Safety of Selegiline Transdermal System in Clinical Practice: Analysis of Adverse Events From Postmarketing Exposures

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ABSTRACT

Objective: The objective of this analysis is to present the safety profile of selegiline transdermal system (STS) in clinical practice after US Food and Drug Administration approval by analyzing reported postmarketing adverse events (AEs).

Method: Deidentified data were obtained on AEs, regardless of causality, as collected and compiled in the pharmaceutical company's adverse event collection systems/databases after the launch of STS in the United States. All reports of hypertensive crisis, suicide attempts, and STS overdoses were carefully examined to independently determine relation of the AE to STS.

Results: From April 2006 to October 2010, a total of 3,155 AEs in 1,516 patients were reported (5.2% of the total exposures; N = 29,141), regardless of causality. The most frequently reported categories of AEs were general disorders (no. of AEs = 1,037, 3.6%) and central nervous system (CNS) disorders (no. of AEs = 574, 2.0%). A total of 266 reports (0.9%) were classified as serious AEs; CNS disorders (no. of AEs = 71, 26.7%) and cardiac and vascular disorders (no. of AEs = 44, 16.5%) were most common. There were 13 self-reports of possible hypertensive events or hypertension, although objective clinical data were not submitted in any of these cases. Thirteen drug-drug interactions (0.04%) were reported, and 5 were classified as serious.

Conclusions: The most commonly reported AEs were application site reactions and insomnia. Very few patients reported a hypertensive event, and there were no objectively confirmed reports of hypertensive crisis with food at any STS dose. Therapeutic doses of STS appear to have a safety profile in clinical practice that is consistent with that observed in clinical trials. However, given the relatively modest exposure numbers, continued safety monitoring is recommended.

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Monoamine oxidase inhibitors (MAOIs) were the mainstay of depression treatment in the mid- to late 20th century due to their consistent antidepressant properties.[1] However, a recent analysis of the utilization of antidepressants in the United States from 2005 to 2007 indicates that MAOIs accounted for less than 0.3% of the antidepressant prescriptions written in a given year.[2]

Selegiline transdermal system (STS) was developed to overcome some of the limitations of oral MAOIs, specifically food-drug interactions. It was approved by the US Food and Drug Administration (FDA) in February 2006. The efficacy of STS in major depressive disorder (MDD) has been established in 3 short-term (6- to 8-week), randomized, double-blind, placebo-controlled trials (RCTs)[3–5] and 1 maintenance (52-week) trial.[6] In a review[7] of the premarketing safety data, 76% of STS-treated patients and 72% of placebo-treated subjects experienced at least 1 adverse event (AE). STS was overall well tolerated; application site reactions (mostly mild to moderate intensity) and insomnia were the most frequently observed side effects. There were no safety concerns on the basis of routine clinical laboratory and electrocardiogram monitoring. Most AEs were rated as "mild" or "moderate" in intensity and did not lead to premature treatment discontinuation. During clinical development, 6 of the 7 clinical trials were conducted without dietary modifications, and no hypertensive crisis at any dose was reported during the trials. Additionally, since hypertensive events are an area of significant concern with MAOI medications, 14 tyramine challenge studies were conducted utilizing STS at different doses and for varying lengths of time to assess the potential for hypertensive events after ingestion of dietary tyramine. Results of these studies showing that the amount of ingested tyramine necessary to achieve a pressor response (increase of ≥ 30 mm Hg) in blood pressure was 7 to 30 times higher than with oral MAOIs have been previously published.[8] Thus, in product labeling, no dietary modifications are required for patients using STS 6 mg/24 h. However, dietary modifications are required with STS 9 mg/24 h and 12 mg/24 h.

After introduction of a new drug in the market, a much larger number of patients are exposed, often with comorbid medical and psychiatric conditions that would have excluded them from controlled clinical trials, and such exposure often continues for longer periods of time. Hence, the safety profile of a drug in clinical practice may be different than the safety profile of the drug observed in clinical trials. As evidence accumulates from clinical experience, the "real world" clinical safety profile of a new drug emerges. Therefore, safety data from clinical development programs combined with postmarketing safety data yield a more complete picture of the overall safety profile of a drug that is relevant to clinical practice.[9]

Clinical Points

- Current evidence based on data from a postmarketing surveillance system supports the safety and tolerability of the use of selegiline transdermal system (STS) in routine clinical practice for patients with major depressive disorder (MDD).
- STS represents another possible option for clinicians to use in treating patients with MDD, in particular those who have compliance issues such as difficulty in using oral formulations.

