Transdermal selegiline
MAO-inhibiting antidepressant in a patch

J. Alexander Bodkin, MD
Assistant professor of psychiatry
Harvard Medical School, Cambridge, MA
Chief, Clinical Psychopharmacology Research Program
McLean Hospital, Belmont, MA

Many psychiatrists do not prescribe monoamine oxidase inhibitors (MAOIs) for fear of causing a potentially fatal hypertensive reaction, even though restricting foods high in the amino acid tyramine usually prevents this effect. Consequently, most depressed patients who might respond well to MAOIs do not receive them.

Transdermal selegiline, FDA-approved for treating major depressive disorder (MDD) (Table 1), offers the clinical efficacy of an MAOI but without adverse interactions with food at the 6-mg strength. Transdermal selegiline may inhibit too much gastrointestinal MAO-A at 9 mg/d and 12 mg/d to clear tyramine from foods, so tyramine-rich foods must be restricted at these dosages (Table 2, page 81).

HOW IT WORKS
MAO enzyme subtypes A and B metabolize CNS monoamines, but primarily MAO-A metabolizes tyramine in the gut before the amino acid enters systemic circulation. At low concentrations, selegiline selectively inhibits MAO-B.

Oral selegiline, approved as a adjunct to levodopa/carbidopa for patients with Parkinson’s disease, has been shown to be effective for treating depression at ≥30 mg/d. Because the drug does not selectively inhibit MAO-B at ≥20 mg/d, dietary tyramine must be restricted when oral selegiline is used off-label at therapeutic dosages for depression. Otherwise, selegiline has been well-tolerated up to 60 mg/d.

The 6-mg “patch” delivers more selegiline to the bloodstream than does low-dose oral selegiline but without inhibiting gut MAO-A. This provides the brain MAO-A and MAO-B inhibition necessary for an antidepressant effect while eliminating the need for dietary restrictions at this lowest dosage.

Transdermal selegiline: Fast facts

<table>
<thead>
<tr>
<th>Brand name:</th>
<th>EMSAM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class:</td>
<td>Monoamine oxidase inhibitor</td>
</tr>
<tr>
<td>FDA-approved indication:</td>
<td>Major depressive disorder</td>
</tr>
<tr>
<td>Manufacturer:</td>
<td>Somerset Pharmaceuticals (marketed by Bristol-Myers Squibb Co.)</td>
</tr>
<tr>
<td>Dosing forms:</td>
<td>6-, 9-, and 12-mg patches</td>
</tr>
<tr>
<td>Recommended dosage:</td>
<td>One 6-mg patch every 24 hours, worn on the chest, back, or stomach. Increase dosage after 2 to 3 months if clinical response is inadequate</td>
</tr>
</tbody>
</table>

continued
CLINICAL IMPLICATIONS
Transdermal selegiline offers an MAOI antidepressant option that might help:
- patients whose depression has not responded satisfactorily to selective serotonin reuptake inhibitors (SSRIs) or serotonin and norepinephrine reuptake inhibitors (SNRIs)
- adults and children with chronic depression marked by atypical features, including reactive mood, rejection sensitivity, anergia, and reversed vegetative symptoms—such as oversleeping, overeating, and psychomotor retardation. Although transdermal selegiline’s efficacy against these features has not been studied, patients with this depressive subtype tend to respond preferentially to MAOIs.

PHARMACOKINETICS
Transdermal selegiline achieves therapeutic blood levels and reaches sustained concentration within 4 to 8 hours of administration. Compared with oral selegiline, transdermal delivery results in higher plasma selegiline concentrations (1,500 pg/mL with the 6-mg patch) with much lower exposure to metabolites.8 The concentration is maintained with successive doses.

Transdermal selegiline clears rapidly upon discontinuation but MAO inhibition persists for 2 weeks, so wait 2 weeks after the last dose before starting a new antidepressant or stopping food restrictions with the 9-mg and 12-mg patches.

EFFICACY
In two randomized, double-blind clinical trials,9,10 a total of 466 adults ages 18 to 65 who met DSM-IV-TR criteria for MDD received transdermal selegiline, 6 mg/d, or placebo for 6 to 8 weeks. Participants had 17-item Hamilton Rating Scale for Depression (HAM-D-17) scores ≥ 20 at baseline.

In the 6-week study,9 transdermal selegiline produced a 46% greater reduction in HAM-D-17 scores, a 52% greater decrease in HAM-D-28 scores, and a 79% greater drop in Montgomery-Asburg Depression Rating Scale (MADRS) scores compared with placebo. In the 8-week trial,10 HAM-D-28 and MADRS scores among the treatment group were significantly improved at endpoint compared with placebo, but HAM-D-17 scores were not.

In a 1-year, double-blind study,11 322 subjects with MDD—who had been rated as responders in a 10-week, open-label transdermal selegiline trial—received the 6-mg patch or placebo. At 6 months and 1 year, relapse was much less frequent among the treatment group compared with placebo. Relapse was defined as:

- HAM-D-17 ≥ 14
- Clinical Global Impressions of Severity score ≥ 3 with a ≥ 2-point increase from baseline
- and meeting DSM-IV criteria for MDD on two consecutive visits ≥ 11 days apart.

