completed at least 1 week of the treatment (N = 30). For these 30 subjects, all analyses were intent to treat with last observation carried forward. Because we used a crossover design to test the effects of MTS on early morning activities, we first needed to determine if there was an ordering effect. To test this, we estimated our main outcome, the ADHD-RS, as a function of time, drug, the time-by-drug interaction, and the time-by-drug-by-order interaction using generalized estimating equations with an independent correlation structure and a log transformation due to departures from normality in the dependent variables.

Figure 1. Subject Disposition



Abbreviations: MTS = methylphenidate transdermal system, PTS = placebo transdermal system.

Table 1. Demographic Characteristics of Sample (N = 30)

	Value[a]
Age, mean (SD), y	9.17 (1.84)
GAF score, mean (SD)	54.43 (1.91)
Sex	
Male	25 (83)
Female	5 (17)
Race	
Asian American	1 (3.33)
White	27 (90)
More than 1	1 (3.33)
Unknown	1 (3.33)
Previous treatment	16 (53)
ADHD subtype[b]	
Combined type	16 (53)
Inattentive type	13 (43)
Hyperactive/impulsive type	1 (3)
Lifetime comorbidity	
Disruptive disorders	
Oppositional defiant disorder	21 (70)
Conduct disorder	2 (7)
Mood disorders	
Major depressive disorder	1 (3)
Anxiety disorders	
Panic disorder	0 (0)
Agoraphobia	5 (17)
Social phobia	3 (10)
Obsessive-compulsive disorder	1 (3)
Generalized anxiety disorder	2 (7)
Separation anxiety disorder	9 (30)
Substance use disorders	0 (0)

[a]N (%) unless otherwise noted.
[b]Subtype was calculated using the *DSM-IV* Kiddie Schedule for Affective Disorders-Epidemiologic Version. A subject must have met 6 of the 9 criteria for the respective subtype. If the subject met 6 of the 9 criteria for both subtypes, then the subject was considered to have the combined subtype.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, GAF = Global Assessment of Functioning.

If the time-by-drug-by-order interaction term was significant, we estimated the effect of MTS on each outcome within strata of drug order. If the interaction term was not significant, we collapsed across order status and estimated the effect of MTS on each outcome (ADHD-RS, Before-School Functioning Questionnaire, Conners' Global Index-Parent Version, the BRIEF, and vital signs). A significant time-by-drug interaction term would indicate a change in the MTS group over time, beyond any change in the PTS group. Because we are analyzing multiple measurements per subject, the assumption that each observation is independent of all other observations is violated in these data. To account for the fact that all subjects received both forms of treatment, we used robust estimates of variance so that *P* values would not be underestimated. The Pearson χ^2 test was used to examine the differences in percent improvement (Clinical Global Impressions-Improvement) between the PTS and MTS groups. We also used the McNemar test to assess differences in the number of adverse events between the treatment groups. An α level of .05 was used to assert statistical significance; all statistical tests were 2-tailed. Data are presented as mean ± SD unless otherwise stated. We calculated all statistics using STATA 10.0 (StataCorp LP, College Station, Texas).

RESULTS

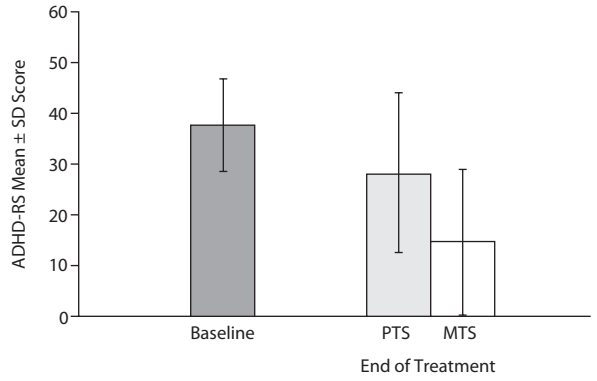
In all, 36 subjects were screened and signed consent forms (Figure 1), while only 30 subjects completed at least 1 week of treatment and were eligible for analyses. Of these 30 subjects, 26 subjects completed the entire protocol; 1 subject receiving PTS withdrew consent at week 3; 1 subject receiving MTS dropped out at week 3 due to low appetite and insomnia (adverse event); and 2 subjects, 1 receiving MTS and 1 receiving PTS, dropped out at weeks 1 and 3, respectively, due to worsening behavior. Demographic features of the sample (N = 30) are presented in Table 1. Subjects were predominantly white males with the combined subtype of ADHD. More than half of subjects (53%) had previous medication exposure, and oppositional defiant disorder was the most common lifetime comorbidity (70%). The mean age was 9.17 ± 1.84 years, and the average past GAF score was 54.43 ± 1.91.

