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Is Methylphenidate Transdermal System (Daytrana®) Safe and Effective for Managing Attention Deficit Hyperactivity Disorder Symptoms in Children?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not methylphenidate transdermal system (Daytrana®) is safe and effective for managing attention deficit hyperactivity disorder symptoms in children.

STUDY DESIGN: A review of three English language studies published from 2006-2010. Includes two randomized, double-blind, controlled trials and one randomized, controlled crossover study.

DATA SOURCES: Randomized, placebo-controlled studies evaluating the effectiveness and safety of methylphenidate transdermal system (MTS) for managing attention deficit hyperactivity disorder (ADHD) symptoms in children were located using the PubMed, CINAHL, and Cochrane Library databases.

OUTCOMES MEASURED: The primary measures of effectiveness used were the ADHD Rating Scale IV and SKAMP Teacher Rating Scale. The secondary measures of effectiveness were the Clinical Global Impressions-Improvement Scale and Parent's Global Assessment. The measures of safety included adverse events (headache, anorexia, insomnia, gastrointestinal symptoms, abdominal pain, dizziness, etc.), skin reactions, vital signs, physical exam findings, EKG findings, and laboratory values.

RESULTS: Three randomized, controlled studies comparing MTS to a placebo transdermal patch were reviewed. All three studies found a statistically significant difference between the two treatment groups in the efficacy measurement scales, with evident improvement noted in MTS participants versus placebo. All three studies also found MTS to be well tolerated. The majority of adverse events were mild to moderate, and the most common events were decreased appetite, headache, gastrointestinal symptoms, and insomnia.

CONCLUSIONS: The results of all three studies in this review support a similar conclusion, that MTS is both effective and safe in the treatment of children 6-12 years of age diagnosed with ADHD. MTS provides the first non-oral administration of stimulant medication in the treatment of ADHD.

KEY WORDS: Transdermal methylphenidate, ADHD.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a serious neurobehavioral disorder associated with persistent inattention, hyperactivity, and impulsivity. ADHD is one of the most common neurobehavioral disorders in youth and often leads to significant academic, home, and social impairments. In the US, the estimated prevalence of ADHD in school-age children is 3-7%, and the annual societal "cost of illness" of ADHD is estimated between $36 and $52 billion (2005).[1] ADHD is a significant financial burden due to the cost of medical care and work loss for patients and family members. The cost annually per individual in 2005 was estimated between $12,005 and $17,458, and there were an estimated 7 million ambulatory care visits in 2006 for ADHD.[1]

ADHD is a complex disorder and can have multiple effects on a child's development. Children with ADHD have difficulty with friendships and peer relationships, are at increased risk of more frequent and serious injuries, and struggle with school work, resulting in lower grades.[1] ADHD also increases the risk for various comorbidities, such as a learning disability, oppositional defiant or conduct disorder, anxiety, depression, and Tourette syndrome.[2] In addition, the majority of children with ADHD continue to have symptoms and the associated impairments of the disorder into adolescence and adulthood. Thus, the diagnosis of ADHD in a child has significant meaning, and physician assistants, regardless of the specialty they may practice in, are bound to encounter patients and families affected by ADHD.

The causes and risk factors for ADHD remain unknown, but current research suggests a genetic component. Recent studies of twins demonstrate a relationship between ADHD and genes, however, like many other conditions, ADHD likely results from a combination of factors.[3] Researchers are studying the link of environmental factors (lead exposure, tobacco and alcohol

use during pregnancy, premature delivery), traumatic brain injuries, and food additives to the development of ADHD.[1,2] A once popular belief that refined sugar causes or worsens ADHD symptoms has since been disproven by numerous studies.[2]

The treatment of ADHD is individualized and multifactorial, including medications, behavioral intervention strategies, and training for parents and teachers. Stimulant medications are the most widely used method to treat ADHD and are considered first-line medical treatment. Seventy to eighty percent of children respond positively to stimulant medication, which has been used for more than 60 years. Stimulants do not cure ADHD, but instead control the symptoms of inattention, hyperactivity, and impulsivity. Stimulants are available in immediate- and extended-release formulations. Immediate-release stimulants require frequent doses and may lead to decreased compliance, lack of privacy, and fear with in-school doses.

