Transdermal selegiline for the treatment of major depressive disorder

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Abstract: Non-selective inhibition of monoamine oxidase (MAO) enzymes (ie, isoforms A and B) in the brain are associated with clinically significant antidepressant effects. In the US, the selegiline transdermal system (STS; EMSAM) is the first antidepressant transdermal delivery system to receive Food and Drug Administration (FDA) approved labeling for the treatment of major depressive disorder (MDD). Currently, the use of orally administered MAO inhibitor antidepressants (eg, phenelzine, tranylcypromine) is limited by the risk of tyramine-provoked events (eg, acute hypertension and headache, also known as the "cheese reaction") when combined with dietary tyramine. The selegiline transdermal system is the only MAOI available in the US for the treatment of MDD that does not require dietary restriction at the clinically effective dose of 6 mg/24 hours. Delivery of selegiline transdermally (EMSAM®) bypasses hepatic first pass metabolism, thereby avoiding significant inhibition of gastrointestinal and hepatic MAO-A activity (ie, reduced risk of tyramine-provoked events) while still providing sufficient levels of selegiline in the brain to produce an antidepressant effect. At dosages of 6–12 mg/24 hours, EMSAM has been shown to improve symptoms of depression, have good tolerability, and have high rates of medication adherence. However, at higher doses of EMSAM (ie, 9 mg/24 hours or more), dietary restriction of tyramine intake is recommended. The introduction of EMSAM overcomes many of the safety concerns affiliated with the conventional oral MAO inhibitors and EMSAM may be considered another strategy for the treatment of MDD, especially in patients who cannot tolerate oral antidepressants, are poorly adherent, who present with atypical depressive symptoms, or have failed other antidepressants.

Keywords: selegiline, transdermal, EMSAM®, major depressive disorder, monoamine oxidase inhibitor

Introduction

Monoamine oxidase inhibitors (MAOIs) have experienced cyclical popularity. Initially used for the treatment of tuberculosis, these agents became recognized and used for antidepressant effects in the late 1950s (Goldberg 1964). However, in the early 1960s, published case reports described an acute hypertensive reaction (tyramine-provoked event), sometimes fatal, between MAOIs and foods containing tyramine (Blackwell 1963; Blackwell and Mabbitt 1965; Blackwell et al 1967). These reports prompted significant publicity concerning food and drug interactions with this class of drugs and, subsequently, prompted a decline in MAOI use. Use of MAOIs further diminished due to replacement by use of tricyclic antidepressants (TCAs) in the 1970s and non-TCAs in the 1980s precisely because of the problems with dietary restrictions and safety concerns. Currently, conventional MAOIs continue to be used in various neurologic (eg, headache) (Evans et al 2006) and psychiatric (eg, anxiety and mood) conditions, albeit not widely. MAOIs have been demonstrated to be superior to TCAs in the treatment of atypical depression (ie, depression marked by symptoms of hypersomnia, hyperphagia, severe lack of energy) (Quitkin et al 1988) and are considered effective alternatives for patients with TCA refractory depression (Roose et al 1986; McGrath

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et al 1987). MAOIs may also be advantageous for treatment of depression in the elderly (Georgotas et al 1986), panic disorder (Liebowitz et al 1990), and phobias (Liebowitz et al 1992). Nevertheless, the use of this very effective class of antidepressants is diminished by concerns about safety and drug interactions (Clary et al 1990).

Currently, selective serotonin reuptake inhibitors (SSRIs) are considered first line in the treatment of major depressive disorder (MDD); however, MAOIs still have a role in the treatment of mood disorders. The American Psychiatric Association recommends that MAOIs may be beneficial in patients with atypical depression and patients who have failed trials with other antidepressants (APA 2000). MAOIs currently available in the US with a Food and Drug Administration (FDA) approved labeling for depression include: phenelzine (Nardil®, Pfizer, Inc, New York, NY, USA), tranylcypromine (Parnate®, GlaxoSmithKline, Research Triangle Park, NC, USA), isocarboxazid (Marplan®, Oxford Pharmaceutical Services, Inc, Totowa, NJ, USA), and most recently, selegiline transdermal system (STS; EMSAM®, Bristol-Myers Squibb, Princeton, NJ, USA). Interest in the use of MAOIs for MDD has re-emerged in part by results from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial (McGrath et al 2006). Treatment refractory patients were randomly assigned to open-label treatment with either tranylcypromine monotherapy or combination of mirtazapine and venlafaxine. Both groups demonstrated similar remission rates and time to remission although the tranylcylpromine group had higher attrition rates due to tolerability issues (McGrath et al 2006).

MAOI pharmacology for depression

Monoamine oxidases are ubiquitous enzymes that exist in mammalian tissues in two genetically distinct forms, referred to as MAO-A and MAO-B (Youdim and Finberg 1983). The physiologic role of MAO is to catalyze the biotransformation of a variety of arylalkylamine neurotransmitters, such as dopamine, norepinephrine, and serotonin as well as to detoxify biogenic amines, such as tyramine (McDaniel 1986). The overall reaction involves oxidative deamination and can be characterized as: $RCH_2NH_2 + H_2O + O_2 \rightarrow RCHO + NH_3 + H_2O_2$. Each isoenzyme demonstrates distinct substrate specificity, inhibitor selectivity, and a unique tissue distribution. MAO-A is primarily responsible for degrading serotonin and norepinephrine, as well as exogenous monoamines such as tyramine. MAO-B is primarily responsible for degrading dopamine. Both MAO isoenzymes are present in tissues of the brain, gastrointestinal tract, and liver; however, MAO-A predominates in the gastrointestinal and hepatic tissues and MAO-B in brain tissue (Saura Marti et al 1990).

