Transdermal Selegiline:

The New Generation of Monoamine Oxidase Inhibitors

By Ashwin A. Patkar, MD, Chi-Un Pae, MD, and Prakash S. Masand, MD

ABSTRACT

The clinical use of monoamine oxidase inhibitors (MAOIs) has declined due to concerns about food and drug interactions and waning physician experience. Evidence indicates that MAOIs are effective in depressive disorders, in particular depression with atypical features. Efforts to address safety issues have led to the development of more selective and reversible MAOIs, such as moclobemide. Selegiline, a selective monoamine oxidase B inhibitor, has been approved for the adjunctive treatment of Parkinson's disease at low doses. At higher doses, oral selegiline is also effective in major depressive disorder (MDD) but loses its selectivity and has the potential for tyramine interactions. To overcome these problems, a transdermal formulation of selegiline, the selegiline transdermal system (STS), was developed with novel pharmacokinetic and pharmacodynamic properties. Compared with oral administration, transdermal selegiline

Needs Assessment

Despite evidence of antidepressant efficacy, the use of monoamine oxidase inhibitors has declined due to concerns about food and drug interactions. To overcome these problems, the selegiline transdermal system (STS) was developed with novel pharmacokinetic and pharmacodynamic properties. STS represents an advance over older monoamine oxidase inhibitors because it can be used as an antidepressant with minimal dietary modifications. STS may have an important therapeutic role in major depressive disorder.

Learning Objectives

At the end of this activity, the participant should be able to:

- List drug interactions and dietary restrictions with monoamine oxidase inhibitors.
- Understand the advantages of transdermal selegiline over older monoamine oxidase inhibitors.
- Understand how to use transdermal selegiline to treat depression.

Target Audience: Neurologists and psychiatrists

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Dr. Patkar is an associate professor in the Department of Psychiatry and Behavioral Sciences at Duke University Medical Center in Durham, North Carolina. Dr. Pae is visiting fellow in psychopharmacology in the Department of Psychiatry and Behavioral Sciences at Duke University Medical Center and assistant professor in the Department of Psychiatry at The Catholic University of Korea in Seoul. Dr. Masand is a consulting professor in the Department of Psychiatry and Behavioral Sciences at Duke University Medical Center.

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Please direct all correspondence to: Ashwin A. Patkar, MD, Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, 4323 Ben Franklin Boulevard, Suite 700, Durham, NC 27704; Tel: 919-471-3826; Fax: 919-620-0346; E-mail: ashwin.patkar@duke.edu.

leads to sustained plasma concentrations of the parent compound, increasing the amount of drug delivered to the brain and decreasing metabolite production. In addition, STS allows targeted inhibition of central nervous system monoamine A (MAO-A) and monoamine B isoenzymes with minimal effects on MAO-A in the gastrointestinal and hepatic systems, thereby reducing the risk of interactions with tyramine-rich foods (the "cheese-reaction"). Clinical trials have found 6 mg/24 hours of STS to be effective in MDD without the need for dietary restrictions. The efficacy and safety profile of STS supports its use in MDD. It is possible that STS may demonstrate benefit in MDD with atypical features or MDD resistant to other antidepressants. However, more research is needed. Clinicians should familiarize themselves with the properties and indications for the new generation of MAOIs.

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INTRODUCTION

Monoamine oxidase inhibitors (MAOIs) are an important class of antidepressants that have been used for over 40 years. Iproniazid, an inhibitor of the enzyme monoamine oxidase (MAO), was originally synthesized as an antituberculosis agent and ushered in the era of antidepressant development.[1,2] By the early 1960s, MAOIs were successfully established as antidepressants.[3] These agents included the hydrazine derivatives phenelzine and isocarboxazid and the nonhydrazine drug tranylcypromine. However, in the early 1960s, iproniazid was withdrawn from the market due to reports of hepatotoxicity.

By the mid-1960s, there were over 40 reports of hypertensive crisis associated with MAOIs, most commonly with tranylcypromine. These episodes often followed ingestion of tyramine-rich cheese, hence the term "the cheese reaction."[4,5] The Food and Drug Administration revised the labeling for MAOIs to include extensive dietary restrictions. Although this dramatically reduced the incidence of hypertensive crises, most patients found the dietary restrictions inconvenient. When tricylic antidepressants (TCAs) rapidly gained acceptance, the use of MAOIs declined. With the advent of selective serotonin reuptake inhibitors (SSRIs), MAOIs were relegated to third- or even fourth-line treatment.

Nevertheless, the efficacy of MAOIs, in particular for atypical and treatment-resistant depresssion (TRD) subtypes, has sustained interest in this class of drugs. Recently, there have been renewed efforts to develop better-tolerated MAOIs leading to the introduction of reversible inhibitors of MAO isoenzyme A (RIMA), such as moclobemide, and a transdermal formulation of selegiline that targets brain MAO while initially bypassing gastrointestinal (GI) MAO. While moclobemide is marketed in several countries, it will not become available in the United States in the foreseeable future. Therefore, this review will focus on critically evaluating the pharmacology, efficacy, and safety data for the selegiline transdermal system (STS) that was introduced in the US in 2006. The purpose of this review is to help clinicians make informed decisions about the appropriate use of new MAOIs for the treatment of depression.

