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Review article

Selegiline transdermal system: Current awareness and promise

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Abstract

Many monoamine oxidase inhibitors (MAOIs) have been used to treat major depressive disorder (MDD). However, the prescription of MAOIs has decreased considerably as a result of side effects such as tyramine-induced hypertensive crisis, which is also known as the 'Cheese Effect'. The drug delivery system itself can affect the bioavailability of certain drugs, which might influence the efficacy and tolerability of medications, as well as improve the compliance and reduce the incidence of recurrence and relapse. Therefore, there is a need for advanced drug delivery techniques that can evade the potentially hazardous toxic effects of the parent compound, including extended-release oral, cutaneous, intravesical and intravaginal routes, etc. In this context, the selegiline transdermal system (STS, EMSAM™) was introduced with improved side effect profiles and efficacy compared with the conventional form of the selegiline oral tablet. STS allows the targeted inhibition of the monoamine A (MAO-A) and MAO-B isoenzymes with minimal effects on the MAO-A in the gastrointestinal and hepatic systems. Hence, STS can reduce the risk of interactions with tyramine-rich foods. Many fundamental clinical and preclinical studies have reported that 6 mg/24 h of STS is effective against MDD without the need for dietary restrictions with an equal efficacy and improved safety profile. In addition, STS might benefit MDD patients with atypical features or who are resistant to other antidepressants. Overall, familiarity with the properties and indications of STS will have the clinicians another option of biological treatments for MDD patients but subsequent more data including actual post-market clinical experiences will be mandatory.

Keywords: Depression; Drug delivery system; Efficacy and tolerability; Monoamine oxidase inhibitor; Selegiline; Selegiline transdermal system (STS, EMSAM™)

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Abbreviations: AD, Alzheimer's disease; ASRs, application site reactions; ADHD, Attention deficiency hyperactivity disorder; BE, benzoylecgonine; PEA, β-phenylethylamine; CAE, catecholaminergic activity enhancer; HAM-D-17, Hamilton Depression Rating Scale-17 item; IC50s, inhibitory concentrations; IDS-SR, inventory for depressive symptoms-self rated; LSASv, Liebowitz Social Anxiety Scale; AMT, l-amphetamine; MET, l-methamphetamine; MDD, major depressive disorder; MAO-A, monoamine A; MAOIs, monoamine oxidase inhibitors; MADRS, Montgomery Asberg Depression Rating Scale; DES, *N*-Desmethylselegiline; Cmax, peak plasma concentration; RCTs, placebo-controlled clinical trials; TYR30, pressor dose; STS, selegiline transdermal system; SPECT, single photon emission computed tomography; SBP, systolic blood pressure; TSF, tyramine sensitivity factor; FDA, U.S. Food and Drug Administration.

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1. Introduction

Before the development of the currently available antidepressants, chlorpromazine was introduced in the mid-1950s to treat agitated, involutional and delusional depression, even though it is not a real primary antidepressant (Ban and Schwarz, 1963). These primitive antidepressant agents were promptly discarded after the introduction of a real prototype of antidepressants, imipramine, iproniazid and hydrazine (Ban, 2001). The introduction of the monoamine reuptake inhibitor (MAOI) agent, iproniazid, is believed to be the cornerstone of modern antidepressant development (Ban, 2001; Robinson, 2002). Iproniazid was originally developed as an antituberculosis medication but was found to induce euphoria and hyperactivity in some tuberculosis patients. MAOIs were among the first compounds to demonstrate consistent antidepressant activity. By the early 1960s, they were successfully established as a mainstream antidepressant as well as for treating anxiety disorders in the absence of depression. However, with the availability of various antidepressant agents, there has been a dramatic decrease in the psychiatrists' prescription and experience of MAOIs over the past several decades (Fiedorowicz and Swartz, 2004). This reluctance might have been driven by a concern about food and drug interactions as well as the potential side effects, even though MAOIs have demonstrated clinical efficacy in the treatment of the following: MDD with atypical features (Jarrett et al., 1999; Liebowitz et al., 1988; McGrath et al., 2000; Quitkin et al., 1988, 1993), treatment resistant depression (McGrath et al., 1993), depression with bulimia and mixed depressive disorder (Rothschild et al., 1994), post-traumatic stress disorder (Frank et al., 1988) and mixed depressive disorder (Robinson et al., 1973).

Although there are many interesting MAOIs available for treat psychiatric disorders including MDD, this review focuses on the clinically updated information regarding the newer MAOI, a selegiline transdermal system (STS, EMSAM™), which is a selective MAO-B inhibitor but is administered through a different route.

Since the U.S. Food and Drug Administration (FDA) approved STS for the treatment of MDD in February 2006, it has officially become the first skin (transdermal) patch indicated for MDD. Our previous paper comprehensively reviewed the MAOIs and briefly introduced STS as a new generation of MAOIs (Patkar et al., 2006). This review focuses on the development and the current status of STS as a new antidepressant for the treatment of MDD as well as its use in the treatment of other psychiatric disorders.

2. Clinical background of STS

2.1. Unmet need of selegiline

Selegiline is a preferential MAO-B inhibitor that is currently used as an adjunct therapy to treat late stage Parkinson's disease. In addition, placebo controlled clinical trials have shown it to have effective antidepressant activity (Mann et al., 1989; McGrath et al., 1989; Sunderland et al., 1994).

However, the antidepressant doses of selegiline are 3 to 6 times higher than those approved for the treatment of Parkinson's disease. This dose might cause the loss of MAO-B selectivity that might be linked to the serious side effect, hypertensive crisis, which also known as the 'Cheese Effect" (Anderson et al., 1993; Blackwell et al., 1967). This effect is believed to develop as a result of the inhibition of MAO-A in the intestinal barrier through systemic tyramine exposure. Therefore, patients who take MAOIs require dietary restrictions of foods or medications containing tyramine (Anderson et al., 1993; Mawhinney et al., 2003). It is for this reason that many psychiatrists have been reluctant to prescribe MAOIs including selegiline.