MAO-A inhibition is required for clinical improvement in depressed patients following the administration of oral or transdermal selegiline. Experimental studies have demonstrated that the antidepressant-like effect of selegiline requires greater than 70% inhibition of MAO-A activity (Gordon et al 1999). Additionally, the metabolites of selegiline (eg, levo-amphetamine derivatives) do not significantly contribute to the parent drug's antidepressant activity nor does phenylethylamine (PEA), an amphetamine-like compound which accumulates when MAO-B is inhibited. In contrast to the potent dextro-amphetamine molecule, levo-amphetamine is several-fold less potent in elicitation of central nervous system effects and thus not likely to exert a clinically significant behavioral effect (Hoffman and Lefkowitz 1996).

Oral selegiline for depression

Selegiline is an irreversible inhibitor of MAO enzymes. Approved in the US as an adjunctive treatment in Parkinson's disease (PD), orally administered selegiline (ie, conventional selegiline [Eldepryl®, Somerset Pharmaceuticals, Inc, Tampa, FL, USA]), up to 10 mg/day and orally disintegrating selegiline [Zelapar®, Valeant Pharmaceuticals International, Costa Mesa, CA, USA] up to 2.5 mg/day), is specific for MAO-B and generally devoid of clinically significant antidepressant activity, as well as the potential for a tyramine-provoked event. However, at high oral dosages of selegiline, the specificity for MAO-B is lost and non-selective inhibition of MAO (ie, MAO-A and MAO-B) confers antidepressant effects with the attendant risk of a tyramine-provoked event.

At oral doses between 30–60 mg/day (3–6 times greater than that used in the treatment of PD), selegiline has been studied for depression in several clinical studies and found to be effective. At these doses, oral selegiline significantly inhibits MAO-A and MAO-B in the peripheral and central tissues. However, because selectivity for MAO-B is lost (at doses exceeding 20 mg/day), the attendant risk of developing a tyramine-provoked event is increased (Schulz et al 1989). In a small double-blind, randomized, crossover study with placebo, treatment-resistant elderly patients who received oral selegiline 60 mg/day for 3 weeks had significant improvements in the Hamilton Depression Rating Scale 17-item (HAM-D-17) score (15.4 ± 9.2 vs 24.6 ± 6.4, $p < 0.01$), the Global Depression score (5.8 ± 2.7 vs 7.5 ± 2.3, $p = 0.05$), and the Brief Psychiatric Rating Scale ($p = 0.01$ for 18- and 28-item scores) (Sunderland et al 1994). In another

double-blind, placebo-controlled study [n = 44], a mean dose of 30 mg/day of selegiline was found to be superior to placebo in reducing the HAM-D mean score (41% vs 10%, respectively) and produced a positive response rate of 50% in those receiving selegiline compared with 13.6% in placebo (Mann et al 1989). All patients followed a low-tyramine diet and the incidence of adverse events, including cardiovascular effects, did not differ between the selegiline and placebo groups.

Selegiline transdermal system

Pharmacology overview

Selegiline transdermal system (STS) was designed to treat MDD and overcome the dietary safety concerns that exist with the conventional oral MAOIs. The STS provides stable and continuous drug delivery over a 24-hour period (Somerset Pharmaceuticals 2006). The STS allows the drug to be delivered directly into the systemic circulation rather than through the intestinal wall or the liver, thereby allowing selegiline to bypass hepatic first pass metabolism. This pharmacokinetic feature of the transdermal delivery system provides sufficient concentrations of selegiline in the central nervous system to inhibit both MAO-A and B for an antidepressant effect while minimizing inhibition of gastrointestinal and hepatic MAO-A activity and the risk of developing a tyramine-provoked reaction (Mawhinney et al 2003). The transdermal patches are composed of three layers (backing, adhesive containing the drug, and the release liner) and contain 1 mg of selegiline per cm^2 (Somerset Pharmaceuticals 2006). Upon administration, approximately 25%–30% of the STS drug content is delivered, in a steady and continuous manner, over 24 hours; this is equivalent to approximately 0.3 mg selegiline per cm^2 over 24 hours. The mean half-life of selegiline is approximately 1.5 hours (Mahmood 1997). Since the drug is an irreversible (suicide) enzyme inhibitor, the drug elimination half-life is less relevant and the duration of MAO enzyme inhibition is dependent on the rate of de novo enzyme synthesis. Selegiline is metabolized by hepatic CYP450 isoenzymes to 3 principal metabolites, N-desmethylselegiline, levo-methamphetamine, and levo-amphetamine (Shin 1997) (Figure 1). When compared with oral administration at equivalent doses, transdermal administration of selegiline to elderly subjects resulted in a 50-fold greater systemic exposure to parent drug and a 70% reduction in exposure to metabolites (Barrett et al 1996). Selegiline is not highly protein bound (89%) and transdermally delivered selegiline has 75% bioavailability (Somerset Pharmaceuticals 2006) compared with approximately 10% for the oral conventional formulation (Mahmood 1997). There is no accumulation of the drug in the skin.

