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# Methylphenidate Transdermal System
## In Attention-Deficit Hyperactivity Disorder in Children

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## Contents



## Abstract

▲ The methylphenidate transdermal system (MTS) patch is approved by the US FDA for use in children aged 6–12 years with attention-deficit hyperactivity disorder (ADHD). This delivery system permits sustained absorption of the drug through the skin and into the bloodstream. Methylphenidate (MPH) is a CNS agent thought to act on dopamine and noradrenaline (norepinephrine) pathways and thereby blocks the reuptake of these neurotransmitters into the presynaptic neuron.

▲ In children with ADHD, MTS patches releasing MPH doses of 10–30mg over a 9-hour period (12.5–37.5cm$^2$ patch size) is steadily absorbed, with mean peak plasma concentrations of *d*-MPH (20–46.5 ng/mL) reached in ≈8 hours.

▲ In well controlled trials in children with ADHD, patients administered MTS patches releasing MPH 10–30mg over ≈9 hours showed significantly greater improvements in their ADHD symptoms than placebo recipients.

▲ MTS patches are generally well tolerated in paediatric patients with ADHD, with treatment-emergent events being similar in nature to those reported with oral MPH. The majority of adverse events were mild to moderate in intensity.

| Features and properties of methylphenidate transdermal system (Daytrana™) | |
|---|---|
| **Indication** | |
| Attention-deficit hyperactivity disorder in children aged 6–12 years | |
| **Mechanism of action** | |
| Possible inhibition of dopamine and noradrenaline (norepinephrine) reuptake into the presynaptic neuron | |
| **Dosage and administration** | |
| Dose delivered over a 9-hour period (patch surface area) | 10mg (12.5cm$^2$)<br>15mg (18.75cm$^2$)<br>20mg (25cm$^2$)<br>30mg (37.5cm$^2$) |
| Frequency of administration | Once daily |
| Route of administration | Transdermal |
| **Pharmacokinetic profile (*d*-methylphenidate doses of 10, 15, 20 and 30mg over a 9-hour period)** | |
| Peak plasma concentration ($C_{max}$) | 20, 23.9, 30.5 and 46.5 ng/mL |
| Time to $C_{max}$ | 7.1–8.8h |
| Area under the plasma concentration-time curve | 145, 181, 229 and 378 ng • h/mL |
| Elimination half-life | ≈3h |
| **Adverse events (≥10% incidence)** | |
| Decreased appetite, insomnia, nausea, vomiting | |

Attention-deficit hyperactivity disorder (ADHD) is estimated to affect ≈8–10% of school-age children.[1] Stimulant medication such as methylphenidate (MPH) is commonly prescribed to treat ADHD. However, immediate-release oral formulations of MPH may require multiple daily doses, which can cause problems and embarrassment for children at school. Extended- or sustained-release oral formulations may not cover the entire school day before the effects of the drug wear off and problems associated with administration of the tablets or capsules may occur.[2,3] The methylphenidate transdermal system (MTS) [Daytrana™][1] is a method of delivering MPH to the systemic circulation via absorption of the drug through the skin. It may also benefit some children who have difficulty swallowing tablets or capsules. The patch, a combination of a multipolymeric adhesive matrix and MPH, allows continuous release of MPH throughout the day.[4] The US FDA-approved MPH doses are 10, 15, 20 and 30mg, which are obtained from MTS 12.5, 18.75, 25 and 37.5cm$^2$ patches, respectively; dosages are based on the MPH content of the patch delivered over a 9-hour wear time (table I). This review examines the use of MTS in the treatment of children with ADHD.

## 1. Pharmacodynamic Profile

The pharmacodynamic properties of MPH in patients with ADHD have been reviewed elsewhere[2,6-9] and are briefly summarised in this section. Pharmacodynamic data relating specifically to MTS are limited. MPH is a racemic compound composed of *d-* and *l-threo* enantiomers, of which the *d*-enantiomer is the more pharmacologically active.[6,10]

**Table I.** Patch surface area and the associated methylphenidate (MPH) dosage (modified from the prescribing information,[5] with permission from Shire Pharmaceuticals Ireland Limited)

| Nominal dose delivered over 9 hours (mg) | Dosage rate[a] (mg/h) | Patch size (cm$^2$) | MPH content per patch (mg) |
|---|---|---|---|
| 10 | 1.1 | 12.5 | 27.5 |
| 15 | 1.6 | 18.75 | 41.3 |
| 20 | 2.2 | 25.0 | 55.0 |
| 30 | 3.3 | 37.5 | 82.5 |

a Nominal *in vivo* delivery rate in paediatric patients aged 6–12 years when applied to the hip for 9 hours.