There is a need for a drug delivery system that can improve the bioavailability of certain drugs, which would be associated with a change in the efficacy and tolerability of medications resulting in improved compliance with a lower incidence of

recurrence and relapse. Therefore, a delivery technique that can evade the potentially hazardous toxic effects of the parent compound metabolism may take alternative paths such as extended-release oral, cutaneous, intravesical and intravaginal routes (Dmochowski and Staskin, 2002).

The repeated continuous subcutaneous selegiline loading on the skin of rats was found to have a larger effect on inhibiting the MAO-A and MAO-B activity in the CNS than in the hepatic tissue, which is linked to a lower risk of hypertensive crisis (Ekstedt et al., 1979; Felner and Waldmeier, 1979; Mawhinney et al., 2003). Therefore, STS was developed in an attempt to achieve a sustained blood concentration of selegiline to have an adequate antidepressant effect through the inhibition of CNS MAO-A without the side effects of the inhibition of intestinal MAO-A.

3. Progression of drug delivery system of selegiline

Selegiline offers benefits to Parkinsonism patients but its amphetamine metabolites can cause cardiovascular side effects. Moreover, Parkinsonism patients are known to suffer from swallowing difficulties, which may limit the use of oral tablets.

Zydis selegiline was developed using a freeze-dried tablet technology (Clarke et al., 2003b). When Zydis selegiline is placed in the mouth, it disintegrates immediately, releasing the drug, which dissolves or disperses in the saliva. The saliva containing the dissolved or dispersed medicament is then swallowed and the drug is absorbed in a normal manner. This might prevent the first-pass metabolism by allowing the administration of a lower dose that is equal to the oral tablet dose whilst maintaining the selegiline bioavailability with the reduced production of amphetamine metabolites (Seager, 1998).

A pharmacokinetic study reported that Zydis selegiline may be more beneficial than the conventional oral form (Clarke et al., 2003a). 1.25 mg of Zydis selegiline produced a similar level of MAO-B inhibition to those used obtained with conventional selegiline 10 mg but without the altered inhibitory effect on MAO-A (Clarke et al., 2003a). In addition, the bioavailability of Zydis selegiline was 8 times higher than the conventional form, as evidenced by the AUC and the peak plasma concentration (Cmax), which showed Zydis selegiline to have a reduced plasma fluctuation than the conventional form (Clarke et al., 2003a).

The level of amphetamine metabolites (DES, AMT, MET, respectively) was significantly lower in patients given 1.25 mg Zydis selegiline (1.19, 0.34, 0.93 ng/ml, respectively) than in those given the conventional form (18.37, 3.60, 12.92 ng/ml, respectively) (Clarke et al., 2003a). In accordance with the improved pharmacokinetic profiles, Zydis selegiline was reported to be more tolerable and preferred by patients than the conventional forms through parallel group and cross-over studies using Zydis selegiline 1.25 mg or 10 mg and oral selegiline 10 mg, in which most (61%) patients had a favorable attitude towards Zydis selegiline 5 mg ($p<0.002$) (Clarke et al., 2003b).

Zydis selegiline did not potentiate the tyramine effect. A pressor effect was elicited after the administration of 400 mg tyramine both before and after 14 days of treatment with 1.25 mg Zydis selegiline. On the other hand, after a 14 day treatment with 10 mg of the conventional form, the threshold dose needed to develop a tyramine pressor response ranged from 400 mg to 200 mg ($p<0.0001$) (Clarke et al., 2003b).

Therefore, an improved drug delivery system may be beneficial to patients, which would result in better drug compliance, and might be associated with reduced recurrence and medical cost.

4. The development of selegiline transdermal system (STS)

4.1. Background of transdermal system

A new drug delivery system would be expected to have greater efficacy, better tolerability, or more convenience than existing compounds. In this context, the transdermal delivery system has been considered. This route might enhance the consistency of the plasma concentration, reduce the gastrointestinal variations associated with the simplification of the range of doses needed to treat patients, bypass the first-pass metabolism associated with enhanced bioavailability, simplify the daily dosing schedule and have a short plasma elimination half-life of the drug (Jenner, 2005).

There are two traditional designs of transdermal patches (Wilkosz, 2003). The first is a membrane system, which contains a reservoir that controls the drug release and maintains a constant serum drug level (Wilkosz, 2003). The second is the matrix patch system. In this system, the active drug is contained in a polymer matrix that releases the drug at a controlled rate. Matrix patches are not designed to provide true zero-order release. However, the decrease in the rate of release is so small that it does not significantly affect the rate of drug absorption (Wilkosz, 2003). Matrix patches may be smaller and thinner than their reservoir predecessors due to advances in their design (Wilkosz, 2003).

4.2. Pharmacokinetics of STS

There is no complete pharmacokinetic data for STS currently available. Selegiline is a weak base with a p*K*a of 7.5, a low molecular weight of 187.3 and a calculated partition coefficient (octanol/water) of 3.4 (Barrett et al., 1997). These properties are optimal for transdermal delivery (Rohatagi et al., 1997). STS has been found to be absorbed extensively with plasma levels being maintained over a 24-hour period, thereby allowing for a once-daily application.

Approximately 20–30% of the selegiline in STS is delivered systemically over a 24-hour period (range of 10%–40%). Consequently, the degree of absorption might be higher with selegiline (Food and Drug Administration, 2005). The 20 mg STS patch delivers 6 mg/24 h of selegiline, while the 30 mg and 40 mg patches deliver approximately 9 mg and 12 mg/24 h of selegiline, respectively (Bristol-Myers Squibb Company, 2006).

