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Systematic review of transdermal treatment options in attention-deficit/hyperactivity disorder: implications for use in adult patients

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Review

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Abstract

Background. Adults with attention-deficit/hyperactivity disorder (ADHD) often face delays in diagnosis and remain untreated, despite significant negative impacts. To evaluate the safety and efficacy of transdermal treatment options in children, adolescents, and adults, a systematic literature review was conducted, with a focus on the implications of transdermal therapies for ADHD in adults.

Methods. A MEDLINE/Embase/BIOSIS/SCOPUS database search was conducted December 4, 2019, for English-language articles of interventional clinical trials using transdermal formulations for the treatment of ADHD without publication date limit. Assessed outcomes included efficacy, safety, adherence, abuse potential, cost efficacy, and health-related quality of life.

Results. Of 23 eligible publications, 18 were in children or adolescents (n = 1699; range 23-305), and 5 in adults (n = 274; range 14-90); all included methylphenidate transdermal system (MTS). All seven pediatric publications reporting change in ADHD symptomology from baseline reported a significant improvement with MTS treatment. Similarly, in three adult publications, ADHD symptoms improved significantly with MTS treatment. Safety findings in pediatric and adult studies were comparable; the most frequently reported treatment-emergent adverse events (TEAEs), namely, headache, decreased appetite, and insomnia, were reported in 13/16 (81%) of publications reporting specific TEAEs. MTS-related dermal reactions were mostly mild and transient. Discontinuation due to dermal reactions was reported in 10 studies (range 0%-7.1% [1 of 14 patients]). MTS compliance was high when assessed (97%-99%).

Conclusions. Transdermal therapies provide a useful treatment formulation for ADHD. Studies of MTS and other transdermal formulations, such as amphetamine, in adult patients are needed in this underserved population.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a relatively common disorder, characterized by inattention, hyperactivity, and impulsivity.[1] In U.S. adolescents, the 12-month prevalence of ADHD is 6.5% (standard error, 0.5),[2] with 76% of patients experiencing moderate to severe ADHD.[3] In many cases, pediatric ADHD will persist into adulthood: 60% of patients display symptoms throughout their lives,[4] with the severity and treatment of pediatric ADHD acting as significant predictors of persistence in adulthood.[5] In cases of "adult-onset" ADHD, in which adult patients did not have a prior medical history of ADHD, patients were more likely to have evidence of psychopathology in childhood, suggesting that they may have displayed symptoms of ADHD below the diagnostic threshold.[6] Recently, the prevalence of adult ADHD diagnoses in U.S. adults has increased from 2.20 per 1000 patients in 1999 to 10.57 in 2010. Despite this increase, approximately half of patients with adult ADHD are untreated, suggesting that this is an underserved patient population.[7] Approximately 66% of adult patients with ADHD have comorbid psychiatric disorders, including substance use disorders (SUDs, 39.2%), anxiety disorders (23%), and mood disorders (18.1%).[8] However, neither an ADHD diagnosis[9] nor treatment with stimulants such as methylphenidate[10] increase the risk of psychotic disorders. Similarly, psychostimulants have not been found to increase the risk for SUDs[11] and have been shown to reduce the risk of smoking.[12]

In adults, untreated ADHD is associated with impaired quality of life (QoL), impaired relationships, reduced employment, impaired driving safety, premature death from accidents, and vulnerability to addiction, depression, and anxiety.[13] Disease trajectory is highly variable,

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and comorbidities such as SUD, antisocial personality disorder, and sleep disorder may emerge in adults with ADHD.[6] Notably, treatment of ADHD has demonstrated a protective benefit against delinquency in adults, with a large epidemiologic study demonstrating a significant reduction in the rate of criminality during periods in which patients received ADHD treatment compared with nonmedication periods (men, −32%; women, −41%)[14]; these findings are consistent with an analysis of recently released prisoners in Sweden, which found a 43% decrease in violent re-offenses in individuals receiving psychostimulants.[15] Despite its increasing prevalence and demonstrated response to medication, adult ADHD has only recently been recognized, and understanding of treatment in adults is hampered by a dearth of long-term data.[16] Treatment for ADHD may include stimulants, such as amphetamine and methylphenidate,[17,18] or other medications, such as atomoxetine (a presynaptic inhibitor of the norepinephrine transporter)[19] and clonidine and guanfacine (α-2 adrenergic agonists).[20] Numerous studies have compared the efficacy of these regimens in children, adolescents, and adults. A meta-analysis of 18 trials found that, compared with placebo, treatment with methylphenidate resulted in a moderate improvement in ADHD symptoms in adults.[21] Additionally, a large analysis of 133 studies (51 of which focused on adults) found that amphetamines, methylphenidate, bupropion, and atomoxetine improved ADHD symptoms relative to placebo in adults; based on the findings, the authors recommended amphetamine as the primary short-term treatment option in adult patients but noted that additional research into long-term treatment was needed.[22]

Methylphenidate is available as an oral medication with a number of formulations, including immediate-release tablets, extended-release (ER) tablets, sustained-release tablets, oral liquid suspension, chewable tablets, and orally disintegrating tablets.[23] The methylphenidate transdermal system (MTS) is approved in the United States for the treatment of children and adolescents with ADHD. Transdermal patches offer a number of benefits over oral formulations, including improved adherence, personalization of wear times, minimization of hepatic side effects and first-pass metabolism, and reduced gastrointestinal adverse events (AEs).[24] MTS is the only transdermal treatment approved for ADHD, and it has demonstrated significant improvement in ADHD symptoms in children and adolescents compared with placebo. Additionally, safety studies have shown that the majority of AEs were mild or moderate, and only 9% of patients discontinued due to AEs.[24] Unique to MTS is the variable duration of action based on the wear time of the patch. Significant improvement in ADHD symptoms from 2 to 12 hours after applying MTS with a 9-hour wear time was observed in clinical trials. Moreover, MTS can be removed before 9 hours if a shorter duration of effect is desired.[25]

