A Review of the Literature on the Selegiline Transdermal System: An Effective and Well-Tolerated Monoamine Oxidase Inhibitor for the Treatment of Depression

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Objective: To provide a narrative review of the properties of the selegiline transdermal system (STS) for the treatment of depression and its subtypes.

Background: Monoamine oxidase inhibitors (MAOIs) once represented the mainstay of therapy for the treatment of major depressive disorder (MDD). However, despite their efficacy, these agents fell from favor due to the risk of acute hypertensive reactions following ingestion of foods containing high concentrations of tyramine. Recent efforts to develop MAOIs that overcome these limitations have resulted in the introduction of the first transdermal formulation of the MAOI selegiline for the treatment of MDD.

Data Sources: A PubMed literature search was conducted in January 2007 using the keyword *selegiline transdermal system.*

Study Selection: Articles retrieved were reviewed and selected for inclusion based on their being randomized, double-blind, placebo-controlled studies that appeared between the years 2000 and 2007 and examined efficacy, safety, and tolerability data from clinical trials of patients with MDD who were treated with the STS. Four articles, including 3 acute trials and 1 long-term prevention of relapse trial, were included in this review based on these criteria.

Conclusions: The selegiline transdermal system provides several advantages compared to orally administered MAOIs, including minimal interaction with dietary tyramine and prolonged exposure to the parent compound, while offering a favorable side effect profile. As a result, treatment at the lowest effective dose of 6 mg/24 hours can be administered without the need for dietary modifications.

(Prim Care Companion J Clin Psychiatry 2008;10:25–30)

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The authors gratefully acknowledge the editorial support of Shahid Salaria, Ph.D., of Medicus International. Editorial support was funded by Bristol-Myers Squibb.

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Many patients with depression remain unrecognized and untreated in both community and primary care settings,[1,2] and for those who are recognized and diagnosed, treatment is often inadequate.[2] As many as 50% of patients who initiate antidepressant treatment do not respond, and up to 30% appear to be treatment resistant.[3] The recent National Institute of Mental Health Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study examined the effectiveness of stepped approaches to depression therapy. It reported a remission rate of 28% using the 17-item Hamilton Rating Scale for Depression (HAM-D) and 33% using the Quick Inventory of Depressive Symptomatology, Self-Report in response to its first 12-week step of therapy treatment with a selective serotonin reuptake inhibitor (SSRI).[4] Even after the fourth step, approximately 30% of patients had not responded adequately. Further, it has been reported that around 75% to 85% of patients with major depressive disorder (MDD) have recurrent depressive episodes,[5] and 10% to 30% of patients live with constant subsyndromal symptoms.[6,7] Unfortunately, these rates reflect the inadequacies of the current state of pharmacotherapy in the treatment of depression.

Treatment is further complicated by the difference in responses to certain antidepressants compared with others for several subtypes of depression. Data suggest that monoamine oxidase inhibitor (MAOI) therapy may provide preferential effects in the treatment of atypical depression,[8] a condition whose definition is still subject to considerable debate,[9] as well as melancholic depression,[10,11] both common in primary care settings.

For both MDD and its variants, the currently available medication treatment options have left a substantial portion of patients with significant impairing symptoms. This article reviews the properties of the new transdermal form of selegiline in the treatment of depression and its subtypes. For this review, a PubMed literature search was conducted in January 2007 using the keyword *selegiline transdermal system*. Articles retrieved were reviewed and selected for inclusion based on their being randomized, double-blind, placebo-controlled trials that appeared between the years 2000 and 2007 and examined

efficacy, safety, and tolerability data from patients with MDD who were treated with the STS. Four articles, including 3 acute trials and 1 long-term prevention of relapse trial, were included in this review based on these criteria.

MONOAMINE OXIDASE INHIBITORS: PAST AND PRESENT

Antidepressant activity of MAOIs was first observed in the 1950s, and by the early 1960s, these agents had become a mainstay of antidepressant therapy.[12–14] However, despite their proven clinical utility, reports in the 1960s of acute hypertensive events (which were sometimes fatal) with the early nonselective MAOIs led to a restriction in their use. The hypertensive reaction was subsequently found to be caused by an interaction between the MAOIs and ingested foods containing high concentrations of tyramine, such as aged cheeses.[15,16] This interaction was quickly characterized,[16,17] and after considerable pressure from psychiatrists, all MAOIs were reintroduced in the United States with revised labeling instructing patients to avoid fermented or aged proteins such as cheese. However, due to these dietary restrictions, the use of MAOIs continued to decline, particularly following the introduction of tricyclic antidepressants (TCAs).