STS is associated with the reduced production of metabolites compared with the selegiline oral tablet by avoiding the extensive

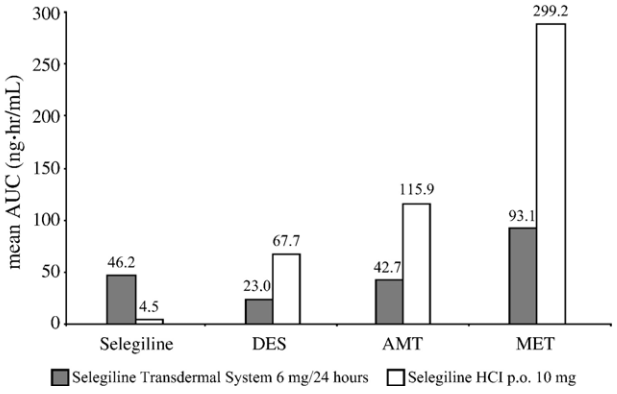

Fig. 1. Average AUC_{inf} (ng h/mL) of selegiline and the three major metabolites [*N*-desmethylselegiline, DES; *l*-amphetamine, AMT; *l*-methamphetamine, MET] estimated for a single, 24-hour application of a selegiline transdermal system (STS) 6 mg/24 h patch and a single, 10 mg oral immediate release dose of selegiline HCl in 12 healthy male and female volunteers. Adapted from the EMSAM prescribing information: available at http://www.bms.com/cgi-bin/anybin.pl?sql=select%20PPI%20from%20TB_PRODUCT_PPI%20where%20PPI_SEQ=112&key=PPI; STS=selegiline transdermal system.

first-pass metabolism (Fig. 1) (Bristol-Myers Squibb Company, 2006).

The drug is metabolized through multiple CYP450 enzyme systems (2C9, 2B6, 3A4, 2D6 and 2A6). A steady-state plasma level of STS is reached after 5 days of treatment, which has little fluctuation resulting in a relatively constant blood level.

Dose adjustments are unnecessary with STS in patients with hepatic and renal failure. It was reported that these patients treated with STS 20 mg showed a similar pharmacokinetic profile to other healthy volunteers (Bristol-Myers Squibb Company, 2006). Table 1 gives a summary of the comparisons between STS and the oral formulation of selegiline.

4.3. Pharmacodynamics and antidepressant activity of STS

Selegiline has a greater affinity for MAO-B than MAO-A. However, selegiline inhibits both isoenzymes at the antidepressant doses. The mechanism for the action of STS as an antidepressant is not completely understood. It is likely that elevated levels of serotonin and norepinephrine and dopamine resulting from the inhibition of MAO play an important role in the antidepressant effects of STS (Cesura and Pletscher, 1992). Selegiline administered through a transdermal patch exhibits antidepressant properties only at the doses that inhibit both MAO-A and MAO-B activity in the brain (Food and Drug Administration, 2005).

Animal studies have shown that the doses of STS that inhibit the activities of both MAO-A and MAO-B by more than 90% in the brain only partially inhibit the enzyme activities in the gastrointestinal tissues, with a maximum 40% inhibition of MAO-A activity and 70%–75% inhibition of MAO-B activity (Wecker et al., 2003). Moreover, the doses of STS that inhibit the brain MAO-A and MAO-B activities by 55%–60% and 85%–90%, respectively, did not alter the gastrointestinal MAO-A activity and produced only 40%–60% inhibition of MAO-B activity (Wecker et al., 2003). These reports support the targeted effect of transdermal selegiline to the brain instead of the gastrointestinal tissues (Wecker et al., 2003) (Mawhinney et al., 2003; Wecker et al., 2003). An animal study showed that the transdermal delivery of selegiline was 10–20 times more potent (on a mg/kg basis) in producing both its antidepressant-like activity and inhibiting the cortical MAO-A than oral selegiline, in which the half maximal inhibitory concentrations (IC50s) for the inhibition of MAO-A after oral and transdermal administration for 7 days were 19.8 and 1.1 mg/kg, respectively (Gordon et al., 1999).

In vitro receptor binding assays demonstrated selegiline to have an affinity for the human recombinant adrenergic α2B receptor (Ki=284 μM), while it showed little or no affinity [Ki>10 μM] for the dopamine receptors, adrenergic β, glutamate, muscarinic M1–M5, nicotinic, or rolipram receptor/sites (Bristol-Myers Squibb Company, 2006).

4.4. Pressor effect and hypertensive reaction

Depressed patients are 1.5 times more vulnerable to a pressor effect or a hypertensive reaction than healthy controls (Barrett et al., 1997), which might be why some psychiatrists are reluctant to prescribe MAOIs including selegiline.

Tyramine is an indirect-acting, sympathomimetic amine that exhibits its pressor effect through active uptake into the sympathetic nerve terminals and the release of norepinephrine from the synaptic vesicles (Barrett et al., 1997).

A pressor response is usually defined as an increase in systolic blood pressure (SBP) of at least 30 mmHg above the baseline or placebo measurements. The minimal dose of

Table 1
Comparisons between oral selegiline and the selegiline transdermal system (STS)[a]

	Selegiline (10 mg)	STS (20 mg/20 cm^2)
Half-life	9.7 h	20.1 h
Metabolisms	CYP450 2A6, 2B6, 3A4/5, 2C9, 2D6	CYP450 2A6, 2B6, 3A4/5, 2C9, 2D6
Time to mean peak plasma concentrations	0.9 h	18.4 h
Metabolites (AUCinfM/P)	MET/DES/AMT (903.1/86.1/320.6)	MET/DES/AMT (2.4/0.6/1.0)
Plasma levels	Variable peak-trough fluctuation	Minimal peak-trough fluctuation
Route of administration	Oral	Skin
Maximum plasma concentrations (pg/mL)	2222	2162
First-pass metabolism	Pass	None
%Fe	0.02	0.07
Intestinal inhibition of MAO-A[b]	Definite beyond 10 mg/day	Less likely at approved dose
Bioavailability	4%	75%

[a] Dietary modifications were not necessary for patients given the 6 mg/24-hour patch, while patients given the 9 mg/24-hour or 12 mg/24-hour patches required some dietary modification.