The coefficient examining the interaction between the order of treatment and the ADHD-RS was not significant ($z = 0.67$, $P = .56$). Thus, we removed the time-by-drug-by-order interaction term and estimated the time, drug, and time-by-drug interaction for all outcomes.

ADHD Rating Scale

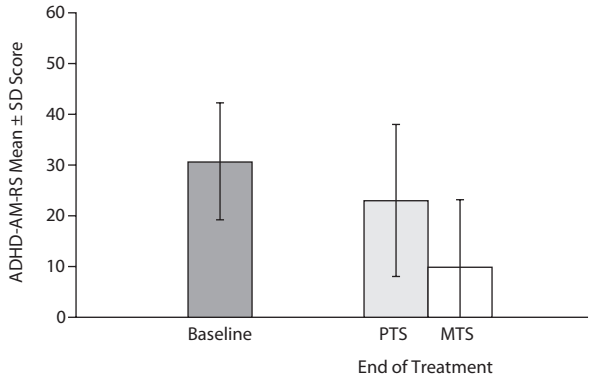
We examined the individual symptoms of ADHD using our primary outcome, the ADHD-RS (Figures 2 and 3). We found a clinically and statistically significant time-by-drug interaction effect for the overall ADHD-RS (baseline:

Figure 2. ADHD-RS Mean Scores (N = 30)[a]



[a]Baseline: 37.80 ± 9.08, versus end of treatment: PTS, 28.33 ± 15.75; MTS, 14.76 ± 14.48; $z = -3.67$, $p < .001$.
Abbreviations: ADHD-RS = ADHD Rating Scale, MTS = methylphenidate transdermal system, PTS = placebo transdermal system.

Figure 3. ADHD-AM-RS Mean Scores (N = 30)[a]



[a]Baseline: 30.83 ± 11.53, versus end of treatment: PTS, 23.22 ± 14.91; MTS, 10.03 ± 13.18; $z = -2.94$, $p = .003$.
Abbreviations: ADHD-AM-RS = ADHD Rating Scale assessing symptoms from 6 AM to 9 AM, MTS = methylphenidate transdermal system, PTS = placebo transdermal system.

Table 2. Individual Functioning Scores on the Before-School Functioning Questionnaire at Baseline and at the End of Treatment of the Placebo Transdermal System (PTS) and Methylphenidate Transdermal System (MTS) (N = 30)