While the persistence of ADHD into adulthood has become increasingly appreciated, few studies have examined optimal treatment options in adults or how to manage the transition of treatment from childhood into adulthood.[26] Adults with ADHD have reported long delays in diagnosis, and access to treatments for adults is limited because of both a lack of dedicated adult services and an unwillingness of psychiatrists to prescribe stimulants to adults.[26] Long-term studies of efficacy and safety in adults with ADHD are also limited, potentially contributing to the undertreatment of adults.[27] Of particular importance is the rate of nonadherence among adult patients. Overall rates of nonadherence have been found to range from 13.2% to 64.0% of patients with ADHD, but predictors of nonadherence included older age and later-onset ADHD, suggesting adherence may be a greater challenge in adult patients.[28] This result is supported by findings from long-term studies of adult ADHD, which found a high rate of nonadherence to ADHD medications, with up to 50% of adults discontinuing treatment after 2 years.[27] This trend is observed in ADHD medications of all types, including long-acting stimulants (discontinuation rate, 19.1% across all ages), short-acting stimulants (99% beyond 12 months in 6-12-year-old patients), and atomoxetine (26.0%-38.3% across all ages).[4] Additionally, it has been demonstrated that patients aged 15 to 21 years are the most likely to discontinue treatment, just as they transition treatment from pediatric to adult services, which is often provided by general practitioners.[29] Several strategies to improve adherence have been proposed, including increasing discussion between patients and physicians regarding the importance of adherence, implementing self-monitoring, addressing AEs, and simplifying dosage and regimens.[28] Long-acting transdermal formulations can reduce the dosing frequency compared with that required for other formulations. In addition, multiple studies in different patient populations have demonstrated improved adherence with transdermal formulations.[24] To this end, the use of transdermal formulations in adults with ADHD has the potential to improve adherence in this underserved patient population. This literature review was conducted to evaluate the safety and efficacy of transdermal treatment options in children, adolescents, and adults, with a focus on the potential for transdermal systems in the treatment of adults with ADHD.

Methods

Search strategy

Because of the relative lack of studies in adults with ADHD, a broad and comprehensive search strategy was designed in order to identify clinical trials of transdermal treatments in patients with ADHD, regardless of patient age or date of publication. On December 4, 2019, a search of the MEDLINE, Embase, BIOSIS, and SCOPUS databases was conducted to identify clinical trials of transdermal treatment conducted in patients with ADHD, using the following search string: TITLE-ABS-KEY(transdermal OR dermal OR *cutaneous) AND TITLE-ABS-KEY("adhd" OR "attention deficit" OR "addh" OR "minimal brain dysfunction" OR "hyperkinetic syndrome") AND TITLE-ABS-KEY(randomized OR randomised OR "equivalence trial" OR "clinical trial" OR "clinical trials" OR "equivalence trials" OR "non inferiority trial" OR "non inferiority trials" OR "noninferiority trial" OR "noninferiority trials" OR "superiority trial" OR "superiority trials" OR "intention to treat analysis" OR "controlled trial" OR "controlled trials" OR "pragmatic trial" OR "pragmatic trials" OR "equivalence design" OR "non inferiority design" OR "noninferiority design" OR "superiority design") AND NOT INDEX(medline).

Results were limited to English language, and the following categories of publications were excluded: Review, Conference Paper, Conference Abstract, Note, Editorial, Letter, Literature Review, Short Survey, Meeting Abstract, Conference Review, and Systematic Review. The search was not restricted by publication date. Eligibility criteria were applied, and a review of the selected hits was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[30] After removal of duplicates, 145 unique hits were identified (Figure 1). Of these, 107 articles were excluded at title and abstract level. Altogether, 38 full text articles were reviewed, and a further 15 were excluded because they were off topic (n = 11; not transdermal

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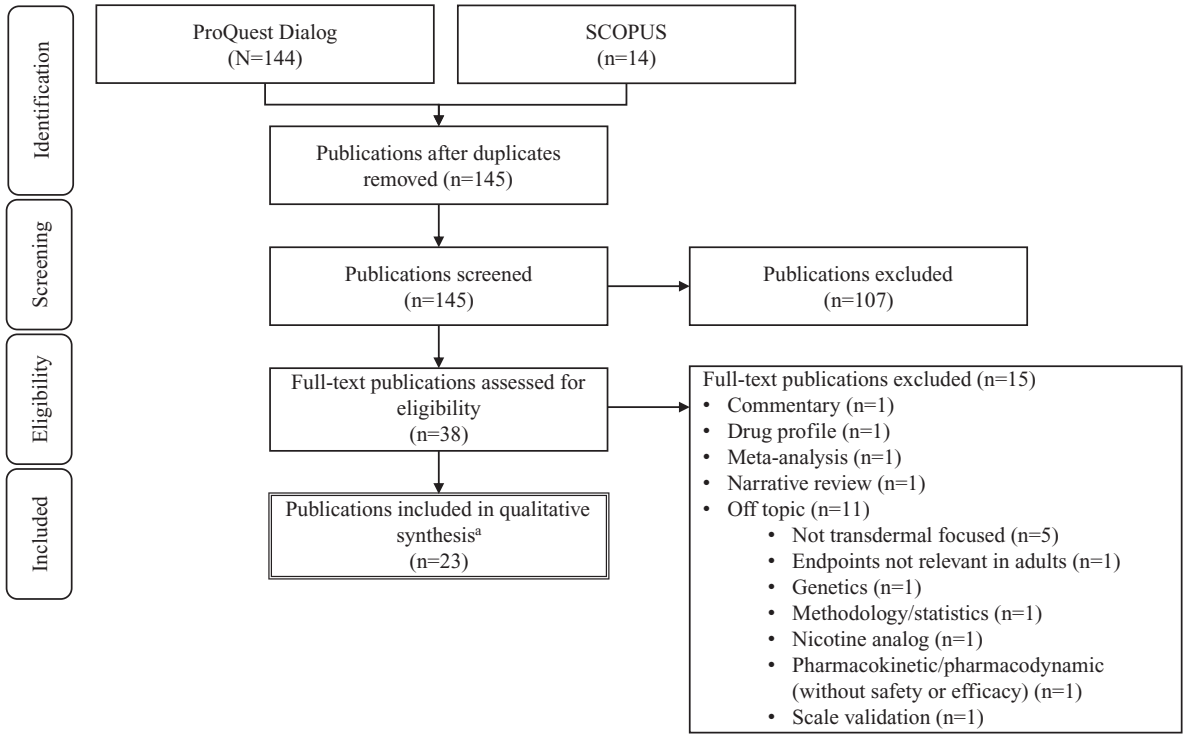