[b] The doses of STS that produced the maximum MAO-A inhibition in the brain inhibited MAO-A in the gastrointestinal tissue by only 30%–40%; DES = *N*-desmethylselegiline; MET = *l*-methamphetamine; AMT = *l*-amphetamine (AMT); AUCinf M/P = ratio of the metabolite to the parent compound area under the concentration-time curve from time zero extrapolated to infinity; %Fe = fraction excreted in the urine unchanged.

tyramine needed to produce a pressor response is referred to as the pressor dose (TYR30) (Blob et al., 2007). It was clearly demonstrated that double the amount of tyramine is needed to provoke a similar effect on the BP at the fed state than at the fasting state, which suggests a decrease in the bioavailability of tyramine when administered with food (Vandenberg et al., 2003). The average level of TYR30 in healthy males in the fasting condition (tyramine capsules without a meal) is approximately 500 mg (Blob et al., 2007). A recent study reported that the tyramine sensitivity factor (TSF, a ratio of the baseline and on-treatment tyramine pressor doses) for STS was similar to that after a treatment with 10 mg/d of oral selegiline capsules but was more than 20 times lower than that observed during a MAOI treatment (tranylcypromine) (Azzaro et al., 2006; Blob et al., 2007). It was also reported that the ingestion of a tyramine-enriched meal containing an estimated 400 mg tyramine produced no clinically significant tyramine effect on the BP in 12 healthy subjects treated with STS 6 mg/24 h, which was approximately double the mean TYR30 measured in the fasted subjects administered the encapsulated tyramine during treatment (Blob et al., 2007). It should be noted that the ingestion of such large quantities of tyramine-containing foodstuffs is highly improbable in real life.

4.5. Dermal safety of STS in human

Preclinical sensitization studies have suggested that STS should be classified as a non-allergen, and that STS is unlikely to cause any dermal sensitization in humans (Pauporte et al., 2004). Short-term, placebo-controlled major depressive disorder studies reported application site reactions (ASRs) in 24% of STS-treated patients and 12% of placebo-treated patients. Most of the ASRs were mild or moderate (Food and Drug Administration, 2005), and none were considered serious. ASRs led to a dropout rate of 2% of the STS-treated patients and 0% of placebo-treated patients. The data from the individual placebo-controlled trials are discussed in the following section.

Table 2
Drug interaction with the selegiline transdermal system (STS)[a]

Drug	Results
Alcohol	No increase in the sedative and cognitive impairing effects
Sympathomimetics	
Pseudoephedrine	No clinically significant change in blood pressure
Phenylpropanolamine (PPA)	Higher incidence of significant blood pressure elevations with the co-administration of STS and PPA
Levothyroxine	No change in T_3 or T_4 concentrations
Olanzapine/risperidone/ Ketoconazole/Ibuprofen/ Alprazolam	No change
Carbamazepine	Increase in selegiline[b]
Warfarin	No effect on warfarin, as measured by INR, factor VII or factor X levels

[a] STS = 6 mg/24 h for various days.
[b] Slightly increased levels of selegiline and its metabolites were observed after the single application of STS 6 mg/24 h in subjects who had received carbamazepine (400 mg/day) for 14 days, even though carbamazepine is an enzyme inducer and typically causes a decrease in the counterpart drug (clinical relevance of these observations is unknown). Adapted from the EMSAM prescribing information: available athttp://www.bms.com/cgi-bin/anybin.pl? sql=select%20PPI%20from%20TB_PRODUCT_PPI%20where%20PPI_SEQ=112&key=PPI; STS = selegiline transdermal system.

4.6. Drug interaction with STS

The prevalence of physical illnesses and the use of over-the-counter medications have dramatically increased, particularly in the elderly. Therefore, polypharmacy in this group is virtually unavoidable in real clinical practice. Furthermore, a combination of different classes of antidepressants in the treatment of MDD is also popular, which will increase in patients in order to meet the potential drug interaction exposure. Table 2 gives a list of the drug–drug interactions.

The use of STS is contraindicated for patients taking selective serotonin re-uptake inhibitors (e.g., fluoxetine, sertraline, and paroxetine), dual serotonin and norepinephrine re-uptake inhibitors (e.g., venlafaxine and duloxetine), tricyclic antidepressants (e.g., imipramine and amitripyline), bupropion hydrochloride; meperidine and analgesic agents such as tramadol, methadone and propoxyphene; the antitussive agent dextromethorphan; St. John's wort; mirtazapine; cyclobenzaprine; oral selegiline or other MAO inhibitors (e.g., isocarboxazid, phenelzine, and tranylcypromine); carbamazepine and oxcarbazepin; sympathomimetic amines (e.g., amphetamines); cold products and weight-reducing preparations that contain various vasoconstrictors (e.g., pseudoephedrine, phenylephrine, phenylpropanolamine, and ephedrine) (Bristol-Myers Squibb Company, 2006).

4.7. Morphological structure of STS

A matrix-type transdermal system consist three layers. Layer 1 is the backing film that provides the matrix system with the occlusivity and physical integrity that protects the adhesive/drug layer. Layer 2 is the adhesive/drug layer. Layer 3 consists of side-by-side release liners that are peeled off and discarded by the patient before applying the STS (Bristol-Myers Squibb Company, 2006).

5. Clinical application of STS

5.1. Approved indication

5.1.1. Major depressive disorder

Six-week (Bodkin and Amsterdam, 2002), 8-week (Amsterdam, 2003) and 52-week placebo-controlled clinical trials (RCTs) (Amsterdam and Bodkin, 2006) have demonstrated the efficacy of STS at a fixed dose of 6 mg/24 h for the acute treatment and prevention of a relapse of MDD. A recent 8-week RCT reported the efficacy of STS for the treatment of MDD with a flexible dose design (range of 6 mg/24 h to 12 mg/24 h) (Feiger et al., 2006). None of these studies (Amsterdam, 2003; Amsterdam and Bodkin, 2006; Feiger et al., 2006) required any dietary modifications with the exception of one study (Bodkin and

Table 3
The results of the published short-term, randomized, placebo-controlled, double-blind clinical trials of Selegiline Transdermal System (STS) in major depressive disorder