Availability, dosing, and administration

EMSAM is available in 3 doses, 6 mg/24 hours (20 mg/20 cm^2), 9 mg/24 hours (30 mg/30 cm^2), and 12 mg/24 hours (40 mg/40 cm^2). Treatment should be initiated at the lowest dose of 6 mg/24 hours (Somerset Pharmaceuticals 2006). There are no dose-response studies but if indicated, the dose can be increased by 3 mg/24 hours every 2 weeks, up to a maximum dose of 12 mg/24 hours. The patch should be applied approximately at the same time every day and dosage adjustment is not required in patients with moderate liver impairment (Child-Pugh classifications of A or B) although there is no data regarding severe liver impairment. EMSAM does not require dose adjustment in mild, moderate, or severe renal impairment. In elderly patients, a target maintenance dose of 6 mg/24 hours is recommended.

The patch should be applied to dry, intact skin on the upper torso (below the neck and above the waist), upper thigh, or the outer surface of the upper arm once every 24 hours. It should be noted that while patients should replace the patch daily, they may still derive therapeutic benefit if the patch is left on the skin for more than 24 hours. EMSAM continues to be released from the patch and this may be a potential advantage in patients who forget to replace the patch daily. Due to application site reactions, patients should be advised to rotate the application sites to avoid re-application to the same site on consecutive days. Patients should wash their hands before and after patch application.

Adverse effects

The most common side effects of the STS include application site reaction, headache, diarrhea, dyspepsia, insomnia, dry mouth, pharyngitis, and sinusitis (Somerset Pharmaceuticals 2006). In placebo-controlled trials, 7.1% of patients discontinued EMSAM treatment versus 3.6% of patients receiving placebo; application site reaction was the only adverse event contributing to discontinuation of treatment. In EMSAM-treated patients, application site reactions occurred in 24% compared with 12% in those receiving placebo. Orthostatic hypotension (9.8% EMSAM, 6.7% placebo) was also reported and was dose-related. Elderly patients were more likely to experience orthostatic hypotension. In both short- and long-term clinical studies, a lack of significant weight gain and sexual dysfunction was observed with STS

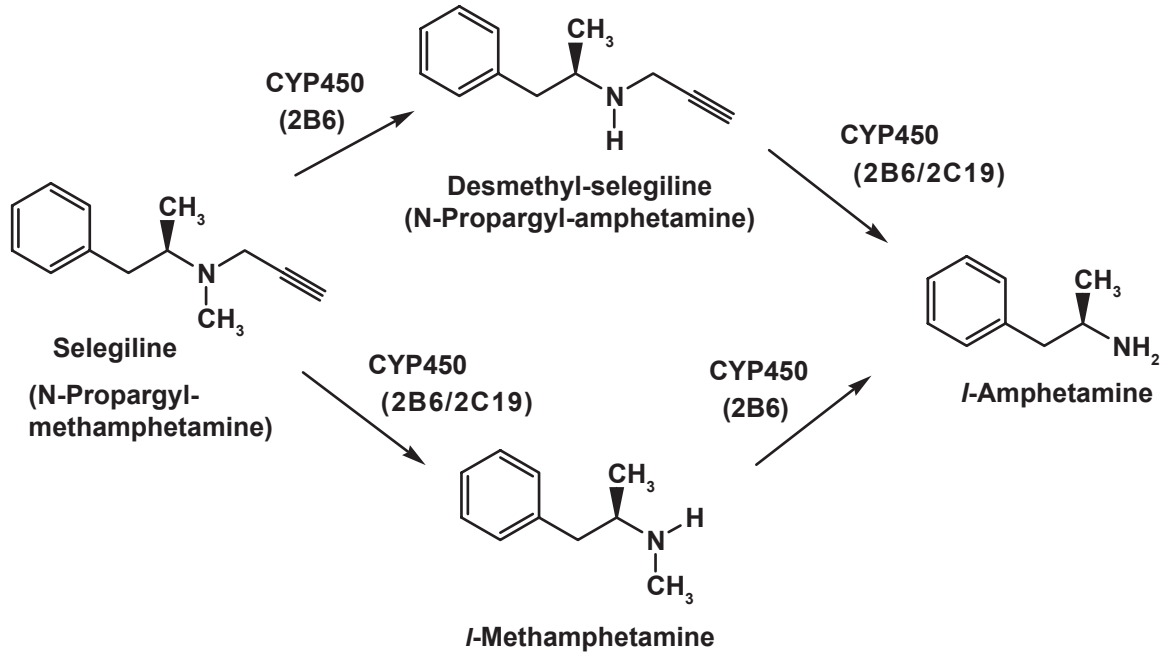

Figure 1 Biotransformation of selegiline.

treatment. This is notable since oral antidepressants (ie, MAOIs, TCAs, SSRIs) are associated with clinically significant effects in these areas (Rabkin et al 1984). Although these observations need to be validated in post-marketing studies, STS may prove to be a viable alternative in patients who experience these symptoms or who prefer medications without these effects.

Food interactions

In 1963, a pharmacist communicated observations to an English psychiatrist named Blackwell. The patient in each observation was the pharmacist's wife and involved a reaction after co-ingestion of tranylcypromine with cheese. The first reaction was described as: "After cheese on toast; within a few minutes face flushed, felt very ill; head and heart pounded most violently, and perspiration was running down her neck. She vomited several times…[and] after about three hours she was normal other than a severe headache…." (Blackwell et al 1967). The reaction also occurred in a subsequent ingestion (ie, rechallenge) of cheese on toast with co-ingestion of tranylcypromine. The pharmacist wrote: "Could there be a link between the effects and the amino acids of the cheese? No effects are caused by butter or milk…If cheese is indeed the factor, it could perhaps explain the sporadic nature of incidence of the side-effect." (Blackwell et al 1967). Over 40 years later, the MAOI-tyramine interaction is one of the most publicized drug interactions in the medical literature. In individuals treated with conventional oral MAOIs, ingestion of small amounts of tyramine (eg, 8 mg) can result in the "cheese reaction".

