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Expert Review of Clinical Pharmacology

ISSN: 1751-2433 (Print) 1751-2441 (Online) Journal homepage: http://www.tandfonline.com/loi/ierj20

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To cite this article: Adam M Bied, Jungjin Kim & Thomas L Schwartz (2015) A critical appraisal of the selegiline transdermal system for major depressive disorder, Expert Review of Clinical Pharmacology, 8:6, 673-681, DOI: 10.1586/17512433.2016.1093416

To link to this article: http://dx.doi.org/10.1586/17512433.2016.1093416

EXPERT REVIEWS

A critical appraisal of the selegiline transdermal system for major depressive disorder

Expert Rev. Clin. Pharmacol. 8(6), 673–681 (2015)

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The selegiline transdermal system (STS) is the first antidepressant transdermal medication approved by the US FDA for the treatment of major depressive disorder. Its unique antidepressant delivery system allows for steady release of selegiline over 24 h with minimal fluctuation in drug serum levels. It is able to deliver high enough central nervous system concentrations required for an antidepressant effect without substantially inhibiting Monoamine oxidase-A in the gastrointestinal and hepatic system, thereby reducing the risk of tyramine hypertensive crises especially at the lowest doses. Patient adherence theoretically could be improved due to ease of use and once-daily dosing when compared to oral counterparts' need for multiple daily doses. Clinical trials have established that doses between 6 and 12 mg over 24 h have been effective for major depressive disorder and tolerated among patients. Episodes of hypertensive crisis with STS have been minimally reported thus far. Overall, STS appears to be an effective agent for major depressive disorder when held to regulatory standards and post marketing analyses. This paper reviews the pharmacologic characteristics of STS and results of studies investigating its clinical efficacy and safety.

Keywords: antidepressive agents • major depressive disorder • MAO inhibitor • pharmacodynamics • pharmacokinetics • selegiline • transdermal system

Monoamine oxidase inhibitors (MAOIs) were some of the first medications to be utilized for the treatment of major depressive disorder (MDD) [1]. Initially developed as an antimicrobial agent to manage tuberculosis infections, they were serendipitously found to have mood-elevating effects in patients infected with tuberculosis [2]. Soon after, reports of MAOIs' antidepressant efficacy emerged and they became widely used to manage clinical depression in the late 1950s [3]. However, due to reports of hypertensive crises associated with dietary tyramine and adverse serotonin syndrome interactions with other drugs, coupled with the advent of other classes of antidepressants with more benign side effect profiles – particularly, the selective serotonin reuptake inhibitors (SSRIs) – MAOIs fell out of prescribing favor among psychiatric clinicians [4–6]. Today use of MAOIs has become largely limited to treatment-resistant depression and they are often deployed just prior to the use of electroconvulsive therapy (ECT).

There is no doubt that MDD remains one of the leading causes of disability worldwide [5], and failure to treat it leaves patients at risk for further medical morbidity and mortality [6]. Unfortunately, less than 50% of patients treated with antidepressants achieve sustained remission and often continue to suffer from MDD. In the landmark STAR*D trial, approximately 30% of patients treated with citalopram, an SSRI, achieved remission [7,8]. Furthermore, 40% of these patients relapsed after a year. This disappointing observation was thought to be due in large part to limited antidepressant efficacy. Patient non-adherence and side effect burden were believed to contribute as well. Despite the risk of hypertensive crisis and serious drug interactions, MAOIs have demonstrated a clear niche of superior efficacy over other antidepressants in the treatment of atypical [9,10] and treatment-resistant depression [11], and have also been found to be effective in the management of melancholic [12] and even bipolar depression [13]. Given the chronicity, treatment-resistant nature,

 10.1586/17512433.2016.1093416 ISSN 1751-2433

morbidity and mortality associated with MDD, efforts were directed to develop safer and better-tolerated forms of MAOIs. Reversible MAOIs that are available outside USA are an example. The use of selegiline transdermal system (STS) may be another example.