	Bodkin and Amsterdam (2002)[a, b]	Amsterdam (2003)	Feiger et al. (2006)[b]
Duration	6 weeks	8 weeks	8 weeks
Number of patients (STS, placebo)	177 (89, 88)	289 (145, 144)	265 (132, 133)
Dose	6 mg/24 h	6 mg/24 h	Flexible dose design (6, 9, and 12 mg/24 h)
Primary endpoint[c] (STS vs placebo)	HAM-D-17 (−8.7 vs −6.1, $p=0.01$)	HAM-D-17 (−8.1 vs −6.1, $p=0.069$)	HAM-D-28 (−11.1 vs −8.9, $p=0.03$)
Additional endpoints[c] (STS vs placebo)	HAM-D-28 (−11.2 vs −7.6, $p=0.004$) MADRS (−9.8 vs −5.7, $p=0.005$)	HAM-D-28 (−10.3 vs −8.5, $p=0.039$) MADRS (−10.2 vs −6.7, $p=0.001$)	HAM-D-17 (−8.7 vs −7.5, $p=0.13$) MADRS (−11.5 vs −8.6, $p=0.02$) IDS-SR (−14.0 vs −10.9, $p=0.03$)
Responder[d] rate (STS vs placebo)	HAM-D-17 ($n=33$, 37.5% vs $n=20$, 22.7%, $p=0.04$) HAM-D-28 ($n=33$, 37.5% vs $n=20$, 22.7%, $p=0.03$)	MADRS ($n=48$, 33.1% vs $n=30$, 20.8%, $p=0.031$) HAM-D-17 ($n=47$, 32.4% vs $n=40$, 27.8%, $p=0.471$) HAM-D-28 ($n=47$, 32.4% vs $n=42$, 29.2%, $p=0.589$)	HAM-D-28 ($n=39$, 32.4% vs $n=42$, 29.2%, $p=0.589$)

HAM-D-17 = 17-item Hamilton Depression Rating Scale; HAM-D-28 = 28-item Hamilton Depression Rating Scale; IDS-SR = Inventory for depressive symptomatology-self rated; MADRS = Montgomery Asberg Depression Rating Scale.
[a] Patients in this study followed a tyramine restricted diet.
[b] Pivotal clinical trials.
[c] Changes in the total score of the rating scales from the baseline.
[d] Rated as a ≥50% reduction in rating scales.

Amsterdam, 2002). Table 3 gives a summary of the published short-term RCTs.

In the first RCT (Bodkin and Amsterdam, 2002), 177 subjects were randomly assigned to the STS ($N=89$) or placebo ($N=88$) groups. The study showed that the STS group achieved statistically significant improvement in all the outcome measures, as shown in Table 3. Additional response analyses revealed the STS to have a better efficacy than the placebo. Moreover, a larger decrease in the mean Hamilton Depression Rating Scale-17 item (HAM-D-17) (STS 17% vs placebo 11%, $p=0.05$), HAM-D-28 (STS 17% vs placebo 11%, $p=0.02$), and Montgomery Asberg Depression Rating Scale (MADRS) scores (STS 11% vs placebo 4%, $p=0.01$) were observed with the STS as early as week 1 of treatment compared with the placebo. In addition, a larger percentage of selegiline patients (22.7%) than the placebo (11.4%) patients demonstrated remission with a final HAM-D-17 scale (<8 on HAM-D-17 score).

The next RCT recruited 289 MDD patients, and showed a modest but statistically significant antidepressant benefit compared with the placebo. One hundred and forty five (145) patients received STS 6 mg/24 h and 144 patients took the placebo patch for 8 weeks (Amsterdam, 2003). The STS had a superior effect on the total MADRS score at week 4 (STS 19.4 vs placebo, $p=0.024$), week 6 (STS 19.2 vs placebo, $p=0.027$) and week 8 (STS 18.1 vs 21.8, $p=0.001$) as well as on the total HAM-D-28 score at week 8 (STS 18.7 vs placebo 21.3, $p=0.039$) than the placebo, even though the HAM-D-17 score similar in the STS failed and placebo groups at any visit. Similar trends were also observed in the percentage of patients rated as being responders experiencing a >50% decrease in each outcome measure, as shown in Table 3. This study partly supported the efficacy and safety reported by a previous study (Bodkin and Amsterdam, 2002).

In an 8-week RCT (Feiger et al., 2006), STS was shown to be superior to the placebo on both the primary (HAM-D-28) and secondary [MADRS and inventory for depressive symptoms-self rated (IDS-SR)] endpoints, as shown in Table 3. The antidepressant efficacy of STS was further substantiated by the significantly greater improvement in the core depression symptoms of the HAM-D (HAM-D Bech-6 subscale = items 1, 2, 7, 8, 10, and 13) (STS-5.5 vs placebo-4.1, $p<0.01$). This study was the first to demonstrate the short-term efficacy of STS at doses of up to 12 mg/24 h, while other short-term studies reported the effect of a fixed dose of 6 mg/24 h. In terms of dose distribution, 230 (87%) out of 265 patients, who were randomized to either the STS or placebo treatments, had their starting dose increased to 9 mg/24 h. In addition, 147 out of 265 patients (55%) had their dose increased to 12 mg/24 h at a certain time of the study period, while only 12 out of 265 patients (4.5%) had their dose reduced (Feiger et al., 2006). However, in most patients, the dose was increased to 12 mg/24 h at week 5 despite there being significant differences in the outcome measures between the two treatment groups. This means that no dose–response relationship could be established in their study (Feiger et al., 2006). A definite clarification regarding the dose–response relationship of STS from different fixed-dose design studies will be needed.

Overall, these three large studies demonstrated the superior efficacy of STS over the placebo in the treatment of patients with MDD with an improved profile after a dietary restriction of tyramine.