Did Your Child Have Difficulty With?[a]	Baseline, Mean ± SD	End of Treatment, Mean ± SD	
		PTS	MTS
Listening (to parents, other caregivers, siblings)	2.43 (0.77)	1.81 (1.21)	0.62 (1.05)**
Following directions (coming to breakfast, getting dressed, picking up necessary things)	2.67 (0.66)	2.07 (1.14)	0.83 (1.10)**
Overall organization (morning routines, getting things together, time awareness)	2.70 (0.70)	2.15 (1.06)	1.03 (1.12)**
Dressing (putting on shirts, blouse, pants, shoes, coats)	1.90 (1.06)	1.52 (1.16)	0.59 (0.82)*
Attention (focusing on morning routines or activities)	2.57 (0.73)	2.00 (1.14)	0.76 (1.06)**
Being quiet (loud, cannot occupy self unless with TV/electronics)	1.37 (1.25)	0.89 (1.09)	0.31 (0.81)
Distraction (easily off task, distracted by objects, noise, others)	2.60 (0.67)	2.07 (1.11)	0.79 (1.05)**
Procrastination (waiting until last moment to complete morning tasks)	2.43 (0.94)	1.81 (1.14)	0.83 (1.17)**
Forgetfulness (memory for specific things; gym clothes, instrument, equipment)	2.30 (0.79)	1.81 (1.27)	0.79 (1.11)**
Misplacing/losing items (bookbag, lunch tickets, school work/projects)	2.40 (0.67)	1.63 (1.28)	0.76 (1.06)*
Hyperactivity (excessive motor activity, running around in morning)	1.07 (1.23)	0.85 (1.13)	0.21 (0.56)*
Talkativeness (talking excessively)	1.13 (1.22)	1.19 (1.14)	0.48 (0.87)**
Interrupt/blurt out (interrupting/intruding, blurting out before question completed)	1.60 (1.10)	1.44 (1.22)	0.38 (0.82)**
Silliness (goofiness, silliness, joking around)	1.17 (1.15)	0.70 (0.82)	0.24 (0.58)**
Awaiting turn (at breakfast, in line for bus or ride, bathroom time)	1.20 (1.25)	0.96 (1.16)	0.31 (0.76)
Breakfast (not sitting down to eat, distracted while eating)	1.90 (1.03)	1.37 (1.11)	0.48 (0.74)**
Hygiene (washing, combing hair, brushing teeth)	2.23 (0.86)	1.89 (1.05)	0.66 (0.97)**
Independence (ability to perform tasks by him/herself)	2.47 (0.90)	2.00 (1.07)	0.93 (1.03)**
Time awareness (not using time correctly, taking too long)	2.57 (0.82)	2.00 (1.11)	1.03 (1.15)*
Getting to school (missing bus, disruptive car/bus ride, walking to school, tardy)	1.80 (0.89)	1.19 (1.04)	0.66 (1.14)
Total	40.50 (11.64)	31.37 (17.79)	12.76 (16.65)**

[a]0 = none, 1 = mild, 2 = moderate, 3 = severe.
*$P < .05$.
**$P < .01$.

37.80 ± 9.08, end of treatment: PTS, 28.33 ± 15.75; MTS, 14.76 ± 14.48; $z = -3.67$, $P < .001$; Figure 2). Compared to baseline, during PTS treatment, there was a 25% reduction in subjects' ADHD-RS score, and during MTS treatment, there was a 61% reduction in their ADHD-RS score.

We then examined if there were significant effects for the symptoms of ADHD specifically between 6–9 AM. We found a clinically and statistically significant time-by-drug interaction effect for the ADHD-AM-RS (baseline: 30.83 ± 11.53, end of treatment: PTS, 23.22 ± 14.91; MTS, 10.03 ± 13.18; $z = -2.94$, $P = .003$; Figure 3). Compared to baseline, during PTS treatment, there was a 25% reduction in subjects' ADHD-AM-RS score, and during MTS treatment, there was a 67% reduction in their ADHD-AM-RS score.

We found the ADHD-RS and the ADHD-AM-RS to be highly correlated. At baseline, the correlation coefficient was 0.87, and at the end of the treatment, the correlation coefficient was 0.95 for PTS and for 0.91 for MTS.

Before-School Functioning Questionnaire

We further examined morning activities using an investigator-completed, before-school functioning questionnaire (Table 2). We found a significant time-by-drug interaction effect for the total questionnaire score

(baseline: 40.50 ± 11.64; end of treatment: PTS, 31.37 ± 17.79; MTS, 12.76 ± 16.65; $z = -3.35$, $P = .001$). Compared to baseline, during PTS treatment, there was a 23% reduction in subjects' total score, versus a 69% reduction during MTS treatment. We also found significant interaction effects for 17 of the 20 questions (all P values < .05). The largest differences between the treatments included listening (to parents, other caregivers, sibling), following directions (coming to breakfast, getting dressed, picking up necessary things), attention (focusing on morning routines or activities), distraction (easily off track, distracted by objects, noise, others), and hygiene (washing, combing hair, brushing teeth) (all P values < .01).