PHARMACOLOGY

The Monoamine Oxidase Enzyme System

MAO is one of the most important enzymes in neurotransmitter metabolism. The human MAO system consists of two isoforms designated MAO isoenzyme A (MAO-A) and isoenzyme B (MAO-B).[6] The ratio of MAO-A to MAO-B in the human brain is 25%:75%, in the liver is 50%:50%, in the intestine is 80%:20%, and in the peripheral adrenergic neurons (adrenal glands, arterial vessels, and sympathetic nerve) is 90%:10%.[7,8] MAO-A preferentially metabolizes serotonin (5-HT) and norepinephrine (NE) and is inhibited by clorgyline. MAO-B preferentially metabolizes phenylethylamine and benzylamine and is inhibited by selegiline. Dopamine and tyramine are metabolized equally by both isoforms.[7] Within the human brain, MAO-A is found in the locus ceruleus and reticular formation, regions that contain a high density of catecholaminergic neurons. MAO-A is also present in the presynaptic terminals of dopaminergic neurons. In contrast, MAO-B is abundant in the dorsal raphe nucleus, which is rich in 5-HT neurons. MAO-B is also found in basal ganglia, primarily within glial cells, that contain dopamine neurons.[9] MAO metabolizes exogenous amines, such as dietary tyramine, and regulates neurotransmitter levels.[10]

Irreversibility and Nonselectivity

Irreversible and Nonselective *Monoamine Oxidase Inhibitors:* Phenelzine and Tranylcypromine

Many of the problems associated with older MAOIs, such as tranylcypromine and phenelzine, result from two pharmacologic characteristics: irreversibility and nonselectivity. Irreversibility refers to the tenacious binding of the drug to the MAO enzyme essentially for the lifetime of the molecule (ie, 14–28 days).[11] Thus, even high concentration of substrate cannot displace an irreversible MAOI from the enzyme. Therefore, normally insignificant concentrations of vasopressors, such as tyramine, can be dangerous when ingested with an irreversible MAOI.

Nonselectivity refers to the tendency of a drug to bind both the A and B isoenzymes.[12] Several MAOIs with selectivity toward either MAO-A or MAO-B have been developed. Table 1 lists the various MAOIs that have been clinically tested. One of the earliest selective MAOIs to be identified was the irreversible MAO-A inhibitor clorgyline.[13] However, clorgyline had the liability to cause hypertensive crisis with high concentrations of tyramine despite its selectivity. To address these limitations, RIMAs were developed.

Reversible Monoamine Oxidase A Inhibitors: Moclobemide

Moclobemide was the first RIMA to be approved as an antidepressant in Europe and is available in over 50 countries, excluding the US.[14] Moclobemide is better tolerated than the older MAOIs and is seldom associated with hypertensive crisis because it is readily displaced from its binding site on MAO-A by tyramine.[15] However, questions remain regarding efficacy of moclobemide compared with the older MAOIs.[16] A meta-analysis[11] found that there was a clinically significant advantage for the older MAOIs (13.3%) over moclobemide. It is hypothesized[1] that MAO inhibition by reversible MAOIs is less profound and sustained compared with the irreversible MAOIs, which may explain the possible efficacy differences. Despite a more favorable tolerability profile, RIMAs have not yet established a strong track record as a preferred treatment for depression.[17]

Selective Monoamine Oxidase B Inhibitors: Selegiline

The accessibility of the blood platelets that contain MAO-B for research facilitated the identification of selective MAO-B inhibitors, such as selegiline. At low oral doses (5–10 mg/day), selegiline inhibits >90% of brain MAO-B while avoid-

TABLE 1.
Classification of MAOIs[9]

Agent	Therapeutic dose (mg/day)	Selectivity	Reversibility	Available in the US
Tranylcypromine	20–90	Nonselective	Irreversible	Active
Phenelzine	15–90	Nonselective	Irreversible	Active
Isocarboxazid	10–30	Nonselective	Irreversible	Active
Selegiline transdermal system	6–12 mg/24 hours	Nonselective*	Irreversible	Active
Oral selegiline	10	MAO-B†	Irreversible	Active
Pargyline	N/A	MAO-B	Irreversible	Discontinued
Clorgyline	N/A	MAO-A	Irreversible	Unavailable
Nialamide	N/A	Nonselective	Irreversible	Unavailable
Befloxatone	N/A	MAO-A	Reversible	Unavailable
Moclobemide	300–600	MAO-A	Reversible	Unavailable
Brofaromine	N/A	MAO-A	Reversible	Unavailable

* Transdermal selegiline is nonselective for brain MAO.

† At antidepressant doses (>20 mg/day), oral selegiline loses its selectivity.

Riederer P, Konradi C, Schay V, et al. Localization of MAO-A and MAO-B in human brain: a step in understanding the therapeutic action of L-deprenyl. *Adv Neurol.* 1987;45:111-118.

MAOIs=monoamine oxidase inhibitors; MAO-B=monoamine oxidase B inhibitor; N/A=not applicible; MAO-A=monoamine oxidase A inhibitor.