- MPH is a CNS stimulant thought to affect the dopamine and, putatively, the noradrenaline (norepinephrine) pathways by blocking the reuptake of the relevant neurotransmitters into the presynaptic neuron.[7,10] As a consequence of the increased concentration of these neurotransmitters in the extraneuronal space, behavioural and cognitive responses may improve in paediatric patients with ADHD;[3] however, the exact mechanism of action of MPH is unknown.

- The beneficial effects of MPH on behaviour, cognition, short-term memory, reaction time, vigilance and learning are well established.[6,9]

- Consistent with these findings, single MTS 12.5 and 25 cm$^2$ patch applications were significantly (all $p < 0.05$) more effective than placebo tablets at improving behaviour in the school setting in children (aged 7–12 years) with ADHD (figure 1);[11] for most parameters assessed, MTS 6.25 cm$^2$ patches also significantly improved behaviour compared with placebo ($p < 0.05$).[11] In this 8-day, double-blind, within patient study, children received single applications of MTS 6.25, 12.5 or 25cm$^2$ patches or placebo in a random order on separate days and at two timepoints (6:00am or 7:00am) [i.e. 8-way crossover]; there were 26–30 children evaluable for each parameter assessed. For discussion of these aspects in 4- to 7-week clinical trials in children with ADHD see section 3. No total MPH dosage was reported in this study, but based on MPH delivery rates of 0.45, 0.9 and 1.8 mg/hr (for 6.25, 12.5 and 25cm$^2$ patches, respectively) over a 12-hour wear time,[11] the MPH content delivered would be approximately 5, 11 and 22mg, respectively. In addition, this study utilised a smaller patch size (6.25cm$^2$) than those used in later clinical trials and those subsequently approved by the FDA.

**1** Daytrana is a trademark of Shire Pharmaceuticals Ireland Limited. The use of trade names is for product identification purposes only and does not imply endorsement.

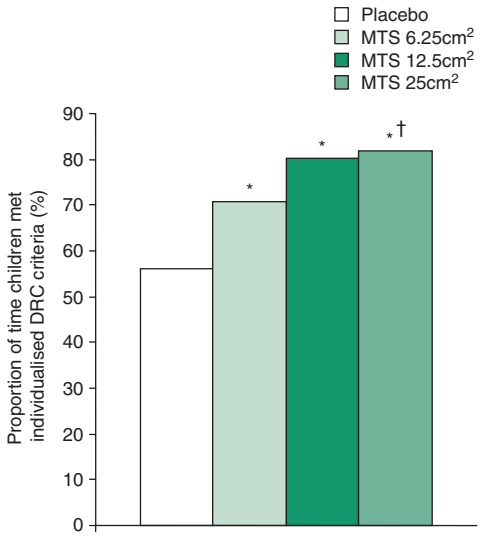


**Fig. 1.** Efficacy of methylphenidate transdermal system (MTS) patches in children (aged 7–12 years) with attention-deficit hyperactivity disorder. In this 8-day, randomised, double-blind, crossover trial, children (n = 26) received once-daily MTS patches 6.25, 12.5 or 25cm$^2$ applied for ≈12 hours, or placebo.[11] The primary endpoint was the proportion of time patients met individualised criteria on the Daily Report Card (DRC) assessment. * $p < 0.05$ vs placebo, † $p < 0.05$ vs lowest dose.

- Moreover, in this 8-day study, MTS treatment had no significant effect on mean pulse rate (≈81 beats/min for all treatments), or systolic (all ≈108mm Hg) or diastolic (all ≈64mm Hg) blood pressure relative to placebo.[11] However, MPH has been associated with increases in blood pressure and heart rate because of its sympathomimetic properties,[2] although the reported range of increases appears to be of minor clinical significance.[8]
- MPH treatment in children has been associated with mild growth suppression, relating to the continuity and length of treatment.[7,12] It is unknown whether the final height of children receiving MPH may be permanently reduced or if growth is merely delayed.