The objective of this postmarketing safety analysis is to present the safety profile of STS in real-world clinical practice after FDA approval by analyzing AE data reported to the pharmaceutical company since the product launch.

METHOD

Data Sources

Adverse events. We obtained deidentified data on AEs, regardless of causality, as collected by the pharmaceutical company after the FDA approval of STS in the United States. For this analysis, data from April 2006 to October 2010 were captured using the company's AE reporting system database. The Adverse Event Reporting System used by Mylan is a global electronic pharmacovigilance system used to record, manage, and report complaints and adverse event data. All adverse event reports are received within the Product Safety and Risk Management Department, where health care professionals receive the information, query the reporter for specific information, and record the incoming information. All events are then further evaluated by a company physician. The AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.[10]

Patient exposure numbers. Data on the total number of patients exposed to STS were collected from the SDI Vector One: Total Patient Tracker system, which captures prescription data longitudinally. This system projects the number of patients with at least 1 drug prescription claim during a specified time period, based on integrated data from a variety of sources.

Data Extraction

Deidentified data were extracted from the postmarketing database by the sponsor and provided to the authors. The safety database was searched by computer algorithm using specified AE preferred terms that might be indicative of untoward events that have been associated with STS treatment, eg, *blood pressure increased, hypotension, drug interaction,* and *serotonin syndrome*. The company's data were limited to the specified parameters requested by the authors and were collated into a database. Tabulation, generation of descriptive statistics, and causality determination were done by the authors independent of the sponsor. Serious AEs (SAEs) were defined as they appeared in the original database.

Clinical information in the analysis extracted when available included the following: patient's gender, patient's age, time to onset of AE after initiation of treatment, dose of STS, treatment given to manage AE, description of AE, clinical outcome of AE, and clinical comments on AE. Additional data that were also systematically collected included a narrative of the events, any associated laboratory data, and assignment of AE seriousness according to FDA reporting criteria.[11]

Outcome Measures

All AEs that were listed in the source database were analyzed as outcome measures. Serious AEs included any fatal, disabling, or life-threatening AEs (eg, suicide attempt); worsening of depression; hospitalization; and incapacity, overdose, malformation, or neoplasm needing intensive and special medical care. For the attribution of AEs to STS, causality was categorized as "definitely related," "probably related," "possibly related," "not related," or "unknown" on the basis of best-available data: knowledge of the case, clinical course (eg, temporal association), clinical experience, and quality of the submitted data (eg, concomitant laboratory and identifiable medical records). All reports of hypertensive crisis, suicide attempts, and STS overdoses underwent an additional systematic and independent review from clinical experts to determine causality of the AE in relation to STS.

Hypertensive crisis represents severe elevation in blood pressure that may be complicated by injury to the brain or another organ and requires immediate blood pressure reduction (not necessarily to normal levels) to prevent or limit organ damage. For this analysis, an event was considered a confirmed hypertensive crisis if there was objective documentation of clinical data (eg, confirmation of blood pressure readings, or organ injury) by a health care provider that was consistent with the reported event. In the absence of objective confirmation, the events were considered self-reports of a hypertensive event. For episodes of reported hypertension/hypertensive crisis, all of the narrative summaries of each event, as recorded in the database, were carefully evaluated by 2 investigators (C.U.P. and A.A.P.) for the purpose of causality attribution.

Data Analyses

The rates of AEs were calculated as the number of AE reactions divided by the total number of patients exposed to STS (N = 29,141) and multiplied by 100. This rate should not be confused with an incidence rate for a particular adverse event, because the numerator is confined to those individuals who notified the manufacturer of an event. It is likely that the rates calculated here reflect substantial underreporting and are lower than the true incidence. Descriptive and narrative analyses are also provided for reported hypertensive events and drug-drug interactions, since these are events of particular interest.

