Selegiline transdermal system (STS) has been approved to treat major depressive disorder in the USA. STS represents a novel generation of monoamine oxidase inhibitors (MAOIs) with a superior safety profile to older MAOIs, in particular with regard to food interactions. The efficacy and safety of STS has been established in short- and long-term clinical trials. STS expands the range of pharmacological treatment options available to clinicians to treat major depressive disorder, in particular major depressive disorder with atypical features or treatment-resistant depression. This article discusses the mechanism of action of STS, summarizes efficacy and safety data from clinical trials, reviews drug and food interactions with STS and offers suggestions for use of STS in clinical practice.

Practice points

- Selegiline transdermal system (STS) has proven its efficacy in the treatment of major depressive disorder and is more tolerable than the older monoamine oxidase inhibitors (MAOIs) in terms of safety concerns regarding food and drug interactions.
- STS may have more favorable effectiveness to atypical depression in selected patients.
- STS may be useful to patients who have failed three trials of different antidepressants, although a 12 mg/24 h dose may often be required.
- In terms of managing patients during washout from previous antidepressants, short-term use of benzodiazepines or a low dose of atypical antipsychotics should be helpful, as is psychological counseling to patients.
- Education about food and drug interaction is critical in alleviating patient anxiety and ensuring compliance while initiating STS (much less with 9- and 12-mg doses of STS than older MAOIs).
- Application-site reaction has been the most common side effect of STS. Patients who experience site reactions should be informed to remove the adhesive liner from the patch and wait for approximately 30 min before applying it to the skin, and apply 1% hydrocortisone cream to affected areas.
- Out-of-pocket cost of STS should be considered in some patients.

SUMMARY

Selegiline transdermal system (STS) has been approved to treat major depressive disorder in the USA. STS represents a novel generation of monoamine oxidase inhibitors with a superior safety profile to older monoamine oxidase inhibitors, in particular with regard to food interactions. The efficacy and safety of STS has been established in short- and long-term clinical trials. STS expands the range of pharmacological treatment options available to clinicians to treat major depressive disorder, in particular major depressive disorder with atypical features or treatment-resistant depression. This article discusses the mechanism of action of STS, summarizes efficacy and safety data from clinical trials, reviews drug and food interactions with STS and offers suggestions for use of STS in clinical practice.
A number of monoamine oxidase (MAO) inhibitors (MAOIs) have been developed and introduced in the market, where they clearly demonstrated consistent antidepressant properties and were successfully established as a mainstream treatment of depressive disorders [1]. However, by the mid-1960s, there were over 40 reports of hypertensive crises associated with MAOIs, especially with tranylcypromine use. These episodes often followed ingestion of tyramine-containing foods and were related to a 10–100-fold increase in the sensitivity to dietary tyramine, a vasoressor, by MAOIs [2]. As a result, the US FDA revised the labeling for MAOIs to include extensive dietary restrictions. While many patients had difficulties following a low tyramine diet, the incidence of hypertensive crises dramatically reduced with the dietary modifications.

After tricyclic antidepressants were introduced, the use of MAOIs declined, while tricyclic antidepressants dramatically gained acceptability in clinical practice. With the advent of selective serotonin reuptake inhibitors (SSRIs) and newer antidepressants, the use of MAOIs became extremely limited.

A study using data from the National Disease and Therapeutic Index, a nationally representative survey of US office-based physicians conducted by IMS HEALTH, analyzed trends in antidepressant prescribing patterns from 1987 through the third quarter of 2001 [3]. In this study, MAOIs were prescribed to only 1% of patients in 1987 and less than 0.1% of patients in 2001 in contrast to aggregate SSRI use in 69% of patients in 2002 [3]. Nevertheless, the efficacy of MAOIs, in particular for patients with atypical and treatment-resistant depression, has sustained the interest in this class of drugs and led to efforts to develop better-tolerated MAOIs with advanced biotechnology. Changes in a drug delivery system may result in an improvement in the efficacy and tolerability of medications leading to improved compliance with a lower incidence of recurrence and relapse [4]. In fact, a number of newer formulations of antidepressants with an improved safety and tolerability profile with different drug delivery technologies have been introduced into the current market.

Selegiline transdermal system (STS), the transdermal formulation of selegiline (EMSAM®, Dey Pharma, L. P., d/b/a Mylan Specialty, NJ, USA) is the first drug patch formulation to treat major depressive disorder (MDD), and was approved by the FDA in February 2006 [5].

