



# Transdermal methylphenidate

Patch designed for flexible, long-acting coverage

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**W**hen prescribing methylphenidate to children with attention-deficit/hyperactivity disorder (ADHD), psychiatrists have had two options:

- immediate-release oral methylphenidate, which works for 3 to 5 hours, necessitating multiple daily doses
- extended-release oral methylphenidate, which can prevent irritability and other rebound symptoms caused by multiple daily dosing.<sup>1</sup> Because its effects last 12 hours, however, once-daily dosing with this formulation is inflexible.

A new option—a transdermal methylphenidate patch FDA-approved for treating ADHD in children ages 6 to 12 (*Table 1*)—offers flexible methylphenidate coverage based on response to or need for the medication.

## CLINICAL IMPLICATIONS

The transdermal patch allows dosing to be tailored—or changed day to day as needed—to maximize effectiveness and reduce side-effect risk. The manufacturer recommends that the patch be worn for 9 hours daily, but it can be removed sooner if children experience appetite loss, insomnia, or other

Table 1

### Transdermal methylphenidate: Fast facts

**Brand name:** Daytrana

**Class:** CNS stimulant

**FDA-approved indication:** ADHD in children ages 6 to 12

**Manufacturer:** Noven Pharmaceuticals (marketed by Shire PLC)

**Dosing forms:** 10-, 15-, 20-, and 30-mg patches

**Recommended dosage:** One 10- to 30-mg patch daily, worn on the hip for 9 hours. Patient can remove patch sooner if side effects become problematic.

adverse effects with 9 hours of exposure to methylphenidate.

Minimizing daily exposure to methylphenidate can also reduce the risk of long-term effects. Findings from one large, randomized clinical trial<sup>2</sup> suggest that chronic exposure to high-dose stimulant medications might suppress growth in height

Table 2

**Transdermal methylphenidate dosage delivery in children ages 6 to 12**

Dose delivered over 9 hours (mg)	Patch size (cm <sup>2</sup> )	Dosage rate (mg/hr)	Methylphenidate content per patch (mg)
10	12.5	1.1	27.5
15	18.75	1.6	41.3
20	25	2.2	55.0
30	37.5	3.3	82.5

Source: Reference 4

**PHARMACOKINETICS**

Methylphenidate, a known CNS stimulant, blocks norepinephrine and dopamine reuptake in the presynaptic neuron, thereby releasing more of these neurotransmitters into the extraneuronal space.<sup>4</sup> Methylphenidate’s precise therapeutic action in ADHD is not known.

and weight, although other data indicate that initial height reductions found in children receiving methylphenidate for ADHD were no longer significant in adulthood.<sup>3</sup>

The patch also could benefit youths who have trouble following dosing schedules and young children who are unable to swallow pills.

**HOW IT WORKS**

The patch contains methylphenidate dispersed in an acrylic multipolymeric adhesive that is further dispersed in a silicone adhesive.<sup>4</sup> The methylphenidate within the acrylic adhesive flows into the skin, then into the bloodstream. The patch is worn on the hip—where it is covered by clothing and unlikely to be dislodged—and changed daily.

The patch comes in four sizes—12.5, 18.75, 25, and 37.5 cm<sup>2</sup>—which, respectively, deliver 10, 15, 20, and 30 mg of methylphenidate over 9 hours.<sup>4</sup> Methylphenidate concentration is the same for all four sizes, so patch size and duration of use determine dose delivery.

In clinical trials, therapeutic effect was seen 2 hours after patch placement and continued through 12 hours.<sup>5</sup> Methylphenidate is delivered continuously while the patch is in place and for as long as 2 hours after it is removed.

Methylphenidate is a racemic mixture of d- and l-enantiomers, the first of which is believed to be more active. Whereas the liver removes the l-enantiomer from oral methylphenidate, the transdermal formulation bypasses the liver and preserves the l-enantiomer, thus increasing exposure to racemic methylphenidate. This means that optimal dosages of transdermal methylphenidate (10 to 30 mg/d) may be lower compared with the oral formulation<sup>5-7</sup> (Table 2).

Methylphenidate’s d-enantiomer has a mean 3- to 4-hour elimination half-life, approximately twice that of the l-enantiomer. This is why transdermal methylphenidate continues to exert therapeutic effect several hours after the patch is removed.<sup>5</sup>

**EFFICACY**

Results from randomized, double-blind, placebo-controlled trials support short-term use of transdermal methylphenidate in ADHD. The following studies recruited children ages 6 to 12 with the disorder.

**Dose-ranging study.** Thirty-three children participating in a summer treatment program received transdermal methylphenidate, 6.25, 12.5, or 25 cm<sup>2</sup> 12 hours daily for 8 days.<sup>6</sup> All three patch sizes were associated with improved academic,

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social, and behavioral functioning based on a range of measures.

Dose response rate diminished with higher dosages, and significant further improvements were difficult to detect as dosages increased. The children also received intensive behavioral treatment during the study, which might have accounted for some therapeutic gains and diminished the researchers' ability to detect subtle improvements with increased dosages.