Figure 1. PRISMA flow diagram. Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses. [a]Representing 19 individual studies.

focused, 5; nicotine analog, 1; endpoint not relevant in adults, 1; genetics, 1; methodology, 1; pharmacokinetic/pharmacodynamic [without safety or efficacy findings], 1; scale validation, 1), commentary (n = 1), drug profile (n = 1), meta-analysis (n = 1), or a narrative review (n = 1). Efficacy, safety, adherence, abuse, cost efficacy, and health-related quality of life (HRQoL) data were extracted from the remaining articles and used in the present qualitative synthesis.

Results

Summary of studies

After applying exclusion criteria, 23 articles were identified by the systematic search (Table 1). These articles represented 19 unique clinical trials: Arnold et al[31] and Bukstein et al[32] concerned the same patient population, as did Wilens et al,[25] Manos et al,[42] and Frazier et al.[41] Findling et al[40] described an open-label extension of Findling et al,[39] and Findling et al[37] reported an open-label extension of four previous trials, two of which were also captured in this search (McGough et al[38] and Findling et al[36]). Altogether, 15 publications described randomized trials (double-blind, n = 10; open-label, n = 4; blinding not specified, n = 1; parallel group = 4, cross-over = 11), and 6 reported nonrandomized open-label studies (extension studies of a randomized trial = 2). All studies included MTS as the transdermal treatment; 12 studies focused on children (N = 1418, range 23-305), 1 on adolescents (N = 217), 1 on both children and adolescents (N = 64), and 5 on adults (N = 274, range 14-90). Patients from manuscripts concerning the same initial trial (eg, *post hoc* analyses or open-label extensions) were counted only once; for Findling et al,[37] only patients not included in McGough et al[38] and Findling et al[36] were included in the n-value (N = 33). The impact of treatment on severity of ADHD symptoms was assessed in 17 publications (children/adolescents, n = 12; adults, n = 5); the 6 papers that did not evaluate ADHD symptoms focused on sleep,[35] effect of patch placement on pharmacokinetics/pharmacodynamics,[43] effect of formulation on pharmacokinetics/pharmacodynamics,[49] and HRQoL improvements.[32,41,42] In children/adolescents, the most common efficacy measure used was the Attention Deficit Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV, 12/18), which evaluates symptom severity as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria. Among the publications related to adults with ADHD, 4 of 5 studies used the Wender–Reimherr Adult Attention Deficit Disorder Scale (WRAADDS), which is based on the Utah Criteria for ADHD in adults and measures ADHD symptom severity in the following seven domains: attention difficulties, hyperactivity/restlessness, temper, affective lability, emotional over-reactivity, disorganization, and impulsivity.

Efficacy: children and adolescents

A total of 12 publications reported on efficacy outcomes in children and adolescents (children, n = 10; adolescents, n = 2). In children and adolescents, treatment with MTS generally improved ADHD symptoms across all rating scales. Of the seven publications that evaluated change in ADHD-RS-IV scale from baseline, all reported a significantly improvement with MTS.[25,33,37,42,51,52] In publications on placebo-controlled trials reporting efficacy findings (n = 6), MTS consistently showed significant improvement over the placebo transdermal system (PTS).[36,38,39,47,48] A placebo-controlled study of oral and transdermal methylphenidate found that MTS (mean total score at endpoint, 18.8) and oral methylphenidate (21.8) significantly improved ADHD-RS-IV scores relative to placebo (placebo, 32.1; $P < .0001$), whereas there was no significant difference in efficacy between the oral and transdermal methylphenidate formulations ($P = .2192$).[36] An open-label extension of

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Table 1. Characteristics of Reviewed Articles