Patkar AA, Pae C-U, Masand PS. *CNS Spectr.* Vol 11, No 5. 2006.

ing inhibition of GI MAO-A, eliminating the need for dietary restrictions.[18,19] At doses >20 mg/day, selegiline loses its selectivity. Oral selegiline in low doses (5–10 mg/day) has been approved for the adjunctive treatment of Parkinson's disease without any dietary restrictions.[20,21]

To date, clinical trials[22-24] have not established oral selegiline as a potent antidepressant at doses selective for MAO-B inhibition (5–10 mg/day). The best evidence for antidepressant efficacy comes from trials[25-27] employing larger, nonselective doses (20–60 mg/day) that required dietary restrictions. This suggests that inhibition of MAO-A alone or in combination with MAO-B is critical to the antidepressant response.[28]

Oral selegiline undergoes extensive first-pass metabolism by the hepatic cytochrome P450 system. Desmethylselegiline, l-methamphetamine, and l-amphetamine are the main metabolites. There is concern that the metabolites with the oral formulation may be associated with cardiovascular side effects and neurotoxicity.[29]

A freeze-dried, orally disintegrating form of selegiline has been developed. It is absorbed through the buccal mucosa directly into the systemic circulation[30,31] and seems to be better tolerated than the conventional formulation and less sensitive to a tyramine challenge.[29] Orally disintegrating selegiline 1.25–2.5 mg/day has been demonstrated to have short-term efficacy as adjunctive treatment for Parkinson's disease. However, its antidepressant efficacy remains to be evaluated.

Rasagiline is a selective, irreversible MAO-B inhibitor that is 10–15 times more potent than selegiline. Unlike selegiline, it does not give rise to methamphetamine metabolites nor does it have the sympathomimetic activity of selegiline.[32] While it is effective in the treatment of Parkinson's disease,[33] its antidepressant efficacy has not been investigated in controlled trials.

THE CHEESE REACTION

The "cheese reaction" occurs when food and alcoholic beverages containing tyramine and other indirectly acting sympathomimetic amines are consumed along with MAOIs.[34] Normally, tyramine is metabolized into inactive substances by GI MAO (primarily MAO-A).[35,36] When peripheral MAO-A is inhibited by at least 80%, tyramine is not metabolized, able to enter the circulatory system, and cause a significant release of NE from the peripheral adrenergic neurons (Figure 1). The consequences can be a severe hypertensive reaction that typically occurs within 10 minutes and can last up to 2 hours after a meal.[37]

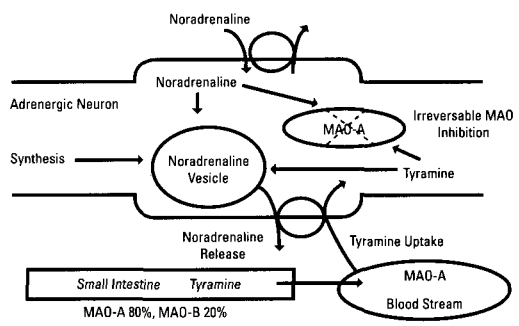
Therefore, dietary restrictions are required for patients receiving older MAOIs. Extensive dietary restrictions were previously recommended, however, due to changes in food processing and more reliable analytical methods, newer recommendations are less restrictive.[38] The tyramine content of foods varies due to the differences in processing. Large quantities of tyramine are formed if products are aged, fermented, or spoiled. Because the cheese reaction is dose-related, it can be minimized without the complete avoidance of tyramine-containing foods.

DEVELOPMENT OF SELEGILINE TRANSDERMAL SYSTEM

From an antidepressant efficacy and safety standpoint, the ideal MAOI should inhibit brain MAO-A and MAO-B but not GI MAO-A. Oral selegiline suffers from the limitations of loss of selectivity for MAO-B at antidepressant doses, thereby introducing the need for dietary restrictions. Recent advances in drug-delivery systems have permitted systemic delivery of a drug via transdermal route.

STS has been developed with novel pharmacokinetic and pharmacodynamic properties. It utilizes selegiline as an amine base embedded in an

FIGURE 1.
The mechanism of the cheese reaction and NE release and metabolism after MAO-A inhibition[15]



Youdim MB, Riederer PF. A review of the mechanisms and role of monoamine oxidase inhibitors in Parkinson's disease. *Neurology.* 2004;63(7 suppl 2):S32-S35. Adapted with permission by Lippincott Williams & Wilkins, Copyright (2004).

NE=norepinephrine; MAO-A=monoamine oxidase isoenzyme A; MAO=monoamine oxidase; MAO-B=monoamine oxidase isoenzyme B.

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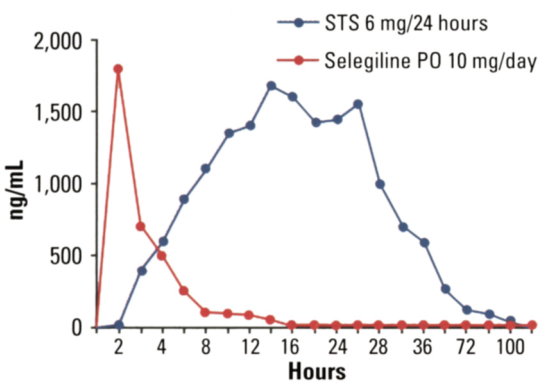
acrylic polymer-adhesive matrix and is released at a controlled rate by the components in the matrix so that a steady plasma-drug level is maintained.[39] STS has undergone extensive evaluation in humans. These studies[40,41] have found that STS offers sustained plasma concentrations, minimal peak-trough fluctuations, higher bioavailability, and reduced concentration of metabolites. STS allows inhibition of brain MAO-A and MAO-B enzymes with reduced effects on GI MAO-A, thereby reducing the risk of possible interactions with tyramine-rich foods at therapeutic doses. The prolonged duration of action with STS permits the lower frequency of administration and possibly improved patient compliance.[1]