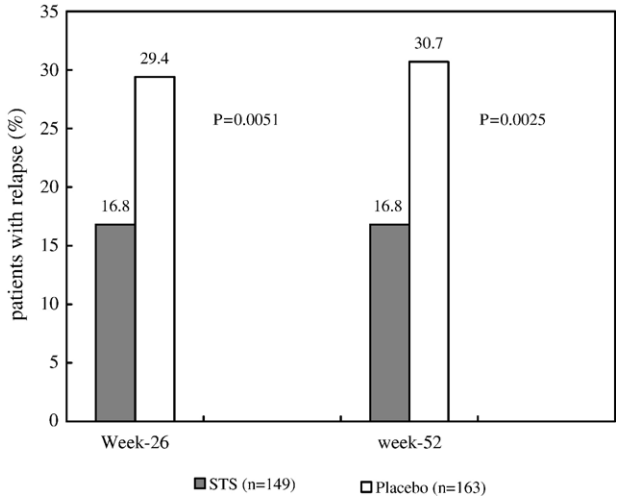

Fig. 2. Percentage of patients who had relapsed in a 52-week long-term study of the selegiline transdermal system (STS). Relapse criteria: 2 consecutive scores (≥3 days apart) of Hamilton Depression Rating Scale-17 item ≥14 and Clinical Global Impression-Severity score ≥3 with a ≥2-point increase from baseline. Data from Amsterdam and Bodkin (2006).

The maintenance efficacy of STS 6 mg/24 h in the treatment of MDD, in terms of the prevention of a recurrence or a relapse for up to 1 year, was assessed in 322 patients (STS-treated $n=149$; placebo-treated $n=163$) with a baseline HAM-D 17 item score of 18 or higher and who responded positively to the initial 10-week open-label treatment (HAM-D 17 item score of 10 or less in two successive occasions during the final two weeks of the open-label treatment) (Amsterdam and Bodkin, 2006). These patients were then randomized to receive either STS 6 mg/24 h or a placebo patch for up to 52 weeks. A recurrence or relapse was defined as a HAM-D-17 score of 14 or more on two successive occasions within a 2-week period. Significantly fewer patients on STS experienced a relapse by week 52 ($p=0.0025$) and week 26 ($p=0.0051$) than those given the placebo. This finding is summarized in Fig. 2.

Interestingly, there is a paucity of data regarding the progression or changes in the relapse rate during the continuation treatment using a placebo-controlled continuation study of patients who initially responded to an acute treatment for MDD (Reimherr et al., 1998). As the authors noted, the patients on STS did not relapse beyond week 14 of the continuation treatment (same relapse rates in both 26-week and 52-week), which is comparable to other trials on antidepressant such as fluoxetine (first 24-week, fluoxetine=26.4% vs placebo=48.6%; second 38-week, fluoxetine=9.0% vs placebo=23.2%; final 62-week, fluoxetine=10.7% vs placebo=16.2%) (Reimherr et al., 1998). Kaplan–Meier survival analysis on the time to relapse also showed significant differences between the two groups favoring the STS treatment ($p=0.0048$). In addition, the cumulative rates of relapse were significantly lower in the STS-treated group than in the placebo-treated group at week-26 (20% vs 37%, $p=0.0115$) and week-52 (20% vs 39%, $p=0.0061$). It should be noted that most of the patients who participated in this study had recurrent MDD (>60%). A substantially larger number of placebo patients (61%) required rescue medication during the first 26 weeks of treatment than the STS patients (29%) (Amsterdam and Bodkin, 2006). This 52-week long-term trial suggests that STS may have beneficial effects in maintaining the treatment effect as well as for preventing a relapse of MDD.

Currently available evidence suggests that STS (6 mg/24 h, 9 mg/24 h, and 12 mg/24 h) is effective in both short-term and long-term treatments of patients with MDD, particularly those who would benefit the most from MAOIs. Importantly, transdermal delivery facilitates the antidepressant properties without the need for dietary restrictions of tyramine.

5.2. Potential indication

5.2.1. Parkinson's disease and movement disease

Oral selegiline has been approved for the treatment of Parkinson's disease as both a monotherapy and as a combination agent with existing antiparkinsonian medications such L-dopa, particularly for patients with motor complications and neuroprotection. The efficacy and safety of oral selegiline in the treatment of Parkinson's disease has been established by numerous RCTs, while there are few studies on STS (Allain et al., 2000; Larsen et al., 1999; Mally et al., 1995; Palhagen et al., 1998; Przuntek et al., 1999; Shoulson et al., 2002).

5.2.2. Alzheimer's disease (AD) and cognitive disorders

Fixed and random effects meta-analyses of oral selegiline in the treatment of AD (Wilcock et al., 2002) were carried out using the standardized mean differences in 14 inclusion criteria fulfilled studies from a total of 27 studies identified. Regarding "cognition" there was a statistically significant difference between the selegiline and placebo at 4–6 weeks and 8–17 weeks after randomization. However, this disappeared at later assessments and the effect size did not justify the clinical significance. This may indicate the potential of STS in the treatment of AD and its related cognitive disorders. Recently, a small RCT reported that STS might be helpful in patients with HIV-associated cognitive impairment (Sacktor et al., 2000). This 10-week study recruited 14 patients suffering from HIV-associated cognitive impairment as a result of high antiretroviral therapy, and produced some meaningful data in relation to the single tests of verbal memory and motor/psychomotor performance, which highlights the need for larger controlled trials (Sacktor et al., 2000). The dose of STS (3.1mg/d) in this trial was lower than that of a similarly designed study with oral selegiline (7.5 mg/d) (Dana Consortium on the Therapy of HIV Dementia and Related Cognitive Disorders, 1998). Therefore, more study will be needed to reach a final conclusion on the efficacy of STS for the treatment of AD and its related cognitive disorders.

5.2.3. Attention deficiency hyperactivity disorder (ADHD)

A small open-label trial evaluated the efficacy of STS for the treatment of ADHD in 30 children and 19 adolescent populations, and reported that STS had some promise in the treatment of ADHD (Mechcatie, 2003). However, after 8 weeks, the dropout rate was 47% and 16% in each group, respectively. This

suggests that the high drop-out rate might be associated with the pharmacokinetic change in STS in the younger age group (Mechcatie, 2003).