Article	Randomized	Placebo-Controlled	Study design	Efficacy Reported (Y/N)	Safety Reported (Y/N)	Patient Population	N	Treatment Arms	Topic	Primary Endpoint	Findings	Notes
Arnold et al[31]	No	No	Open-label	Yes	Yes	Children	171	MTS	Abrupt PO to TD conversion	Change from baseline in clinician-completed ADHD-RS-IV total score at week 4	Mean ADHD-RS-IV score at week 4 improved over baseline (9.9 ± 7.47 vs 14.1 ± 7.48; $P < .0001$)	Same patient population as Bukstein et al[32]
Ashkenasi[33]	Yes	No	Open-label, cross-over	Yes	Yes	Children	26	• 9-h wear time • 10-h • 11-h • 12-h	Effect of wear time on sleep	Sleep latency	Wear time did not have a significant effect on sleep latency	
Bukstein et al[32]	No	No	Open-label	No	Yes	Children	171	MTS	Abrupt PO to TD conversion	Primary not specified, secondary endpoints (subject of article) were AIM-C and MSS	AIM-C improved by endpoint; 93.8% of caregivers reported high MSS scores	Same patient population as Arnold et al[31]
Cox et al[34]	Yes	No	Open-label, cross-over	Yes	Yes	Adults	17	• No medication → MTS • MTS → no medication	Effect of MTS on driver inattention	Not specified	MTS improved ADHD symptoms, driving safety, and ADL	
Faraone et al[35]	Yes	Yes (PTS & PO)	Double-blind, parallel	No	Yes	Children	268	• MTS • ER-MPH (PO) • Placebo (TD) • Placebo (PO)	Effect of long-acting methylphenidate formulation on sleep	Primary endpoint not specified; secondary endpoint (subject of article) was CSHQ	No significant effect of methylphenidate dosage on sleep scores was observed	
Findling et al[36]	Yes	Yes (PTS & PO)	Double-blind, parallel	Yes	Yes	Children	282	• MTS + placebo (PO) • ER-MPH (PO) + placebo (TD) • Placebo (PO) + placebo (TD)	Efficacy and safety of MTS in children	Change in ADHD-RS-IV total score at endpoint	Mean change from baseline in ADHD-RS-IV scores was greater with MTS and oral MPH relative to placebo ($P < .001$)	
Findling et al[37]	No	No	Open-label, extension (enrolled from 4 previous studies; 2 unpublished [data on file], McGough et al[38], and	Yes	Yes	Children	326	MTS	Long-term safety of MTS in children	Primary efficacy outcome was ADHD-RS-IV, but focus of article was 12-mo tolerability of MTS	AEs were mild to moderate in severity, with the exception of dermal reactions	293 patients were reported in McGough et al[38] and Findling et al[36] and were not counted towards the total n values for this analysis; Findling et al[37] therefore

Table 1. *Continued*

Article	Randomized	Placebo-Controlled	Study design	Efficacy Reported (Y/N)	Safety Reported (Y/N)	Patient Population	N	Treatment Arms	Topic	Primary Endpoint	Findings	Notes
			Findling et al[36])									represents 33 patients not captured elsewhere in this search.
Findling et al[39]	Yes	Yes (PTS)	Double-blind, parallel	Yes	Yes	Adolescents	217	• MTS • Placebo (PO)	Efficacy and safety of MTS in adolescents	ADHD-RS-IV	MTS resulted in a greater reduction in ADHD-RS-IV scores from baseline relative to PTS ($P < .0001$).	
Findling et al[40]	No	No	Open-label, extension (enrolled from Findling et al[39])	Yes	Yes	Adolescents	162	MTS	Long-term efficacy and safety of MTS in adolescents	ADHD-RS-IV	MTS significantly improved ADHD-RS-IV scores from baseline to endpoint ($P < .001$)	
Frazier et al[41]	Yes	No	Double-blind, cross-over	No	No	Children	127	MTS	Predictors of HRQoL and MSS with MTS	Primary endpoint reported in Wilens et al[25]; focus of article was correlation of ADHD-RS-IV scores with AIM-C and MSS scores	ADHD-RS-IV, AIM-C, and MSS scores improved simultaneously	Same patient population as Manos et al[42] and Wilens et al[25]
González et al[43]	Yes	No	Open-label, cross-over	No	Yes	Children	23	• MTS (hip) → MTS (scapular area) • MTS (scapular area) → MTS (hip)	Effect of patch placement on PK	Not specified	Bioavailability of MPH differed between hip and scapular placement, but two sites had similar dermal reactions	
Manos et al[42]	Yes	No	Double-blind, cross-over	No	Yes	Children	128	MTS	Impact of MTS on HRQoL and MSS	Primary endpoint reported in Wilens et al[25]; secondary endpoints from this publication included AIM-C and MSS	Mean AIM-C scores improved over time; MSS scores were high	Same patient population as Frazier et al[41] and Wilens et al[25]
Marchant et al[44]	Yes	Yes (PTS)	Double-blind, cross-over	Yes	Yes	Adults	90	• MTS • Placebo (TD)	Efficacy of MTS in adults	Improvement in total WRAADDS scores	MTS improved WRAADDS scores in patients with ADHD, ADHD/ED, ADHD/ODD, and ADHD/ED/ODD	

Table 1. *Continued*

Article	Randomized	Placebo-Controlled	Study design	Efficacy Reported (Y/N)	Safety Reported (Y/N)	Patient Population	N	Treatment Arms	Topic	Primary Endpoint	Findings	Notes
McGough et al[38]	Yes	Yes (PTS)	Double-blind, cross-over	Yes	Yes	Children	93	• MTS - > Placebo (TD) • Placebo (TD) - > MTS	Efficacy of MTS in children	SKAMP deportment subscale	MTS significantly improved SKAMP scores relative to placebo	
McRae-Clark et al[45]	No	No	Open-label	Yes	Yes	Adults	14	MTS	Efficacy and abuse liability of MTS in adults with history of stimulant SUD	WRAADDS scale measured longitudinally over the course of 8 wk	MTS was associated with significant improvement in WRAADDS scores from baseline to endpoint	
Olsen et al[46]	Yes	Yes (PTS)	Double-blind, cross-over	Yes	No	Adults	67	• MTS • Placebo (TD)	Efficacy of MTS in adults with ADHD and PD	Proportion of responders, as defined by a 50% improvement in WRAADDS score	71% of patients without PD or with one PD responded to MTS compared with 38% of patients with 2 or more PDs	
Pelham et al[47]	Yes	Yes (PTS)	Double-blind, cross-over	Yes	Yes	Children	27	• MTS w/o BMOD • Placebo w/o BMOD • MTS w/ BMOD • Placebo w/o BMOD	Efficacy of MTS in combination with behavior modification	Not specified	Counselor-provided behavioral observations and daily report cards improved with MTS treatment	
Pelham et al[48]	Yes	Yes (PTS)	Double-blind, cross-over	Yes	Yes	Children	33	• MTS • Placebo	Efficacy of MTS in children with ADHD	Not specified	Low doses of MPH were associated with enhanced improvement in counselor-reported behavioral observations, classroom measures, and daily report cards when combined with BMOD	
Pierce et al[49]	Yes	No	Open-label, parallel	No	Yes	Children/ Adolescents	64	• MTS • ER-MPH (PO)	PK/PD of TD and PO methylphenidate formulations	Not specified	Plasma concentration time profiles for both *d*- and *l*-MPH enantiomers after single and multiple MTS doses was consistent with previous data	
Reimherr et al[50]	Yes	Yes (PTS)	Double-blind, cross-over	Yes	No	Adults	86	• MTS • Placebo (TD)	Evaluation of ODD symptoms in adult patients with ADHD treated with MTS	Not specified	69% of adults with ADHD met ODD criteria. ODD and ADHD symptoms improved significantly with MTS ($P < .001$).	