The typical features of a MAOI-associated tyramine-provoked event are occipital headache radiating forward, nausea, palpitations, and tachycardia which occur acutely and subside within hours. Other features include dilated pupils, hypertension, neck stiffness, photophobia, reflex bradycardia with chest tightness, and sweating.

Tyramine challenge studies

Using an oral tyramine pressor test, as little as 8 mg of tyramine is sufficient to cause an increase in systolic blood pressure of 30 mmHg in 50% of tranylcypromine-treated subjects (Bieck and Antonin 1988). Cooper notes that prior to the recognition of the need for dietary restrictions, up to 25% of MAOI-treated patients experienced a tyramine-provoked event (eg, acute hypertension, headache) with serious sequelae such as stroke or death occurring in up to a quarter of the affected patients (Cooper 1989). However, this potentially severe side effect could have been largely avoided by the implementation of simple dietary precautions. Unfortunately, at that time, suspicion and fear burgeoned, and both the seriousness and the frequency of risk were dramatically inflated. This was a major factor in the subsequent general disuse of the irreversible MAOIs. In contemporary clinical practice, dietary restrictions are less of a concern, although concerns do persist.

Studies indicate that the actual risk of a clinically significant tyramine-provoked event with the STS is rare and

may be considered negligible (Azzaro et al 2006; Blob et al 2007). Healthy male subjects were challenged with encapsulated tyramine HCl under various conditions (Table 1) (Azzaro et al 2006). In one group of 12 subjects treated with STS 6 mg/24 hours for 9 days and then 33 days (with a 3 month washout between treatments), the mean tyramine pressor doses (ie, dose of tyramine HCl required to achieve a sustained increase above baseline in systolic blood pressure (SBP) of ⩾30 mmHg for 3 consecutive readings), in the absence of food, at 9 and 33 days were 292 mg and 204 mg, respectively ($p < 0.05$). Although the difference is statistically significant, no clinically meaningful differences in safety were noted. An ingestion of tyramine 200 mg or more, derived from a single meal, is highly unlikely and approximately 6 times more than that contained in a tyramine-rich meal and 20 times greater than that contained in a normal meal (Da Prada et al 1988; Shulman et al 1989; Walker et al 1996). One study examined the tyramine content of high-tyramine meals (5 course) from 6 different restaurants and found that the tyramine content ranged from approximately 10 to 36 mg per meal (Da Prada et al 1988). Cheeses made from pasteurized milk contain very low amounts of tyramine (less than 50 mg/kg) (Da Prada et al 1988) and a whole pizza with a double-cheese topping has been reported to contain less than 1 mg tyramine (Shulman and Walker 1999).

A study was performed to assess for differences in tyramine pressor dose between STS and conventional oral selegiline treatment. Following a crossover design with a washout period of 3 months between active treatments, the pressor effects of tyramine following treatment with STS was compared with that obtained with oral selegiline (10 mg/day). The mean tyramine pressor doses for oral selegiline and STS 6 mg/24 hours were not significantly different (385 mg and 338 mg, respectively, $p = 0.19$), indicating that the dietary safety of STS 6 mg/24 hours is similar to conventional oral selegiline 10 mg/day.

The STS 6 mg/24 hours has a much wider margin of dietary safety than conventional oral tranylcypromine. A study was performed to assess for differences in tyramine pressor dose between STS 6 mg/24 hours and oral

Table 1 Tyramine pressor doses (TPD) obtained in subjects administered the selegiline transdermal system, oral conventional selegiline 5 mg twice daily, and tranylcypromine sulfate 30 mg/day[a]

	N	Duration of treatment (days)	Baseline tyramine pressor dose[b], mg (mean ± SEM)	On-treatment tyramine pressor dose[b], mg (mean ± SEM)
Changes in TPD after extended dosing				
STS 6 mg/24 h	12	9	508 ± 29	292 ± 23[c]
STS 6 mg/24 h	12	33	483 ± 40	204 ± 25[c,d]
STS 12 mg/24 h	11	33	568 ± 27	95 ± 23[c,e]
STS 12 mg/24 h	11	63	568 ± 27	72 ± 15[c,e]
STS 12 mg/24 h	11	93	568 ± 27	88 ± 18[c,e]
Changes in TPD before and after a meal				
STS 12 mg/24 h Fasted	8	93	606 ± 24	64 ± 10[c]
STS 12 mg/24 h Fed	8	96	606 ± 24	172 ± 32[c,f]
TPD differences between STS and oral selegiline[g]				
STS 6 mg/24 h	13	9	550 ± 30	338 ± 31[c]
Oral selegiline (5 mg bid)	13	9	550 ± 28	385 ± 36[c,h]
TPD differences between STS and tranylcypromine				
STS 6 mg/24 h	10	10	480 ± 28	270 ± 26[c]
Tranylcypromine 30 mg/day[a]	9	8	400 ± 24	10 ± 0[c,i]

[a]Tranylcypromine sulfate administered orally as 20 mg in the morning and 10 mg the afternoon.

[b]Tyramine pressor dose = dose of tyramine HCl required to achieve a sustained increase above baseline in systolic blood pressure (SBP) of ⩾30 mmHg for 3 consecutive readings. Following tyramine challenge, blood pressure was monitored at 5-minute intervals from 0 to 2 hours and at 15-minute intervals from 2 to 6 hours. If the SBP exceeded the baseline. measurement by ⩾25 mmHg, the interval for monitoring was decreased to 3-minute intervals.