This review examines methylphenidate transdermal system (MTS), a discrete, colorless patch. It is the only non-oral medication approved specifically for the treatment of ADHD and provides an option for patients who have difficulty swallowing or tolerating oral medications or for those who need improved control of the duration of medication effect.[7] The once-daily application provides continuous, consistent delivery of methylphenidate for the standard nine-hour wear time. The transdermal delivery bypasses the first-pass metabolism in the liver, so more methylphenidate is available in the body. MTS offers a unique, new ADHD treatment option.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not methylphenidate transdermal system (Daytrana®) is safe and effective for managing attention deficit hyperactivity disorder symptoms in children.

METHODS

The three studies in this review were researched by the author using PubMed, CINAHL,

and Cochrane Library databases using the following keywords: transdermal methylphenidate,

ADHD. All articles were published in English, in peer-reviewed journals, and selected by the

author based on relevance and significance of the outcomes to patients. Inclusion criteria were

randomized, controlled studies published after 1996, children aged 6-12 years diagnosed with

ADHD by the *Diagnostic and Statistical Manual of Mental Disorders IV* criteria, and patient-

oriented outcomes. Patients outside of the 6-12 year age range or with comorbid psychiatric

disorders, concurrent illness or skin disorder, or mental retardation were excluded.

This review includes two randomized controlled trials and one randomized, controlled

crossover study, all of which compared the methylphenidate transdermal system to a placebo

patch. The outcomes measured include the effects of MTS on ADHD symptoms and severity,

and the safety of the transdermal patch. The studies reported statistical summaries with the

following: mean change from baseline, confidence interval (CI), p-value, F-value, number

needed to treat (NNT), and number needed to harm (NNH). Demographics and characteristics of

the specific studies are found in Table 1.

Table 1. Demographics & Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Findling et al, 2008.[4]	Double-blind RCT.	274	6-12	ADHD diagnosis; responsive or naïve to stimulants; IQ $\geq$80; ADHD Rating Scale score $\geq$26; normal lab parameters and vital signs.	Comorbid psychiatric disorders; history of seizures, tics, or skin disorders; use of clonidine, antidepressants, hepatic enzyme altering agents, sedatives, or antipsychotics in past 30 days.	105	MTS – 2 weeks at pt's optimized dose (10, 15, 20, or 30 mg); delivered over 9-hour wear time.

McGough et al, 2006.[5]	Double-blind RCT.	93	6-12	ADHD diagnosis; responsive or naïve to stimulants; IQ ≥80; ADHD Rating Scale score ≥26; normal laboratory parameters and vital signs.	Comorbid psychiatric disorders; history of seizures, tics, or skin disorders; mental retardation; use of clonidine, antidepressants, hepatic enzyme altering agents, sedatives, or antipsychotics in past 30 days.	13	MTS – 1 week at pt's optimized dose (10, 16, 20, or 27 mg); delivered over 9-hour wear time.
Wilens et al, 2010.[6]	Random-ized, controlled, crossover study.	36	6-12	ADHD diagnosis and a clinical psychiatric interview.	Dermatologic atopy; structural cardiac defects; IQ <70; seizure or psychological disorder; history of no response or intolerable adverse effects to methylphenidate.	10	MTS – 10 or 20 mg; delivered over 9-hour wear time.