Pharmacology of MAOIs

Monoamine oxidases (MAOs) are enzymes that catalyze the oxidative deamination of neurotransmitters, many of which are central to the theoretical biological underpinning of MDD [14]. Humans have two forms of MAO isoenzymes: MAO-A and MAO-B. Both are found in the neurons of the brain. Outside the brain, MAO-A is present primarily in the gastrointestinal mucosa and hepatic tissue and MAO-B is present mostly in platelets. MAO-A mainly metabolizes norepinephrine, serotonin and tyramine, an exogenous monoamine and a pressor agent, whereas MAO-B mainly metabolizes dopamine [15]. MAOIs exert their antidepressant effects in the brain by inhibiting the breakdown of norepinephrine, dopamine and serotonin by MAO enzymes, which then leads to enhanced neurotransmission by these neurotransmitters. While the monoamine theory of depression has been superseded by additional explanations of mood disturbance, such as hypofrontality, the significance of brain-derived neurotrophic factor deficiencies, monoamine receptor over expressivity and amygdala hyperactivity among others, it remains a useful model which readily explains the utility of multiple classes of antidepressants including the MAOIs [16]. Recent studies have also suggested that selegiline, an MAOI, facilitates enhanced activity of mitochondrial metallothioneins to provide neuroprotection by inhibiting Charnoly body formation involved in impaired mitochondrial bioenergetics and progressive neurodegeneration [17–19]. Regardless of the precise mechanism of action responsible for the antidepressant effects observed, the MAOIs, including STS, have passed the usual regulatory process and have been approved for the treatment of MDD.

MAOIs have varying degrees of selectivity for each of the MAO isoenzymes. The older, oral, first-generation MAOIs, such as phenelzine, tranycypromine and isocarboxazide, were largely irreversible and nonselective for both forms of MAO isoenzymes. These agents blocked first-pass metabolism of dietary tyramine, a vasopressor, in the intestines and liver. Resultant increases in tyramine can cause acute elevation of blood pressure which is known as tyramine-induced hypertensive crisis. To overcome this potentially fatal side effect, second-generation MAOIs (e.g., selegiline or rasagliline) and third-generation MAOIs (e.g., moclobemide or brofaromine) were developed.

Among these agents, selegiline has consistent antidepressant efficacy when used at very high oral doses. Selegiline is a second-generation MAOI that selectively and irreversibly inhibits MAO-B at oral doses up to 10 mg daily [20]. Selectivity for MAO-B was thought to reduce the risk of tyramine-associated hypertension. However, much of selegiline's antidepressant effects are observed at much higher doses above 30 mg, where facilitation of both serotonin and norepinephrine is more likely to occur [21,22]. At these doses, selegiline loses its selectivity and inhibits both MAO-A and MAO-B in the brain and peripheral tissues. Gastrointestinal and hepatic MAO-A inhibition is more pronounced at these doses and may potentially induce tyramine release and an associated malignant hypertension. Given this, a tyramine-restrictive diet is often necessary to provide adequate safety to patients when high-dose oral selegiline is used in practice.

Theoretically, a desirable MAOI would selectively block brain MAO enzymes (A and B) without inhibiting peripheral first-pass metabolism. Several experimental compounds thought to have such properties have been studied, though their use in clinical practice has been minimal thus far. The STS has been thought to display such properties, offering a standard by which investigational compounds have even sometimes been judged [23]. Recent studies utilizing PET functional neuroimaging have demonstrated MAO subclass selectivity for STS in dosages up to 10 mg daily, with diminishing selectivity for the MAO B observed at higher dosages [24]. Efforts to develop medications which confer antidepressant efficacy and maintain a robust safety profile with good clinical tolerability have led to the creation of STS.

Selegiline patch formulation – dosage & administration

The STS is a formulation developed to deliver sustained plasma concentrations of selegiline sufficient to induce a clinically relevant antidepressant effect without significantly impairing MAO-A activity in the duodenal mucosa and ideally lowering the risks for tyramine-associated hypertensive crises. The STS comes as a patch applied every 24 h to the upper torso, upper thigh or upper arm. The patch is composed of three layers: the outermost polyester backing, the middle adhesive drug reservoir and the innermost layer that attaches to the skin and delivers the medication. According to the manufacturer's regulatory insert, 20–30% of selegiline is dermally absorbed when the STS is used every 24 h. The STS is applied for 24 h and comes in three dosages: 6 mg (20 mg/20 cm^2), 9 mg (30 mg/30 cm^2) and 12 mg (40 mg/40 cm^2). The 6 mg daily dose is widely accepted to be the starting dose as well as the minimum therapeutic dose, while doses of 12 mg daily are frequently considered an upper therapeutic dose and dosages of 20 mg daily or more have sometimes been used. At present, regulatory standards permit dosages of up to 12 mg daily, while off-label anecdotal use of 20 mg or more has been used in clinical practice, often when managing treatment-resistant patients. A clear enhanced therapeutic benefit and dose–response curve has yet to be established for such dosages, however [22].