Since the late 1980s, pharmacotherapy development has been directed toward increased specificity, and the SSRIs and serotonin/norepinephrine reuptake inhibitors (SNRIs) have supplanted the TCAs as the treatments of choice by targeting specific neurotransmitters. This newer class of antidepressants has a more specific and selective pharmacologic profile than the older antidepressants and, as a result, has a better tolerability profile.[18] With the introduction of SSRIs and SNRIs and their improved safety and tolerability profile, along with their general ease of administration, the use of MAOIs fell to such low levels that, by the end of the 1990s, only 2% of antidepressants prescribed in the United States were MAOIs.[19] As a result, much of the literature relating to MAOIs is derived from the 1970s and 1980s, since little additional research has taken place in the interim. Nevertheless, many psychiatrists believe that MAOIs are seriously underutilized in clinical practice,[20,21] particularly in light of their proven efficacy in MDD and its variants, atypical depression,[22–26] psychotic depression,[27,28] dysthymic disorder,[11] and treatment-resistant depression.[29–33] Current guidelines issued by the American Psychiatric Association and the British Association for Psychopharmacology suggest that MAOIs should be considered for treating MDD patients with atypical features and patients in whom other antidepressant medications have failed.[34,35] These agents have also demonstrated efficacy in patients with bipolar depression.[8,30,36]

SELEGILINE AND THE SELECTIVE MONOAMINE OXIDASE INHIBITORS

The therapeutic effect exerted by MAOIs is achieved by inhibition of monoamine oxidase (MAO) in the brain; this prevents the oxidative deamination of the naturally occurring monoamines: dopamine, serotonin, and norepinephrine.[37,38] Two subtypes of MAO isoenzymes have been identified: MAO-A and MAO-B. MAO-A is concentrated in the brain and the intestine; in the brain, the primary substrates are epinephrine, norepinephrine, dopamine, and serotonin.[39] In the intestine, MAO-A plays an important role in the metabolism of dietary tyramine to restrict uptake of tyramine into the systemic circulation.[40] Once in the systemic circulation, tyramine triggers norepinephrine release from sympathetic nerve terminals, causing an increase in blood pressure; if sufficient levels of dietary tyramine enter the circulatory system, a hypertensive crisis can occur.[25,26] MAO-B is concentrated in anatomic brain regions that are rich in serotonergic neurons, such as the dorsal raphe nucleus,[37] and can also be found in platelets, which led to a method of monitoring treatment effect in the 1970s and 1980s.[41]

Several selective MAOIs are currently available. Selective MAO-A inhibitors and nonselective MAOIs are equally effective. The use of both oral MAO-A inhibitors and nonselective MAOIs is limited owing to the need to restrict the dietary intake of tyramine. Several selective and reversible inhibitors of MAO-A (RIMAs) have been developed. This group of antidepressant agents is distinguished from the older MAOIs by their selective reversibility. As a result, dietary restrictions are not required during RIMA therapy; however, moclobemide, the most widely studied RIMA (available in Europe but not the United States), has been demonstrated to be less effective than nonselective MAOIs.[42]

Oral selegiline is a selective MAO-B inhibitor and is currently approved as an adjunctive treatment of Parkinson's disease at a dose of 10 mg/day without the need for dietary restrictions.[37] Although selegiline has also demonstrated antidepressant efficacy in a number of placebo-controlled trials at oral doses of 30 to 60 mg/day,[43–47] these doses are too high to confer selectivity for MAO-B,[47–49] and lower doses of selegiline are not effective for depression treatment because selective MAO-B inhibition is not linked to antidepressant activity.[39] Accordingly, dietary adjustments are required when selegiline is administered as an oral formulation for the treatment of depression.

THE SELEGILINE TRANSDERMAL SYSTEM: A NOVEL DELIVERY SYSTEM

A transdermal formulation of selegiline, the first antidepressant of this type, has now been approved by the

U.S. Food and Drug Administration (FDA) for the treatment of MDD. The transdermal delivery of selegiline was investigated to further enhance the safety of the drug by a systemic delivery via a route of administration other than oral. The aim was to attain therapeutic concentrations of drug in the brain, while minimizing exposure of the drug to the gastrointestinal tract. The dermal application allows selegiline to be directly absorbed into the systemic circulation, bypassing the gastrointestinal tract and hepatic first-pass metabolism.[37] As a result, MAO-B within the brain is inhibited without significantly impairing peripheral MAO-A activity, while avoiding the need to restrict dietary tyramine intake at the effective dose of 6 mg/24 hours.[37]