OUTCOMES MEASURED

The outcomes measured in the three studies were patient oriented and included the effects of MTS on ADHD symptoms and the safety of the transdermal patch. The primary measures of effectiveness were the ADHD Rating Scale IV (Findling et al[4], Wilens et al[6]) and SKAMP Teacher Rating Scale (McGough et al[5]). The ADHD Rating Scale is an 18-item scale linked directly to DSM-IV ADHD diagnostic criteria and used for diagnosing ADHD and assessing the response to treatment. The SKAMP Teacher Rating Scale is a 15-item scale describing typical behaviors in a classroom setting; items are rated on a 7-point impairment scale. The secondary measures of effectiveness were the Clinical Global Impressions-Improvement Scale, a 3-item observer-rated scale to measure the overall severity and improvement of the patient (Findling et al[4], McGough et al[5], Wilens et al[6]), and the Parent's Global Assessment, a parent measurement

of the overall severity and improvement of ADHD in the patient (Findling et al[4], McGough et al[5]).

In all three studies, the safety of MTS was measured by adverse events (headache, anorexia, insomnia, gastrointestinal symptoms, abdominal pain, dizziness, etc.), skin reactions, vital signs, physical exam findings, EKG findings, and laboratory values. These events were spontaneously reported by the participant or noted at the study visits.

RESULTS

This review includes two randomized controlled trials and one randomized, controlled crossover study, all of which compared methylphenidate transdermal system to a placebo patch, and all analyses were intention-to-treat. In all three studies, the patches were applied on the child's hip between 6-7 am, alternating sides so that the same application site was not used for two consecutive days, and worn for approximately nine hours daily. All studies included children 6-12 years of age diagnosed with ADHD by the *Diagnostic and Statistical Manual of Mental Disorders IV* criteria because MTS was at the time FDA-approved only for persons six years of age or older, and children are the population most affected by ADHD. Children with comorbid conditions or mental retardation were excluded from the studies to specifically look at the efficacy of MTS on ADHD only. Children with any concurrent illness or skin disorder were also excluded from all studies because those factors may have compromised safety or study assessments. All three studies recorded medical compliance at 80%-100% for all subjects by counting both the used and unused patches at each follow-up visit.[4,5,6]

Findling et al and Wilens et al used the ADHD Rating Scale (ADHD-RS) as the primary measure of efficacy, recorded at baseline and then weekly thereafter until the end of the study.

Findling et al found the ADHD-RS mean total scores were rather severe and similar at baseline, but not at endpoint (Table 2). Compared to the placebo, the MTS treatment group showed significant improvements in the change in ADHD-RS mean total scores from baseline to study endpoint (95% CI = -18.062 to -9.724).[4] There was a roughly 2-fold greater improvement in ADHD symptoms in those treated with MTS compared to placebo.[4] Wilens et al also found a clinically and statistically significant effect of MTS on ADHD symptoms compared to a placebo using the ADHD-RS at baseline and study endpoint (Table 2). Compared to baseline, there was a 25% reduction of ADHD-RS mean total scores in the placebo group and a 61% reduction in MTS treatment group.

Table 2. ADHD-RS Mean Total Scores

Study	Baseline Score (MTS; Placebo)	Endpoint Score (MTS; Placebo)	Change from Baseline (MTS; Placebo)	p-value
Findling et al[4]:	43.0; 41.9	18.8; 32.1	-24.2; -10.3	p < 0.0001
Wilens et al[6]:	37.80 ± 9.08; 37.80 ± 9.08	14.76 ± 14.48; 28.33 ± 15.75	61%; 25% reduction	p < 0.001

McGough et al used the SKAMP Teacher Rating Scale as the primary measure of efficacy and analyzed the results with analysis of variance and least square mean. The teacher measured the subject's deportment (SKAMP-D score) and attention (SKAMP-A score) at multiple time points during the laboratory classroom sessions of the study. At all individual postdose time points measured, the mean SKAMP-D scores were considerably lower (i.e. improved) for MTS than the placebo group and statistically significant. Table 3 demonstrates that the least square mean for the SKMAP-D scores in the MTS treatment group was significantly lower than that for the placebo patch treatment group. Analysis of the SKAMP-A scores showed similar results, as seen below in Table 3.