Children also had fewer negative behaviors during the first hour when the patch was applied at 6 AM instead of 7 AM. This suggests that the patch might produce optimal effect when placed first thing in the morning.

**Randomized crossover trial.**<sup>7</sup> Across 6 weeks, 27 children were given placebo or transdermal methylphenidate, 12.5, 25, or 37.5 cm<sup>2</sup>/d. The children also received behavior modification treatment on alternating weeks. Medication was randomly assigned and varied daily for 4 days per week over 6 weeks, and behavioral treatment was varied weekly for 4 weeks. Each subject took each dosage for 2 days without behavioral treatment and for 4 days with behavioral treatment.

Academic productivity, interactions with peers and adults, and compliance during class improved with all dosages compared with placebo. Although most children removed the patch by 3:30 PM after 9 hours of use, parents reported

that positive behavioral effects lasted into the evening.

As in the dose-ranging study, dose response diminished with higher dosages. Optimal effects were achieved on some measures with 12.5 cm<sup>2</sup> of transdermal methylphenidate, which produces the same plasma drug level as 10 mg of oral methylphenidate.<sup>7</sup>

**Multisite crossover study.**<sup>5</sup> Eighty children received transdermal methylphenidate—12.5, 18.75, 25, or 37.5 cm<sup>2</sup> based on response to medication—over 5 weeks for 9 hours daily. Dosages were titrated by changing patch sizes until each child reached his or her optimal dosage. Children then received their optimal dosage or placebo for 1 week, then received the opposite treatment for another week. Results were measured in a simulated classroom.

Overall, children showed statistically significant improvement in Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) Teacher Rating Scale scores while receiving their optimal dosage. Improvement was seen 2 hours after patches were applied and continued for 12 hours. Children also were more able to solve math problems during optimal dosage periods than while using placebo.

Nearly 80% of children were rated as significantly improved while receiving transdermal methylphenidate based on Clinical Global Impressions of Improvement scores. Roughly 12% of children showed significant improvement with placebo. Parents reported that their children were markedly less hyperactive and impulsive and more attentive during optimal dosage periods.

#### TOLERABILITY

No serious side effects were reported during clinical trials of transdermal methylphenidate in children ages 6 to 12.<sup>5-7</sup> Side effects commonly associated with oral methylphenidate—*anorexia, decreased appetite, headache, insomnia, and*

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abdominal pain—were most frequently reported with the patch.<sup>5</sup>

In one study,<sup>6</sup> 61% of children who wore the patch for 12 hours/day reported appetite loss and 47% reported insomnia. Insomnia prevalence diminished substantially when daily wear was limited to 9 hours.<sup>2,5</sup> Loss of appetite was reported less often with lower-dose patches (12.5, 18.75 cm<sup>2</sup>) than with higher-dose patches (25, 37.5 cm<sup>2</sup>).

Although many children complained of erythema at the patch site,<sup>5,7</sup> most reported minimal irritation or discomfort.<sup>5</sup> Redness usually dissipated about 8 hours after the patch was removed.<sup>6</sup>

Despite concerns that youths with impulsive behaviors might remove the patches prematurely, very few children did so during clinical trials.<sup>5,7</sup> Those who did had comorbid symptomatic conduct disturbances. Compliance with patch placement and maintenance was very high during dose optimization (98%) and analog classroom analysis (97%).<sup>5,7</sup>

## DOSING

Start transdermal methylphenidate at 12.5 cm<sup>2</sup> (10 mg) for children who have never taken methylphenidate or were previously stabilized on the drug. If the child does not respond after 1 week, switch to the 18.75 cm<sup>2</sup> (15-mg) patch; keep switching to the next largest patch each week until optimal response is achieved. In clinical trials,<sup>5,7</sup> 18.75 or 25 cm<sup>2</sup> (10 mg) of transdermal methylphenidate produced optimal response for most children.

Advise the child and parents to place the patch on the right and left hip on alternate days to minimize irritation. Counsel children to inform parents if the patch causes itching, burning, or irritation; tell parents to call you if they notice or the child complains of irritation. Children who experience intolerable skin sensitivity with the patch can resume taking oral methylphenidate the day after the patch is removed.

## Related resources

- ▶ Transdermal methylphenidate Web site. [www.daytrana.com](http://www.daytrana.com).
- ▶ Greenhill LL, Pliszka S, Dulcan MK, et al. Practice parameter for the use of stimulant medications in the treatment of children, adolescents, and adults. *J Am Acad Child Adolesc Psychiatry* 2002; 41:26S-49S.

### DRUG BRAND NAMES

Methylphenidate (oral) • Concerta, Ritalin, Metadate      Methylphenidate (transdermal) • Daytrana

### DISCLOSURES

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

As with oral methylphenidate, the transdermal formulation may be discontinued without a taper and another formulation or medication may be started the next day. Ask the child and parents about side effects at each visit. See the child every 2 to 4 weeks during the titration period and monthly after symptoms are stabilized.

Consider trying a “drug holiday” for at least 2 weeks during the summer to see how the child behaves without methylphenidate, then evaluate the need for medication and determine the optimal dosage close to when the school year begins.

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