In regard to the before-school functioning self-report section of the questionnaire, there were no clinically significant time-by-drug interactions. There was however, a significant interaction effect for one of the questions: "Over the past week, in the morning, I felt happy." Subjects reported that they were significantly happier while receiving MTS than while receiving PTS (baseline: 1.37 ± 0.76; end of treatment: PTS, 1.37 ± 0.74; MTS, 1.25 ± 0.75; $z = -2.49$, $P = .01$).

Conners' Global Index-Parent Version

We also assessed activities using the Conners' Global Index-Parent Version. There were no statistically significant time-by-drug interaction effects for the total score or for each of the subscales: restless/impulsive, emotional/lability (all P values > .05).

Clinical Global Impressions-Improvement Scale

We examined response to treatment using the categorical Clinical Global Impressions-Improvement scale. On the basis of categorical Clinical Global Impressions-Improvement scores, there was a significant difference in the percentage of subjects with much to very much improvement from baseline to the end of treatment when they were receiving MTS compared to placebo (MTS, 83%; PTS, 30%; $\chi^2 = 16.12$, $P \leq .0001$).

BRIEF Subscales

We also examined the effects of MTS using an instrument sensitive to the clinical features of executive function, the BRIEF. There was a significant time-by-drug interaction effect for the BRIEF subscale: initiation (baseline: 69.03 ± 10.19; end of treatment: PTS, 63.71 ± 12.07; MTS, 60.41 ± 12.11; $z = -2.101$, $P = .045$). We did not find significant interaction effects for any of the other BRIEF subscales: inhibition ($P = .56$), shifting ($P = .71$), working memory ($P = .14$), emotional control ($P = .14$), plan/organize ($P = .10$), organization of material ($P = .25$), or monitor ($P = .90$).

Safety/Tolerability

We compared the frequencies of adverse events between the MTS and PTS groups (Table 3). While receiving MTS, subjects experienced a significantly higher number of the most commonly occurring adverse events (decreased appetite, other [including being dizzy or shaky], gastrointestinal problems, and insomnia) compared to when they were receiving PTS (all P values < .05). Also, while receiving MTS, subjects experienced a higher frequency of events of pruritus at application site compared to when they received PTS ($P < .05$).

Table 3. Adverse Events Experienced by Patients Receiving Placebo Transdermal System (PTS) and Methylphenidate Transdermal System (MTS) (N = 30)

Adverse Event	MTS, n (%)	PTS, n (%)	χ^2	P[a]
Loss of appetite	13 (43)	0 (0)	12.25	**< .001**
Other[b]	10 (33)	3 (10)	5.44	**.02**
Gastrointestinal	9 (30)	0 (0)	9.00	**.003**
Insomnia	8 (27)	0 (0)	8.00	**.005**
Headaches	5 (17)	1 (3)	2.67	.10
Irritability	5 (17)	1 (3)	2.67	.10
Pruritus at site	4 (13)	0 (0)	4.00	**.045**
Rhinitis	3 (10)	2 (7)	0.20	.65

[a]Boldface indicates statistical significance.
[b]Including the following: for MTS, feeling sad, shaky, dizzy; increase in tics/tremors; increase in energy; itchy eyes; and infected molluscum; for PTS, feeling weak, shaky, sad; and upper respiratory infection.

Vital signs and electrocardiogram. We compared the MTS and PTS groups on safety parameters measured throughout the study (ie, heart rate, diastolic blood pressure, and systolic blood pressure). There were no clinically or statistically meaningful time-by-drug interaction effects (all P values > .05). There were no clinically significant ECG findings at endpoint for any subject.