Table 3. SKAMP Teacher Rating Scores[5]

	F-score	Least Square Mean, MTS	Least Square Mean, Placebo	p-value
SKAMP-Deportment	$F(1,77) = 71.48$	3.2 ± 0.58	8.0 ± 0.58	$p < 0.0001$
SKAMP-Attention	$F(1,77) = 83.04$	6.2 ± 0.50	9.9 ± 0.50	$p < 0.0001$

All three studies used the Clinical Global Impressions-Improvement Scale (CGI-I), a 3-item observer-rated scale used to measure the overall severity and improvement of the patient. The CGI-I score was recorded in both the MTS and placebo treatment groups at the start and end of the study. These scores were dichotomized into two groups, where group one included very much improved and much improved and group two included the remaining levels. As seen in Table 4, all studies found a statistically significantly greater proportion of MTS subjects were rated as improved, compared with placebo. All three studies also determined the number needed to treat to produce one additional good outcome was only two patients. Furthermore, two of the studies (Findling et al[4], McGough et al[5]) used the Parent's Global Assessment (PGA) and found similar results after dichotomizing the data (Table 5). The results of all three studies support that MTS is not only effective in reducing the severity of symptoms based on an ADHD rating scale, but also produces a noticeable improvement in the patient by observers, teachers, and parents.

Table 4. Clinical Global Impressions-Improvement Scale Scores

Study	% Improved (MTS; Placebo)	RBI	ABI	NNT	p-value
Findling et al[4]	71.9%; 23.5%	2.1%	48.4%	2 patients	$p < 0.0001$
McGough et al[5]	79.8%; 11.6%	5.9%	68.2%	2 patients	$p < 0.0001$
Wilens et al[6]	83%; 30%	1.76%	53%	2 patients	$p \leq 0.0001$

RBI (relative benefit increase), ABI (absolute benefit increase), NNT (number needed to treat).

Table 5. Parent's Global Assessment Scores

Study	% Improved (MTS; Placebo)	RBI	ABI	NNT	p-value
Findling et al[4]	69.8%; 24.7%	1.8%	24.7%	4 patients	$p < 0.0001$
McGough et al[5]	71.1%; 15.8%	3.5%	55.3%	2 patients	$p < 0.0001$

RBI (relative benefit increase), ABI (absolute benefit increase), NNT (number needed to treat).

All three studies examined the safety of MTS compared to a placebo patch and found MTS to be well tolerated overall. Findling et al and McGough et al both demonstrated no serious adverse events, including deaths or suicides, with ≥99% of adverse events classified as mild to moderate.[4,5] The most common adverse events across all studies were decreased appetite, headache, gastrointestinal problems (nausea, vomiting, abdominal pain), and insomnia.[4,5,6] All three studies found the absolute number of reported events higher for the MTS group. Findling et al used a post-hoc analysis to find this difference to be statistically insignificant for the ten most common adverse events. Whereas Wilens et al found a significant increased number of MTS subjects with loss of appetite compared to placebo (MTS 13%, PTS 0%, x^2 12.25, p<0.001). Table 6 displays the number needed to harm for each study reviewed and were calculated with different adverse events for each study. The values in Table 6 for Findling et al and McGough et al used patients with one or more adverse event, whereas the Wilens et al study used patients with loss of appetite, which was the most common side effect and occurred in 13% of MTS patients and 0% of placebo patients. Wilens et al determined the number needed to harm with appetite loss was only two patients. All studies noted that the effects were known adverse effects of methylphenidate and transdermal applications.

Table 6. Adverse Events – Number Needed to Harm

Study	RRI	ARI	NNH	p-value
Findling et al[4]	0.3%	17.9%	6 patients	n/a
McGough et al[5]	0.33%	7.5%	13 patients	n/a
Wilens et al[6]	43/0	43%	2 patients	p < 0.001

RRI (relative risk increase), ARI (absolute risk increase), NNH (number needed to harm).