Clinical efficacy

The clinical efficacy of STS has been demonstrated in multiple placebo-controlled and randomized trials. An 8-week, double-blinded, placebo-controlled trial of STS in 289 participants meeting DSM-IV criteria for MDD was conducted using STS, in a 6 mg, 9 mg or 12 mg dose, and a control placebo patch.

The study was blinded, but the clinician and patient were permitted to titrate up or down the dosage as clinically indicated. STS resulted in improvement ($p \leq 0.05$) in four depression scales, the Montgomery–Åsberg Depression Rating Scale (MADRS), Hamilton Depression Rating Scale-28 item (Ham-D28), Hamilton Depression Rating Scale-6 item (Ham-D6), the inventory of depressive symptomatology self-reported, and nearly statistically significant improvement in a fifth scale, the Hamilton Depression Rating Scale-17 item (Ham-D17). When evaluating improvement in MADRS, Ham-D28, Ham-D6, the inventory of depressive symptomatology self-reported and HAM-D17 scores, the STS arm performed better than the control arm in all five measures, and was statistically significantly better in the first four, with an aggregate number needed to treat (NNT) of 10. The results were as follows: MADRS (−11.5/−39.2 vs −8.6/29.4%, p: 0.02), HAM-D28 (−11.1/39.9 vs −8.8/30.1%, p: 0.03), Ham-D6 (−5.5/44.4 vs −4.1/32.5%), the inventory of depressive symptomatology self-reported (−14/37.5 vs −10.9/29.9%) and Ham-D17 (−8.7/37.2 vs −7.5/32.2%, p: 0.11). Based on these findings, the authors concluded that STS was efficacious at managing MDD [25].

Another study affirmed these findings in an 8-week, double-blinded, placebo-controlled, trial. Three hundred and sixty-five participants were assigned either to STS 20 mg daily or a placebo patch and were evaluated using the MADRS, Ham-D28 and Ham-D17 scales. When evaluating improvement in MADRS, Ham-D28 and Ham-D17 scores, the STS performed better than the control arm in the first two measures and was similar to control, though statistically insignificant, in the third. The results were as follows: MADRS (−10.3/36.4 vs −6.7/23.5%, p: 0.031), Ham-D28 (−8.5/29.4 vs −8.5/23.5%, p: 0.039) and Ham-D17 (−8.1/35.5 vs −13.7/45.7%, p: 0.07). The aggregate NNT was estimated to be 11.4. The authors concluded that STS conferred a measurable clinical benefit in patients with MDD [26].

An additional double-blind, placebo-controlled, parallel-group study was conducted for evaluating the efficacy of STS in an adult outpatient setting. After a weeklong placebo lead in, 177 participants experiencing MDD were provided either STS, 20 mg daily, or a placebo patch for 6 weeks and evaluated using the Ham-D28, Ham-D17, MADRS and the Clinical Global Impression scale. When evaluating improvement in the four scales, STS performed better than the control arm in all four measures with an aggregate NNT of 7.5. The results were as follows: Ham-D17 (−8.7/38.2 vs −6.1/26%, p: 0.01), Ham-D28 (−11.2/38 vs −7.6/25%, p: 0.004), MADRS (−9.8/34 vs −5.7/19%, p: 0.005), Clinical Global Impression (improvement in all substrata with respective $p < 0.05$). The authors concluded that STS was an effective antidepressant [27].