PHARMACOKINETICS OF SELEGILINE TRANSDERMAL SYSTEM

Over 30 human pharmacokinetics studies[42] have examined dermally applied selegiline in over 650 subjects. STS is extensively absorbed through the skin with plasma levels maintained over a 24-hour period permitting once-daily application. About 25% to 30% of selegiline in STS is delivered within 24 hours. Selegiline delivered by 20 mg/20 cm^2, 30 mg/30 cm^2, and 40 mg/40 cm^2 STS approximates 6 mg, 9 mg, and 12 mg over 24 hours, respectively. Steady-state levels are reached after 5 days of STS treatment.[23] The bioavailability of selegiline is ~75% following STS compared with 4.4% after oral administration due to first-pass metabolism. Therefore, STS produces higher and more sustained steady-state levels compared with oral selegiline. Figure 2[43] shows differences in plasma concentrations with oral selegiline 10 mg/day versus STS 6 mg/24 hours. Protein binding is ~90% and it rapidly penetrates the central nervous sytem. Selegiline is metabolized by multiple cytochrome P450 isoenzymes 2C9, 2B6, 3A4/5 to form *N*-desmethylselegiline or R-methamphetamine. Both these metabolites can be further transformed into R-amphetamine. The increase in selegiline concentration after STS compared with oral administration occurs with a 70% reduction in the formation of amphetamine-like metabolites that may be associated with toxic effects on brain neurochemistry and behavior.[44,45] The pharmacokinetics of STS does not seem to be significantly influenced by gender, renal function, or mild to moderate hepatic impairment. Table 2 describes the pharmacokinetics of STS.

FIGURE 2.
Pharmacokinetics of STS compared with oral selegiline[43]



Adapted from Krishnan R. Advances in psychopharmacology: MAOIs. Scientific report session. *American Psychiatric Association*, New York, NY, 2004.

STS=selegiline transdermal system; PO=oral.

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PHARMACODYNAMICS OF SELEGILINE TRANSDERMAL SYSTEM

Studies[46] have shown that selegiline doses that produce at least 70% inhibition of brain MAO-A and 90% inhibition of brain MAO-B predict antidepressant activity. STS also was 10–20 times more potent than oral selegiline in producing its antidepressant-like effect and inhibiting cortical MAO-A.[10]

Animal studies[24] have demonstrated that doses of STS that inhibit activities of both MAO-A and MAO-B in the brain by >90% only partially inhibit GI enzyme activities, with a maximal 40% inhibition of MAO-A and 70% to 75% inhi-

TABLE 2.
Pharmacokinetics of STS[47]

Pharmacokinetic Parameters	STS
Half-life	20.1 hours
Steady-state	5 days
Bioavailability	75%
Hepatic metabolism	CYP 2C9, 2B6, 3A4
Metabolites	l-methamphetamine, *N*-desmethylselegiline

Adapted from EMSAM [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2006.

STS=selegiline transdermal system; CYP=cytochrome P450.

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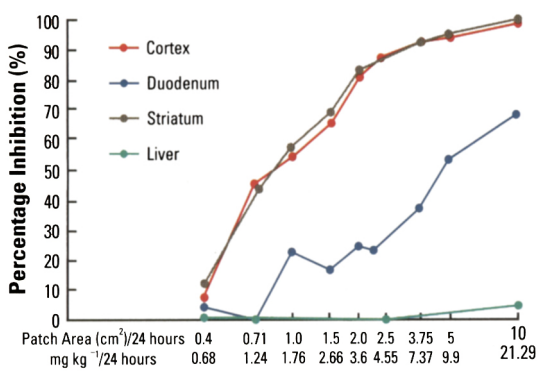
bition of MAO-B. In addition, doses of STS that inhibit brain MAO-A and MAO-B by 60% and 90%, respectively, do not alter GI MAO-A activity. This supports a targeted effect of STS on the brain versus the periphery (Figure 3).[10,24] Because >80% inhibition of GI MAO-A is necessary to affect the ability of the enzyme to catabolize tyramine, STS 6 mg/24 hours does not seem to significantly impair tyramine metabolism in the gut.

TYRAMINE CHALLENGE TESTS

Tyramine is a vasopressor and can produce clinically significant increases in blood pressure (>30 mmHg) in healthy volunteers at extremely high doses (~1 gram/meal).[48,49] About 2–3 times more tyramine is required with food compared with fasting condition to induce a pressor response. Tyramine pressor sensitivity to STS 6 mg/24 hours and 12 mg/24 hours has been investigated under both fasting and fed conditions. Studies[48,49] have found that, on average, at least 200 mg of tyramine in fasting state (well above the content of a tyramine-rich meal, which is 40 mg) was necessary to produce a 30 mm increase in blood pressure. In contrast, as little as 10–25 mg of tyramine can produce a 30 mm increase in blood pressure with tranylcypromine.[49,50] Even with long-term STS 6 mg/24 hours treatment, there is only a slight increase in tyramine sensitivity compared with that seen with oral selegiline 10 mg/day.[51]

FIGURE 3.
Effect of STS at steady-state on MAO-A inhibition*[42]



* Even at the highest observed STS-induced brain MAO-A inhibition, hepatic MAO-A function (and presumed tyramine-metabolizing capacity) remained robust.