### Transdermal System Technology

MPH is delivered through the skin using a transdermal patch, which utilises DOT Matrix™ [2] technology (figure 2).[13] Acrylic and pressure-sensitive adhesive make up the novel formulation for the third generation DOT Matrix™ patches, with the acrylic designed to hold the MPH and silicone supplying the adhesive qualities. This allows a high concentration of the drug to be contained within a patch without compromising the patch's adhesive characteristics.[4] The earliest patch formulations generally solubilised the active drug in alcohol leading to localised skin irritation, while the second-generation formulations used acrylic to both hold the drug and to act as the adhesive. This meant that high drug concentrations could only be obtained at the expense of adhesion, whereas lower drug concentrations required skin permeation enhancers, which could also lead to problems with skin irritation.[4] DOT Matrix™ technology allows the required MPH dosage to be delivered in a thin, discreet and conveniently sized patch, which retains its adhesive properties and causes less skin irritation than found with earlier generation patches.

## 2. Pharmacokinetic Profile

The pharmacokinetic profile of MTS patches has been evaluated in several studies in paediatric patients with ADHD[14-16] and in healthy volunteers.[15] Additional pharmacokinetic data are available from the US prescribing information in children aged

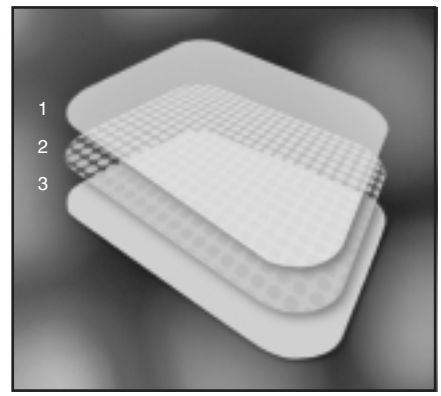


**Fig. 2.** Methylphenidate transdermal patch incorporating DOT Matrix™ technology. The patch is made up of (1) backing layer, (2) drug/adhesive mix and (3) release liner.[13]

**2** DOT Matrix is a trademark of Noven Pharmaceuticals, Inc.

6–12 years with ADHD.[5] In a randomised, double-blind, multicentre trial, children aged 6–12 years wore an MTS patch releasing MPH 10, 15, 20 or 30mg (12.5, 18.75, 25 or 37.5cm$^2$ patch size; n = 7, 36, 28 and 8, respectively) over ≈9 hours (poster presentation).[14] Blood samples were taken after 1 week of MTS treatment, following a 5-week dose optimisation phase titrating MTS to clinical effect.[14]

The pharmacokinetic properties of MPH in children with ADHD and healthy adults have been reviewed previously, and these data are included where relevant.[6]

### Absorption and Distribution

- With MTS patches releasing MPH 10–30mg over ≈9 hours (12.5–37.5cm$^2$ patch size), *d*- and *l*-MPH absorption increased in a dose-proportional manner in children with ADHD.[14] Mean peak plasma concentrations ($C_{max}$) for *d*-MPH were 20, 23.9, 30.5 and 46.5 ng/mL with MTS patches releasing MPH 10, 15, 20 or 30 mg/day, respectively, with a mean area under the plasma concentration-time curve from zero to 12 hours ($AUC_{12}$) of 145, 181, 229 and 378 ng • h/mL. Corresponding $C_{max}$ values for *l*-MPH were 14.6, 15, 18.4 and 29.5 ng/mL, with $AUC_{12}$ values of 86.2, 100, 129 and 229 ng • h/mL. The median time taken to achieve $C_{max}$ (i.e. $t_{max}$) ranged from 7.1–8.8 hours with *d*-MPH and 7.1–7.3 hours with *l*-MPH.[14]

- With chronic MTS therapy there appears to be an increase in the transdermal absorption of MPH.[5] In an MTS single-dose study,[5] the average time before *d*-MPH could be detected in the circulation (lag time) was 3.1 hours; however, this may not be clinically relevant as the efficacy of MTS was apparent at 2 hours in a multiple-dose study (see section 3, figure 3).[17] In another clinical trial,[5] 66% and 40% of children had *d*-MPH concentrations of <5 ng/mL at 2 and 3 hours, respectively. On day 4 of MTS treatment in a multiple-dose study in children aged 8–16 years with ADHD (n = 12),[16]