DISCUSSION

The results of this controlled, crossover study support our primary hypothesis that transdermal application of methylphenidate very early in the morning has a positive effect on ADHD symptoms throughout the day. Secondarily, results of a questionnaire focused on morning behaviors showed that methylphenidate improved a multitude of before-school behavioral symptoms and functioning. Despite very early administration of the MTS (ie, 6–7 AM), adverse effects that emerged with MTS compared to placebo were similar to previously reported studies. Despite no formal psychometric testing, the Before-School Functioning Questionnaire may have utility in addressing before-school functioning, requiring further testing.

The results of this study are consistent with those of other studies of stimulants in general[5,6] and with MTS in particular.[11,14–17] In studies of stimulants, for instance, improvement in ADHD symptoms and impairment as well as executive functioning has been shown acutely with treatment.[6,29–31] While we collected information naturalistically, results from the current study are similar to those derived from analog classroom studies of MTS in showing improvement not only in ADHD across the day, but also in morning ADHD symptoms.[11,14,15] In laboratory studies using MTS,

improvement in ADHD symptoms and performance (measured by permanent product measure of performance [PERMP]) was demonstrated by the first time point of 2 hours after administration.[11,15–17] For example, McGough et al[11] found significant efficacy for MTS with a 9-hour patch wear-time, from the first postdose time point and continuing through 12 hours.

While the bulk of our findings showed robust effects of MTS versus PTS, the Conners' Global Index-Parent Version did not show improvement; perhaps this was related to the fewer number of items (10) in that instrument in comparison to the others used in this study (ie, Before-School Functioning Questionnaire). It is also possible that we found a significant difference in improvement with the Clinical Global Impressions-Improvement scale (an investigator-completed rating based on parent report), while we did not find a significant result in the Conners' Global Index-Parent Version (parent-rated scale), because the Clinical Global Impressions scale collected information for the entire day and the Conners' Global Index assessed morning functioning in a predefined set of domains. In aggregate, however, transdermal application of methylphenidate around 6 AM resulted in improved ratings of ADHD symptoms in the morning, afternoon, and throughout the day, as well as improved before-school functioning reflective of ADHD (Figure 2).

The current study is unique in that we also included a questionnaire capturing real-life before-school functioning that is referable to ADHD. The investigator-completed section of the questionnaire indicated improvement in all aspects of functioning in the morning compared to placebo (Table 2). For instance, improvements in listening, following direction, attention, and independence were observed in youth receiving active medication compared to placebo. Moreover, the youth self-report section signaled improved mood associated with active treatment. While the current study lacks a group of children without ADHD, the clear differences in scores reflective of before-school functioning in those youth receiving MTS compared to PTS suggest the high level of before-school impairment and subsequent reversal with treatment. The findings from this study suggest the potential utility of instruments such as this Before-School Functioning Questionnaire in naturalistically identifying before-school functioning and the importance of examining before-school dysfunction in ADHD.

Another important finding of the current study was the utility of very early morning administration of the MTS with resultant improvement in ADHD symptoms without problematic adverse effects. Given that many parents report difficulties upon awakening and during early activities in children with ADHD, administration of MTS in the early morning appeared to result in full coverage of ADHD symptoms prior to school onset with resultant improvement in ADHD and before-school functioning. Additionally, adverse effects of MTS during the active (compared to placebo) phase were similar to those ascertained in other controlled trials of MTS.[15,16]

Specifically, there was no increased rate of appetite suppression, anxiety, or edginess in the early morning hours with very early administration. Interestingly, ratings on the Before-School Functioning Questionnaire indicated significant improvement in breakfast-related activities in youth treated with active medication. These findings seem to offer a therapeutic option to parents with children who experience ADHD symptoms and resultant impairment in the morning: allowing parents to administer methylphenidate to their children while still in bed or when arising early without concern of effects such as appetite suppression adversely affecting breakfast.