5.2.4. Cocaine addiction

A recent placebo-controlled, crossover study indicated that STS might attenuate the physiological and subjective effects of cocaine, which highlights the need for randomized trials to evaluate the efficacy of selegiline for the treatment of cocaine abuse (Houtsmuller et al., 2004). The pharmacokinetics and subjective, physiological, and endocrinological effects of intravenous cocaine (0.2 mg and 40 mg) in 12 cocaine-dependent subjects were examined both before and during STS (20 mg/20 cm^2, 10 days). STS clearly reduced the cocaine-induced increases in the subjective ratings of the typical cocaine effects. The cocaine-induced increases in the ratings of "Drug effect", "Liking", "Good drug effect", "High", "Stimulated", and "Desire for cocaine" were attenuated during the selegiline treatment compared with those before treatment. This attenuation by selegiline was substantial. For example, on a scale of 0–100, the peak scores for "High" after cocaine (40 mg) decreased from 46 before the selegiline treatment to 23 after 10 days of the selegiline treatment, which is in line with previous reports (Bartzokis et al., 1999). In addition to the subjective cocaine effects, STS decreased the cocaine-induced increases in both the heart and systolic blood pressure but had no effect on the level of cocaine metabolites (Houtsmuller et al., 2004). This study provides further evidence that STS might be a useful agent for treating substance abuse. However, a recent RCT on 300 cocaine dependent subjects examined the efficacy of selegiline using the subject self-reported cocaine use as the primary outcome measure. This was also substantiated by urine benzoylecgonine (BE). The results showed that selegiline had no significant effect compared with the placebo (Elkashef et al., 2006). However, more data will be needed to clarify the efficacy of STS in the treatment of substance abuse.

5.2.5. Other uses

A recent large and small RCT showed that oral selegiline of 5 mg/d successfully reduced the craving for cigarettes as well as the need for nicotine replacement therapy, even though there were no significant differences in the long-term abstinence rate (Biberman et al., 2003; George et al., 2003).

A recent single photon emission computed tomography (SPECT) study suggested that the striatal dopamine reuptake site density was significantly lower in those patients with social phobia than in their age- and gender-matched comparison subjects (Tiihonen et al., 1997). Given that a decreased dopaminergic function is linked to the development of social phobia, it was suggested that STS might be beneficial for the treatment of social phobia. To date, there has been only one small study ($n=16$, 6-week) of oral selegiline (10 mg/day) with regard to the treatment of social phobia, where modest efficacy of selegiline was shown (a 32% decrease in anxiety symptoms from the baseline as measured by the Liebowitz Social Anxiety Scale [LSAS]) (Simpson et al., 1998).

Animal studies have shown that the ability of selegiline to increase the dopaminergic response might be translated into a clinical application for the treatment of erectile dysfunction. This was supported by other evidence showing that selegiline is associated with an increase in β-phenylethylamine (PEA), which increases the level of dopaminergic neurotransmission in the brain (Allard et al., 2002). PEA and amphetamines induce the continuous release of noradrenaline and dopamine from their intraneuronal stores, while selegiline lacks this property leading to fewer side effects (Knoll, 2000, 1985). Preclinical studies also suggested that selegiline might slow or mitigate the age-related decreases in sexual performances (Knoll, 1985). The catecholaminergic activity enhancer (CAE) activity of selegiline was found to be effective against the age-related decrease in sexual performance as well as learning and memory by enhancing the impulse propagation mediated release of noradrenaline and dopamine in the brain (Knoll, 1998).

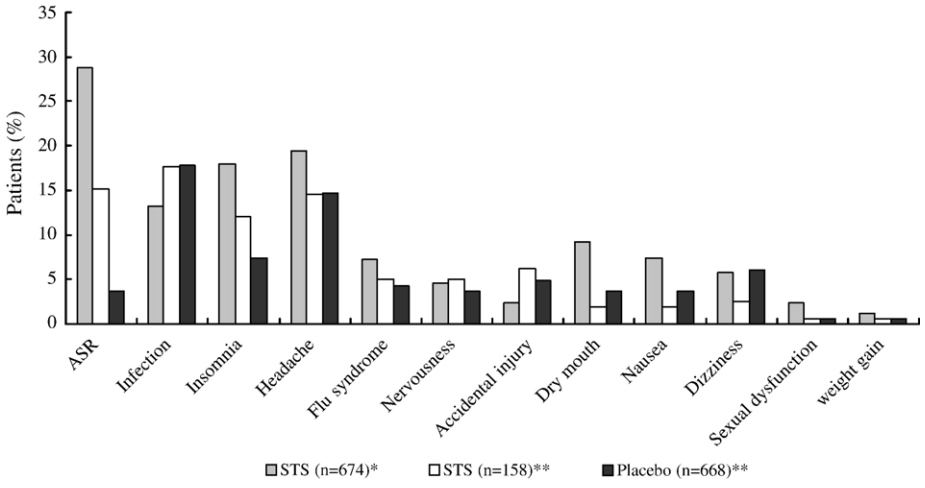

Fig. 3. Treatment-emergent adverse events in the selegiline transdermal system (STS) and placebo groups in a 52-week, double-blind, placebo-substitution, parallel-group study. ASR = application site reaction. *Open-label phase for 10-weeks; **Double-blind phase for 52-weeks. ASRs occurred at a rate of only approximately 5% and was double that of the placebo. Data from Amsterdam and Bodkin (2006).

However, a suitable number of adequately powered RCTs will be needed to demonstrate the advantages of STS in these potential indications.

6. Safety of STS

In the first controlled study (Bodkin and Amsterdam, 2002), ten patients (11%) given STS and 15 patients (17%) given the placebo dropped out of the study before week 6. Of these, only four patients (4.5%) in the STS group and five patients (5.6%) in the placebo group discontinued the treatment as a result of adverse events. ASRs such as rashes, itching, redness, or irritation were more common in those patients treated with the STS (N=32, 36%) than in those given the placebo (N=15, 17%) (p=0.006). However, only 5 of the 32 STS patients required symptomatic treatment with topical corticosteroids or oral diphenhydramine, and only three patients in the STS group discontinued treatment due to this reaction. The patients in the STS group had a slightly larger decrease in the orthostatic blood pressure (p=0.0001), which was not considered to be clinically meaningful. Although not clinically meaningful, the QTc interval at the endpoint was slightly lower in the STS group (mean=0.005 s) but slightly higher in the placebo group (mean=0.001 s) (p=0.04).