Table 1. *Continued*

Article	Randomized	Placebo-Controlled	Study design	Efficacy Reported (Y/N)	Safety Reported (Y/N)	Patient Population	N	Treatment Arms	Topic	Primary Endpoint	Findings	Notes
Warshaw et al[31]	No	No	Open-label	Yes	Yes	Children	305	MTS	Dermal reactions and sensitization in patients receiving MTS	Not specified	The majority of DRS scores with MTS were between 0 and 3; 1% of patients had definite edema (DRS score = 4)	
Wilens et al[25]	Yes	Yes (PTS)	Double-blind, cross-over	Yes	Yes	Children	127	• MTS • Placebo (TD)	Effect of wear time on MTS efficacy and safety	SKAMP Deportment subscale	4- and 6- h wear times improved SKAMP scores	Same patient population as Manos et al[42] and Wilens et al[25]
Wilens et al[52]	Yes	Yes (PTS)	Double-blind, cross-over	Yes	Yes	Children	30	• MTS • Placebo (TD)	Efficacy of MTS in children	ADHD-RS-IV	Compared with PTS, there was a significant decrease in ADHD-RS scores ($P < .001$)	

Abbreviations: ADHD-RS-IV, Attention Deficit Hyperactivity Disorder Rating Scale-IV; ADL, activities of daily living; AIM-C, ADHD Impact Module-Child; CSHQ, Children's Sleep Habits Questionnaire; ED, emotional dysregulation; ER-MPH, extended-release methylphenidate; HR-QoL, health-related quality of life; MSS, Medication Satisfaction Survey; MTS, methylphenidate transdermal system; ODD, oppositional-defiant disorder; PO, oral administration; PTS, placebo transdermal system; SKAMP, Swanson, Kotkin, Agler, M-Flynn, and Pelham; TD, transdermal; WRAADDS, Wender-Reimherr Adult Attention Deficit Disorder Scale.

a randomized MTS vs PTS trial demonstrated that ADHD-RS-IV scores significantly improved from baseline of the antecedent study (mean change in score, −23.0; $P < .001$).[40] Importantly, patients abruptly transitioning from oral extended-release methylphenidate (ER-MPH) to MTS reported improved ADHD-RS-IV scores with MTS (mean score [standard deviation, SD], 9.9 [7.47]) over baseline scores with ER-MPH (14.1 [7.48]; $P < .0001$).[31]

Efficacy: adults

All five studies of adults with ADHD reported efficacy findings. A double-blind, placebo-controlled, randomized, cross-over trial of MTS and PTS in adults found that, compared with placebo, MTS significantly improved total WRAADDS (mean score [SD]; MTS, 11.2 [7.2]; placebo, 17.9 [6.6]), Clinical Global Impression-Improvement scale (CGI-I; proportion moderately improved; MTS, 65%; placebo, 15%; $\chi^2 = 26.9$, $df = 1$, $P = .001$), and Clinical Global Impression-Severity scale (CGI-S) scores ($\chi^2 = 24.5$, $df = 1$, $P = .001$).[44] Importantly, two publications reported on the comorbidity of adult ADHD with one or more personality disorders (PDs), such oppositional defiant disorder (ODD), emotional dysregulation (ED), generalized anxiety disorder, and major depression.[44,46] Reimherr et al[50] demonstrated that 42% of adult patients with ADHD in their study met diagnostic criteria for ODD and that a further 27% reported childhood ODD that had previously resolved. The proportion of responders, defined as patients who demonstrated a 50% improvement in the self-reported WRAADDS-ODD scale, significantly improved with MTS relative to placebo (MTS, 66%; placebo, 33%). Using the same criteria to define responders, an additional trial of adults with ADHD with or without PD found that 71% of patients without PD or with one PD responded to MTS ($P < .001$). However, this effect was not significant in patients with more than one comorbid PD (37%, $P = .24$).[46] Another study found that, relative to placebo, MTS improved both ADHD and ODD symptoms in adult patients, regardless of underlying ODD or ED.[44]

MTS has also been demonstrated to improve other important related dimensions of ADHD. In a study of young adults (mean age, 20.82 years; SD, 2.40), patients treated with MTS self-reported fewer total ADHD ($P < .04$) and inattentive symptoms ($P = .014$).[34] Risky driving behaviors ($P = .059$) and collisions ($P < .005$) were also significantly reduced during periods in which patients took MTS compared with periods in which patients took no medication.[34]

Adherence

Adherence parameters were reported in six publications (children, n = 5; adults, n = 1), as summarized in Table 2. Two papers assessed adherence based on the return of unused study medication and defined compliance as use of between 80% and 100% of dispensed medication. In general, adherence was high among pediatric patients treated with MTS, ranging from 97% to 99% in the two aforementioned studies.[36,38] The study by Cox et al,[34] which included the use of MemsCaps, showed that, during the MTS condition, the MemsCap was opened on 56% of the days medication was to be taken, ranging from 4% to 91% across participants. Bukstein et al[32] found that the percentage of patients with missed doses decreased numerically when patients switched from oral formulations (28.6%) to MTS (23.6%). Furthermore, data reported by Manos et al[42] showed that the score for the ADHD Impact Module-Children (AIM-C) missed-doses items decreased over the study period (proportion missing ≥4 doses: baseline, 17.2%;

