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Updates in Psychopharmacology: Two New Patches

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Adhesive transdermal patches have been available on the U.S. market for more than 20 years. Since the first scopolamine transdermal patch was approved in 1981, the Food and Drug Administration has approved more than 35 transdermal patch products.[1] Methylphenidate, a stimulant medication used to treat attention deficit hyperactivity disorder, and selegiline, a monoamine oxidase inhibitor used for the treatment of depression, have both been reformulated into a transdermal delivery system. The evidence supporting their efficacy and their appropriate use are discussed.

Transdermal drug delivery is the distribution of drugs across the skin into systemic circulation. Not all human skin is the same and minor variations can affect drug delivery.[2] Neonates and elderly patients have more permeable skin than other ages and the skin of Caucasian patients is more permeable than that of African Americans. The most permeable regions of the body include: mucous membranes, scrotal skin, and eyelids. Areas of intermediate permeability include the: face/head, chest/back, buttocks, abdomen, and upper arms/legs. The least permeable areas of the body are the palmar/plantar surfaces and nails. Well hydrated skin is more permeable than dry skin. Skin that is broken or irritated have increased permeability.

The transdermal patch is an alternative to oral medications for patients who cannot swallow and may improve adherence by providing a slow release of medication over an extended period of time. The disadvantages of transdermal medications include: application site reactions, delayed onset of activity, and the potential for toxicity if handled inappropriately. In order to maintain consistent release rates, transdermal patches contain a surplus of active drug. Most transdermal patches contain 20 times the amount of drug that will be absorbed during the time of application.[2] Thus, after removal, many patches contain 95% of the total drug initially contained in the patch and patients need to exercise care when disposing of them. Each patch should be folded in half and the adhesive sides should be stuck together. As an additional precaution, patches may be flushed down the toilet rather than discarded in household trash. The appropriate use and disposal of patches becomes even more important in transdermal delivery systems that are indicated for use in children.

Transdermal Methylphenidate (*Daytrana*)

Methylphenidate (MPD) is used in the treatment of attention deficit/hyperactivity disorder (ADHD). The short duration of action of the immediate release preparation has led a number of manufacturers to market once-daily products (e.g. *Concerta, Metadate CD*, and *Ritalin LA*). The long-acting transdermal formulation of MPD, Daytrana® (Shire) was approved in April 2006.

Compared to other long-acting products, the methylphenidate transdermal system (MTS) has a more delayed onset. After application, MPD is not detected in plasma for about 3 hours (range 1-6 hours). In children, following a single MTS application of about 9 hours, plasma concentrations were similar to those found with equivalent doses of long-acting oral methylphenidate (*Concerta*). But, after repeated daily dosing, concentrations were almost double those of the oral drug, suggesting increased absorption with chronic dosing.[3] To prevent excessive absorption, the MTS should not be exposed to sources of heat. The mean elimination half-life of d-MPD (active isomer) after removal of the patch (8-10 hours of wear time) is about 3-4 hours. Even after the MTS is removed, MPD distribution from the skin may continue to occur.[3]

In several clinical trials, each limited by size and/or duration, MTS exhibited greater activity than placebo in the treatment of ADHD.[4-8] The most notable trials are available in Table 1. Studies directly comparing MTS with methylphenidate oral or other stimulant therapies have not been published, but one study comparing MTS and methylphenidate extended-release tablets (*Concerta*) to placebo is included in the FDA briefing documents.[4] Unpublished data cited in another study suggest the methylphenidate 20 cm^2 transdermal system produced effects comparable with those of methylphenidate 10 mg immediate-release administered 3 times daily.[6]

Systemic effects with the patch are dose-related and are similar to oral forms of MPD. In the trial using long-acting oral MPD (*Concerta*) as an active control, nausea, vomiting, decreased appetite, anorexia, weight loss, emotional lability and insomnia occurred more frequently with the patch than with oral MPD.[4] Tics were reported in 7% of patients using the patch compared to 1% of those taking oral MPD. In a long-term, open-label study that included 191 children wearing the patch for 12 hours a day for up to 40 months, the incidence of anorexia was 46% and that of insomnia was 30%.[4]

Dermal side effects, erythema and pruritus, at the application site were common in clinical studies.[3] Contact sensitization to the patch has led to the development of systemic sensitization to other forms of MPD. Sensitization should be suspected if erythema is accompanied by evidence of a more intense local reaction (edema, papules, vesicles) that does not significantly improve within 48 hours or spreads beyond the patch site. This occurrence would prevent the future use of any MPD product.

The MTS needs to be applied daily 2-3 hours before an effect is needed and should not be worn for more than 9 hours. The dosage should be titrated to effect, with all patients initiated at the 10 mg dose and increased to the 15, 20, and 30 mg doses as needed at weekly intervals. With chronic administration, dosage reduction may be necessary. Although comparative studies are needed, the transdermal application of MPD does not appear to confer additional benefit over oral long-acting MPD and may cause an increased rate of side effects. Prescribers and caregivers should be cautioned about the misuse and potential subsequent toxicity associated with MPD "stickers." The average monthly cost of *Daytrana* is $130 (Table 2).