Of the three studies reviewed, Findling et al recorded the most detailed dermal response to the transdermal applications. Findling et al scored dermal effects from zero to seven, ranging from none to vesicular eruption to strong reaction spreading beyond test site. The highest score reported for MTS was 4, definite edema, compared to a 3, erythema and papules, for placebo.[4]

Also, in both treatment groups 97.7% subjects reported no discomfort (87.3%) or minimal discomfort (10.4%).[4] In addition, McGough et al noted patch adhesion to very good as >90% of patch surface was judge adhered to the skin for most (86%) patches by the end of the day. Findling et al had similar results, where 63.2% of subjects had >90% of the patch attached after nine hours of wear time. Lastly, all studies found no clinically significant effects of MTS on mean vital signs and other clinical parameters (i.e. EKG findings, laboratory values).

DISCUSSION

This review supports the use of MTS as a safe and effective treatment option for children 6-12 years of age diagnosed with ADHD. MTS was the first non-oral medication FDA-approved for the treatment of ADHD in persons 6-12 years in April 2006, and is now approved and proven effective for use in adolescents 13-17 years of age.[7,8] Additional research is required to examine the use of MTS in adults.

MTS is a valuable option for treatment of ADHD, however as with every medication, there are warnings and contradictions for its use. MTS is a schedule II controlled substance, as are other methylphenidate products, because it can be abused or lead to dependence. MTS should be given cautiously to patients with a history of drug dependence or alcoholism.[9] Contraindications to MTS include patients with a known hypersensitivity to methylphenidate, acrylic adhesive, or silicone adhesive (does not contain latex); marked anxiety, tension, and agitation; glaucoma; motor tics or family history of Tourette syndrome; or are being treated with monoamine oxidase inhibitors. MTS should only be prescribed for the treatment of ADHD in patients 6-17 years of age.

MTS is a central nervous system stimulant, as are all the stimulant medications for ADHD, and associated with the risk of cardiovascular side effects. Sudden death has been reported with the use of CNS stimulants at usual doses in children, adolescents, and adults. Therefore, stimulant products should not be used in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious heart problems.[9] In this review, no significant cardiovascular events related to treatment, no clinically significant changes from baseline EKG findings, and no reports of death were observed.

A limitation of this review is that it only examines the use of MTS in children 6-12 years of age, and MTS is now FDA-approved for up to age 17 years, as of July 2010[8]. Looking ahead, studies investigating the use of MTS in adults would be beneficiary. Another limitation of this review is that all three studies involved relatively small sample sizes that were predominately white males with combined ADHD type. So the use of MTS in females, other races, and patients with only inattentive or hyperactive type is not as specifically studied in this review. An additional limitation of the studies included in this review is that the participants who were withdrawn from the studies were not specifically analyzed. Findling et al had the largest number of withdrawn patients at 105 due to various reasons after receiving the double-blind medication. McGough et al had 13 patients withdrawn prior to randomization and Wilens et al had 10 patients withdrawn. All three studies reported adverse events, protocol violation, withdrawn consent or lost to follow-up as reasons for withdrawn participants.

CONCLUSION

This review of three randomized, controlled studies determined methylphenidate transdermal system to be safe and effective for managing ADHD symptoms in children 6-12 years of age. MTS provides children diagnosed with ADHD, and their parents and medical providers, with a new treatment option. Future research should be designed to examine the effects of MTS in older patients, as well as how its efficacy compares to oral stimulant medication for ADHD. The focus of this review was whether or not MTS is safe and effective, and additional research evaluating the optimal dose and wear time of MTS is necessary. Also, because of the high rates of comorbidities in patients diagnosed with ADHD, future research is needed to study the effects of MTS in patients with coexisting illnesses. Despite the need for additional studies, methylphenidate transdermal system remains a safe and effective, once-daily administration of stimulant medication for children diagnosed with attention deficit hyperactivity disorder.

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