**Indications & usage**

STS is indicated for the treatment of MDD. Efficacy and safety of STS for acute treatment of MDD was supported by data from short-term trials. The long-term benefit of maintaining patients with MDD on STS treatment for up to 52 weeks duration was demonstrated in a controlled clinical trial [6–9].

**Dosage & administration**

The STS comes in patches of three sizes: 20, 30 and 40 mg/40 cm², which deliver 6, 9 and 12 mg/24 h, respectively. Dietary modifications are not required with the starting and target doses of 6 mg/24 h but are recommended with the 9- and 12-mg doses. It is preferable to wait for 3–4 weeks after starting the 6-mg STS before deciding to increase the dose to 9 mg and to wait for at least 2 weeks before titrating to the 12-mg dose. STS should be applied at approximately the same time of the day, preferably in the morning. A minimum washout period from existing antidepressants equivalent to 4–5 half-lives (1 week for most antidepressants, 5 weeks for fluoxetine) is recommended before starting STS to washout the previous antidepressant. A minimum 2-week washout period before switching from STS to other antidepressants is required as 2 weeks is approximately the amount of time needed to regenerate the MAO enzyme.

**Clinical pharmacology**

**Mechanism of action**

Selegiline selectively inhibits MAO-B at lower doses and has been found to potentiate dopamine transmission in the brain primarily from this MAO-B inhibition [10]. At higher doses of selegiline, such as those delivered via STS, selegiline loses its selectivity for MAO-B and inhibits both MAO-A and MAO-B, and thus 5-HT and noradrenaline levels are also elevated [11,12,101]. It is likely that elevated levels of 5-HT, norepinephrine and dopamine resulting from MAO inhibition play some role in the antidepressant effects of STS [13]. Selegiline also has several pharmacological effects in the brain other than its MAO inhibition, such as antioxidant and neuroprotective properties (Figure 1) [14].

MAO-A has been the target of recent interest in the role monoamines play in depression. An intriguing study showed that MAO-A levels in the brain are elevated approximately 34% in depressed patients compared with healthy controls [15]. In another study examining SSRI treatment...
in depressed patients, MAO-A binding in certain brain regions remained consistently elevated before and after SSRI treatment, even in subjects in remission. While this has not been demonstrated in healthy controls, it may indicate that depressed patients exhibit a persistent abnormality that is inadequately targeted by SSRI treatment [16]. Finally, a similar brain imaging study examined MAO-A density both before and during treatment with the MAOI moclobemide, and found that after moclobemide treatment, MAO-A density was significantly reduced in all brain areas assessed [17]. These studies clearly suggest a critical role of MAO-A activity in the pathophysiology of MDD.

**Pharmacodynamics**

Studies 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 was ten–20-times more potent than oral selegiline in producing both its antidepressant-like effect and inhibiting cortical MAO-A [18]. Animal studies have demonstrated that doses of STS that inhibit activities of both MAO-A and MAO-B in the brain by greater than 90% only partially inhibit gastrointestinal enzyme activities, with a maximal 40% inhibition of MAO-A and 70–75% inhibition of MAO-B [19,20]. In addition, doses of STS that inhibit brain MAO-A and MAO-B by 60 and 90%, respectively, do not alter gastrointestinal MAO-A activity. As over 80% inhibition of gastrointestinal MAO-A is necessary to affect the ability of the enzyme to catabolize tyramine, the 6 mg/24 h dose of STS does not seem to significantly impair tyramine metabolism in the gut [18].

**Pharmacokinetics**

Over 30 human pharmacokinetic studies have examined dermal application of selegiline in over 650 subjects [21,22]. STS is extensively absorbed through the skin with plasma levels maintained over a 24-h period permitting once a day application. Approximately 25–30% of selegiline in STS is delivered within 24 h. Steady-state levels
are reached after 5 days of STS treatment [23]. The bioavailability of selegiline is approximately 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. Protein binding is approximately 90% and it rapidly penetrates the CNS. Selegiline is metabolized by multiple CYP450 isoenzymes (2C9, 2B6, 3A4/5) to form N-desmethylselegiline or R-methamphetamine [24,25]. The pharmacokinetics of STS do not appear to be significantly influenced by gender, renal function or mild-to-moderate hepatic impairment.