Table 1. Clinical trials comparing transdermal methylphenidate to placebo.

STUDY	DURATION	POPULATION	TREATMENT	ENDPOINT	FINDINGS
R, DB, PC Phase III trial[4]	2-weeks	N=270 6-12 year olds	1. MTS 2. CON 3. PCB	Change in ADHD-RS-IV	MTS = -24.2 CON = -22.0 PCB = -9.9 (p<0.0001) Study not designed nor powered to detect differences between MPD products, but did show more adverse effects with patch. No apparent advantage to 30mg over 20mg patch.
R, DB, PC-crossover Phase II trial[5]	5-week dose optimization phase; 2-week trial; 1 week each treatment	N=79 6-12 year olds with ADHD	MTS vs. PCB	SKAMP-D	MTS = 3.2 vs PCB = 8 (p<0.0001)

R=randomized, DB=double blind, PC=placebo controlled
MTS=methylphenidate transdermal system, CON=Concerta, PCB=placebo
ADHD-RS-IV=ADHD rating scale IV, SKAMP-D= Swanson, Kotkin, Agler, M-Flynn, and Pelham-Deportment scale

Table 2. Cost of long-acting stimulant medications.

Drug	*Cost/Month*
Methylphenidate SA	$30
Concerta	$110
Adderall XR (all strengths)	$120
Daytrana (all strengths)	$130
Average 30-day retail cost to OHP Q2-06, excludes rebate	

Transdermal Selegiline (*Emsam*)

Selegiline is an irreversible monoamine oxidase inhibitor (MAOI) traditionally used for the treatment of Parkinson's Disease. At low oral doses, selegiline is a selective inhibitor of MAO-B; at higher doses it inhibits both MAO-A and MAO-B.[9] To be an effective MAOI antidepressant, oral selegiline needs to be given at a higher dose. The transdermal patch (indicated for the treatment of major depressive disorder) was developed to deliver sustained blood concentrations of selegiline to the central nervous system without extensively inhibiting MAO-A in the intestinal mucosa and liver thus decreasing the need for dietary restrictions. Due to its absorption and avoidance of first-pass metabolism, transdermal selegiline (TS) is associated with a 2- to 5-fold increase in selegiline levels compared to the oral dosage form.

Transdermal selegiline has been shown to be effective in clinical trials at dosages of 6mg/24 hours to 12mg/24 hours; however, studies were not designed to determine if the higher dosages are more effective than the 6mg/24 hours doseage. There are two main clinical trials comparing TS to placebo (Table 3).[10,11] Both trials included the same outcome measures. The larger of the two studies failed to demonstrate the superiority of TS over placebo at any time point as measured by the 17-item Hamilton Depression Scale (HAM-D). In addition, the 17- and 28-item HAM-D response rates (defined as ≥50% score reduction) for TS were no better than placebo.

In another unpublished double-blind study, 322 patients meeting DSM-IV criteria for major depressive disorder who had responded during open-label therapy with TS 6 mg/24 hours were randomized to continue therapy at the same dose (159 patients) or to placebo (163 patients). Approximately 52% of patients in both groups discontinued therapy by week 12 of the double-blind phase; however, patients continuing therapy in the TS group experienced a longer time to relapse.[12]

Adverse reactions reported during therapy with TS included application-site reactions, headache, diarrhea, dizziness, insomnia, somnolence, and dry mouth.[9] Application-site reactions (rash, itching, redness, irritation, swelling, urticaria) and insomnia occurred more frequently in patients treated with TS than placebo.[9, 10, 11, 13] Drug interactions with TS are identical to those found with oral MAOIs.

TS should be applied to dry, intact skin on the upper torso, upper thigh, or the outer surface of the upper arm once every 24 hours. Although higher strengths are available, the recommended starting dose and the target dose of TS is 6mg/24 hours. Studies comparing the efficacy of different doses have not been done, so the optimal dose for the treatment of depression is not known. If the dose is raised over 6mg/24 hours, then liver and intestinal MAO-A is inhibited and dietary restrictions should be in place. If higher doses are necessary, then the patch does not confer any benefit over the oral MAOIs and should be reserved for patients who cannot swallow. Like oral MAOIs, TS at all doses is associated with numerous potential drug interactions. The average monthly cost of *Emsam* is $410 (Table 4).

Table 4. Cost for selected antidepressant medications.

Drug	Cost/Month
Fluoxetine	$5
Citalopram	$10
Zoloft	$100
Wellbutrin XL	$125
Cymbalta	$130
Effexor XR	$140
Emsam (all strengths)	$410
Average 30-day retail cost to OHP Q2-06, excludes rebate	

Conclusion

The transdermal application of methylphenidate and selegiline does not appear to offer clinical advantages over oral products. Because they require daily application, neither patch would be expected to improve adherence. The MTS is associated with an increased rate of adverse effects and has a high potential for intentional or accidental diversion. TS is limited by a narrow dosing range. Both products should be reserved for patients who cannot swallow.