Both animal and clinical studies[50–53] have demonstrated that when transdermal selegiline is used at doses efficacious for the treatment of depression (6 mg/24 hours), the recommendation of a modified diet with tyramine restriction is not required. However, it should be noted that dietary restrictions are still required at the higher doses of 9 mg/24 hours and 12 mg/24 hours. Azzaro et al.[53] administered the oral tyramine pressor test to healthy males during treatment with the STS (6 mg/24 hours) in order to determine the risk of hypertensive crisis following oral ingestion of dietary tyramine. They demonstrated a tyramine sensitivity factor (TSF) value following 9 days of treatment with the STS of 1.85 ± 0.10. An additional investigation following 33 days of treatment with STS 6 mg/24 hours showed a small, clinically nonmeaningful increase in this value. A larger increase in the TSF (10.99 ± 2.33) was observed following extended STS treatment (33 days) at a higher dose (12 mg/24 hours). These results suggest that the 6 mg/24 hours dose of the STS can be administered safely without the need for dietary tyramine restrictions.

Despite limitations in the STS clinical trial program, including a lack of direct comparator controlled trials as well as studies in patients with a history of intolerance or nonresponse to SSRIs and SNRIs, the efficacy and tolerability of the STS in MDD have been established in several placebo-controlled clinical trials that led to FDA approval.[54–57]

Acute Efficacy of the Selegiline Transdermal System in Major Depressive Disorder

Two acute, randomized, double-blind, placebo-controlled studies of 6 and 8 weeks' duration[55,56] enrolled adult outpatients with moderate-to-severe depression, all of whom met the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) criteria for MDD and had a HAM-D 17-item score of ≥ 20. Efficacy was assessed in both trials using the HAM-D (17-item and 28-item versions) and the Montgomery-Asberg Depression Rating Scale (MADRS). In the study performed by Bodkin and Amsterdam,[55] patients received either STS 6 mg/24 hours (N = 89) or placebo (N = 88) once daily and followed a tyramine-restricted diet for 6 weeks. At study endpoint (6 weeks), the STS demonstrated significantly superior efficacy compared with placebo according to the HAM-D 17-item (–8.7 ± 7.5 vs. –6.10 ± 6.67; p = .01), HAM-D 28-item (–11.2 ± 9.8 vs. –7.5 ± 8.7; p = .004), and MADRS (–9.7 ± 11.5 vs. –5.6 ± 9.07; p = .005). Greater reductions in mean 17-item and 28-item HAM-D and MADRS scores were observed as early as week 1 of STS treatment compared with placebo. In addition, a larger percentage of selegiline patients achieved ≥ 50% reduction in both the 17-item (33% vs. 20%; p = .04) and 28-item (33% vs. 20%; p = .03) total HAM-D scores at endpoint compared with placebo.[55]

In the second study,[56] 289 patients received either transdermal selegiline 6 mg/24 hours (N = 145) or placebo (N = 144) once daily for 8 weeks. These patients were not required or advised to follow a tyramine-restricted diet. The results demonstrated that at study endpoint, the STS treatment group experienced significantly greater reductions compared with the placebo group on the basis of mean HAM-D 28-item scale (18.6 ± 9.4 vs. 21.2 ± 9.3; p = .039) and MADRS (18.05 ± 10.06 vs. 21.75 ± 9.93; p = .001) scores. The HAM-D 17-item scale demonstrated a nonsignificant superiority (selegiline, 14.7 ± 7.2 vs. placebo, 16.3 ± 7.1; p = .069). Furthermore, significantly more patients achieved ≥ 50% reduction in total baseline MADRS score at endpoint compared with placebo (33.1% vs. 20.8%; p = .03).[56]

In a third and more recent study conducted by Feiger et al.,[57] 265 patients were randomly assigned to blinded treatment with STS 6 mg/24 hours (N = 132) or a matching placebo (N = 133) for 8 weeks. Patients were not required to follow a tyramine-restricted diet. At week 2, doses were increased to 9 mg/24 hours and 12 mg/24 hours based on individual patient response. Of the 265 patients, 230 had their starting doses increased, with similar percentages of patients in the STS (88%) and placebo (86%) groups having their doses titrated to the STS 9 mg/24 hours or the equivalent placebo patch. Overall, 147 of the 265 patients had their doses increased further to the 12 mg/24 hours dose (or placebo). Selegiline transdermal system treatment resulted in significantly greater improvements compared with placebo on the 3 depression rating scales at endpoint (week 8): the HAM-D 28 (STS baseline = 28.3 ± 3.7, mean change = –11.1 ± 8.6; placebo baseline = 28.6 ± 4.0, mean change = –8.9 ± 9.1; p = .03), the MADRS (STS baseline = 29.3 ± 4.2, mean change = –11.6 ± 9.8; placebo baseline = 29.3 ± 4.2, mean change = –8.6 ± 10.3; p = .02), and the Inventory for Depressive Symptomatology-Self Rated (STS baseline = 37.3 ± 8.8, mean change = –13.9 ± 12.1; placebo baseline = 37.6 ± 9.4, mean change = –10.6 ± 12.5; p = .03). Importantly, in spite of an absence of dietary restrictions, there were no occurrences of hypertensive