Adapted from EMSAM® selegiline transdermal system new drug application 21,336/21,708. Food and Drug Administriation Web site. Available at: http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4186B2_01_01_Somerset-EMSAM.pdf. Accessed October 26, 2005.

STS=selegiline transdermal system; MAO-A=monoamine oxidase isoenzyeme A.

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The results of tyramine challenge studies[48-50] suggest that STS 6 mg/24 hours is equivalent to oral selegiline 10 mg/day in pressor responses at 10 days and is ~20 times less sensitive than tranylcypromine. Doses of STS 12 mg/24 hours are ~4 times less sensitive than tranylcypromine. With STS 6 mg/24 hours, it seems virtually impossible that an individual can consume sufficient amounts of tyramine-rich food to produce a hypertensive crisis. Even at 12 mg/24 hours, the mean pressor dose (172±92 mg/24 hours) in the fed state represents >4 times the amount in a tyramine-rich meal. However, the most sensitive subject had a pressor dose of tyramine 75 mg. Given individual variabilities in tyramine sensitivity and unusual dietary habits, dietary modifications are required with STS 9 mg/24 hours and 12 mg/24 hours. McCabe and Gurley[52] reviewed tyramine content of over 360 samples in >17 food categories and could identify only seven items (mostly aged or fermented cheese, meat, or fish products) that, when consumed in large amounts (>5 servings at a time), could reach the mean tyramine threshold in the fed state that may produce a pressor effect with 12 mg/24 hours. The lists of food to avoid are available in local pharmacies and are shown in Table 3.[53]

Consistent with these findings, phase III trials[42] of >2,500 patients exposed to STS 6 mg, 9 mg, and 12 mg over 24 hours without dietary modifications revealed no episodes of hypertensive crises. Oral selegiline has been used to treat Parkinson's disease without dietary restrictions since 1989 with >1.5 million patient exposures. Pharmacovigilance data from 1997[42] found that the rate of hypertensive crisis per 100,000 exposure years was 1.56 for oral selegiline compared with 43.36 for tranylcypromine. Of the four reported events, three were not tyramine related and possibly due to interactions with multiple dopaminergic drugs.

DRUG INTERACTIONS

Older MAOIs were liable to produce hypertensive episodes when taken concomitantly with indirectly acting sympathomimetics, such as pseudoephedrine. Therefore, several cough and cold medications carry a specific warning against using such preparations with MAOIs. Pharmacologic studies[54,55] have shown that the oral decongestants pseudoephedrine or phenylpropanolamine did not produce significant blood pressure increases when given to individuals administered STS 6 mg/24 hours. However,

due to the limited number of subjects exposed in these two studies, sympathomimetic drugs are contraindicated with STS.

Another potentially life-threatening complication of MAOI therapy is the development of serotonin syndrome characterized by confusion, fever, diaphoresis, ataxia, or diarrhea. The most common drug combinations that cause serotonin syndrome are MAOIs with SSRIs, tryptophan, TCAs, or meperidine (opioids).[56] This syndrome is rare. Since 1950, ~225 cases of serotonin syndrome have been reported and have included cases due to non-MAOI drug combinations.[57] The syndrome is usually mild and, if managed with drug withdrawal and supportive therapy, generally improves within 24 hours.[57] As in the case of older MAOIs, these agents are contraindicated during STS treatment.

A survey of 47 investigators involved in the Parkinsons Study Group[58] found that of the 4,568 patients treated with a combination of oral selegiline and an antidepressant (commonly an SSRI), 11 (0.24%) experienced symptoms possibly consistent with serotonin syndrome. Only two (0.04%) had serious symptoms. There were no fatalities.[58] Currently, there is insufficient evidence to determine whether STS has a decreased risk to induce the serotonin syndrome in depressed patients. Therefore, it is prudent to observe a minimum washout period equal to 5 half-lives (~1 week with all antidepressants, 5 weeks with fluoxetine) when switching from an antidepressant to an MAOI and to allow at least 2 weeks of washout when switching from an MAOI to an SSRI.

Comprehensive data are not available for drug interactions with STS. Therefore, STS should not be used in combination with several drugs that affect monoamine activity for at least 2 weeks *after discontinuation of STS*. *Table 4 provides a* list of contraindicated medications with STS.

ANTIDEPRESSANT EFFICACY OF SELEGILINE TRANSDERMAL SYSTEM

The efficacy of STS in MDD has been evaluated in five short-term, randomized, dou-

TABLE 3.
Dietary Modifications with MAOIs*[53]

Type of Food and drink	Tyramine-Rich Foods and Drinks to Avoid	Acceptable Foods containing little or no tyramine
Vegetables	Broad bean pods (fava bean pods)	All other vegetables
Meat, Poultry, and Fish	Air dried, aged and fermented meats, sausages and salamis, including cacciatore, hard salami, and mortadella Pickled herring Any spoiled or improperly stored meat, poultry and fish. These are foods that have a change in color, odor, or become moldy. Spoiled or improperly stored animal livers	Fresh meat, poultry and fish, including fresh processed meats (eg, lunch meats, hot dogs, breakfast sausage, and cooked sliced ham)
Dairy (milk products)	Aged cheeses	Processed cheeses, mozzarella, ricotta cheese, cottage cheese, and yogurt
Drinks	All tap beers and other beers that have not been pasteurized	As with other antidepressants, concomitant use of alcohol with STS is not recommended (bottled and canned beers and wines contain little or no tyramine)
Other	Concentrated yeast extract, such as Marmite Sauerkraut Most soybean products, including soy sauce and tofu OTC supplements containing tyramine	Brewer's yeast, baker's yeast, soy milk, commercial chain restaurant pizzas prepared with cheeses low in tyramine

* All foods you eat must be fresh or properly frozen. Avoid foods when you do not know their storage conditions.
Shulman KI, Walker SE. A reevaluation of dietary restrictions for irreversible monoamine oxidase inhibitors. *Psychiatr Ann.* 2001; 31: 378-384.
MAOIs=monoamine oxidase inhibitors; STS=selegiline transdermal system; OTC=over the counter.