Table 1. Adverse Events Reported in Patients Exposed to Selegiline Transdermal System[a]

Event	No. of Reports of Adverse Reaction (total = 3,155 reactions)	% Reactions (total N = 29,141)[b]	Patients With Reaction, n (total n = 1,516)	Patients With Reaction, % (total N = 29,141)
General disorders and administration site conditions	1,037	3.6	820	2.8
CNS disorders	574	2.0	391	1.3
Skin and subcutaneous tissue disorders	267	0.9	218	0.7
Gastrointestinal disorders	198	0.7	144	0.5
Investigations	149	0.5	140	0.5
Musculoskeletal and connective tissue disorders	91	0.3	71	0.2
Vascular disorders	77	0.3	74	0.3
Injury, poisoning, and procedural complications	66	0.2	61	0.2
Respiratory, thoracic, and mediastinal disorders	56	0.2	40	0.1
Cardiac disorders	50	0.2	48	0.2
Metabolism and nutrition disorders	40	0.1	38	0.1
Eye disorders	39	0.1	34	0.1

[a]Calculated on the basis of the dataset including 3,155 reactions in 1,516 patients (total exposure N = 29,141). Data are not shown for categories with adverse events reported in < 0.1% of 3,155 reactions. These categories included infections and infestations; ear and labyrinth disorders; reproductive system and breast disorders; renal and urinary disorders; immune system disorders; surgical and medical procedures; pregnancy, puerperium, and perinatal conditions; hepatobiliary disorders; social circumstances; benign, malignant, and unspecified neoplasms; blood and lymphatic disorders; unclassified; endocrine disorders; and congenital, familial, and genetic disorders.
[b]Rates of adverse events, calculated as the number of adverse reactions divided by the total number of patients exposed to selegiline transdermal system (N = 29,141) multiplied by 100.
Abbreviation: CNS = central nervous system.

RESULTS

Subject Disposition

From April 2006 to June 2010, a total of 29,141 patients were exposed to STS (n = 25,378 to 6-mg/24 h; n = 10,225 to 9-mg/24 h; n = 6,112 to 12-mg/24 h doses). A total of 3,155 AEs in 1,516 patients (5.2% of the total exposure N of 29,141) were reported, regardless of causality. More than half of the patients were female (n = 911/1,516; 60.1%). The patients' mean age was 53.1 years, and the median age was 53 years.

The distribution of AEs is presented in accordance with the System Organ Class (SOC) classification of the World Health Organization.[10]

Overall AEs

The most frequently reported AEs categorized by SOC were general disorders (no. of AEs = 1,037/29,141; 3.6%) and CNS disorders (no. of AEs = 574/29,141; 2.0%) (Table 1). Among the reported AEs in the general disorders category, application site reactions (application site reactions, 577/1,037; 55.6%) were most frequent.

Among total exposures, 266 reports were classified as SAEs (0.913%). Among total SAEs, CNS disorders (no. of AEs = 71/266, 26.7%) and cardiac and vascular disorders (no. of AEs = 44/266, 16.5%) were the most common categories.

Cardiovascular Events

Cardiac and vascular AEs were reported by approximately 0.4% of the total exposed patients (no. of AEs = 127/29,141), with palpitation (no. of AEs = 28/127, 22.0%) and hypotension (no. of AEs = 25/127, 19.7%) being the most common among cardiovascular AEs (Tables 1 and 2).

Eleven cases reported as hypertensive events, as well as 1 tyramine reaction, were found in the database. One more case was coded with 2 events—suicide attempt and multiple drug overdose—but upon review of the narrative, the possible diagnosis of hypertensive crisis arose, and this additional case was also included in the total of 13 possible reports of hypertensive events.

Table 2. Cardiac and Vascular Events Reported in Patients Exposed to Selegiline Transdermal System[a]

Event	No. of Adverse Reactions	% Reactions (N = 29,141)[b]
Hypertensive events	11	0.037
Tyramine reaction	1	0.003
Myocardial infarction	1	0.003
Rate and rhythm disorders	13	0.045
Others	101	0.347

[a]Calculated on the basis of the dataset including 3,155 reactions in 1,516 patients (the total exposure N = 29,141).
[b]Rates of adverse events were calculated as the number of adverse reactions divided by the total number of patients exposed to selegiline transdermal system (N = 29,141) multiplied by 100.

A review of the narrative summary for each case in the series led the investigators to categorize 5 of the 13 cases as possibly fitting the criteria for hypertensive crisis. However, objective clinical data that would have confirmed the diagnosis of hypertensive crisis were not available in the records. In 3 cases, the narrative included coadministration of STS with food, and in 2 cases, STS was taken with contraindicated drugs (tranylcypromine and amphetamine). Three of the 5 cases were reported to have resolved; however, information about resolution was not available in the other 2 cases (Table 3).