A long-term, multicenter study of 322 participants evaluating the efficacy of STS, 6 mg daily, in preventing relapse was subsequently conducted. After recruiting patients to an open-label trial of STS lasting 10 weeks, participants who responded with a Ham-D17 score of 10 or less were enrolled in a 52-week, double-blinded, placebo-controlled study of STS versus a placebo patch to observe for an MDD relapse. Relapse was defined as experiencing a Ham-D17 score of 14 or more after experiencing remission. The authors showed that STS reduced the number of participants experiencing relapse (16.8 vs 30.7%) with an NNT of 7.2. The time to relapse was also found to be longer in the STS arm (mean duration among relapsers: 80 vs 51 days). These findings supported the authors' argument that STS may facilitate prevention of MDD-related relapses [28].

Another study expanded the target patient population to adolescents. Adolescent populations have been known to experience lower oral antidepressant efficacy in general. In this 12-week-long, double-blinded, placebo-controlled study of 308 adolescents, they failed to show a statistically significant level of improvement in the STS versus placebo patch. The patients were provided a starting dose of 6 mg daily and titrated upward, as tolerated, in 4-week intervals until observable treatment response occurred, up to a final dose of 12 mg daily. This study differed from the other studies in that it used the children depression rating scale-revised, a validated measure of depressive symptomatology used in child and adolescent populations. Despite this difference, a non-statistical degree of improvement (STS: 62.5%, placebo: 57.7%) was observed when using the children depression rating scale-revised. The findings of these double-blinded, placebo-controlled trials is summarized in Table 1 [29].

Treatment adherence

Data evaluating STS treatment adherence, in general, and in comparison with its oral counterpart, in particular, are limited, though have been hypothesized to be superior. STS's dermal route of administration has been considered a possible advantage with regard to treatment adherence. In individuals experiencing dysphagia or gastrointestinal pathology, STS would confer a superior route of administration over oral alternatives in regards to allowing consistent drug absorption. STS has been shown to have less pronounced orthostatic, sedative, sexual and gastrointestinal adverse reactions at therapeutic doses (6–12 mg daily) than its oral counterpart and is also a once-daily formulation in contrast to the typical three-times daily dosing of oral selegiline [22]. Both of these attributes have been hypothesized to improve treatment adherence, though data are presently limited. A disadvantage to STS, skin irritation [30], has not been shown to lead to significant discontinuation rates in regulatory studies, but can be problematic in clinical practice. As such, STS is expected to confer a higher degree of patient compliance than the present alternative, though no firm conclusion can yet be made based upon literature review.

Safety & tolerability

A Phase I clinical study was conducted to evaluate the safety and tolerability of STS. The dermal safety of STS was examined with 154 volunteers. The participants received STS 20 mg daily, a placebo patch and a commercial bandage and were

Table 1. Summary of clinical efficacy of selegiline transdermal system.

Study (year)	Dosage	Study design	Demographic	Participant size	NNT	Ref.
Feirger *et al*. (2006)	6 mg, 9 mg, 12 mg	8-week, double-blinded, placebo-controlled trial of the STS	Adults	289	10	[25]
Amsterdam (2003)	20 mg	8-week, double-blinded, placebo-controlled trial	Adults	365	11.4	[26]
Bodkin and Amsterdam (2002)	6 mg	6-week, double-blinded, placebo-controlled study	Adults	177	7.5	[27]
Amsterdam and Bodkin (2006)	6 mg	52-week, double-blinded, placebo-controlled study	Adults	322	7.2	[28]
DelBello *et al*. (2014)	6 mg, 9 mg, 12 mg	12-week, double-blinded, placebo-controlled study	Children and adolescents	308	Not statistically significant	[29]

The table summarizes the findings from the four studies which evaluated the clinical efficacy of the STS. The author, STS dosage utilized, study design, population evaluated, participant size and NNT are listed.
NNT: Number needed to treat; STS: Selegiline transdermal system.

evaluated using a Dermal Safety Assessment at 48 and 96 h post-application. The STS displayed similar scoring in low (0) and moderate levels (1–2) to both the placebo and the commercial bandage. It displayed a modest propensity (7.4% of participants) toward more pronounced reactions (score ≥3) than either the placebo patch (0%) or the commercial bandage (0%). A Phase III clinical study of 24 weeks duration followed, enrolling 1326 patients for a mean of 74.6 days and using both an open-label and blinded design. It showed a generally mild and self-resolving rash presumed to be caused by the STS adhesive glue. It was associated with a minority of subjects (21.8%) and, when compared to the placebo patch (9.7%), had a number needed to harm (NNH) of 8.3. Despite this, adverse skin reactions led to rare discontinuation (four participants/<1%) in the STS arm [30].