Patkar AA, Pae C-U, Masand PS. *CNS Spectr.* Vol 11, No 5. 2006.

ble-blind, placebo-controlled trials and one maintenance trial.[47,59-61] Four trials compared a fixed-dose of STS (6 mg/24 hours) while one study[62] had a flexible-dosing strategy (STS 6–12 mg/24 hours). In the pivotal trials, STS produced significantly greater improvement on primary and secondary outcome measures, which included the 28-item Hamilton Rating Scale for Depression (HAM-D_{28}) and Montgomery-Åsberg Depression Rating Scale (MADRS) scores and Clinical Global Impression (CGI) ratings.

To date, results from two randomized controlled trials (RCTs)[59,60] have been reported. In a 6-week, fixed-dose, RCT of 176 subjects, STS 6 mg/24 hours was significantly more effective compared with placebo on the primary (17-item HAM-D and secondary endpoints.[59] Tyramine-restricted diet was recommended in this study. STS was separated from placebo by week 1, raising the possibility of accelerated response due to a systemic drug-delivery route.[61] About 38% of subjects on STS responded (≥50% reduction in HAM-D_{17}) and 23% remitted (HAM-D_{17} score <8) compared with 23% response and 11% remission rate in the placebo group. The compliance with the patch was high, with nearly 90% of STS subjects completing the trial.

TABLE 4.
Contraindicated Drugs with STS*[47]

Drug Classes	Examples
Antidepressants	
TCAs	Amitriptyline, imipramine
SSRIs	Fluoxetine, paroxetine, sertraline,
Newer antidepressants	Bupropion, venlafaxine, mirtazapine, duloxetine
MAOIs	Oral selegiline, isocarboxazid, phenelzine, tranylcypromine
Antitussive agents and cold products	Dextromethorphan, phenylpropanolamine, pseudoephedrine, ephedrine, phenylephrine
Sympathomimetic amines	Amphetamine
Narcotics	Meperidine
Muscle relaxants	Cyclobenzaprine
Analgesics	Tramadol, methadone, propoxyphene
Others	St. John's wort, carbamazepine, oxcarbazepine

* *STS should be discontinued at least 10 days before surgery requiring* general anesthesia.

Adapted from EMSAM [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2006.

STS=selegiline transdermal system; TCAs=tricyclic antidepressants; SSRIs=selective serotonin reuptake inhibitors; MAOIs=monoamine oxidase inhibitors.

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The second trial[60] was an 8-week, dose titration (STS 6–12 mg/24 hours) trial of 289 subjects without dietary restrictions. Primary and secondary efficacy endpoints included scores on the HAM-D_{17}, HAM-D_{28}, and the MADRS. STS was significantly superior to placebo according to HAM-D_{28} and MADRS scores and showed a nonsignificant superiority on the HAM-D_{17} (P=.07) and Clinical Global Impression ratings (P=.055). Responders (≥50% reduction in MADRS scores) were significantly higher in the STS group (33%) than the placebo group (21%). Responder differences were not striking when defined by HAM-D_{17} or HAM-D_{28} scores. Overall, there was a modest but statistically significant improvement with STS compared with placebo. Data from this trial were supportive of STS but the drug did not significantly separate from placebo on the primary endpoint.

In a long-term trial,[62] 322 subjects with MDD who had responded during an initial, open-label, 10-week trial of fixed-dose STS, were randomized to STS 6 mg/24 hours or placebo for up to 12 months. Relapse rates at 6 and 12 months favored STS (17% at 12 months) over placebo (31% at 12 months). Substantially greater numbers of placebo patients (61%) received rescue medication during the first 26 weeks of treatment than STS patients (29%).[62] It seems that improvement seen in short-term trials is maintained for at least 1 year with continued STS treatment. The data from the three trials as well as an unpublished trial (data submitted to the FDA) are summarized in Table 5.

SAFETY OF SELEGILINE TRANSDERMAL SYSTEM

Data from clinical trials[60] indicate that STS has a favorable side-effect profile. No drug-placebo differences in cardiovascular side effects were observed in the trial that did not restrict tyramine. Although orthostatic changes in blood pressure (ie, a decrease of ≥10 mmHg in mean blood pressure when changing position from supine or sitting to standing) were slightly higher with STS (–2.3 mmHg) than placebo (–0.8 mmHg) at week 6 in one trial,[59] these were not judged to be clinically meaningful. In short-term STS trials,[59,60] the incidence of orthostatic

hypotension was 9.8% in STS-treated patients and 6.7% in placebo-treated patients. However, orthostatic hypotension and falls are more of a concern in the elderly. Such patients should be monitored for postural changes in blood pressure throughout treatment. Dose increases should be made cautiously in patients with preexisting orthostasis. Postural hypotension may be relieved by having the patient recline until the symptoms have abated or asking patients to change positions gradually. Patients displaying orthostatic symptoms may need their dose adjusted.