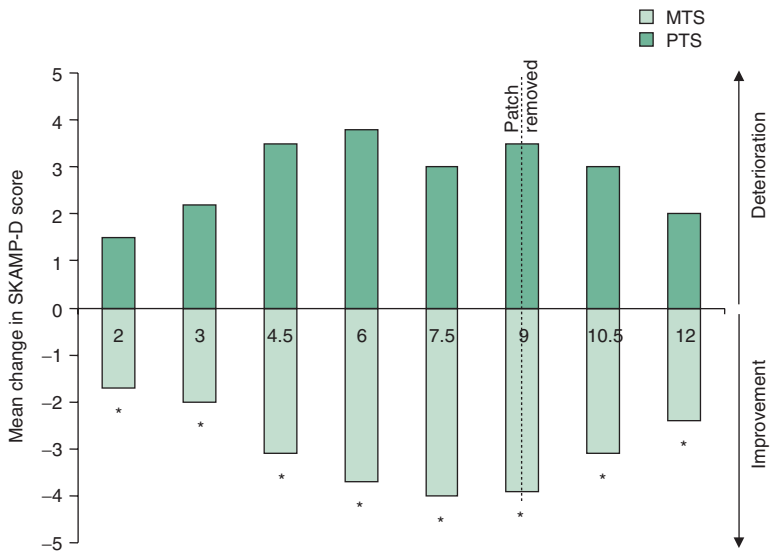


**Fig. 3.** Efficacy of methylphenidate transdermal system (MTS) patches in children (aged 6–12 years) with attention-deficit hyperactivity disorder. Changes from baseline in overall scores on the SKAMP-D rating scale at post-application timepoints (primary endpoint) [values estimated from graph].[17] In this 7-week, randomised, flexible-dose, multicentre, crossover trial, children (n = 79) received once-daily methylphenidate (MPH) titrated to clinical effect using MTS patches releasing MPH 10, 15, 20 and 30mg over 9 hours (12.5, 18.75, 25 and 37.5cm$^2$ patch size, respectively) or placebo transdermal system patches (PTS), applied for 9 hours.[17] The trial comprised a 5-week, open-label, dose optimisation phase followed by a 2-week, double-blind treatment phase. The number on the MTS bar represents the time (hours) after patch application at which SKAMP-D scores were assessed, with the patch removed at 9 hours. SKAMP-D = Swanson, Kotkin, Agler, M-Flynn and Pelham Ratings Scale-deportment subscale; * $p < 0.001$ vs PTS.

plasma *d*-MPH could be detected after 1 hour in 17% and 33% of patients receiving MTS 37.5 and 50cm$^2$ patches; 3 hours after patch application, plasma *d*-MPH levels were quantifiable.[16]

- In healthy volunteers, application of a 20mg (25cm$^2$) MTS patch resulted in similar plasma *d*-MPH concentrations to those achieved with three oral immediate-release MPH 20mg doses.[15] $AUC_{16}$ and $C_{max}$ values for MPH were ≈31% higher when the MTS patch was placed on a child's hip than when it was applied to the scapula for a 16-hour wear time.[15]
- MPH may continue to be distributed by the skin after the patch has been removed, as plasma MPH concentrations decline biexponentially in children with ADHD.[5] The binding of MPH to plasma proteins is reported to be low (10–33%);[10] a small (n = 8) study in paediatric patients indicated that ≈15.2% of MPH is bound to plasma protein.[6] After intravenous administration of a single dose of MPH 10mg in healthy adults (n = 11) the volume of distribution at steady state ($V_{ss}$) was 2.65 and 1.8 L/kg for *d*-MPH and *l*-MPH.[6]

### Metabolism and Elimination

- MPH is mainly metabolised through de-esterification to a carboxylic acid, α-phenyl-piperidine acetic acid (ritalinic acid), its primary metabolite.[6,10] Less than 2% is metabolised through minor pathways and there is no evidence that any of the metabolites have significant pharmacological activity.[6,10] The transdermal route of administration of MPH is subject to less first-pass effect than occurs with the oral route. Because first-pass metabolism greatly reduces the level of *l*-MPH, when racemic MPH is administered transdermally, the systemic level of *l*-MPH is approximately 27–45% lower on average than exposure to *d*-MPH.[5]
- A total body clearance of 0.4 and 0.73 L/h/kg for *d*- and *l*-MPH and a renal clearance rate of 0.005 L/h/kg for both enantiomers was observed in healthy adults receiving a single dose of methylphenidate 10mg intravenously.[6]
- In children receiving a once-daily, 9-hour application of MTS patches releasing MPH 10–30mg, the mean elimination half-life ($t_{1/2}\beta$) for *d*-MPH was ≈3 hours (specific values not reported).[14] The $t_{1/2}\beta$ for *l*-MPH was 1.8, 1.2, 1.3 and 1.5 hours for MTS patches releasing 10, 15, 20 and 30mg, respectively.[14]
- Cytochrome P450 does not appear to play a role in the metabolism of MPH[7] and there are few clinically significant interactions between methylphenidate and other drugs, although monoamine oxidase inhibitors have a potential for serious adverse events (e.g. a hypertension crisis) when coadministered with MPH.[7] Serious adverse events when MPH and clonidine have been used concomitantly have been reported, although the causality is unknown.[5] Interactions between MPH and drugs such as tricyclic antidepressants, coumarin anticoagulants, selective serotonin reuptake inhibitors, anticonvulsants, antipsychotics and antihypertensives may occur to some extent, although these interactions usually only warrant caution and monitoring of patients by the prescribing physician. If necessary, adjustments to drug dosages may be required to ensure plasma drug concentrations remain at therapeutic levels.[5,7]