Another research group conducted a meta-analysis of four 6–8-week-long, randomized, doubled-blinded, placebo-controlled trials of STS, 6 mg daily, in patients with MDD. In total, 789 participants were evaluated with similar portions enrolled in the STS arm and the placebo arm. The Medex Sexual Dysfunction Subscale and the MADRS, validated measures of sexual dysfunction and depression severity, respectively, were utilized to assess participant response. The authors found minimal changes in Medex Sexual Dysfunction Subscale scoring in men and a non-significant modest improvement in Medex Sexual Dysfunction Subscale scoring in women. Depressive symptoms, though not a primary measure of the study, also improved ($p = 0.016$). The authors concluded that STS could be an option to manage MDD without inducing sexual side effects [31].

A case series consisting of two patients who received STS, 6 mg daily, and were concurrently subjected to ECT was published. The two patients experienced depressive episodes in the context of MDD and bipolar depression, respectively. Anesthesia management consisted of methohexital, succinylcholine, nitroglycerin and esmolol. Both patients experienced no adverse effects, leading the authors to conclude that STS may be a safe option in the context of ECT-induced sympathetic discharge and ECT-related anesthesia agents [32].

In regards to hypertensive crises, Pae *et al*. observed that 3155 adverse events were reported to regulatory authorities and 266 were classified as serious [33]. Thirteen reports documented increased blood pressure, but none of these were defined as hypertensive crises. The findings of these studies are summarized in Table 2.

According to regulatory agencies and the STS package insert, the most common daily side effects include skin reaction, headache, insomnia, diarrhea, dry mouth, dyspepsia, rash, pharyngitis and sinusitis. All of these were noted to be greater than 2% over placebo side effect rates. Sexual dysfunction side effects and weight gain were equal to placebo rates. Weight loss occurred in 2% of STS patients compared with placebo. After reviewing clinical data in USA, regulatory agencies declared that the low dose (6 mg daily) of STS did not require any dietary modifications, but that higher doses (9 mg, 12 mg daily) should follow an MAOI diet. This labeling likely resulted from researcher-conducted tyramine challenge tests where subjects were permitted to take the 6 mg daily dose. The finding suggested an innocuous profile characterized by minimal to no increases in blood pressure and determined that the STS had 20-times less of a pressor effect than the oral MAOI tranylcypromine [34].

Pharmacokinetics

According to the regulatory data and the 2014 Mylan Pharmaceuticals Emsam package insert, it is noted that 20–30% of the STS's selegiline is dermally absorbed over 24 h of use. Absorption may increase upward of 33% with increased dosage strengths, as the patches are larger and have more surface area of absorption. Selegiline would not accumulate in skin or skin structures and would become 90% protein bound. Selegiline is ultimately metabolized by many CYP450 hepatic enzymes (CYP2B6, CYP2C9, CYP3A4 and CYP3A5), but the STS preparation greatly reduces first-pass hepatic metabolism.

Table 2. Summary of studies evaluating aversive reactions to selegiline transdermal system.

Study (year)	Dosage	Study design	Participant size	Aversive reaction studied	Results	Ref.
Pauporte *et al.* (2004)	20 mg	24-week, double-blinded, placebo-controlled study	1326	Dermal reaction	NNH: 8.3	[30]
Clayton *et al.* (2007)	6 mg	Meta-analysis of 6–8-week-long, randomized, doubled-blinded, placebo-controlled studies	Four studies consisting of 789 participants	Sexual dysfunction	According to authors, minimal adverse effects were observed with improvement in sexual function in women	[31]
Horn *et al.* (2010)	6 mg	Case series	Two patients	ECT-related aversive reactions	None	[32]

The table summarizes the findings from the three studies which evaluated the aversive effects of the selegiline transdermal system. The table lists the authors, selegiline transdermal system dosage utilized, study design, participant size, aversive reaction studied and results as published.
ECT: Electroconvulsive therapy.