Rates of sexual, digestive, and central nervous system side effects with STS were comparable with those with placebo. In 6–8-week studies,[59,60] there were no significant changes in weight between STS (mean change: –1.2 pounds) compared with placebo (mean change: 0.3 pounds). The incidence of ≥5% weight gain or loss was no different between drug and placebo. In long-term studies (3–12 months),[42] the average weight change with STS was –1.6 pounds.

Skin Reactions

Application site reactions (ASRs), such as rash, itching, redness, or irritation, were more common in STS-treated patients (36%) than in placebo patients (17%) (P=.006).[59] Pauporte and colleagues[63] found that the rate of skin reactions was significantly higher with STS (22%) compared with placebo (12%) in 1,326 subjects with a mean duration of exposure of 75 days. In general, few subjects required symptomatic treatment for the ASRs in the trials and <10% discontinued treatment due to ASRs.

The potential for ASR can be minimized by proper precautions while applying the patches. These include applying the patch on intact, dry skin on the upper torso, upper thigh, or upper arm; rotating the patch site daily; washing the site with soap and water and drying it before application; ensuring that the patch adheres properly by pressing it flat against the skin; removing the patch every 24 hours; and gently rinsing the skin site with warm water after removal. Most reactions subside without treatment. If reactions persist or are severe, local corticosteroids and/or oral antihistaminic agents, such as diphenhydramine, should be used.

Insomnia has been reported, particularly with higher doses of STS (eg, 12 mg/24 hours). To minimize potential insomnia, STS should be initiated at 6 mg/24 hours, preferably in the morning. Benzodiazepine or nonbenzodiazepine hypnotics can be used if insomnia is troublesome.

Teratogenic Effects

STS is a Category C drug like most antidepressants and there are no data on secretion in human milk.

In clinical studies of STS,[42] there have been no differences in efficacy between elderly and young patients, though the elderly appear at higher risk for skin rash. There are no data on pediatric population.

TABLE 5.
STS: Randomized, Placebo-Controlled, Double-Blind Trials in MDD[42]

	Bodkin and Amsterdam (2002)	Amsterdam (2003)*	P9303-P0052*	S9303-P9806 (unpublished)*
Duration	6 weeks	8 weeks	8 weeks	52 weeks
N	176	289	265	322
Dose	6 mg/24-hour patch	6–12 mg/24-hour patch	6–12 mg/24-hour patch	6 mg/24-hour patch
Primary	HAM-D_{17}	HAM-D_{17}	HAM-D_{28}	K-M relapse
Endpoint	P=.018	P=.069	P=.033	P=.006

* Patients were not required to follow a tyramine modified diet.

Adapted from EMSAM® selegiline transdermal system new drug application 21,336/21,708. Food and Drug Administriation Web site. Available at: http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4186B2_01_01_Somerset-EMSAM.pdf. Accessed October 26, 2005.

STS=selegline transdermal system; MDD=major depressive disorder; HAM-D_{17}=17-item Hamilton Rating Scale for Depression; HAM-D_{28}=28-item Hamilton Rating Scale for Depression; K-M relapse=Kaplan-Meier time to relapse analysis.

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MECHANISM OF ANTIDEPRESSANT ACTION OF SELEGILINE TRANSDERMAL SYSTEM

Selegiline has been found to potentiate dopamine transmission in the brain primarily due to MAO-B inhibition.[7] Additionally, STS would be expected to elevate brain 5-HT and NE levels due to inhibition of brain MAO-A.[64,65] Interestingly, the acute increases in brain 5-HT and NE with MAOIs subside with continued treatment and the levels gradually return to the pre-treatment state due to end-product inhibition of biosynthesis and adaptive changes in the neurotransmitter receptor sensitivity.[1] Chronic MAOI administration has been shown to enhance 5-HT neurotransmission by altering the rate of 5-HT neuron firing and the release of 5-HT from nerve endings.[66,67] It is likely that elevated levels of 5-HT, NE, and dopamine resulting from MAO inhibition play some role in the antidepressant effects of STS.[68] Selegiline also has several pharmacologic effects in the brain other than its MAO inhibition. For example, selegiline has been found to have antioxidant and neuroprotective properties.[69] In this context, defects in antioxidative systems have been found in depression.[70]

DOSAGE AND INDICATION

STS has been FDA approved for the treatment of MDD. STS comes in three strengths: a 6 mg/24-hour patch (20 mg/20 cm^2), a 9 mg/24-hour patch (30 mg/30 cm^2), and a 12 mg/24-hour patch (40 mg/40 cm^2) in separate boxes of 30 patches. Dietary modifications are not necessary with the 6 mg/24-hour patch but are required with the 9 mg/24-hour and 12 mg/24-hour patches. The starting and target dose should be 6 mg/24 hours. Dose increases, if required should occur in 3 mg/24 hours increments at ≥2-week intervals until the maximum recommended dose of 12 mg/24 hours is reached. No data are available to support a greater efficacy at higher doses. Generally, the STS should be applied at the same time of the day, preferably in the morning. A minimum washout period equal to 5 half-lives from existing antidepressants (~1 week for most antidepressants, 5 weeks for fluoxetine) is recommended before initiating STS treatment. Patients should be informed that tyramine-rich foods should be avoided from the first day of using the 9 mg/24 hours or 12 mg/24 hours patch. The dietary modifications should continue for at least 2 weeks after dose reduction to 6 mg/24 hours or discontinuation of the 9 mg or 12 mg 24-hour patch.