### Factors Affecting Pharmacokinetics

- When the MTS application site was inflamed, the *d*-MPH lag time was less than 1 hour, the $C_{max}$ and AUC were ≈3-fold higher than normal and the $t_{max}$ dropped to 4 hours.[5] Exposure of the applied patch to heat reduced the median lag time by 1 hour, the median $C_{max}$ and AUC was increased (2- and 2.5-fold higher) and the $t_{max}$ was reduced by 0.5 hours.[5]

## 3. Therapeutic Efficacy

The efficacy of MTS patches in children with ADHD has been evaluated in three, 4- to 7-week, randomised trials (n = 79–270 intent-to-treat population).[17-19] Two of these were double-blind, placebo-controlled, multicentre studies;[17,18] no design details were reported for the other study.[19] In addition, a 6-week, dose-ranging, single-centre trial in 27 children investigated the efficacy of MTS treatment with or without a behavioural modification

program; this small study is only briefly discussed.[20] One of the well controlled trials[17] and the 6-week trial[20] are fully published; the other data are available as an abstract[19] and poster presentation.[18] Analyses were based on the intention-to-treat population unless stated otherwise.

Eligible children were aged 6–12 years[17-20] and diagnosed with ADHD using Diagnostic Interview Schedule for Children Version IV criteria[20] or from Diagnostic & Statistical Manual for Mental Disorders.[17,18]

Two 7-week trials had an initial 5-week, double-blind[18] or open-label[17] dose-optimisation phase.[17,18] After this period, in one trial,[18] responders (i.e. those who had achieved a ≥25% reduction in their ADHD Rating Scale-IV [ADHD-RS-IV] score) entered a 2-week, double-blind maintenance phase and, in the other trial,[17] patients were randomised to double-blind MTS patches for 1 week followed by placebo transdermal system (PTS) patches for 1 week, or vice versa, in a cross-over manner. Children received MTS patches,[17,18] OROS® [3] MPH tablets,[18] placebo tablets[18] or PTS[17,18] once daily in the morning, with the patches worn for ≈9 hours. Dosages were titrated to clinical effect using MTS patches releasing MPH 10, 15, 20 and 30mg over 9 hours (12.5, 18.75, 25 and 37.5cm$^2$ patch size, respectively)[17,18] or OROS® MPH 18, 27, 36 and 54mg tablets.[18] Another 4-week study optimised the dosage (based on efficacy and tolerability of the MTS patch) using an initial dosage of 0.9 or 1.35 mg/h (dependent on previous MPH treatment and bodyweight) and titrating up to a maximum dosage of 3.6 mg/h (patch size not reported).[19]

The primary efficacy endpoints were change from baseline at study endpoint in the ADHD-RS-IV total score[18] and the least square mean in the Swanson, Kotkin, Agler, M-Flynn, and Pelham Ratings Scale-deportment subscale (SKAMP-D) overall score at study end.[17] Other measures included the change in teacher inattention/overactivity (I/O) scores at study end,[19] the proportion of patients who reached individual target goals in Daily Report Card (DRC) scores,[20] improvements in Clinical Global Impressions-Severity (CGI-S) and -Improvement (CGI-I) scores at study end,[17-19] improvements in Parent Global Assessment (PGA) scores at study end,[17,18] changes in mean SKAMP Attention (SKAMP-A) and Permanent Product Measure of Performance (PERMP) scores,[17] investigator rated ADHD-RS-IV score at study end,[17] mean score in Conners' Parent Rating Scale-Revised Short Version (CPRS-R) and mean scores for point system and classroom behavioural measures.[20] Rating scales used for assessments in one trial[20] included Abbreviated Conners, Inattention/Overactivity With Aggression (IOWA) Conners (with two subscales of I/O and Oppositional/Defiant), Pittsburgh Modified Conners, effectiveness and stress ratings and child self-ratings.[20] For the ADHD-RS-IV, SKAMP-D and teacher I/O scores, a reduction in score corresponds with an improvement in ADHD symptoms, whereas the DRC scores are a proportional measure of individual behavioural goals and criteria that have been met each day.