Regarding the potential advantage of minimizing first-pass hepatic metabolism, an open-label, two-phase, cross-over study was conducted to evaluate the pharmacokinetic properties and bioavailability of STS, compared to its oral counterpart. Twelve healthy volunteers were enrolled into a three-part cross-over study providing STS 6 mg daily and a 10 mg selegiline oral tablet. Blood and urine drug levels were measured. The authors found that STS was more bioavailable than its oral counterpart (73 vs 4%) and displayed a more sustained blood concentration. These were considered as pharmacokinetic advantages by the authors [20].

In another pharmacokinetic study involving 13 subjects, researchers determined that the STS concentrations were qualitatively similar to those of intravenous infusions [35]. Both routes of administration allowed for high plasma levels of sustained selegiline to be detected over 24 h. In contrast, oral selegiline administration in this study allowed for plasma levels reaching a peak quickly followed by a rapid decline. Furthermore, oral use of selegiline was followed by a more rapid detection of metabolites (primarily R-methamphetamine and secondarily R-amphetamine and N-desmethyl selegiline) suggesting a faster and more complete first-pass hepatic metabolism compared with STS. Intravenous, STS and oral selegiline produced metabolites in the same chronologic order (N-desmethyl selegiline, R-methamphetamine, R-amphetamine). Due to the avoidance of initial hepatic metabolism, the half-lives of intravenous and STS were similar and ranged from 15 to 25 h, whereas that of oral formulation was less at 9–15 h. Renal excretion rates were similar for all preparations. R-amphetamine and R-methamphetamine were found in a 1:2 ratio after selegiline use and the STS preparation afforded the lowest concentrations. These urine metabolites may create a false-positive amphetamine urine drug screen for any of the preparations. Finally, considering area under the curve (AUC) findings after dosing adjustments for intravenous versus STS versus oral (9336.01, 12667.10 and 542.10, respectively) formulations, it was shown that selegiline exposure was 17-times greater with STS over oral selegiline. Cmax ratios suggested that STS was 1.7-times greater as well (456.26 vs 265.48).

In conclusion, these findings suggest that the STS preparation may avoid much of the first-pass hepatic metabolism, minimize metabolites and allow more active drug to be present in the blood stream and theoretically in the CNS. Compared to the oral agent, this may allow a clinical effectiveness and tolerability profile which is discussed elsewhere in this paper.

Drug interaction

Polypharmacy is quite common in clinical practice. As such, drug–drug interactions are an important clinical consideration when prescribing psychiatric medications. One of the most important, potentially fatal adverse reactions with STS is serotonin syndrome – a phenomenon characterized by hyperreflexia, myoclonus, tremor, hyperthermia, tachycardia, hypertension, confusion, hallucinosis, coma, cardiovascular and cerebrovascular events, and potentially death. It occurs when STS or oral selegiline is combined with SSRIs (e.g., fluoxetine, sertraline, paroxetine, escitalopram, citalopram), SNRIs (e.g., venlafaxine, desvenlafaxine, milnacipran, levomilnacipran or duloxetine) or other MAOIs. Some primarily noradrenergic tricyclic antidepressants (TCAs) (desipramine, nortriptyline, protriptyline) are contraindicated by regulatory agencies. Other TCAs are robust serotonin reuptake inhibitors (SRIs; clomipramine, imipramine, amitriptyline) and likely carry a greater risk of drug interaction. Despite these warnings, there is a small evidence base that TCAs may be combined with MAOIs for highly refractory cases of MDD. There are different protocols in small samples where both agents may be combined at initiation of treatment or their titrations alternated. These should be specifically referenced prior to use, in order to provide maximum safety [36]. Theoretically, any drug with a SRI mechanism may induce serotonin syndrome. The antihistamine chlorpheniramine and the opioid tramadol, for example, both exhibit SRI properties, but are not antidepressants, and could cause serotonin syndrome. Cyclobenzaprine and carbamazepine (for muscle spasm and epilepsy, respectively) both have TCA structures and theoretically could cause such an adverse reaction, though they have weak to no SRI properties. A washout period of at least four to five half-lives of the conflicting drug is,

therefore, warranted upon discontinuation of these agents before initiating treatment with STS. Fluoxetine, displaying a prolonged half-life, is a notable exception to the typically brief washout periods displayed for the above medications. Instead, it typically requires a minimum of 5 weeks after discontinuation before initiating an MAOI [37].