CNS Disorders

CNS events were reported by 2.0% of the total exposed patients (no. of AEs = 574/29,141). As summarized in Table 4, insomnia (no. of AEs = 144/574, 25.1%) was the most frequent CNS AE. The other reported AEs included changes in

Table 3. Summary of Hypertensive Events Reported in Patients Exposed to Selegiline Transdermal System

Case	Age (y)/Sex	STS Dose	Concomitant Food/Drug	Past History	Self-Reported BP; Clinical Course	Objectively Defined Hypertension	Comment
1[a]	74/F	6 mg	Soy-containing meal Clonazepam	Irritable bowel syndrome	195/110; 2-day hospitalization	Not reported	Interaction with food: resolved. STS restarted
2[a]	76/M	9 mg	White wine and chocolate Propranolol 140 mg prn	Hypertension	150/95–165/105; no hospitalization	Not reported	Interaction with food: resolved
3[a]	55/F	6 mg	Tranylcypromine sulfate	Refractory depression without effect from several prescribed antidepressants No medical history	200/100; event occurred immediately after prescription of tranylcypromine and cessation of STS 6 mg; no washout. No hospitalization	Checked by a physician, but no objective BP reading	Interaction between STS and immediate use of tranylcypromine sulfate: resolved
4[a]	Unknown/F	6 mg	Ziprasidone and clonazepam Dexamphetamine + amphetamine	No medical history	170/unknown; event occurred 1 day after STS use began	Checked by a physician at ER; no objective reading	Drug interaction: resolution unknown
5[a]	44/F	9 mg	Soy sauce	Asthma, GERD, allergy to tetracycline	216/143; no information on onset time or course	None	Interaction with food: resolution unknown
6	72/F	6 mg	Fluticasone propionate and salmeterol, 1 puff twice daily; albuterol inhaler, 2 puffs twice daily; triazolam 0.5 mg at night; clonazepam 0.25-mg tablet at night; esomeprazole 40 mg/d; phenelzine sulfate (discontinued 2 wk prior to visit); montelukast 10 mg/d; sulindac 150 mg twice daily; verapamil HCl twice daily	Asthma, hypertension, and arthritis	Very high blood pressure (no specific BP info); event occurred 6 days after STS use began	Possibly by ER physician; no objective reading	Drug interaction: resolved
7	22/F	6 mg	Quetiapine 600 mg, no tyramine-containing food	Bipolar I disorder and borderline personality disorder	No specific BP info	Not confirmed	Resolved
8	Unknown/F	6 mg	…	…	High BP (no values)	Not confirmed	Resolved
9	Unknown/F	6 mg	Four-cheese pizza	…	Very high BP reported (no values)	Not confirmed	Resolved
10	Unknown/F	12 mg	Tranylcypromine sulfate	…	Headache. No specific BP information	Not confirmed	Unknown
11	Unknown/unknown	12 mg	Soy sauce	…	Report of tyramine reaction. No specific BP information	Not confirmed	Unknown
12	Unknown/M	Unknown	…	…	Increased BP (no specific BP information)	Not confirmed	Unknown
13	23/M	6 mg	STS patch overdose (28 6-mg patches), bupropion, amphetamine	…	Hospitalization	Not confirmed	Resolved

[a]Self-report as a hypertensive crisis and defined as a possible hypertensive crisis by investigators.
Abbreviations: BP = blood pressure, ER = emergency room, F = female, GERD = gastroesophageal reflux disease, M = male, STS = selegiline transdermal system.
Symbol: … = no further information available.

mood, behavior, and consciousness and sleep and seizures. There were 16 reports (2.8%) of manic/hypomanic AEs among CNS AEs.

Suicidal Behavior and Suicide

There were 29 reports of suicidal ideation (0.01%), 4 suicide attempts (0.01%), and 4 completed suicides (0.01%); no causal role was apparent for STS on the basis of available follow-up information.