crisis during treatment at higher STS doses, and treatment with the STS was generally well tolerated, with the most frequent adverse events being application site reactions (40% for STS vs. 20% for placebo) and insomnia (30% for STS vs. 14% for placebo). However, it should be emphasized that this was not a dose-response trial, and only 116 patients of the 265 participants were exposed to the STS at higher doses, which means the risk of hypertensive crisis without dietary restrictions at higher doses cannot be fully evaluated from the results of this trial.

Prevention of Relapse: Long-Term Results

A long-term, 52-week, double-blind, placebo-substitution study was conducted in 322 patients with MDD who had achieved remission after 10 weeks of open-label treatment with STS 6 mg/24 hours.[54] Patients were randomly assigned to receive either STS 6 mg/24 hours or placebo once daily. A dietary tyramine restriction was not imposed or advised in this study. Relapse was defined as meeting the following criteria on 2 consecutive visits: (1) HAM-D 17 score of ≥ 14, (2) a Clinical Global Impressions scale score of ≥ 3 with a 2-point increase from baseline, and (3) DSM-IV criteria for MDD. There was a significant reduction in the percentage of STS-treated patients who had relapsed at weeks 26 (16.8% vs. 29.4%; $p = .005$) and 52 (16.8% vs. 30.7%, $p = .0025$) compared with placebo. In addition, patients receiving STS experienced a significantly longer time to relapse compared with those receiving placebo ($p = .0048$).[54]

Safety and Tolerability of Transdermal Selegiline

In the 2 short-term studies outlined above,[55,56] transdermal selegiline (6 mg/24 hours) was well tolerated. In the study by Amsterdam,[56] there were no differences in treatment withdrawal rates between the STS treatment and placebo groups (10 vs. 8 patients, respectively). Adverse event profiles were similar, with the exception of STS application-site reactions (it is advisable not to apply the patch to an area of skin that is irritated, broken, scarred, or calloused and to select a new application site with each new patch in order to avoid application-site reactions). The incidence of patient-rated sexual dysfunction was low and comparable between the STS and placebo treatment groups (0.6% vs. 0.6%; $p = .559$). Similar results were derived from the Bodkin-led study.[55] Similarly, in the long-term, 52-week study (6 mg/24 hours),[54] weight change, gastrointestinal irritation, and the incidence of sexual dysfunction were low and comparable between STS- and placebo-treated patients. Mean scores on the Medex Depression evaluation scale sexual activity symptom complex improved during the open-label phase (13.4 to 10.4; $p > .05$) but did not change substantially during the double-blind period for either treatment. Importantly, no cases of hypertensive crisis were reported despite the absence of dietary restrictions.

Drug Interactions

The potential for drug interactions between STS (6 mg/24 hours) and a variety of drugs has been examined in several human studies.[58] The potential for interactions between STS (6 mg/24 hours) and alcohol, alprazolam, ibuprofen, levothyroxine, olanzapine, and warfarin has been the subject of several studies, none of which have demonstrated an altered pharmacokinetic profile of either selegiline or the test agent.[58] The STS is not metabolized in human skin and does not undergo extensive hepatic first-pass metabolism. Several cytochrome P450 (CYP)–dependent enzymes (CYP2B6, CYP2C9, and CYP3A5/5) are involved in the metabolism of selegiline, with CYP2B6, CYP2C9, and CYP3A5/5 being the major contributing enzymes in the formation of selegiline metabolites.[58]

A potentially fatal central nervous system toxicity referred to as the serotonin syndrome has been reported with the combination of nonselective MAOIs with certain other drugs, including SSRIs, SNRIs, and TCAs.[59] Accordingly, contraindicated medications (Table 1) include other antidepressant medication: SSRIs (e.g., citalopram, escitalopram, fluoxetine, sertraline, and paroxetine), SNRIs (e.g., venlafaxine and duloxetine), and TCAs (e.g., imipramine and amitriptyline). Furthermore, oral selegiline and other MAOIs should not be used concomitantly with STS. Carbamazepine, cough or cold preparations containing dextromethorphan, cyclobenzaprine, amphetamines, cold products or weight-reducing agents containing vasoconstrictors (e.g., pseudoephedrine, phenylephrine, phenylpropanolamine, or ephedrine), buspirone, and the herbal supplement St. John's wort are also contraindicated, as are analgesics such as meperidine, tramadol, and methadone. The recommended washout period for contraindicated medications is about 1 week (4–5 half-lives) prior to and 2 weeks after STS treatment (with the exception of fluoxetine, which requires a 5-week washout because of its long half-life).