Combination with other sympathomimetic agents, such as a decongestant (pseudoephedrine or phenylpropanolamine), is also not recommended due to risk of hypertensive episodes. However, a small trial showed no pressor effect or hypertensive effects. Without a tyramine interaction that synergistically increases blood pressure to crisis levels, adding noradrenergic drugs likely gives a milder additive pressor effect in practice [38]. Other contraindicated agents may include buspirone, carbamazepine, oxcarbazepine, cyclobenzaprine, meperidine, methadone, tramadol, propoxyphene, amphetamines, dextromethorphan and St. John's wort [37–39].

Other clinical considerations

Approximately 19–29% of patients afflicted with MDD experience the atypical subtype of the disease characterized by reverse neurovegetative symptoms (hypersomnia, hyperphagia, anergia), mood reactivity and/or rejection sensitivity [40]. Patients with atypical depression pose a clinical challenge as they can be poorly responsive to SSRIs, as shown in the STAR*D trial. A meta-analysis pooling outpatients experiencing atypical depression across eight studies comparing the efficacy of an MAOI (phenelzine), a TCA (imipramine) and a placebo found the greatest clinical efficacy with the MAOI [41]. Interestingly, the US FDA requires an antidepressant to be capable of statistically improving a majority of patients by 50% and with these moderate benchmarks, suggests all antidepressants are equal in treating MDD [42]. Patients in these trials have a mixture of depressive symptoms, some melancholic, some atypical and some undifferentiated. It appears that an attempt to look at a homogenous group of atypical depressed patients can reveal a drug response edge to the MAOIs. Other data would suggest that TCAs may help severe afflicted inpatients with MDD more often than other agents. Though evidence in atypical MDD is currently lacking for STS, historical and preliminary findings suggest that STS may also be effective for this population. In a small case series and *post-hoc* analysis of five patients, STS was shown to be equally efficacious in patients with atypical and non-atypical depression [43]. Furthermore, other studies have demonstrated clinical utility of MAOIs in treatment-resistant depression [44,45], psychotic depression [46], dysthymic disorder [47], anxious depression [48] and bipolar depression [49].

MAOIs have shown promise in treating a range of psychiatric and neurologic conditions other than depression, though the evidence base is limited. While a detailed discussion of the use of STS in non-depressive illnesses is outside the scope of this paper, a terse overview is warranted. Oral selegiline is clinically approved for the treatment of Parkinson's disease and its clinical efficacy and safety is well established [50]. STS could prove useful in this population if co-morbid with MDD. Usage of selegiline has also been explored for the treatment of attention-deficit/hyperactivity disorder [51–53]. Low-dose (3 mg daily) STS has proven useful for the treatment of HIV-associated cognitive impairment as well. Selegiline augmentation to antipsychotic treatments has been suggested to be helpful for negative symptoms in schizophrenia and schizoaffective disorder [54]. These studies are often more limited in design and statistical strength, but nonetheless are in the evidence base for STS. Finally, safety studies have been reported for potential use of selegiline in the treatment of cocaine addiction and studies regarding cigarette smoking cessation have failed to show benefit [55–57].