There are no data on discontinuation of STS. In the absence of data on downtitration of STS, it is difficult to make specific recommendations about abrupt versus gradual discontinuation. In clinical trials, subjects were abruptly discontinued at the end of the trials; however most of the studies were short-term. From a clinical standpoint, abrupt discontinuation of the 6 mg/24 hours patch may be reasonable. Whether the 12 mg- or 9 mg/24 hours patches should be discontinued abruptly or tapered to the 6 mg/24-hour patch prior to discontinuation will depend upon the clinical history as well as patient and clinician preferences. A better understanding of taper strategies may occur with wider clinical use of the drug. At least 2 weeks should elapse after stopping STS before commencing treatment with another antidepressant or a drug that is contraindicated with STS.

THERAPEUTIC IMPLICATIONS

Major Depressive Disorder with Atypical Features

MDD with atypical features characterized by reverse vegetative symptoms (eg, hypersomnia, hyperphagia, retardation) and mood reactivity is viewed as distinct from other forms of depressive disorders. Prevalence rates of 30% in depressive outpatients and 5% in the community have been reported.[69-73] A recent large meta-analysis[74] showed that MAOIs are superior to TCAs (effect size=0.27; 95% CI: 0.16-0.42) in MDD with atypical features, replicating results from an earlier meta-analysis.[28] Only three RCTs[28] have directly compared SSRIs with MAOIs in atypical depression. Both drugs were found to have comparable efficacy in atypical depression. However, the results should be interpreted cautiously because two included the RIMA moclobemide that may be less efficacious than the irreversible MAOI.[75] While MDD without atypical features responds equally well to MAOIs and TCAs or SSRIs, it seems that atypical depression may preferentially respond to MAOIs.[28]

Treatment-Resistant Depression

Results from Sequenced Treatment Alternatives to Relieve Depression[28] trial showed that ~30% of patients with MDD achieve remission of their symptoms with SSRI monotherapy. Evidence suggests MAOIs may benefit up to 50% of patients who have failed other antidepressants[28,76] and

practice guidelines have recommended MAOIs in TRD.[77] A recent retrospective study[78] of 59 patients with TRD found that 56% of MAOI trials in patients with early TRD (defined as those who had failed to respond to ≤3 previous antidepressant trials) resulted in a CGI-Improvement score of 1 (very much better) or 2 (much better). However, only 12% of MAOI trials in patients with advanced TRD (failed >3 antidepressant trials) resulted in remission.[78] The MAOIs studied included older MAOIs and oral selegiline. Similar results supporting efficacy of MAOIs in TRD have been reported previously.[16,76,79] STS may benefit patients with TRD and clearly prospective, controlled studies to examine this issue should be conducted.

Therapeutic Areas Needing Further Study

Oral selegiline and STS has been shown to hold promise in the treatment of attention-deficit/hyperactivity disorder (ADHD).[80,81] STS was also shown to block cocaine-induced euphoria and cardiovascular effects in a controlled study,[82] consistent with results from an earlier trial of oral selegiline in cocaine dependence.[83] Studies[84,85] have also found that oral selegiline was effective in reducing craving for nicotine and reduced the need for nicotine replacement therapy, although it did not influence long-term abstinence from smoking. A 6-week augmentation trial[86] with oral selegiline was found to lead to reduction in negative and depressive symptoms in 21 patients with chronic schizophrenia or schizoaffective disorder with prominent negative symptoms who were receiving antipsychotic medications. Interestingly, positive symptoms did not worsen in this study.[86] Another case series[87] also supported selegiline use in schizophrenia patients with prominent negative symptoms who were smokers. Older MAOIs have been found to be effective in panic disorder, posttraumatic stress disorder, phobia, and anxiety disorders,[88] although oral selegiline or STS has not been studied in these populations.

CONCLUSION

There is a large unmet need in patients with MDD. Although SSRIs and newer antidepressants are effective, a significant proportion of patients fail to respond and the remission rates are not high. This is coupled with high rates of noncompliance, troublesome side effects, and the risk of withdrawal syndrome. Despite evidence of efficacy, older MAOIs have been mostly avoided by clinicians due to safety issues and dietary restrictions. STS represents a new generation of MAOI that seems to have safety advantages over the older MAOIs. Available evidence shows that 6 mg/24 hours of STS is effective in MDD and can be safely taken without dietary modifications. Although higher doses of STS (9 mg and 12 mg/24 hours) also demonstrate a superior safety profile than older MAOIs, the limited clinical and experimental evidence suggest that dietary modifications should be instituted at these doses. Due to paucity of data, it is premature to infer whether STS will offer any incremental value in efficacy over currently available antidepressants or whether its side-effect profile may differ with long-term use. Nevertheless, introduction of STS expands the range of therapeutic options for clinicians to treat MDD. Further studies are necessary to compare STS with conventional antidepressants and to suggest evidence-based guidelines for the use of STS in clinical practice. ***CNS***

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