Multiple drugs were involved in all 4 of the completed suicides. In 1 patient, death was attributed to acute bupropion toxicity following bupropion overdose in a patient who was previously exposed to STS; 1 patient abused crystal methamphetamine along with STS; 1 patient was taking lamotrigine

Table 4. CNS Adverse Events Reported in Patients Exposed to Selegiline Transdermal System[a]

Event	No. of Adverse Reactions	% Reactions (total N = 29,141)[b]
Behavioral		
Anxiety	61	0.209
Irritability	29	0.100
Agitation	40	0.137
Restlessness	10	0.034
Nervousness	15	0.051
Mood		
Depression	66	0.226
Mania/hypomania	16	0.055
Delirium		
Delirium	2	0.007
Confusion		
Confusional state	12	0.041
Seizures		
Partial seizures	1	0.003
Convulsion	5	0.017
Sleep		
Insomnia	144	0.494
Somnolence	18	0.062
Other sleep disorders	11	0.038
Others		
Headaches	89	0.305
Migraines	11	0.038
Change in consciousness	5	0.017

[a]These reactions were calculated based on that dataset including 3,155 reactions in 1,516 patients (the total exposure N = 29,141). Data are not shown for categories with adverse events reported in < 0.1% of 3,155 reactions.
[b]Rates of adverse events were calculated as the number of adverse reactions divided by the total number of patients exposed to selegiline transdermal system (N = 29,141) multiplied by 100.
Abbreviation: CNS = central nervous system.

and zolpidem along with STS for at least 3 months; and 1 patient was taking lamotrigine for 3.5 years along with STS for 16 months and had possibly discontinued all medications prior to the attempt. A causal role for STS was not attributed by any of the reporting physicians on the basis of available information.

Drug Overdose

Eleven cases were coded as drug overdoses (0.04%). An independent review of the narratives revealed that only 2 of these 11 cases had received medical attention upon discovery of the overdose attempt. One patient was reported to have self-administered 28 STS patches along with several tablets of amphetamine salts, bupropion, and "MAOI," but recovered. Another patient was reportedly found with multiple STS patches and had apparently overdosed on diazepam and alcohol after ingesting tyramine-rich food.

Drug-Drug Interactions

There were 13 drug-drug interactions reported (a rate of 0.05%); 5 (38.5%) of them were classified as serious and required medical attention (Table 5). The clinical outcomes of such cases were mostly unknown, and 1 case (patient was taking lithium and trazodone) was reported to have a fatal outcome. One case was reported as serotonin syndrome, with no further clinical information.

DISCUSSION

Analysis of reported adverse events via large database systems provides clinicians with updated safety information, in particular regarding medical risks that may not have been observed in clinical trials.[9]

The overall AE profile of STS in the present postmarketing safety analysis appears similar to that reported in clinical trials. For analysis, we paid particular attention to 2 areas, cardiac/vascular events and CNS events, because of concerns about potential hypertensive crisis and serotonin syndrome, respectively. Among 29,141 total exposures, 5.2%, or 1 in approximately 20, of treated patients in clinical practice reported any AEs. As expected, this rate is considerably lower than those observed in the MDD RCTs for STS, in which 76% of STS-treated subjects and 72% of placebo-treated subjects experienced at least 1 AE.[3–6] Although postmarketing safety analyses invariably underrepresent the actual occurrence of specific AEs, the 5.2% rate appears reassuring. Consistent with the data from the RCTs for MDD, the most commonly reported AEs during STS treatment were application site reaction and insomnia.

It is not surprising that application site reactions and CNS symptoms such as insomnia, anxiety, and depression were the most frequent AEs in view of STS's approved indication in MDD, its pharmacologic profile, and its application method. The overall AE rate of 2% for application site reactions and CNS disorders is lower than those reported in clinical trials. For instance, in the MDD trials, the incidence rate of application site reaction was 24% in the STS-treated group and 12% in the placebo-treated group.[12] Application site reactions led to dropout in 2% of STS-treated patients and no placebo-treated patients in those RCTs.[12] In MDD RCTs, orthostatic hypotension was also reported at rates of approximately 10% in the STS-treated group and 7% in the placebo-treated group, with a trend toward a dose-related effect.[12] In the present analysis, cardiovascular AEs accounted for only 0.4% of reported AEs, which is lower than in short-term and long-term MDD RCTs.

It is estimated that approximately 1% of patients with hypertension will at some point spontaneously develop a hypertensive crisis, and it has also been estimated that hypertensive emergencies account for 25% of all patient visits to the emergency department.[13] In the present postmarketing safety analysis, there were 13 cases categorized as a hypertensive event. Five of the 13 cases were considered to have experienced possible hypertensive crisis, although objective clinical information that may have definitively established the occurrence of hypertensive crisis was not completely available for any of the 5 self-reported events. Hence, only 0.017% of patients exposed to STS experienced a possible hypertensive crisis, and none were objectively confirmed. In addition, 3 of the 5 cases were reported to have resolved, although specific information about resolution was not available in 2 cases. These results are consistent with those from efficacy clinical trials for STS in patients with MDD that showed no hypertensive reaction during study treatment, despite the