Clinical evidence

Overview of clinical trials

Major depressive disorder

The efficacy of STS as an acute treatment for MDD was established in two, randomized, double-blind, placebo-controlled studies of 6 and 8 weeks duration in adult outpatients (aged 18–70 years) with moderate-to-severe depression and meeting Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for MDD [8,9]. In the 6-week trial (n = 176), fixed-dose STS 6 mg/24 h was significantly more effective than placebo on the 17-item Hamilton Depression Rating Scale (HAM-D) and statistical separation from placebo was seen as early as week 1. Significantly more STS patients achieved a reduction of 50% or more in total HAM-D-17 scores (37.5 vs 22.7%; p = 0.04) at the end point than the placebo group. Also, significantly more patients on STS achieved remission as defined by a HAM-D-17 <8, compared with patients on placebo (22.7 vs 11.4%; p = 0.04). As this was the first large clinical trial with STS, patients in the trial were required to follow dietary modifications to avoid foods high in tyramine. All subsequent trials were conducted without dietary modifications at any dose. The 8-week dose titration trial (n = 265) showed that STS at a starting dose of 6 mg/24 h, with possible increases to 9 or 12 mg/24 h based on clinical response, showed significant improvement compared with placebo on the primary outcome measure, the 28-item HAM-D score and the secondary outcome measures, including Montgomery–Asberg Depression Rating Scale (MADRS) and the Inventory for Depressive Symptomatology–Self Rated (IDS-SR). Table 1 summarizes the changes in the primary efficacy measure in the pivotal, short-term trials [8,9]. Three additional 8-week, short-term trials were conducted with STS. One of these did not reach statistical significance on the primary efficacy measure of HAM-D-17 (p = 0.06) but was significant for multiple secondary outcome measures of depression including HAM-D-28 and MADRS [7]. The other two trials were negative at end point on all primary and secondary end points (internal study numbers E113 and E114 [Dey Pharma, L.P., d/b/a Mylan Specialty, Unpublished Data]).

In a meta-analysis of the five short-term, placebo-controlled trials, STS exhibited significant treatment effects on core depression symptoms (HAM-D Bech 6 items: depressed mood, guilt, work and activities, retardation, psychic anxiety, general somatic symptoms), reverse vegetative symptoms (oversleeping, overeating), motor retardation, suicide and genital symptoms (libido) [26]. Significant STS treatment effects were noted for each MADRS item except for reduced sleep and appetite. The most prominent MADRS effects were improvement in sadness (effect size: 0.38), lassitude (effect size: 0.38) and poor concentration (effect size: 0.36).

The long-term efficacy and safety of STS was assessed in a 52-week relapse prevention study [6]. In this study, 322 patients meeting DSM-IV criteria for MDD who had responded during an initial 10-week open-label treatment phase with STS 6 mg/24 h were randomized to continuation of STS at the same dose, or to placebo, for up to 52 weeks of observation for relapse. By week 52, significantly fewer STS-treated patients experienced a relapse when compared with

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Duration</th>
<th>n</th>
<th>Age (mean, range)</th>
<th>Dose</th>
<th>Primary end point</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bodkin and Amsterdam (2002)</td>
<td>6 weeks</td>
<td>176</td>
<td>42 (20–65)</td>
<td>STS 6 mg/24 h vs placebo</td>
<td>HAM-D-17 (p = 0.018)</td>
<td>[8]</td>
</tr>
<tr>
<td>Feiger et al. (2006)†</td>
<td>8 weeks</td>
<td>265</td>
<td>42 (18–70)</td>
<td>STS 6–12 mg/24 h vs placebo</td>
<td>HAM-D-17 (p = 0.033)</td>
<td>[9]</td>
</tr>
<tr>
<td>Amsterdam and Bodkin (2006)†</td>
<td>52 weeks</td>
<td>322</td>
<td>43 (18–81)</td>
<td>STS 6 mg/24 h vs placebo</td>
<td>K–M relapse (p = 0.006)</td>
<td>[6]</td>
</tr>
</tbody>
</table>

*Patients in these studies had no dietary modifications.

HAM-D: Hamilton Depression Rating Scale; K–M relapse: Kaplan–Meier time to relapse analysis; STS: Selegiline transdermal system.
placebo-treated patients (17 vs 30.7%; p = 0.003) and STS patients experienced a significantly longer time to relapse over the 52 weeks compared with those receiving placebo (p = 0.005).

