Novel Transdermal Delivery Formulation of the Monoamine Oxidase Inhibitor Selegiline Nearing Release for Treatment of Depression

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A novel formulation of the monoamine oxidase inhibitor (MAOI) selegiline has been approved by the U.S. Food and Drug Administration (FDA) for treatment of depression and should be introduced at some point in the spring or early summer of 2006. Marketing of selegiline coincidently occurs almost 50 years after Nathan Kline and colleagues first recognized the therapeutic effects of the first MAOI, iproniazid.[1] Administered via a skin patch, selegiline transdermal delivery system (TDS; brand name: EMSAM; manufacturer: Somerset Pharmaceuticals and distributed by Bristol-Myers Squibb Pharmaceuticals) will be the first new MAOI to be introduced in the United States for the indication of depression in more than 30 years.

Most physicians are familiar with medications with transdermal delivery systems for indications such as smoking cessation and hormone replacement. In addition, child psychiatrists may be aware that recent research has established the efficacy of a methylphenidate skin patch for treatment of attention-deficit/hyperactivity disorder (see, for example, reference 2), which is pending FDA approval. Although negotiations between the manufacturer and the FDA are ongoing, it is likely that—at least at the minimum therapeutic dose—selegiline TDS will be the first MAOI ever to be available in the United States for use without dietary restrictions.[3]

Three of the older MAOIs—isocarboxazid, phenelzine, and tranylcypromine—are still available in the United States. Despite their storied history (see, for example, reference 4), these MAOIs have a very limited role in the contemporary treatment guidelines (see, for example, reference 5). The major reasons that the older MAOIs are not more widely used include relatively poor tolerability (including common side effects such as orthostatic hypotension, sexual dysfunction, insomnia, and weight gain), greater difficulty of use (divided daily dosing and the need to titrate), the absolute requirement of dietary restrictions to avoid hypertensive reactions (i.e., the notorious "cheese effect," which is mediated by intake of foods and beverages with high concentrations of the amino acid tyramine), and the risk of potentially lethal drug-drug interactions. These limitations were sufficient to result in the second- or third-line use of MAOIs when the tricyclic antidepressants (TCAs) were the standard of comparison; subsequent introduction of safer and more user-friendly antidepressants, beginning with fluoxetine and bupropion in the late 1980s, largely relegated the MAOIs to use by subspecialists for treatment of the most therapy-resistant patients.[4] However, the unique therapeutic properties of the MAOIs for patients with so-called atypical depressive features (i.e., hypersomnolence, increased appetite, and weight gain)[6] coupled with the lack of progress in developing effective and well-tolerated medications with truly unique mechanisms of action have led to continued efforts to develop safer and easier-to-use MAOIs.

The holy grail of this search for a better MAOI has been identification of a drug that (1) did not require a special diet, (2) has a tolerability and ease-of-use profile comparable to the selective serotonin reuptake inhibitors (SSRIs), and (3) is as effective as tranylcypromine or phenelzine. Two aspects of the pharmacology of the older MAOIs—lack of selectivity for the 2 subtypes of MAO (i.e., type A and type B) and the irreversibility of inhibitory effect—have been targets for drug development. The subtyping of the 2 types of MAO is based on the preferred substrates of enzymatic activity. The A type of enzyme, which is found in the gut, liver, and brain, metabolizes norepinephrine, serotonin, and tyramine. Thus, it is inhibition of MAO A in the gut and, to a lesser extent, the liver that is the mechanism that underlies the "cheese effect." The B type of enzyme, which is found in blood platelets and the brain, metabolizes phenethylamine and dopamine. Irreversible MAOIs bind tightly to the enzyme, functionally deactivating the enzyme for its "life" (e.g., about 14 days).

One approach to develop a better MAOI led to a class of medications known as reversible inhibitors of monoamine oxidase type A (RIMAs; see, for example, reference 7). Selective inhibition of the MAO A type is sufficient for an antidepressant effect,[7,8] yet the reversible nature of enzymatic binding essentially protects against the "cheese effect" because high levels of dietary tyramine displace the drug from enzyme binding sites. Despite considerable promise, the RIMAs have not been a particularly successful class of medications. To date, only 1 of the RIMAs (moclobemide) has made it to the worldwide marketplace, and both clinical experience and results of a meta-analysis of controlled studies suggest that it is probably not as effective as the older nonselective MAOIs.[8] Moreover, moclobemide has not received FDA approval and—in most of the countries in which it was approved—has not been a "blockbuster" drug.[7,8]

Selegiline, unlike the RIMAs, is a relatively selective inhibitor of MAO type B. Although selegiline is an irreversible inhibitor, at doses low enough to ensure selectivity for MAO B there is no risk of hypertensive crises. Selegiline is actually not a new drug: initially synthesized in the 1970s in Hungary,[9] it is currently approved in oral formulation in doses of 5 and 10 mg/day for treatment of Parkinson's disease (see, for example, reference 10). At these low doses, selegiline does not significantly inhibit MAO A and, thus, therapy does not require any dietary restrictions.