[c]$p < 0.001$ compared with baseline.

[d]$p < 0.05$ compared with crossed-over subjects administered STS 6 mg/24 h.

[e]$p < 0.005$ compared with 6 mg/24 h for 33 days.

[f]$p < 0.005$ compared with fasted.

[g]A 3-month washout between STS and oral selegiline was imposed.

[h]$p = 0.19$ compared with STS 6 mg/ 24 hours.

[i]$p < 0.01$ compared with crossed-over subjects administered STS 6 mg/24 h.

Abbreviations: STS, selegiline transdermal system.

Derived from Tables II, III and IV from Azzaro et al (2006).

tranylcypromine sulfate 30 mg/day (Azzaro et al 2006). Following a crossover design with a washout period of 8 weeks between active treatments, the pressor effects of tyramine following treatment with STS was compared with that obtained with tranylcypromine. The mean tyramine pressor dose for STS 6 mg/24 hours was 270 mg, whereas all tranylcypromine-treated subjects experienced a pressor response following an initial tyramine HCl dose of 10 mg and this difference was statistically significant ($p < 0.0001$).

To determine the effects of a higher STS dose, 12 mg/24 hours, on tyramine pressor responses, 11 subjects were treated and tyramine pressor doses were assessed after 33, 63, and 93 days of treatment. Results, listed in Table 1, reveal that at higher STS doses, the mean tyramine dose required to elicit a pressor response is significantly decreased. With the STS 12 mg/24 hours-treated group, the tyramine pressor doses ranged from 25 to 200 mg. Thus the dietary safety margin is dose dependent. Within the treatment duration of 33–93 days, difference in the mean tyramine pressor dose were not statistically significant ($p = 0.36$), suggesting that a pharmacodynamic steady state (tyramine pressor sensitivity) is achieved by 33 days of treatment.

When co-administered with food, the risk of tyramine-provoked events appears to be minimal even at 12 mg/24 hours. Tyramine pressor responses were assessed in fasted and fed states. In STS 12 mg/24 hours-treated subjects, the presence of food significantly increased, by approximately 3-fold, the mean tyramine dose required to elicit a clinically significant pressor response (Table 1).

Realistically, it is not reasonably possible to consume sufficient amounts of tyramine in the form of cheeses to induce a clinically significant tyramine response in STS-treated patients. In an open-label study, 16 healthy adult male subjects were enrolled to receive STS 6 mg/24 hours for 13 days (Blob et al 2007). At baseline and on the final day, subjects ingested aged cheeses for breakfast (equivalent to approximately 100 mg tyramine content) and for dinner (equivalent to approximately 320 mg tyramine content). Cardiovascular response was monitored after the meals and no clinically significant changes in vital signs (eg, SBP) were observed. Of note, 4 of the 16 (25%) enrolled subjects were unable to consume the protocol defined amount of cheese during baseline testing.

In summary, the results of several tyramine challenge studies confirm that treatment with STS is associated with a wide margin of safety compared with the non-selective MAOI antidepressants in terms of dietary interactions (Azzaro et al 2006; Blob et al 2007). The data from these tyramine challenge studies should allay concerns regarding treatment with STS and dietary interactions. However, it should be noted that the tyramine challenge studies enrolled male subjects, and sex-based differences in tyramine response have been observed, with females tending to show greater pressor sensitivity than males (Reimann et al 1992). However, in the STS clinical studies (vide post), the majority of patients were female and dietary tyramine was allowed in all but one of these studies.

Despite the data supporting the dietary safety of EMSAM, the manufacturer does recommend that when initiating therapy with 9 mg/24 hours or 12 mg/24 hours, tyramine-containing foods should be avoided (Table 2). Furthermore, the dietary restrictions are advised for at least 2 weeks after either dose reduction (eg, from 9 mg or 12 mg/24 hours to 6 mg/24 hours) or discontinuation of the 9 mg or 12 mg/24 hour patches. Patients should be educated on the signs and symptoms of the "cheese reaction" (eg, headache occurring after ingestion of certain food and beverages).

Drug interactions

Drug interaction precautions are recommended for the STS (Table 3), similar to those recommended for high dose oral selegiline and other non-selective MAOIs. Most of the restrictions for STS, however, are extrapolated from known experience with or theoretical concerns about drug interaction sequelae involving other MAOIs, rather than specific data from oral selegiline or STS drug interaction studies. The actual risk of various drug interactions with MAOIs is not always clearly established. Given the unique pharmacokinetic profile of STS (in which transdermally administered selegiline bypasses the gut and liver), studies specifically investigating drug interactions with STS are warranted.

Although the EMSAM product labeling states that the drug is contraindicated with sympathomimetic amines (due to risk of hypertensive crisis), the combination of an MAOI with a stimulant has been used safely in depression. A review of the recent literature revealed no documented reports of clinically significant hypertensive events or fatalities occurring when the stimulant was cautiously added to a MAOI (Feinberg 2004). Additionally, other studies have found no significant adverse effects in patients receiving STS together with cocaine (Houtsmuller et al 2004) or pseudoephedrine (Azzaro et al 2007a). However, an increase in SBP (without clinical symptoms) with combination STS 6 mg/24 hours and phenylpropanolamine has been reported (Azzaro et al 2007a).