**Adverse events**

- **Adverse reactions**

  The overall discontinuation rate due to adverse reactions in the short-term, placebo-controlled trials for STS was 7.1% for STS compared with 3.6% for placebo. The only specific adverse event (AE) associated with discontinuation in at least 1% of STS-treated patients and at a rate at least twice that of placebo was application-site reaction (STS: 2%; placebo: 0%) [101].

  In the short-term, placebo-controlled trials, reported AE rates were comparable in STS and placebo groups (STS: 76% vs placebo: 72%). The only ‘common’ treatment-emergent AE (defined as ≥5% and twice the rate of placebo) in the pool of short-term clinical trials was application-site reaction (STS: 24%; placebo: 12%). All of the application-site reactions were mild or moderate in severity and generally did not require further treatment such as topical steroids [101]. Table 2 summarizes all AEs reported by at least 2% of STS-treated patients.

  Reported incidence rates of sexual side effects in patients with MDD were comparable to placebo rates in placebo-controlled trials [101]. In addition, results from a meta-analysis of four short-term STS studies (one study did not have the sexual dysfunction measure) showed that treatment with STS is associated with low-risk of sexual side effects and did not statistically differ from placebo on any measured parameter of sexual dysfunction [27]. In terms of effects on weight, mean weight change in the short-term placebo-controlled trials was -1.2 lbs for STS and 0.3 lbs for placebo [101] and in the 52-week long-term relapse prevention study, STS patients lost on average 1.6 lbs over approximately 1 year [6].

- **Changes in vital signs**

  There were no clinically meaningful changes in blood pressure between the STS and placebo groups, nor were there any apparent trends in the vital signs over time except for the higher STS dose groups (9 and 12 mg/24 h), which had a decrease from baseline in resting and standing systolic blood pressure of -4.5 and -6.0 mmHg, respectively, at the end of the study [7,8]. In the pool of short-term MDD trials, 9.8% of STS-treated patients versus 6.7% of placebo patients experienced a notable (decrease of at least 10 mmHg) orthostatic change in blood pressure. There were no hypertensive crises reported in any of the Phase III clinical trials [101].

  A recent analysis of AEs reported to the drug manufacturer validates the safety and tolerability

<table>
<thead>
<tr>
<th>Table 2. Treatment-emergent adverse events: incidence of major depressive disorder with selegiline transdermal system in placebo-controlled clinical trials.</th>
</tr>
</thead>
<tbody>
<tr>
<td>COSTART body system preferred term</td>
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<tr>
<td>-----------------------------------</td>
</tr>
<tr>
<td><strong>Body as a whole</strong></td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td><strong>Digestive</strong></td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Dyspepsia</td>
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<tr>
<td><strong>Nervous system</strong></td>
</tr>
<tr>
<td>Insomnia</td>
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<tr>
<td>Dry mouth</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
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<tr>
<td>Pharyngitis</td>
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<tr>
<td>Sinusitis</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
</tr>
<tr>
<td>Application-site reaction</td>
</tr>
<tr>
<td>Rash</td>
</tr>
</tbody>
</table>

Events reported by at least 2% of patients treated with STS are included. Events that had higher incidence with placebo treatment than STS are not included. These are: infection, nausea, dizziness, pain, abdominal pain, nervousness, back pain, asthenia, anxiety, flu syndrome, accidental injury, somnolence, rhinitis and palpitations.

†% of patients reporting event.

COSTART: Coding symbols for a thesaurus of adverse reactions terms; STS: Selegiline transdermal system.

Data taken from [101].
profile of STS seen in clinical trials [28] and 5.2% of the population exposed to STS (out of ~29,000 post-marketing exposures) reported an AE. The most common AEs reported post-marketing were application-site reactions and insomnia. There were very few reports of hypertensive events, and there were no objectively confirmed reports of hypertensive crisis with food at any STS dose. Table 3 summarizes the data on hypertensive events in the post-marketing study. Serious drug–drug interactions were reported in <0.05% of the exposed population.

Serious AEs
The overall rate of serious AEs in the STS clinical trials program was comparable between STS (0.7%) and placebo (1%) [101]. There were no deaths in the controlled clinical trials for STS although there was one suicide attempt by a patient on STS. In the post-marketing study [28], there were 266 (0.09%) reports classified as serious AEs.

Drug interactions
Drug–drug interactions
The Phase I clinical pharmacology development program for STS included several drug interaction studies conducted in healthy, nondepressed subjects. Drug interaction studies between alprazolam, risperidone, or olanzapine and STS 6 mg/24 h have been previously reported [24,25]. There were no clinically meaningful pharmacokinetic interactions with STS and any of these drugs, with the exception of a twofold increase in plasma selegiline during carbamazepine administration.