There were a number of methodological limitations of the current study. We do not have κ coefficient data that are calculated exclusively from this study or from child interviews. The κ coefficients we present may not be accurate, as the reliability may vary by the age of the subject. We conducted only indirect assessments of psychopathology. The lack of direct psychiatric interviews with children younger than 12 may have decreased the sensitivity of some diagnoses, particularly "internalizing" disorders. However, since children younger than 12 have limited expressive and receptive language abilities, there is a question about whether their lifetime history of psychopathology and behavior can be reliably assessed through self report.[32] Although limited, studies of interview techniques for children under the age of 12 suggest that their responses are unreliable.[33] We chose not to control for multiple comparisons. Using the Bonferroni adjustment alters the statistical inference of a study from the testing of a number of specific hypotheses to a test of the universal null hypotheses.[34–36] This method increases the type II error rate[34,35] and raises the issue of the number of tests to be included in the adjustment.[34] Conclusions about the long-term effects of MTS are limited by the short 4-week duration of the present study (2 weeks of active medication).

Further, because of the forced dose increase of the medication to a lower than US Food and Drug Administration–approved dose of 30 mg, it is unclear if the results of this study represent maximal or even optimal response. Since subjects received a maximum dose of only 20 mg, it is possible that subjects may have benefited from, and results may have been more robust with, the higher approved dose. While we attempted to examine morning functioning of patients with ADHD in a naturalistic setting, given limited available expanded instruments, we relied upon validated overall ADHD scales and adaptations of valid and reliable ADHD symptom scales. While promising in showing robust changes compared to placebo for early morning functioning, the Before-School Functioning Questionnaire lacks formal psychometric testing (which will be presented in a future manuscript) in regard to reliability and validity in ADHD and non-ADHD groups of various

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ages and sex. Clearly, further work with valid and reliable instruments in assessing ADHD symptoms and associated impairment during the before-school hours would be useful. Unlike analog classroom derived data, our data do not allow a definitive time to onset of action given the nature of our rating scales. Similarly, this study was designed to examine before-school and not afternoon/early evening activities. As a result, by administering the patch in the early morning, ADHD coverage may have been compromised in the late afternoon/early evening.

Despite these limitations, the aggregate findings from our study show that very early administration of MTS was associated with improved ADHD symptoms and before-school functioning in children with ADHD with similar adverse effects to previous MTS studies. Before-school functioning appears to be a major area of impairment related to ADHD. Future research should examine the effects of comorbid disorders like oppositional defiant disorder and the subtypes of ADHD. In the end, more work examining the relationship between before-school ADHD symptoms and functioning and later academic and daytime performance is needed.

Drug names: atomoxetine (Strattera), methylphenidate transdermal system (Daytrana).

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Author contributions: Dr Wilens wrote the first draft of the manuscript. No honorarium, grant, or other form of payment was given to anyone to produce the manuscript. All authors listed on the manuscript have seen and approved the submission of this version of the manuscript and take full responsibility for the manuscript.

Potential conflicts of interest: **Dr Wilens** receives or has received grant support from Abbott, McNeil, Eli Lilly, NIH (NIDA), Merck, and Shire; has been a speaker for Eli Lilly, McNeil, Novartis, and Shire; has been a consultant for Abbott, AstraZeneca, McNeil, Eli Lilly, NIH (NIDA), Novartis, Merck, and Shire; and has a published book with Guilford Press, *Straight Talk About Psychiatric Medications for Kids*. **Dr Hammerness** has received research support from or participated in CME activities/professional talks supported by Abbott, Eli Lilly, Forest, McNeil, Shire, and Elminda; has participated in speaker training with Shire; has participated as an investigator in research studies funded by Abbott, Bristol-Myers Squibb, Cephalon, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, McNeil, Merck, New River, Organon, Pfizer, Shire, and Takeda; and has received honoraria from Reed Medical Education (logistics collaborator for MGH Psychiatry Academy)—educational programs are supported through Independent Medical Education grants from pharmaceutical companies along with participant tuition. **Mss Martelon, Brodziak, Utzinger,** and **Wong** report no conflict of interest.

Funding/support: This study and medication/placebo were funded by an investigator-initiated grant through Shire Pharmaceutical Company.

Role of sponsor: The Shire Pharmaceutical Company had no further role in study design, collection, analysis, interpretation of data, writing of the report; or in the decision to submit the paper for publication.

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