In vitro experiments have identified CYP2B6-, CYP2C9-, and CYP3A isoenzymes as having a significant role in the

Table 2 Foods and beverages that contain tyramine[a]

Aged and fermented meats
Sausages and salamis
Pickled herring
Spoiled or improperly stored meat, poultry, and fish
Spoiled or improperly stored animal livers
Broad bean pods
Aged cheeses
Beers that have not been pasteurized (ie, tap beer)
Red wine
Concentrated yeast extract
Sauerkraut
Soybean products (including soy sauce and tofu; excluding soy milk)
Over-the-counter products containing tyramine

[a]Tyramine content varies widely within each food or beverage category.
Derived from Shulman et al (1989).

metabolism of selegiline. Other isoenzymes such as CYP1A2-, CYP2A6-, CYP2C8-, CYP2D6-, and CYP2C19 also may be involved (Taavitsainen et al 2000; Hidestrand et al 2001; Kamada et al 2002; Salonen et al 2003; Azzaro et al 2007b).

Plasma concentrations of selegiline following steady-state treatment with STS are in the range of 0.01 μM to 0.08 μM. In vitro, selegiline causes a concentration-dependent inhibition of several CYP450 isoenzymes but at concentrations of 10 μM or greater. As this is several orders of magnitude greater than the observed plasma concentrations at clinically relevant doses of STS, significant inhibitory effects on the biotransformation of CYP450 substrates is not to be expected.

Table 3 Medications to avoid with the selegiline transdermal system

Amphetamines[a]
Bupropion[a]
Buspirone
Carbamazapine[a] and oxcarbazepine[a]
Cold products with vasoconstricting properties (eg, pseudoephedrine, phenylephrine, phenylpropanolamine, ephedrine)[a]
Cyclobenzaprine[a]
Dextromethorphan[a]
Linezolid
Meperidine,[a] methadone,[a] propoxyphene,[a] and tramadol[a]
Mirtazapine[a]
Monoamine oxidase inhibitors (eg, rasagiline, oral selegiline, isocarboxazid, phenelzine, tranylcypromine)[a]
Selective serotonin reuptake inhibitors (eg, fluoxetine, paroxetine, sertraline)[a]
Serotonin norepinephrine reuptake inhibitors (eg, venlafaxine, duloxetine)[a]
St. John's wort[a]
Tricyclic antidepressants (eg, amitriptyline, imipramine)[a]

[a]Contraindicated as per EMSAM product labeling.
Derived from Somerset Pharmaceuticals (2006), Taylor et al (2006).

Experimental studies fail to show significant drug–drug interactions between STS and psychotropic drugs such as olanzapine, risperidone, and alprazolam, that are CYP1A2, 2D6 and 3A4 substrates, respectively (Azzaro et al 2007b). This may be an important feature as a majority of patients diagnosed with MDD also meet criteria for an additional psychiatric diagnosis (Kessler et al 2003) and may be co-prescribed other psychotropic medications that are CYP450 substrates.

There is, however, a pharmacokinetic interaction with carbamazepine in which increased levels of selegiline and its metabolites were seen with concomitant administration of EMSAM (Somerset Pharmaceuticals 2006) and therefore the use is contraindicated. The plasma concentrations of selegiline were increased approximately two-fold in patients who received carbamazepine 400 mg/day for 14 days. In addition, because molecular scaffolds of carbamazepine and oxcarbazepine are tricyclic, the use of these two agents is contraindicated with EMSAM due to theoretical concerns of serotonin syndrome.

Prior to initiating EMSAM, contraindicated drugs (Table 3) should be discontinued and the equivalent of at least 5 half-lives should elapse before initiating EMSAM. For example, due to a risk of serotonin toxicity, several weeks should elapse after discontinuing antidepressants (5 weeks for fluoxetine and 2 weeks for other antidepressants) before starting therapy with EMSAM. Conversely, if EMSAM is discontinued, at least 2 weeks should elapse before initiating therapy with a drug that is contraindicated.

Clinical efficacy

The clinical efficacy of transdermal selegiline monotherapy has been established in 4 published double-blind, placebo-controlled studies (Table 4) (Bodkin and Amsterdam 2002; Amsterdam 2003; Feiger et al 2006; Amsterdam and Bodkin 2006). The criteria for all three short-term efficacy studies were the presence of single or recurrent unipolar major depression in out-patients with a HAM-D-17 score of ⩾20. In the first published multi-center study, 177 adult patients aged 18–65 years with MDD were randomized to receive 20 cm^2 selegiline transdermal patch (equivalent to 6 mg/24 hours) or placebo (Bodkin and Amsterdam 2002). In this fixed-dose study, selegiline showed significant reduction in the mean HAM-D-17 (46%, $p = 0.01$) and HAM-D-28 (52%, $p = 0.004$) scores compared with placebo as well as the Montgomery-Asberg Depression Rating Scale (MADRS) (79%, $p = 0.005$). These reductions on all three scales were observed as early as week 1. There was also

significant improvement on the Clinical Global Impression (CGI) severity (p = 0.02) and global improvement (p = 0.007) scales in the selegiline group versus the placebo group. The efficacy analyses were conducted in the intent-to-treat study group using the last observation carried forward (LOCF) analysis and included all patients who were randomized to treatment with selegiline and had at least one evaluation. At the end of the study, 152 subjects (86%) had completed the trial and 9 of these patients dropped out of the study due to adverse events (4 patients in selegiline, 5 patients with placebo). The only reported adverse events that were significantly different between selegiline and placebo were skin and application site reactions. Selegiline-treated patients exhibited a significantly improved sexual function compared with placebo-treated patients (F = 4.78, df = 1, 145, p = 0.03). Additionally, during the close monitoring of blood pressure, subjects who received selegiline had greater mean change in orthostatic blood pressure (–2.3 mmHg) versus those who received placebo (–0.8 mmHg) (F = 15.75, df = 1, 170, p = 0.0001), although these changes were not considered clinically meaningful. Since all patients followed a tyramine-restricted diet, the study was not able to establish safety with a non-restricted diet.