In addition, some pharmacodynamic drug interactions were examined by studying STS with oral decongestants pseudoephedrine and phenylpropanolamine [25]. No significant differences in mean maximum changes in vital signs occurred in patients on STS and pseudoephedrine. However, there were small, isolated minimalpressor responses in three subjects on STS and phenylpropanolamine without concurrent AEs. While the authors concluded that STS did not significantly alter the pharmacokinetics or pharmacodynamics of either pseudoephedrine or phenylpropanolamine, it is prudent to avoid combining STS with sympathomimetic agents [24].

Prescribing information [101] for STS specifies that due to the potential for serotonin syndrome, which is potentially life-threatening, STS should not be used with antidepressants, certain opioid analgesics that have serotonergic properties and cyclobenzaprine. Due to the risk for hypertensive crisis, the use of STS is contraindicated for use with sympathomimetic amines, including amphetamines as well as cold products and weight-reducing preparations that contain vasoconstrictors (e.g., pseudoephedrine, phenylephrine, phenylpropanolamine and ephedrine). Carbamazepine and oxcarbazepine are contraindicated in patients taking MAOIs, including STS, due to the tricyclic structure of these compounds. After stopping treatment with any of these drugs, approximately 1 week (5 weeks for fluoxetine) should elapse before starting therapy with STS. At least 2 weeks should elapse after stopping STS before starting any drug that is contraindicated with STS because it takes 2 weeks to regenerate enough MAO enzyme in the brain to catalyze monoamines [101]. Box 1 summarizes the list of contraindicated medications.

Drug–food interactions
Oral MAOIs have long been associated with a risk of tyramine-induced hypertensive crisis when patients ingest foods containing high levels of tyramine; however, STS was designed to overcome these dietary limitations of oral MAOIs. The transdermal delivery of STS bypasses first-pass metabolism and thus MAO-A levels in the gut remain intact and able to process dietary tyramine. To further explore the cardiovascular safety of the concomitant administration of STS with tyramine, Somerset Pharmaceuticals conducted a tyramine challenge program consisting of 14 trials with a total of 214 subjects who were challenged multiple times with oral encapsulated tyramine, both before and after treatment with STS [29,101]. Tyramine sensitivity was studied with respect to the following variables and comparators:

- Time of exposure (10, 21, 30, 60, 90 and 96 days);

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Table 3. Cardiac and vascular events.

<table>
<thead>
<tr>
<th>Adverse reactions (n)†</th>
<th>Reaction (%)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive events</td>
<td>11</td>
</tr>
<tr>
<td>Tyramine reaction</td>
<td>1</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1</td>
</tr>
<tr>
<td>Rate and rhythm disorders</td>
<td>13</td>
</tr>
<tr>
<td>Others</td>
<td>101</td>
</tr>
</tbody>
</table>

†Reactions: n = 3155.
‡Patients: n = 29,141.
[Data on file.]
• Dose (6, 9, and 12 mg/24 h STS);
• Fasting versus fed conditions;
• Comparator drugs (oral selegiline, tranylcypromine and fluoxetine).

Results of these studies are published [29]. Briefly, a tyramine pressor dose is the dose of tyramine needed to increase systolic blood pressure by 30 mmHg. Tyramine pressor doses for STS 6 mg, STS 12 mg, and oral tranylcypromine were 204, 95 and 10 mg, respectively. For comparison, a high tyramine meal contains approximately 40 mg of tyramine.

Thus, at the starting dose of STS 6 mg/24 h there are no dietary modifications. However, due to limited data at the higher doses, patients on 9 and 12 mg/24 h doses of STS must follow dietary modifications. Foods and beverages high in tyramine must be avoided while on STS 9 or 12 mg/24 h, and for 2 weeks following discontinuation of STS at these doses or reducing the dose to STS 6 mg/24 h. Table 4 summarizes the list of foods and beverages to be avoided on the 9- and 12-mg STS doses.