- At study end, least square mean overall SKAMP-D scores were significantly ($p < 0.0001$; 95% CI −5.89, −3.64) lower in MTS than PTS recipients (3.2 vs 8) in a crossover study ($n = 79$ in the intent-to-treat group) [primary endpoint].[17] Moreover, the beneficial effects of MTS patches were observed at all time points after application of the patch and were still seen for ≈3 hours after the patch had been removed (i.e. throughout the 12-hour assessment period) [figure 3]. SKAMP-A scores also showed significantly (all $p < 0.0001$) greater reductions in MTS than placebo recipients at all post-application timepoints, as did the PERMP scores (all $p < 0.0001$) in both the number of maths problems attempted and the number of problems correct categories.[17] Similarly, mean ADHD-RS-IV and CPRS-R scores were significantly (both $p < 0.0001$) lower in MTS versus PTS recipients, and significantly (both $p < 0.0001$) greater proportions of patients receiving MTS showed improvement in both the CGI-I and PGA scores compared with those receiving PTS.[17]

**3** OROS® is a trademark of ALZA Corporation.

● MTS patches significantly improved ADHD symptoms compared with placebo in paediatric patients in a 7-week, flexible-dose trial.[18] Reductions in the mean total ADHD-RS-IV scores (primary endpoint) in MTS (n = 96), OROS® MPH (n = 89) and placebo (n = 85) recipients were 24.2 (95% CI −18.062, −9.724 vs placebo; $p < 0.0001$), 22 (95% CI −15.579, −7.059 vs placebo; $p < 0.0001$) and 9.9, respectively (figure 4). Although the study was not designed to compare MTS with OROS® MPH directly, there was no significant between-group difference in reductions in ADHD-RS-IV scores at study end. In the intent-to-treat population, mean baseline ADHD-RS-IV total scores were 43, 43.8 and 41.9 in the MTS, OROS® MPH and placebo groups.[18]

● MTS and OROS® MPH treatment also resulted in significant improvement in ADHD symptoms according to secondary endpoints for this trial.[18] A significantly (all $p < 0.0001$) greater proportion of MTS (73%) and OROS® MPH (67%) recipients showed an improvement in CGI-I ratings than placebo recipients (25%) and in the PGA rating scale (70%, 60% and 24% of MTS, OROS® MPH and placebo recipients, respectively) [all values estimated from graphs].[18]

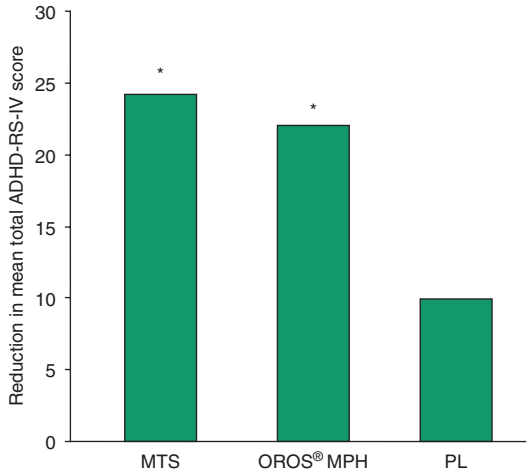


**Fig. 4.** Efficacy of methylphenidate transdermal system (MTS) patches in children (aged 6–12 years) with attention-deficit hyperactivity disorder. Reduction from baseline in mean total ADHD-RS-IV scores (primary endpoint).[18] In this 7-week, randomised, flexible-dose, multicentre trial, children received once-daily methylphenidate (MPH) titrated to clinical effect using MTS patches (n = 96) releasing MPH 10, 15, 20 and 30mg over 9 hours (12.5, 18.75, 25 and 37.5cm$^2$ patch size, respectively), OROS® MPH 18, 27, 36 and 54mg tablets (n = 89) or placebo (PL) [n = 85].[18] The trial comprised a 5-week, double-blind, dose optimisation phase followed by a 2-week, double-blind treatment phase. The study was not powered to directly compare MTS with OROS® MPH. **ADHD-RS-IV** = attention-deficit hyperactivity rating scale-IV; * $p < 0.0001$ vs PL.