CONCLUSIONS

There are a substantial number of patients who do not respond adequately to, or are intolerant to, existing antidepressant therapy, for whom alternative therapies are required. Oral MAOIs have proven to be efficacious in the treatment of many subgroups of MDD; however, their safety and tolerability profile limits their use. As the first transdermal administration of an antidepressant, the STS provides several advantages over orally administered MAOIs, including minimal interaction with dietary tyramine, as well as the possibility of a more rapid onset of therapeutic action. Alongside its favorable safety profile, which includes a paucity of sexual side effects, the transdermal delivery of selegiline offers the same benefits of an effective MAOI without the need for dietary modifications

Table 1. Medications Contraindicated With the Selegiline Transdermal System[a]

Class	Specific Examples	Evidence Level for Class[b]
Narcotic analgesics	Meperidine	Probable
Analgesics	Tramadol Methadone Propoxyphene	Not noted[c]
Muscle relaxant	Cyclobenzaprine	Not noted[c]
Antitussive agents (found in cold and cough medications)	Dextromethorphan	Suspected
Vasoconstrictors (found in cold products and weight-reducing preparations)	Pseudoephedrine Phenylephrine Phenylpropanolamine Ephedrine	Established
Selective serotonin reuptake inhibitors	Fluoxetine Sertraline Paroxetine	Probable
Dual serotonin and norepinephrine reuptake inhibitors	Venlafaxine Duloxetine	Probable
Tricyclic antidepressants	Imipramine Amitriptyline	Suspected
Tetracyclic antidepressant	Mirtazapine	Not noted[c]
Monoamine oxidase inhibitors	Oral selegiline Isocarboxazid Phenelzine Tranylcypromine	Not noted[c]
Antianxiety agent	Buspirone	Not noted[c]
Aminoketone	Bupropion hydrochloride	Suspected
Herbal	St John's wort	Not noted[c]
Antiepileptics	Carbamazepine Oxcarbazepine	Suspected
Amphetamines	Dextroamphetamine Di-amphetamine	Suspected
Methylphenidates	Dexmethylphenidate Methylphenidate	Suspected

[a]The recommended washout period for contraindicated medications is about 1 week (4–5 half-lives) prior to and 2 weeks after STS treatment. One exception is fluoxetine, which requires a 5-week washout period prior to STS. Note that more rapid switches of 1 to 8 days have also been performed safely for monoamine oxidase inhibitors.
[b]Level of evidence for interaction with monoamine oxidase inhibitor class based on Facts and Comparisons 4.0,[60] in which "established" = proven to occur in well-controlled studies; "probable" = very likely but not proven clinically; "suspected" = may occur, some good data, needs more study; "possible" = could occur, but data are limited.
[c]Evidence level not noted by Facts and Comparisons 4.0.
Abbreviation: STS = selegiline transdermal system.

at the starting and target dose of 6 mg/24 hours. The STS is thus a viable therapeutic option for the treatment of MDD and its subtypes including atypical depression and melancholic depression.

Drug names: alprazolam (Xanax, Niravam, and others), bupropion (Wellbutrin and others), buspirone (BuSpar and others), carbamazepine (Equetro, Carbatrol, and others), citalopram (Celexa and others), cyclobenzaprine (Amrix, Flexeril, and others), dexmethylphenidate (Focalin and others), dextroamphetamine (Dexedrine, Dextrostat, and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), ibuprofen (Motrin, Ibu-Tab, and others), imipramine (Tofranil and others), isocarboxazid (Marplan), levothyroxine (Synthroid, Levo-T, and others), meperidine (Demerol and others), methadone (Methadose and others), methylphenidate (Ritalin, Daytrana, and others), mirtazapine (Remeron and others), olanzapine (Zyprexa), oxcarbazepine (Trileptal and others), paroxetine (Paxil, Pexeva, and others), phenelzine (Nardil), propoxyphene (Darvon and others), selegiline (EMSAM, Eldepryl, and others), sertraline (Zoloft and others), tramadol (Ultram and others), tranylcypromine (Parnate and others), venlafaxine (Effexor and others), warfarin (Coumadin, Jantoven, and others).

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