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Table 3. Clinical trials comparing transdermal selegiline to placebo.

STUDY	DURATION	POPULATION	TREATMENT	ENDPOINT	FINDINGS
R, DB, PC fixed dose study[10]	6-weeks	N=177 adult outpatients with MDD	TS 6mg/24hr vs. PCB Tyramine-restricted diet	17- and 28-item HAM-D MADRS Response defined as ≥50% reduction in HAM-D scales	$HAM\text{-}D_{17}$ Δ at endpt (TS-8.73, PCB -6.10; p=0.01) $HAM\text{-}D_{28}$ Δ at endpt (TS-11.23, PCB-7.59; p=0.004) MADRS Δ at endpt (TS-9.77, PCB-5.69; p=0.005) RR (TS 33%, PCB 20%; p=0.04)
R, DB, PC fixed dose study[11]	8 weeks	N=289 adult outpatients with MDD	TS 6mg/24hr vs. PCB No diet restrictions	MADRS 17- and 28-item HAM-D Response defined as ≥50% reduction in MADRS and HAM-D scales	MADRS Δ at endpt (TS-10.21, PCB-6.72; p=0.001) $HAM\text{-}D_{28}$ Δ at endpt (TS-10.28, PCB-8.53; p=0.039) $HAM\text{-}D_{17}$ TS not SS better than PCB at any pt. RR only SS better than PCB with MADRS scale (TS 33%, PCB 30%, p=.031)

R=randomized, DB=double blind, PC=placebo controlled
MDD=major depressive disorder, TS=transdermal selegiline,
HAM-D= Hamilton Depression Scale, MADRS=Montgomery Asberg Depression Rating Scale,
PCB=placebo, RR=response rate, SS=statistically significant

References

1. Electronic Orange Book. Food and Drug Administration. Available at www.fda.gov/cder/ob. Accessed August 7, 2006.
2. Wilkosz MF, Bogner RH. Transdermal Drug Delivery; Part 1: Current status. U.S. Pharmacist. 2003;28. Available at http://www.uspharmacist.com. Accessed August 7, 2006.
3. *Daytrana* [package insert]. Wayne, PA: Shire Pharmaceuticals. Available at http://www.daytrana.com/pdf/pdf1.pdf Accessed July 31, 2006
4. Levin R, for the Food and Drug Administration Psychopharmacologic Drugs Advisory Committee. Clinical review for NDA 21-514 (methylphenidate transdermal system). December 2, 2005. Available at: http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4195B1_01_01-Noven-Briefing-Document.pdf. Accessed August 7, 2006.
5. McGough JJ, Wigal SB, Abikoff H, Turnbow JM, Posner K, Moon E. A randomized, double-blind, placebo-controlled, laboratory classroom assessment of methylphenidate transdermal system in children with ADHD. *J Atten Disord*. 2006;9:476-485.
6. Pelham WE, Manos MJ, Ezzell CE, et al. A dose-ranging study of a methylphenidate transdermal system in children with ADHD. *J Am Acad Child Adolesc Psychiatry*. 2005;44:522-529.
7. Pelham WE, Burrows-Maclean L, Gnagy EM, et al. Transdermal methylphenidate, behavioral, and combined treatment for children with ADHD. *Exp Clin Psychopharmacol*. 2005;13:111-126.
8. Fabiano GA, Gnagy EM, Burrows-MacLean L, Hoffman MT, Pelham WE, Morse G. Onset and offset time-course of a methylphenidate transdermal system [abstract]. American Psychiatric Association 155th Annual Meeting; May 18–23, 2002; Washington, DC. Abstract NR337.
9. *Emsam* [package insert]. Tampa, FL: Somerset Pharmaceuticals Inc.; February 2006. Available at http://www.emsam.com. Accessed August 1, 2006.
10. Bodkin JA, Amsterdam JD. Transdermal selegiline in major depression: a double-blind, placebo-controlled, parallel-group study in outpatients. *Am J Psychiatry*. 2002;159:1869-1875.
11. Amsterdam JD. A double-blind, placebo-controlled trial of the safety and efficacy of selegiline transdermal system without dietary restrictions in patients with major depressive disorder. *J Clin Psychiatry*. 2003;64:208-214.
12. Preskorn S, for the Food and Drug Administration Psychopharmacologic Drugs Advisory Committee. Clinical review for NDA 21-336/21-708 (selegiline transdermal system). October 26, 2005. Available at: http://www.fda.gov/ohrms/dockets/ac/05/ briefing/2005-4186B2_01_01_Somerset-EMSAM.pdf Accessed August 1, 2006.
13. Robinson DS, Campbell BJ, Amsterdam JD. Safety and tolerability of the selegiline transdermal system 20 mg for treatment of major depression [abstract]. *Neuropsychopharmacology*. 2005;30(suppl 1):S234.

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