In a second multi-center, 8 week study, 289 adult patients with moderate to severe MDD were randomized in a double-blind fashion to either selegiline transdermal system 20 mg/20 cm^2 (6 mg/24 hours) or placebo (Amsterdam 2003). In contrast to the former study, patients in this study were not required to adhere to a tyramine-restricted diet. Patients, however, were instructed to check with the study investigator prior to initiating medications that have been historically known to interact with monoamine oxidase inhibitors (eg, over-the-counter cold preparations, narcotic and non-narcotic analgesics, antidepressants, antihypertensives). Most of the patients had recurrent major depressive episode and the mean HAM-D-17 scores at baseline were similar for selegiline and placebo groups. At the end of the 8 week study using the LOCF analysis, patients who received selegiline transdermal had significantly lower MADRS scores at week 4 (p = 0.024) and the effect persisted until week 8 (p = 0.001). The STS was also associated with lower mean HAM-D-28 scores but the effect was not observed until week 8. The discontinuation rate due to adverse effects was low, 6.7% and 5.3% in the selegiline and placebo groups, respectively, and application site reaction was the only adverse event that differed significantly between the two groups (31.5% for selegiline vs 15.1% for placebo, p = 0.001). Reductions in the mean SBP and DBP were observed in the STS group compared with the placebo group (–0.5 ± 10.7 mmHg vs –0.8 ± 11.7 mmHg for systolic BP; –0.5 ± 7.7 mmHg vs –1.0 ± 7.5 mmHg for DBP, respectively) although the difference was not statistically significant. Differences in other cardiovascular measures (eg, heart rate, electrocardiogram) were not observed.

In a third study enrolling 265 patients with MDD, patients were randomized, in a double-blind manner, to STS or placebo (Feiger et al 2006). This was an 8 week,

Table 4 Summary of published studies

Study	Method	N (% females)	Duration	Primary efficacy outcome measures	Adherence rate	Tyramine restricted diet
Bodkin and Amsterdam (2002)	Fixed dose (6 mg)	177 (60%)	6 weeks	♦HAM-D-17, -28 ♦MADRS ♦CGI	94% (average)	Yes
Amsterdam (2003)	Fixed dose (6 mg)	301 (64%)	8 weeks	♦MADRS ♦HAM-D-17, -28 ♦CGI-S, CGI-C	>98%	No
Feiger et al (2006)	Flexible (6 mg, 9 mg, 12 mg)	265 (61%)	8 weeks	Mean change in ♦HAM-D-28 ♦MADRS ♦IDS-SR	STS: 96% Placebo: 89%	No
Amsterdam and Bodkin (2006)	Fixed dose (6 mg)	322 (68.5%)	10 weeks (open label) 52 weeks (double-blind)	In double-blind phase ♦HAM-D-28 ♦MADRS ♦CGI-S ♦CGI-I	Open label: 88.1% Double-blind: STS: 84.2% Placebo: 89.6%	No

Abbreviations: CGI-S, Clinical Global Impression-Severity of Illness Scale; CGI-C, Clinical Global Impression-Change Scale; MADRS, Montgomery Asberg Depression Rating Scale; HAM-D-17, -28, 17 and 28 item Hamilton Depression Rating Scales; IDS-SR, Inventory of Depressive Symptomatology (Self-reported).

flexible-dose study utilizing STS doses of 6 mg/24 hours to 12 mg/24 hours and did not require dietary restriction of tyramine. Patients were also limited to use of concomitant medications that may interact with selegiline, although sleep agents such as chloral hydrate, zolpidem, and antihistamines were allowed. At the end of the 8 week study, 206 patients completed the study with approximately 22% drop out rate due to primary reasons of "lost to follow up" and "adverse event." Most of the patients were Caucasian female with recurrent major depression, similarly to the two previous studies. During the study period, 88% and 96% of patients received 9 mg/24 hours or the equivalent-sized placebo patch, respectively. Furthermore, 48% of patients received 12 mg/24 hours of selegiline versus 63% of patients in the placebo group. Patients who received STS had significant improvement in the primary efficacy measure, HAM-D-28, compared with patients who received placebo ($p = 0.03$) at weeks 5 and 8. Other significant differences were observed for the MADRS ($p = 0.02$) and the Inventory for Depressive Symptomatology-Self Rated (IDS-SR) ($p = 0.03$) at week 8 and the HAM-D (6-item Bech) at weeks 5 and 8 ($p < 0.01$). Although there was a difference in the HAM-D-17 scores between the treatment groups, the difference was not statistically significant. Overall, 80% and 74% of patients in the STS and the placebo groups had an adverse event and the most frequent event observed was application-site reaction (40% and 20%, respectively). No episodes of hypertensive crises were observed although insomnia was also a frequent occurrence with the STS group (30%) compared to the placebo group (14%). There was a higher incidence of sedative hypnotic use in the STS group (14%) compared with the placebo group (8%). The STS appeared to be well-tolerated at the higher doses since approximately half of the patients received the higher doses of 9 and 12 mg/24 hours.