Selegiline is structurally most similar to tranylcypromine among the currently available MAOIs (see reference 11 for a comprehensive review of its pharmacology). Not surprisingly, there has been evidence from controlled trials for more than 20 years that selegiline has significant antidepressant effects.[12–16] However, these studies revealed that selegiline has minimal antidepressant effects at 5 to 10 mg/day (i.e., the orally administered doses of selegiline that are selective for inhibition of MAO B) and, at the doses necessary to achieve reliable antidepressant effects (typically >20 mg/day), selegiline is essentially an irreversible, nonselective MAOI comparable to tranylcypromine or phenelzine. Thus, orally administered selegiline did not seem to convey any significant advantage over the older MAOIs and it was not until the transdermal delivery system was developed that the commercial potential of this medication could be tapped (see, for example, reference 17 or 18).

It is not certain to what extent patients receiving selegiline TDS therapy will be vulnerable to the effects of drug-drug interactions. The possibility of serotonin syndrome when used in proximity with an SSRI or serotonin-norepinephrine reuptake inhibitor is a serious concern and, in all likelihood, at least a 14-day washout will be needed between termination of

selegiline therapy and starting a reuptake inhibitor. Interactions with drugs of abuse, particularly psychostimulants, also are an area of concern, although the results of 1 study of intravenous methamphetamine users were reassuring.[19]

The minimum therapeutic dose of selegiline TDS appears to be 20 mg/20 cm^2.[20,21] One critical aspect of transdermal delivery is that it yields plasma drug levels that are sufficiently high to achieve nonselective inhibition of both MAO A and B in the brain without resulting in high levels of inhibition of MAO A in the intestine or liver.[22] It is not yet clear if higher doses might convey additional therapeutic activity for patients with more difficult-to-treat depressive syndromes. It is also not clear if selegiline TDS therapy is particularly more or less effective for patients with specific clinical presentations of depressions.

To date, there are no studies comparing the antidepressant efficacy of selegiline TDS with standard antidepressants such as fluoxetine. Response to selegiline TDS therapy also has not yet been studied systematically in relation to past treatment history. Obviously, efficacy among patients with reverse neurovegetative features and for patients who have not responded to first-line therapies are areas of great interest.

The selegiline TDS is formulated such that a 20 mg/20 cm^2 patch strength delivers the equivalent of 6 mg of drug over 24 hours. As noted earlier, the critical aspect of transdermal delivery is that it avoids direct inhibition of MAO A in the gut wall that occurs as orally ingested medication is absorbed. Thus, tyramine-rich foods can be ingested during selegiline therapy (at least at the 6 mg/24 h or 20 mg/20 cm^2 patch strength) with only minimal effects on blood pressure.[17] Transdermal delivery also avoids "first pass" hepatic metabolism, which minimizes inhibition of MAO A activity in the liver. Experimental studies measuring pressor responses to escalating doses of tyramine indicate larger increases in blood pressure can be expected at higher doses of transdermally administered selegiline (i.e., 9 or 12 mg/24 h or 30 or 40 mg/30 or 40 cm^2 patches), so it is possible that at least some dietary restrictions may be necessary when doses above 6 mg/24 h (or 20 mg/20 cm^2 patches) are utilized.[17]

Transdermally administered selegiline also may have a more favorable tolerability profile than the older MAOIs. This could be because drug absorption through the skin is slow, often taking 8 to 12 hours to achieve peak plasma levels.[18] In the published clinical trials,[20,21] selegiline therapy was generally well tolerated (as compared with inert placebo), although insomnia and local dermatologic reactions to the patch can be troublesome. Clinical experience suggests that insomnia may be lessened with minimal loss of efficacy by taking the patch off before bedtime. Rotating patch application sites and prompt topical treatment of skin eruptions minimize dermatologic reactions.

In summary, for the first time in decades, a new MAOI will be available to U.S. clinicians. The novelty of selegiline TDS—both the administration by skin patch and the lack of a need for dietary restrictions—may help clinicians who are reluctant to prescribe the older MAOIs to give this venerable class of medication a new look.

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