Conclusion

STS is the only antidepressant administered transdermally and achieves a continuous release of selegiline over 24 h. The clinical efficacy of STS in patients with MDD is well established as shown in several randomized controlled trials highlighted in this paper and it has garnered FDA approval as an indication for treating MDD. STS's safety and tolerability over its oral counterparts is demonstrable. Compared to other MAOI oral agents, STS has the adherence advantage of being a once-daily medication and has much less risk of dietary hypertensive reactions. It also has clearly comparable antidepressant efficacy when held to the same standards of clinical response on clinician-administered ratings as other classes of antidepressants. It has advantages of less sexual dysfunction, weight gain and sedation than more mainstream SSRI and SNRI antidepressants. It causes sedation and weight gain, compared to the non-SSRI antidepressant agents (trazodone, nefazodone, mirtazapine). It has less anticholinergic side effects than the TCA antidepressants. Despite these advantages, however, STS continues to be underutilized among prescribers [58,59]. This has been suggested to be due to a combination of the fear of side effects, actual side effects, inadequate studies addressing use in co-morbid disorders in MDD (i.e., anxiety disorders), inadequate studies comparing STS to other antidepressants and minimal marketing efforts [60]. In clinical practice, STS appears to avoid the common intolerability side effects of sedation, weight gain or sexual dysfunction, but may induce more activating side effects such as agitation, anxiety and insomnia. STS has a significant chance of creating local, allergic skin reactions that may limit its use as well. Given the risk of drug–drug interactions causing serotonin syndrome and the need for tyramine dietary restrictions at higher doses of STS, the outright risk of cerebrovascular insults limits its use as other antidepressants do not carry an immediate life-threatening risk due to hypertensive crisis [37,61]. Administering an MAOI in clinical psychopharmacological practice may be difficult and limited due to the greater requirements in the informed consent process and psychoeducation portion of clinical management. Further studies addressing these unanswered clinical questions, including comparison of STS to other antidepressants with regard to efficacy and tolerability in MDD, are clearly needed.

Regardless of these, prescribers should be aware of the availability of STS as an important addition to the armamentarium in treating MDD.

Expert commentary

MDD is increasingly being considered a chronic and recurrent disorder characterized by incomplete symptom remission and persistent psychosocial disability. In clinical practice, logistically easier and medically safer antidepressants, such as SSRIs and SNRIs, are typically utilized initially. Treatment-resistant patients often require older antidepressants, such as TCAs and MAOIs. This paper focuses on the selegiline transdermal preparation, a member of the latter class of drugs. Unique among psychopharmacology treatments, STS is notable for being one of the few transdermal treatments in psychiatric practice, conferring greater safety in the deployment of an MAOI, and reducing drug–diet interactions. STS may be considered an entry-level MAOI with an FDA approval similar to alternative antidepressants and with regulatory benchmarks revealing comparable antidepressant efficacy.

Five-year view

Antidepressant use in the treatment of MDD will persist given the high prevalence and disabling nature of that disorder. The MAOI mechanism of antidepressant treatment dates back to the 1950s and for some time, there was ongoing research into use of reversible and safer MAOIs, but these research endeavors appear to be at a minimum. Due to fear of drug–drug and drug–diet interactions and reticence among clinicians about the initiation of MAOI therapy, much research appears to be directed toward non-MAOI treatments. Recently, the SSRI class of drugs has grown to include SSRIs that can also modulate multiple serotonin receptors. Prescribing trends will likely continue to favor drugs with less-severe side effect profiles, greater ease in initiation and less burdensome monitoring in an increasingly demanding clinical environment. Treatment-resistant patients will remain a challenge to prescribers and ultimately MAOI therapy can and will be offered when appropriate.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Key issues

- The monoamine oxidase inhibitor (MAOI) class of antidepressants has been utilized since the 1950s.
- Presently, MAOIs are largely used as a last line of pharmacotherapy, given the relative risk among the antidepressants for both serotonin syndrome and hypertensive crisis.
- The older oral preparations of MAOIs confer the greatest risk of tyramine-related hypertensive crises, though all MAOI preparations confer some risk of serotonin syndrome when combined with other serotonergic agents.
- Certain reversible MAOIs have been researched and developed, but have not been approved for clinical use in USA. Moclobemide, approved in the UK and Australia, is an example.
- The selegiline transdermal system, or dermal patch, has received regulatory approval in USA and elsewhere for the treatment of major depressive disorder and is equally as effective as other antidepressants based upon regulatory findings and processes.
- Compared with selective serotonin reuptake inhibitors, SNRIs, and modern-day sedating antidepressants, the selegiline transdermal patch confers a better tolerance profile with minimal weight gain, sexual dysfunction and fatigue.
- Compared to oral MAOIs, the selegiline transdermal patch is absorbed by means of skin contact bypassing the gastrointestinal tract and reducing the danger of drug–diet (tryamine hypertensive crisis) adverse reactions, particularly at its lowest dose. This is novel among irreversible MAOI preparations. At moderate-to-high therapeutic doses, the usual MAOI, low tyramine diet is suggested.

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