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Table 2. Summary of Adherence Parameters

Publication	Patient Population	N	Method of Reporting	Adherence Parameter	Adherence Rate	Notes
Ashkenasi et al[33]	Children	26	Caregiver-completed diaries	Patch wear time (9, 10, 11, and 12 h)	Actual patch wear-time closely matched target wear times	
Bukstein et al[32]	Children	171	AIM-C	Percentage of patients with missed dose	Percentage of patients with missed dose decreased from baseline (28.6%) to endpoint (23.6%)	Patients were abruptly switched from oral MPH to MTS, suggesting an improvement in adherence when transitioning from oral to TD formulation
Cox et al[34]	Adults	17	MemsCap	Percentage of days medication container was opened	MemsCap opened 56% of days (range 4-91%) under the MTS condition	Authors noted that improved adherence could have increased efficacy findings
Findling et al[36]	Children	282	Medication was dispensed on a weekly basis; compliance was determined based on the weekly return of unused medication	Percentage of patients meeting compliance criteria, defined as use of 80–100% of dispensed medication	Dose-optimization period - MTS, 98% - OROS, 98% - Placebo, 97% Dose-maintenance period - MTS, 99% - OROS, 98% - Placebo, 97%	
Manos et al[42]	Children	128	AIM-C	Percentage of patients with missed dose	Percentage of patients with a missed dose decreased from baseline (17.2% missed ≥4 doses) to endpoint (0 missed ≥4 doses)	
McGough et al[38]	Children	93	Medication was dispensed on a weekly basis; compliance was determined based on the weekly return of unused medication	Percentage of patients meeting compliance criteria, defined as use of 80–100% of dispensed medication	Dose-optimization period - Overall, 98% Randomized period - MTS, 97% - Placebo, 96%	

Abbreviations: AIM-C, ADHD Impact Module-Child; MPH, methylphenidate; MTS, methylphenidate transdermal system; OROS, osmotic-release oral system; TD, transdermal.

endpoint, 0), suggesting that compliance increased as patients became more familiar with the transdermal treatment.

Safety

Altogether, 16 publications reported specific treatment-emergent adverse events (TEAEs), 14 in children and adolescents and 2 in adults (Table 3). The proportion of MTS-treated patients experiencing TEAEs ranged from 22% to 81.3% (median, 67%) in the 11 publications reporting this endpoint.[31,32,36–40,43–45,51] In publications concerning children and adolescents, the median proportion of patients experiencing TEAEs was 73.5% (range 22%-81.3%); in adults, two publications reported the proportion of patients with TEAEs (57% and 67%).[44,45] The most commonly reported TEAEs were headache (13 of 16 studies; range of proportion of patients affected, 3.8%-28.6%), decreased appetite (13/16; 4.0%-29.8%), insomnia (13/16; 3.5%-47.2%), abdominal pain (9/16; 2.7%-30.0%), nausea (8/16; 3.7%-12.5%), nasopharyngitis (5/16, 1.3%-7.4%), decreased weight (5/16, 3.0%-10.1%), and tics/abnormal jaw movement (5/16; 2.8%-7.4%; Table 3). The proportion of patients reporting specific TEAEs other than skin reactions was largely comparable between children and adults.

A total of 13 publications reported on TEAE severity; in these 13 publications, the majority (>92%) of TEAEs were mild to moderate in severity. Across 16 publications reporting specific adverse events, only 2 patients in 2 separate trials experienced a serious adverse event that was considered related or possibly related to study treatment: 1 patient in Bukstein et al[32] experienced acute depression and suicide attempt, and 1 patient in Findling et al[39] experienced two episodes of syncope.

Studies in the present analysis reported that while dermal reactions tended to be worse with MTS compared with placebo,[25,44] the majority of erythema cases were mild and transient. In McRae-Clark et al,[45] 57.1% of adult patients reported a skin reaction, a greater proportion of study subjects than was observed in any of the pediatric studies (n = 3, 1.3%-3.7%).[38,43,51] This difference may be partially related to small sample size, as McRae-Clark et al[45] included only 14 patients. In other studies, patients generally had low skin reaction and dermal response scores.[25,31,33,36–40,43,44,47,49,51] Furthermore, Warshaw et al[51] (N = 305) demonstrated that >90% of patients experienced either mild or no discomfort resulting from skin reactions and that their severity diminished quickly over time.

Even though most skin responses were mild, 10 studies had at least 1 patient discontinue treatment due to application site reactions.[25,31,32,36,37,39,40,42,43,45,48,51] The proportion of patients discontinuing due to skin reactions ranged from <1% to 7.1% in McRae-Clark et al.[45] However, due to small sample size, the latter percentage reflected the discontinuation of only one patient.[45] One trial of 64 children and adolescents did not report any discontinuations due to adverse events, including application site reactions.[49]

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Table 3. Percentage of Specific Treatment-Related Adverse Events in MTS-Treated Patients Reported in 4 or More Studies[a]