Use in specific populations
A post-hoc analysis of three short-term (one 6 weeks and two 8 weeks) double-blind placebo-controlled trials of STS (6, 9 and 12 mg/24 h) in patients with anxious depression defined as a HAM-D-17 anxiety/somatization factor score ≥seven was conducted to determine if STS was effective at treating MDD in this historically difficult-to-treat subpopulation. Both anxious and nonanxious depressed patients treated with STS had significantly greater overall improvement at end point on MADRS and HAM-D total scores as well as higher remission rates than patients treated with placebo [30]. Results of a similar post-hoc analysis of a subset of patients with recurrent depression (n = 305) indicated that STS produced higher end point MADRS remission rates than did placebo in patients with recurrent depression (STS: 27.9%; placebo: 13.3%; p < 0.01) [31].

An examination of population subgroups in the STS clinical development program for adults did not reveal any clear evidence of differential responsiveness on the basis of age, gender or race [101].

One hundred and ninety-eight elderly (≥65 years of age) patients participated in clinical studies of STS. While there were no overall differences in effectiveness between elderly and younger patients, patients aged 50 years and older appeared to be at a higher risk for rash (4.4% STS vs 0% placebo) than younger

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**Box 1. Drugs contraindicated with selegiline transdermal system.**

- Due to the risk of serotonin syndrome, STS should not be used with:
  - Most antidepressants
  - St John’s Wort
  - Other MAOIs, including oral selegiline
  - Certain analgesics
  - Dextromethorphan
  - Buspirone
  - Approximately 1 week (four to five half-lives) should elapse before initiating STS treatment†
- Due to the structural similarity to tricyclic antidepressants, STS should not be used with:
  - Carbamazepine and oxcarbazepine
- Due to the risk of hypertensive crisis, STS should also not be used with:
  - Sympathomimetics
    - General anesthesia for elective surgery
    - Cocaine and local anesthetics containing vasoconstrictors‡
  - Any herbal or dietary supplement that contains tyramine
- After stopping STS, a 2-week washout period is required prior to initiating any agent that should not be used with STS

*Due to the long half-life of fluoxetine and its metabolites, a 5-week washout is necessary.
‡STS should be discontinued 10 days prior to elective surgery; if surgery is necessary sooner, benzodiazepines, mivacurium, rapacuronium, fentanyl, morphine and codeine may be used cautiously.
MAOI: Monoamine oxidase inhibitor; STS: Selegiline transdermal system.
Data taken from [101].
patients (3.4% STS vs 2.4% placebo). In addition, it is recommended that elderly patients treated with STS be observed closely for postural changes in blood pressure throughout treatment.

Safety and effectiveness in pediatric patients was examined as part of an FDA post-marketing commitment. Adolescent (aged 12–17 years) outpatients (n = 308) meeting DSM-IV criteria for moderate-to-severe MDD without psychotic features were entered into a 12-week double-blind, randomized controlled trial of flexible dose STS (6, 9 or 12 mg/24 h) versus placebo [32]. Patients in both STS and placebo groups had significant reductions from baseline on the Children’s Depression Rating Scale – Revised, however, STS was not statistically superior to placebo, perhaps due to a large placebo response. Overall, STS was generally safe and well tolerated in adolescents. Incidence of reported AEs was 62.5% in the STS group and 57.7% in the placebo group. Most commonly reported AEs in both STS and placebo groups were application-site reactions (STS: 24.3%; placebo: 21.8%), headache (STS: 17.1%; placebo: 16.7%) and nausea (STS: 7.2%; placebo: 7.7%). STS is not approved for use in pediatric patients and anyone considering the use of STS in a child or adolescent must balance the potential risks with the clinical need. STS should not be used in children under the age of 12 years even when administered with dietary modifications.

Practice points
- Commentary from real-world experience
MAOIs including STS are underutilized by clinicians today despite a strong evidence base for their efficacy in MDD. STS is viewed by many clinicians to be comparable to the older MAOIs in terms of safety concerns regarding food and drug interactions. Therefore, with the exception of a few experienced psychiatrists, STS is not considered as a psychopharmacological treatment option for MDD in clinical practice. This is despite data from large trials such as the STAR*D trial [33] demonstrating that nearly 65% of patients with MDD do not fully remit after monotherapy with SSRI such as citalopram and only an additional 25–30% remit with a switch or addition of a different SSRI, serotonin and norepinephrine reuptake inhibitor (SNRI) or other antidepressants.