SIDE EFFECTS
Transdermal selegiline, 6 mg/d, has been well-tolerated in clinical trials. Inflammation at the application site was the most commonly reported side
effect, occurring in 32% to 36% of treatment group subjects compared with 15% to 17% of the placebo groups. Inflammation was usually mild, but approximately 3% of patients dropped out of one study, citing this effect as the reason. Fair-skinned women are at highest risk for this reaction.

In the 1-year relapse prevention study, 12% of treatment group patients reported insomnia compared with 7% of the placebo group. Insomnia incidence was the same in the selegiline and placebo groups during the 6- to 8-week clinical trials.

Unlike conventional oral MAOIs, the 6-mg selegiline patch has not been found to impair sexual function, alter appetite, or change body weight or blood pressure compared with placebo. The toxicity of the 9- and 12-mg patches has not been studied in humans, but 8 mg/d and 12 mg/d of transdermal selegiline across 3 months were shown not to cause drug toxicity in dogs.

### Pediatric Use

Although transdermal selegiline has not been studied in children and adolescents, the 6-mg patch could benefit some youths with depression. Before starting the drug, discuss with the child’s parents/guardians the FDA’s black box warning describing a possible association between selegiline and increased suicidal behavior in youths. This applies to all antidepressants.

### Geriatric Use

The patch might also help some older patients with depression. In a double-blind trial of high-dose oral selegiline (60 mg/d) involving 16 older patients (mean age 65.6), both the treatment and placebo groups remained almost free of side effects across 3 weeks. Although the sample was small, the findings suggest that older patients can tolerate selegiline at high dosages. Side effects also were minimal among treatment-group

---

#### Table 2

<table>
<thead>
<tr>
<th>Food/beverage class</th>
<th>Foods to avoid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beverages</strong></td>
<td>Tap beer</td>
</tr>
<tr>
<td></td>
<td>Beer that has not been pasteurized*</td>
</tr>
<tr>
<td></td>
<td>Red wines</td>
</tr>
<tr>
<td><strong>Dairy</strong></td>
<td>Aged cheeses</td>
</tr>
<tr>
<td><strong>Meat, poultry, fish</strong></td>
<td>Air-dried, aged, and fermented meats, sausages, and salamis (including cacciatore and mortadella)</td>
</tr>
<tr>
<td></td>
<td>Pickled herring</td>
</tr>
<tr>
<td></td>
<td>Spoiled or improperly stored fish, meat, poultry, or animal livers (check for mold, discoloration, or odor)</td>
</tr>
<tr>
<td><strong>Vegetables</strong></td>
<td>Broad bean pods (fava beans)</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td>Concentrated yeast extract (such as Marmite)</td>
</tr>
<tr>
<td></td>
<td>Fermented soybean products (including soy sauce)</td>
</tr>
<tr>
<td></td>
<td>Over-the-counter supplements containing tyramine</td>
</tr>
<tr>
<td></td>
<td>Sauerkraut</td>
</tr>
</tbody>
</table>

* Bottled and canned beer and white wine contain little or no tyramine, but more than moderate alcohol use while taking selegiline is not recommended.

patients age ≥ 65 in the yearlong relapse prevention study.\textsuperscript{11}

Treatment adherence rates with transdermal selegiline have been high in published studies, suggesting that the patch’s visibility might reduce the risk of forgetting to take the medication. Observing whether the patch has been changed might help older patients and family members/caregivers keep track of dosing.

**CONTRAINDICATIONS**

As with the oral form, do not prescribe transdermal selegiline to patients taking SSRIs, SNRIs, tricyclic antidepressants, mirtazapine, or bupropion.

When switching antidepressants, allow enough time for the previous agent to “wash out” before starting transdermal selegiline. How much time to allow for wash-out depends on the previous agent’s half-life.

The patch is also contraindicated for patients taking:

- carbamazepine or oxcarbazepine
- meperidine
- analgesics such as tramadol, methadone, and propoxyphene
- St. John’s wort
• cough syrups containing dextromethorphan
• amphetamines, such as mixed amphetamine salts
• cyclobenzaprine
• or cold remedies or weight-loss products that contain vasoconstrictors, such as pseudoephedrine, phenylephrine, phenylpropanolamine, or ephedrine.

Do not give transdermal selegiline during pregnancy, as its effect on fetal development has not been studied.

DOSING
Start transdermal selegiline at 6 mg/d. Instruct the patient to wear the patch on the upper torso, where vascularity is richer compared with the buttocks and legs. Tell the patient to change the patch daily and to apply it to a different spot each day to prevent inflammation. Consider increasing the dosage after 2 or 3 months if response is unsatisfactory.

For treating first, second, and some third depressive episodes, continue transdermal selegiline for 6 months to 1 year of sustained recovery; consider longer-term maintenance treatment for highly recurrent depression. Transdermal selegiline has not been tapered in clinical trials, and subjects have not reported withdrawal symptoms after 1 year of continuous treatment.

References
11. Robinson DS, Moonsammy G, Azzaro AJ. Relapse prevention study shows the long-term safety and efficacy of transdermal selegiline, a new generation MAOI. Poster presented at: Annual Meeting, American College of Neuropsychopharmacology, Dec 11, 2002; San Juan, PR.

In clinical trials, the 6-mg transdermal selegiline patch has shown efficacy in treating major depressive disorder with few reported side effects and no adverse interactions with food. Clinical experience will determine which patients might benefit most from this formulation.