The most recent study was a fixed-dose relapse prevention study of 322 patients that lasted 1 year (Amsterdam and Bodkin 2006). All patients received STS 6 mg/24 hours for 10 weeks in open-label fashion. Responders (those with HAM-D-17 scores of ≤ 10 in the final 2 weeks of the lead-in) were randomized in a double-blind manner to continue STS or placebo for 52 weeks. The primary efficacy measure was the proportion of patients achieving relapse based on a combination of HAM-D-17 score ≥ 14, CGI severity of illness score ≥ 3 (with at least a 2 point increase from double-blind baseline), and meeting the DSM-IV criteria for MDD. STS-treated patients experienced significantly less relapse (16.8%) than placebo-treated patients (30.7%) ($p = 0.0025$) at the end of the study. In those who did experience a relapse, the time to relapse was longer in the STS group ($p = 0.0048$). The most notable adverse effect in the STS group was application site reaction, and no cases of hypertensive reaction were reported. Adherence was high in both the selegiline and placebo groups (84.2% and 89.6% respectively) and discontinuation rates due to adverse event were higher for the STS group (13.2% vs 6.1%, respectively). It should also be noted that 56% of patients who were randomized were prematurely discontinued from the study for reasons other than meeting relapse criteria.

In summary, STS 6 mg/24 hours is effective as monotherapy for MDD. Only one of the four studies assessed dosages exceeding 6 mg/24 hours; therefore, it is uncertain whether higher doses correspond to better efficacy. The majority of patients in the clinical studies were females (Table 4), which is consistent with the higher prevalence of depression in this population. In addition, three of the four studies did not require a tyramine-restricted diet and the most frequently reported adverse effect was application site reaction.

Precautions and contraindications

Patients who are prescribed EMSAM should be counseled on the issue of dietary safety and potential drug interactions. Patients receiving EMSAM should be warned against undergoing elective surgery that requires general anesthesia or sympathomimetic vasoconstricting agents. EMSAM should be discontinued at least 10-days prior to the surgery, if necessary. Patients with pheochromocytoma should not receive EMSAM. Prolonged exposure to external heat sources such as electric blankets, heaters or direct sunlight may potentially enhance dermal absorption of selegiline from the patch matrix (Somerset Pharmaceuticals 2006).

Although EMSAM is not indicated for use in children or adolescents, a black box warning for suicidality in this population exists for EMSAM and stems from literature on SSRIs and other antidepressants (not EMSAM) suggesting increased suicidality. Patients and clinicians should monitor for signs of suicidality, worsening of symptoms, and/or changes in behavior, especially at the initiation of treatment and during dosage changes. Interpretation of the actual risk of suicidality in children and adolescents seen in studies is complex and has resulted in controversy over the decision to treat or not to treat this population. While analysis of all antidepressant trials in pediatric patients found that the

risk of suicidal behaviors was approximately twice as high in those who received an antidepressant versus those who received placebo (Simon 2006), others argue that the benefits of antidepressants outweigh the risk of suicide or suicide attempt (Bridge et al 2007).

There are no well-controlled studies in pregnant women with EMSAM (Pregnancy Category C). The potential benefits of using EMSAM in the mother should be weighed against the risk to the fetus. It is unknown whether selegiline is excreted in breast milk in humans. In animal studies, the levels of selegiline and metabolites in milk were approximately 15 and 5 times the steady-state levels in maternal plasma (Somerset Pharmaceuticals 2006).

Place in therapy, future directions

The efficacy of the MAOI class in treatment-resistant patients and patients with atypical depression may provide a rationale for the use of selegiline transdermal system given its favorable tolerability profile and recent data supporting improved dietary and drug interaction safety. Transdermal selegiline may also be potentially advantageous in patients who are not able to tolerate oral medications due to systemic side effects or who prefer a transdermal dosage formulation. While adherence rates for taking oral medications daily compared with a daily patch is debatable, adherence to antidepressant medications remains a significant challenge to ensuring appropriate treatment of depression and preventing relapse (Lin et al 2003). In a recent study, adherence rates for antidepressant medications for more than 90 days after initiation of medication was less than 30% (Olfson et al 2006). When evaluating the impact of inadequate treatment of depression on relapse rates, quality of life and economic burden, any measure that may increase adherence rates to antidepressants should be explored. In the published studies for EMSAM, the adherence rate to the novel delivery system ranged from 84% to >98%. Although post-marketing experience may have varying effects on adherence, the potential benefit of a patch versus an oral medication should be a therapeutic consideration. As mentioned previously, the added benefit of the residual drug remaining in the patch for more than 24 hours may offer a slight advantage to oral medications.

Transdermal selegiline may potentially play a role in conditions other than MDD. A small placebo-controlled study found that STS was modestly efficacious in patients with HIV-associated cognitive impairment (Sacktor et al 2000). In addition, there is interest in studying the effects of STS in the treatment of cocaine abuse (Houtsmuller et al 2004) and nicotine dependence (ClinicalTrials 2007).

Conclusion

The selegiline transdermal system (STS; EMSAM), is the only MAOI available in the US for the treatment of MDD that does not require dietary restriction at the clinically effective dose of 6 mg/24 hours. The STS may also play a role in the treatment of atypical depression, treatment resistant MDD, and anxiety disorders. The unique delivery system also may provide an advantage for patients unable to tolerate the systemic effects of oral antidepressants or who prefer an alternative dosage formulation. Overall, the STS appears to be well-tolerated with application site reactions as the most common adverse reaction and low rates of weight gain and sexual dysfunction. Additionally, the STS is associated with minimal CYP450 mediated drug–drug interactions.

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