● In the 4-week flexible-dose study in 212 children with ADHD, I/O scores significantly improved with MTS patches compared with placebo tablets (reduced by 5.3 vs 1.1; $p < 0.0001$).[19] A significantly ($p < 0.0001$) greater proportion of MTS than placebo recipients responded to treatment (68.9% vs 13.6%), as assessed by CGI-I ratings.

● MTS treatment in combination with a behavioural modification programme was more effective than MTS treatment alone or behavioural treatment at improving ADHD symptoms in 21 evaluable children.[20] In this 6-week, dose-ranging, single-centre study, children received MTS 12.5, 25 or 37.5cm$^2$ patches (no dosage reported) or placebo tablets; patches were applied for ≈8.5 hours. Each child had 2 days on each treatment without concomitant behavioural modification therapy and 4 days on each treatment with concomitant behavioural treatment, with the children, parents and teachers blind with regard to the medication being used.

● For example, the percentage of individualised target criteria met by children in their DRC assessment was significantly (all $p < 0.05$) higher in the MTS 12.5, 25 and 37.5cm$^2$ groups than in placebo recipients, both without (41.9%, 63.1% and 66.2% vs 20.8%) and with (73.7%, 87.5% and 86.2% vs 54.7%) concomitant behavioural modification.[20] These response rates were higher in the MTS 25cm$^2$ group than in the 12.5cm$^2$ group, both with and without behavioural modification (both $p < 0.05$); increasing the size of the patch to 37.5cm$^2$ gave no further added advantage.

## 4. Tolerability

MTS patches were generally well tolerated in children with ADHD participating in clinical trials discussed in section 3.[17-20] To date, no long-term tolerability data are available.

• In the largest trial, most (99%) treatment-emergent adverse events were mild to moderate in severity.[18] Four severe adverse events were reported, three of which were thought to be unrelated to the study medication and one (syncope) of which was deemed possibly related to the study drug. There were no serious life-threatening adverse events or deaths reported.

• Treatment-emergent adverse events that occurred in ≥5% of MTS or OROS® MPH recipients and with a 2-fold higher incidence than in the placebo group are summarised in figure 5.[18] Those occurring with a ≥10% incidence in MTS recipients were decreased appetite, insomnia, nausea and vomiting. Moreover, the nature of treatment-emergent adverse events was similar in MTS recipients to those occurring in OROS® MPH recipients (figure 5).

• MTS patches have the potential for skin irritation and sensitisation.[5] In a clinical trial discussed in section 3,[17] the incidence of skin irritation in MTS versus PTS recipients was low (1.3% vs 2.5%), with the numerically higher proportion of PTS recipients experiencing a skin reaction suggesting that their skin rash was a response to the patch itself rather than the drug *per se*. In a small study (n = 27),[20] one child withdrew due to irritation from the patch. Another small, 8-day study (n = 36)[11] reported a high incidence of skin rash (≈40–50% of all patients) when the adhesive patch was removed (see section 1); however, the patch had an application time of 12 hours, which is longer than that used in the clinical trials[17,18,20] discussed in section 3 (≈9 hours application time) and longer than the recommended application time.[5]