	Headache (%)	Decreased Appetite (%)	Insomnia (%)	Abdominal Pain[b] (%)	Nausea (%)	Nasopharyngitis (%)	Decreased Weight (%)	Tic/ Abnormal Jaw Movement (%)	Irritability (%)	Anorexia (%)	Upper Respiratory Tract Infection (%)	Dizziness (%)	Rash/ Skin Reaction (%)	Pruritus (%)
Children/Adolescents														
Arnold et al[31]	7	6	5	4	NR	4	3	NR	NR	4	NR	NR	NR	NR
Bukstein et al[32]	5.1	4.7	3.5	2.7	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Findling et al[36]	NR	25.5	13.3	NR	12.2	5.1	9.2	7.2	NR	5.1	NR	NR	NR	NR
Findling et al[37]	16.6	24.8	8.9	8.3	6.1	7.4	10.1	NR	6.1	NR	12.3	NR	NR	NR
Findling et al[39]	12.4	25.5	6.2	NR	9.7	NR	5.5	NR	11	NR	10.3	5.5	NR	NR
González et al[43]	NR	NR	NR	NR	3.7	NR	NR	7.4	NR	NR	3.7	3.7	3.7	NR
Manos et al[42]	21	28	20	12	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
McGough et al[38]	3.8	NR	NR	NR	3.8	1.3	NR	NR	NR	2.5	NR	NR	1.3	NR
Pelham et al[47,c]	NR	4	4	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Pelham et al[48]	25	61	47.2	19.4	NR	NR	NR	2.8	27.8	NR	NR	NR	NR	NR
Pierce et al[49]	Children, 4.2 Adolescents, 8.0	Children, 8.3 Adolescents, 8.0	NR	Children, 12.5 Adolescents, 4.0	Children, 12.5 Adolescents, 0	NR	NR	NR	NR	NR	Children, 0 Adolescents, 4.0	Children 0 Adolescents, 8.0	NR	Children, 4.2 Adolescents, 0
Warshaw et al[51]	8.9	29.8	9.8	3.3	5.2	NR	3.3	NR	5.9	3.6	NR	NR	2.3	4.6
Wilens et al[25]	21	28	20	12	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Wilens et al[52,d]	17	43	27	30	NR	NR	NR	Yes	NR	NR	NR	Yes	NR	13
Adults														
Marchant et al[44]	13	11	31	NR	7	NR	NR	7	11	NR	NR	NR	NR	NR
McRae-Clark et al[45]	28.6	NR	7.1	NR	NR	7.1	NR	NR	NR	NR	NR	NR	57.1	NR

Abbreviation: NR, not reported.[a]Ashkenasi,[33] Cox et al,[34] Faraone et al,[35] Findling et al,[40] Frazier et al,[41] Olsen et al,[46] and Reimherr et al[50] did not report the incidence of specific AEs.
[b]Including general, lower, and stomachache.
[c]Reporting only parent-reported adverse events.
[d]The frequency of some adverse events were not reported; these have been captured as "yes."

Sleep

Insomnia was reported as a TEAE in 13 of 16 studies reporting specific TEAEs, including 2 publications in adults and 11 in children/adolescents (Table 3).[25,31,32,36,37,39,42,44,45,47,48,51,52] The proportion of patients experiencing insomnia varied widely between studies, and the reported values ranged from 7.1% to 31.0% in adults and 3.5% to 47.2% in child/adolescent patients (Table 3).

Four pediatric studies evaluated sleep dysfunction; none reported a change in sleep latency or total sleep time in patients using MTS.[35–37,40] Rather, improvements in certain sleep parameters from baseline to endpoint were noted, with an increased proportion of patients reporting sleeping through the night (baseline, 51.5%; endpoint, 66.7%) and a shorter time spent awake in those who woke during the night (baseline, 13.2 minutes; endpoint, 7.5 minutes).[40] Ashkenasi[33] found no association between sleep latency or sleep time and patch wear time and reported a trend toward improved sleep quality with longer wear times.

Health-related quality of life

While the studies of adult ADHD in this analysis did not address QoL, four publications on MTS trials in children and adolescents universally reported improved QoL scores across several assessments. AIM-C and family HRQoL scores improved in all domains in patients initiating MTS treatment.[42] In children switching from oral ER-MPH to MTS, AIM-C scores improved, including child and family impact, worry, behavior, and missed-dose items.[32] An open-label extension trial of MTS in adolescents found that scores in the four perceptual domains (self, relationship, environment, and general quality of life) of the Youth Quality of Life-Research instrument improved from baseline of the antecedent study.[40] Medication Satisfaction Survey scores were generally high with MTS, with the majority of caregivers expressing satisfaction with the medication.[32,42] In a time course analysis of children initiating MTS treatment, medication satisfaction and AIM-C child HRQoL increased with dosage.[41] This analysis also found that improvements in symptomology and HRQoL occurred simultaneously, rather than HRQoL "lagging behind" improved symptoms.

Abuse liability

In the only open-label study of MTS reporting on abuse liability, WRAADDS and CGI-S scores of 14 adult ADHD patients with a history of SUD significantly improved across all domains measured, and urinalysis throughout the trial period indicated that all patients were negative for stimulants.[45] One patient self-reported abuse of oral stimulants, but no other indications of stimulant abuse were identified in the study.

Cost efficacy

In two studies conducted in children, the AIM-C economic impact items improved with MTS treatment. The proportion of patients reporting parental missed days of work and extra tutoring, nursing, or other home healthcare decreased with MTS treatment.[32,42]

Discussion

Despite being an increasingly recognized subset of the ADHD patient population, few trials have been conducted to examine ADHD in adult patients, and fewer still have focused on treatment with MTS in the adult population. The current analysis identified 23 manuscripts concerning the treatment of ADHD in adult and pediatric patients using MTS.