In the second controlled study (Amsterdam, 2003), forty-one patients from each group dropped out of the study before week 8. Of these, 10 (6.7%) and 8 patients (5.3%) in the STS and placebo groups, respectively, discontinued the treatment due to adverse events. ASRs were more common in the patients treated with STS (N=47, 31.5%) than in those given the placebo (N=23, 15.1%) (p=0.001). However, these reactions were clinically mild or moderate and did not require active treatment.

Similar trends regarding the safety profile were also observed in another placebo-controlled clinical trial (Feiger et al., 2006). The only significant difference in adverse event reporting between the STS and the placebo groups was mild to moderate ASRs (31.5% vs 15.1%, p=0.001).

Table 4
Potential advantages of the selegiline transdermal system (STS) relative to the oral formulation of selegiline

Improvements in STS
Tissue specificity in drug targeting: targeted specific inhibition on MAO in the brain versus the intestine
Increased bioavailability (↑ drug delivery to brain): no first-pass metabolism
Easy administration route : skin patch
Convenience and simplicity: single-daily dose, easily removed when adverse side effects are experienced
Good alternative use according to the patient's medical condition: e.g., swallowing difficulties
Decreased gastrointestinal side-effects: skin absorption and no first-pass metabolism
Minimizing serious adverse effects: reduced risk of hypertensive crisis
Less restriction in food consumption: no food restriction on a recommended and target dose at 6 mg/24 h
Improved quality of life: no exposure to others when taking medication
Improved medication adherence/compliance: possibly by complex factors e.g., easy accountability, difficult to miss a dose, and a more acceptable form for long-term treatment

In contrast to other antidepressants, STS was found to have negligible effect on weight changes. Based on the short-term RCTs, STS was found to be associated with an average weigh loss of 1.2 lb, while the placebo was related to an average weigh gain of 0.3 lb. No studies have specifically examined the incidence of sexual dysfunction with STS. However, a low incidence of sexual side effects in both men (delayed ejaculation was the most common) and women (Anorgasmia) has been reported in short-term RCTs, which is comparable to that of the placebo (Food and Drug Administration, 2005). As there may be differences between clinical practice and the data from RCTs, the actual incidence of sexual dysfunction might be different from what is reported for RCTs.

Overall, with the exception of ASRs, none of the short-term RCTs showed any clinically significant differences in the adverse event profile as well as the findings from a clinical laboratory, ECG parameter, and physical examination between the STS and placebo groups.

The long-term tolerability profile of STS suggests it to be safe and well tolerated. In addition, the long-term data are similar to the data obtained from studies examining an acute treatment. Headache, insomnia, ASRs and nervousness were the main side effects encountered in 5% or more of patients in both groups without any group differences. The most frequent side effects were ASRs, headache and insomnia in that order. Twenty-one (13.2%) STS-treated and 11 (6.7%) placebo-treated patients discontinued the treatment as a result of side effects. In a double-blind phase, ASRs were more common (p=0.0004) in the STS-treated group (15.2%) than in the placebo-treated group (3.7%) (Amsterdam and Bodkin, 2006). However, there were no clinically significant differences in the other adverse event profiles between the treatment groups. Fig. 3 summarizes the published data regarding the treatment-emergent adverse events reported in a 52-week long-term RCT of STS for the treatment of MDD (Amsterdam and Bodkin, 2006).

Several controlled studies have shown that an STS treatment at doses between 6 mg/24 h to 12 mg/24 h had no clinically significant adverse events or meaningful changes in the laboratory values or ECG parameters including a prolongation of the QT intervals. STS is classified as category C for use during pregnancy. It should be noted that there was no incidence of dietary tyramine associated hypertensive crisis or clinically meaningful blood pressure changes despite the lack of dietary requirements in the all RCTs of STS.

7. Potential advantages of STS

Since the first skin patches that release scopalamine for the prevention of motion sickness and a system for releasing nitroglycerine for the prevention of angina pectoris, were approved by the FDA in 1981, several pharmaceutical companies began developing new therapeutic patches (Henzl).

New formulations for existing antidepressants are still under development. Formulations for the extended or controlled release for once-daily and even once-weekly administration, and orally disintegrating tablets have already been released onto the market. Indeed, the use of these new formulations has been

found to be useful for enhancing the patients' satisfaction with the treatment and compliance, thereby meet the ultimate requirements of clinicians and patients in short-term and long-term treatments (Keith, 2006). The FDA approved STS for the treatment of MDD after a series of tests that were aimed at developing innovative dosage forms or delivery systems to improve the success of pharmacotherapy for the treatment of MDD. As has been shown in previously available transdermal patches, STS would have clinically important advantages, as summarized in Table 4.

However, it should also be noted that transdermal patches also have several limitations, such as cosmetic concerns, adhesion to skin, absorption depending on the patient's skin condition such as skin thickness, temperature and continuity, degradation issues as a result of the external environment such as exposure to heat or water, individual skin reactions, frequent changes in the skin site to be placed on, and manufacturing issues associated with producing a high molecular weight drug.

8. Conclusion

The STS is a novel MAO-A and -B inhibitor with a new delivery system that allows the consistent administration of selegiline over a 24-hour period with minimal plasma fluctuations. This promising new antidepressant delivery system allows the MAOI class to be retained, and has fewer of the potential risks of classical MAOIs. Well-controlled clinical trials have shown STS to be another option as a first-line treatment of MDD. Clinical studies suggest that the currently available dose ranges of STS (6 mg/24 h, 9 mg/24 h, 12 mg/24 h) would be effective and safe in the short- and long-term treatment of patients with MDD, even in some other neuropsychiatric disorders such as parkinsonism and Alzheimer's disease. With regard to the unique drug delivery that is associated with prolonged, 24-hour drug delivery, STS might help patients adhere to the necessary treatment regimen, which would reduce the incidence of recurrence and the relapse of MDD and related psychiatric disorders.

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