Several meta-analyses [34,35] have highlighted the efficacy of MAOIs in particular in atypical depression, and treatment-resistant depression and practice guidelines such as the American Psychiatric Association and the British Association of Psychopharmacology have recommended their consideration in MDD with these features. However, it must be noted that most of the comparative data regarding the benefit of MAOIs in atypical and treatment-resistant depression involved older MAOIs and tricyclic antidepressants. Also, in the STAR*D trial, tranylcypromine – which was a level four treatment option – showed high dropout and only modest remission rates in treatment-resistant depression. Nevertheless, in our experience, atypical depression (symptoms of hypersomnia, hyperphagia, retardation and mood reactivity) has shown a favorable response to STS in selected patients. We also found that patients who have failed up to three trials of different antidepressants, have responded to STS, however, a 12 mg/24 h dose

### Table 4. Foods and beverages to be avoided while taking the 9- and 12-mg/24 h selegiline transdermal system doses.

<table>
<thead>
<tr>
<th>Food to avoid on 9- and 12-mg STS dose</th>
<th>Food allowed on any dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air-dried, aged and fermented meats, sausages and salamis; pickled herring; and any spoiled or improperly stored meat, poultry and fish (e.g., foods that have undergone changes in coloration, odor, or become moldy; spoiled or improperly stored animal livers)</td>
<td>Fresh meat, poultry and fish, including fresh processed meats (e.g., lunch meats, hot dogs, breakfast sausages and cooked sliced ham)</td>
</tr>
<tr>
<td>Broad bean pods (fava bean pods)</td>
<td>All other vegetables</td>
</tr>
<tr>
<td>Aged cheeses</td>
<td>Processed cheeses, mozzarella, ricotta cheese, cottage cheese and yogurt</td>
</tr>
<tr>
<td>All varieties of tap beer and beers that have not been pasteurized so as to allow for ongoing fermentation</td>
<td>As with other antidepressants, concomitant use of alcohol with STS is not recommended (bottled and canned beers and wines contain little or no tyramine)</td>
</tr>
<tr>
<td>Concentrated yeast extract, sauerkraut, most soybean products (including soy sauce and tofu); OTC supplements containing tyramine</td>
<td>Brewer’s yeast, baker’s yeast, soy milk, commercial chain restaurant pizzas prepared with cheeses low in tyramine</td>
</tr>
</tbody>
</table>

OTC: Over the counter; STS: Selegiline transdermal system.
Data taken from [101].

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**Table 4. Foods and beverages to be avoided while taking the 9- and 12-mg/24 h selegiline transdermal system doses.**
was often required. In terms of managing patients during 1 week washout from previous antidepressants, we found that short-term use of benzodiazepines, or a low dose of atypical antipsychotics such as quetiapine and aripiprazole has been helpful, as is psychological counseling to patients. We observed much less incidence of hypotension, sexual dysfunction or weight gain with STS, compared with the older MAOIs in their practice. Education about food and drug interaction is critical in alleviating patient anxiety and ensuring compliance while initiating STS. This includes informing patients about the magnitude of risk with food interaction, which is much less with 9- and 12-mg doses of STS than older MAOIs. In clinical practice, application-site reaction (e.g., skin erythema) has been the most common side effect of STS, and has been severe enough to lead to discontinuation of STS in some cases. Patients who experience site reactions should be informed to remove the adhesive liner from the patch and wait for approximately 30 min before applying it to the skin, and apply 1% hydrocortisone cream to affected areas. Out-of-pocket costs associated with STS use has been an issue with several patients, even with those who have insurance coverage, because the drug typically has a higher co-pay on most commercial insurance plans.

**Conclusion & future perspective**

The vast majority of patients with MDD are currently treated with antidepressants belonging to the SSRI, SNRI or norepinephrine dopamine reuptake inhibitor class. Although these classes of compounds are efficacious and safe, there is a significant proportion of patients who fail to remit or are unable to tolerate these medications. From a neurobiological standpoint, MAOIs belong to a distinct class of antidepressants whose clinical utility was limited by safety concerns about dietary and drug interactions. STS represents a new generation of MAOIs with the potential to offer therapeutic advantages of older MAOIs with less of the safety concerns, especially food interactions. Availability of an antidepressant with a different mechanism of action to SSRIs or SNRIs has the potential to broaden the range of pharmacological options for MDD. In this context, STS provides an important therapeutic option for clinicians in the treatment of depressive disorders. However, further studies are necessary to compare STS with conventional antidepressants and to suggest evidence-based guidelines for the use of STS in clinical practice.

**Disclaimer**

The authors would like to state that their clinical experience may not necessarily reflect the experience of other clinicians.

**Financial & competing interests disclosure**

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