While more publications focused on children and adolescents than adults (18 vs 5), efficacy and safety parameters were largely comparable between adult and pediatric publications. In pediatric papers, all studies measuring change from baseline in ADHD-RS-IV score reported that MTS significantly improved symptoms of ADHD. In publications concerning adult trials, ADHD symptomology also improved with MTS treatment, as evidenced by improved WRAADDS, CGI-I, and CDI-S scores. While direct comparison of improvements in ADHD-RS-IV in children and adolescents and WRAADDS scores in adults is complicated by the difference in the underlying diagnostic criteria used for the evaluations (DMS-IV and the Utah Criteria, respectively),[53,54] criteria largely overlapped, and the directionality of the improvements was nonetheless consistent. Additionally, other domains improved in patients treated with MTS, such as dangerous driving in young adults[34] and improved classroom scores in children.[38] These findings are comparable to a large meta-analysis conducted in children and adults, which found that methylphenidate was superior to placebo in both age groups.[22]

Although two publications on ADHD in adults included evaluation of comorbid ODD, this is not the most common comorbid disorder typically observed with adults with ADHD. More commonly observed psychopathologies include mood and anxiety disorders, SUDs, and PDs.[55] Therefore, while interesting, the impact of MTS on comorbid ODD needs to be interpreted with caution and does not reflect effects on the most relevant comorbidities observed in adults with ADHD.

While fewer studies in adults reported on the proportion of patients experiencing TEAEs (n = 2, range 57%-67%), the range was comparable to the median proportion of patients experiencing TEAEs in children and adolescents (n = 9; median, 73.5%). The majority of articles detailing specific TEAEs reported headache, decreased appetite, insomnia, abdominal pain, and nausea (Table 3); however, it is difficult to compare the occurrence of specific TEAEs between pediatric and adult populations due to the small number of studies available in adults.

Insomnia, which was identified as a TEAE in the majority of studies that provided detailed TEAE data, varied widely in incidence between publications, occurring at a rate of 7.1% to 31.0% of adults and 3.5% to 47.2% of pediatric patients (Table 3). However, despite this, four studies of the effect of MTS on sleep dysfunction in pediatric patients did not demonstrate a significant effect on sleep latency or total sleep time.[35–37,40] Therefore, while stimulants have the potential to increase insomnia and sleep latency, the extent to which stimulants contribute to sleep dysfunction in patients with ADHD is unclear.[33]

In one trial evaluating abuse liability in adults with a prior history of SUD, there was no evidence of abuse of MTS.[45] However, the potential for abuse is an important factor to consider when treating adult ADHD with stimulants, especially as adult ADHD is known to be associated with SUD,[46] and patients with ADHD and comorbid ODD may be more likely to have a SUD,[50] although this trend was not consistently observed.[46] More studies in larger populations of adults are necessary to critically evaluate the risk of abuse liability of methylphenidate and other ADHD treatment options, including by formulation type.

While MTS was generally associated with worse skin reactions than placebo, these reactions were largely mild and transient. Ten studies identified skin reactions as a reason for treatment

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discontinuation in at least one patient, including one study of adults. The percentage of patients discontinuing treatment was relatively small across all studies, ranging from 0% to 7.1%.[49]

Among the articles reporting on adults, three papers assessed MTS in adult ADHD patients with comorbid psychiatric disorders.[44,46,50] These studies provide a unique opportunity to compare findings in adults and pediatric studies; previous findings have indicated that, in the pediatric population, comorbid ODD is associated with greater functional impairment. However, treatment with stimulants and nonstimulants can improve symptoms even in patients with very poor baseline functioning scores and can preclude the need for additional medications to control symptoms.[56,57] These findings are corroborated by articles identified in the present search, in which MTS improved symptoms of ADHD, PD, ODD, and ED in adult patients.[44,46,50]

While some studies of MTS have included adults, amphetamine patch data are missing. Recently, a large meta-analysis recommended the use of amphetamines as the primary oral short-term treatment option in adult ADHD.[22] Given the benefits observed with MTS in both children and adults, transdermal application of amphetamines may serve to increase adherence while providing comparable safety and efficacy outcomes, as observed with oral amphetamines. It should be noted that in adults with a history of SUD, MTS treatment was not associated with stimulant abuse.[45] While this finding would have to be confirmed in a similar population with a transdermal amphetamine preparation, the lack of an abuse signal is encouraging. As amphetamines have been recommended for adults over other ADHD treatments, including methylphenidate, this suggests a role for transdermal amphetamine formulation in this underserved population. However, such potential benefits will need to be confirmed by trials in adult patients with ADHD.

This study has several limitations. First, only five studies reported on transdermal stimulants in adults, limiting the extent to which findings in adults and children/adolescents could be compared. This low number was especially limiting in studies reporting safety outcomes, as only two articles discussed TEAEs in adults. Furthermore, in-depth studies of sleep disturbance were not identified in adults, and there were limited data reported for domains such as adherence, HR-QoL, and HRU. Future studies of adult ADHD should include these important domains.

Second, variability in endpoint reporting between studies complicated direct comparison between trials. Only two trials, both in adults, reported responder rates.[46,50] Similarly, while multiple studies reported on skin reactions, variability in the scales and definitions used precluded direct and simple cross-comparison of results. Standardization of endpoint reporting would improve future trials, facilitating comparison between various studies and populations.

Third, although the search was not limited by transdermal treatment type, all studies identified for this analysis evaluated transdermal formulations of methylphenidate; studies that focused on alternative transdermal treatments, such as amphetamines, were not found. This result is despite evidence of the efficacy of amphetamines in ADHD.[22] As there are currently no approved transdermal amphetamine formulations, their development represents an important unmet need.

Finally, due to the heterogeneous nature of the data, only a qualitative/semiquantitative summary and synthesis were possible. Results in pediatric vs adult samples could only be broadly extrapolated for some key efficacy and safety outcomes. Nevertheless, to our knowledge, this is the first systematic review of transdermal treatments for patients with ADHD across all ages. These data should inform future studies of MTS and transdermal amphetamine treatment options in adults, and such studies should provide results from a comprehensive battery of symptomatic, functional, and adverse effect outcomes.

In summary, MTS has demonstrated considerable efficacy with a tolerable safety profile in both children and adults. However, adult ADHD remains an understudied area with few treatment options. This analysis supports the applicability of transdermal treatment options in adults and provides a strong rationale for the development of other transdermal systems, such as transdermal amphetamine, in this underserved patient population.

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