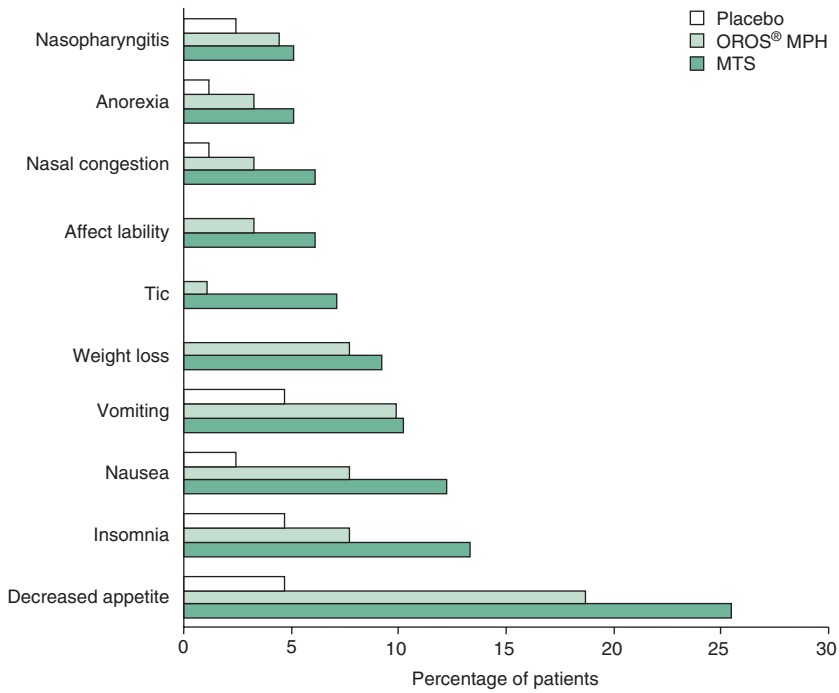


**Fig. 5.** Tolerability profile of methylphenidate transdermal system (MTS) and comparators in children with attention-deficit hyperactivity disorder.[18] Treatment-emergent adverse events occurring with an incidence of ≥5% and a 2-fold higher incidence in MTS patch recipients than in placebo recipients. In this randomised, double-blind, placebo-controlled study, children aged 6–12 years received once-daily methylphenidate (MPH) titrated to clinical effect using MTS patches releasing MPH 10, 15, 20 and 30mg (12.5, 18.75, 25 and 37.5cm$^2$ patch size, respectively) applied for ≈9 hours (n = 96), once daily OROS® MPH 18, 27, 36 and 54mg tablets (n = 89) or placebo (n = 85) for 7 weeks.[18] Where placebo bars are absent, the incidence of that adverse event was 0%.

- Skin sensitisation, after continuous same-site MTS contact, was observed in a study designed to elicit this effect (study reported in the prescribing information[5] and in a safety summary for the Psychopharmacologic Drugs Advisory Committee[21]). Adult patients had the same skin site exposed to MTS for 3 weeks, followed by a 2-week break and re-exposure to MTS.[5,21] Compared with a placebo patch or saline, MTS was shown to be more irritating and 13.5% of the patients (challenge phase of study, n = 133) became sensitised to MTS.[5]
- When MTS has been used as prescribed no cases of contact sensitisation have been reported.[5] For further guidance on the administration of MTS, see section 5.
- Methylphenidate may aggravate existing conditions involving agitation and tics and the use of stimulant treatments in children with structural heart abnormalities has been associated with sudden death.[5] In addition, there is a possibility that drug dependence could develop because of the stimulant nature of the active drug.[5]

## 5. Dosage and Administration

MTS should be administered once daily, 2 hours before the effect of MPH is required, as an application of the patch to the hip area and should be removed after 9 hours' wear time.[5] MPH should be titrated to clinical effect using MTS 10mg ($12.5cm^2$), 15mg ($18.75cm^2$), 20mg ($25cm^2$) and 30mg ($37.5cm^2$) patches (dosage based on a 9-hour application time). If a shorter period of effect is preferred, or adverse events appear late in the day, the patch can be removed earlier than the recommended 9 hours, as directed by the physician.[5]

The adhesive side of the MTS patch should be applied to a clean, dry part of the hip free from oil, damage or irritation.[5] The patch should be placed on different sites each day, preferably on the opposite hip, and placed so as to prevent clothing from rubbing it. To ensure good contact with the skin, the patch should be pressed firmly with the palm of the hand and held for ≈30 seconds. If the patch comes off at any stage a new patch may be used on a different area of the hip; however, the total daily wear time should not exceed 9 hours. While the patch is being worn, exposure of the application site to direct heat sources, for example electric blankets, should be avoided. Used or unnecessary patches should be folded so that the adhesive sides stick to each other and then discarded into a lidded container or flushed down the toilet.[5]

If contact sensitisation develops, systemic sensitisation or other systemic reactions may develop if agents containing MPH are administered at any subsequent time, by any route.[5] Consequently, the administration of MPH following MTS treatment should be carried out under close medical supervision.

MTS is contraindicated in patients with hypersensitivity to MPH, agitation, glaucoma and tics and in those being treated with monoamine oxidase inhibitors.[5] Treatment with CNS stimulants is associated with sudden death in patients with structural cardiac abnormalities and caution is necessary for patients with a history of drug dependence or alcoholism. For further information on warnings, contraindications, precautions and potential drug interactions, consult the manufacturer's prescribing information.[5]

## 6. Methylphenidate Transdermal System: Current Status in Attention-Deficit Hyperactivity Disorder in Children

MTS patches are approved in the US for the treatment of ADHD in children. This novel delivery system for MPH is the only approved method of administering the drug transdermally. In two well designed trials, MTS treatment using 10mg ($12.5cm^2$), 15mg ($18.75cm^2$), 20mg ($25cm^2$) and 30mg ($37.5cm^2$) patches (dosage obtained after 9 hours of wear time) improved ADHD symptoms and was generally well tolerated in children aged 6–12 years.

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