Table 5. Summary of Drug-Drug Interaction Adverse Events Reported in Patients Exposed to Selegiline Transdermal System

Case	STS Dose	Concomitant Drugs	Type of Interaction in Terms of Symptoms	Outcomes
1	Unknown	Trazodone, lithium	Cardiac disorder	Fatal
2[a]	Unknown	Methylphenidate, clomipramine	Dizziness, syncope	Ongoing
3	10 mg	Pramipexole, levodopa	Gambling, dopamine dysregulation syndrome	Unknown
4	12 mg	Calcium (soy excipient)	Headaches	Resolved
5	Unknown	Unknown breathing treatment	Increased blood pressure	Resolved
6	6 mg STS	Tamsulosin	Orthostatic hypotension, postural dizziness	Ongoing
7[a]	6 mg STS	Alcohol	Balance disorder, fall	Unknown
8	Unknown	Fluticasone and salmeterol	Blood pressure increased	Unknown
9	Unknown	Eletriptan, topiramate	Migraine, muscle spasm, paresthesia, visual impairment, pain in extremity, fatigue, dizziness, polymenorrhea, galactorrhea, irritability, night sweats, dysacusis	Unknown
10[a]	9 mg STS	Scopolamine patch	Disorientation, insomnia, nausea	Unknown
11	6 mg STS	Modafinil, levofloxacin	Heart rate increased, musculoskeletal stiffness, headache, insomnia	Unknown
12	6 mg STS	Cyclobenzaprine	Application site rash	Unknown
13[a]	Unknown	Valacyclovir, ethanol	Depressed level of consciousness, ataxia, confusional state	Unknown

[a]Cases with altered consciousness. One additional case was recorded as serotonin syndrome with no other information.
Abbreviation: STS = selegiline transdermal system.

fact that a tyramine-restricted diet was not required in 3 out of 4 trials.[3,5,6] In these trials, 2.2% of patients were found to show elevated blood pressure.[3,5,6] Furthermore, most of such cardiac AEs occurred in patients with preexisting hypertension, and blood pressure elevations were judged as being unrelated to STS.[3,5,6] Additionally, the results of several tyramine challenge studies confirm that treatment with STS is associated with a wide margin of safety compared with the oral MAOI antidepressants in terms of dietary interactions. For example, the tyramine sensitivity with the highest dose of STS (12 mg/d given for 33 days) was about 10-fold lower than that with tranylcypromine (30 mg/d given for 8 days) in the challenge tests.[8]

It is important to note that several clinical factors, such as preexisting cardiovascular disease, concomitant medication with cardiac side effects, smoking, alcohol or drug abuse, and metabolic issues, may contribute to cardiovascular adverse events in patients exposed to STS. In the absence of sufficient clinical information, it is difficult to determine causality determination, and the extent to which STS was the sole contributor to the hypertensive events is unclear.

In short- and long-term MDD RCTs, weight gain and sexual dysfunction with STS treatment were comparable to placebo.[3–6] This is notable since the major oral antidepressant classes such as selective serotonin reuptake inhibitors have been found to be significantly associated with these AEs, leading to early dropout. In the present analysis of postmarketing safety, only 0.1% of patients reported weight- or sexual dysfunction–related AEs. Hence, STS may prove to be a viable alternative in patients who experience these AEs with other antidepressants or who prefer medications without such undesirable effects.

There were 11 cases coded as drug overdoses. As of the date of this analysis, no deaths had been reported to have been solely attributable to STS overdose. Two patients required significant medical attention, although they eventually fully recovered. On the basis of these data, it could be inferred that the fatal toxicity index[14] of STS should be regressed to zero, although careful monitoring of overdose events should be continued in order to confirm such a favorable fatal toxicity index. It should be noted that mixed overdoses of STS with other antidepressants can be life-threatening due to cumulative toxicity of the drugs as well as serious interactions such as serotonin syndrome. Hence, it is strongly recommended that patients suspected of taking any combined overdose should be hospitalized immediately and intensive care should be provided.

Thirteen drug-drug interactions (0.045%) were reported; 5 of them were classified as serious and required medical attention. The median number of substances taken was 1.4 (range, 1–2). One death was reported in a patient who was also taking lithium and trazodone. Due to limited information, it was difficult to conclude whether STS, lithium, trazodone, cumulative toxicity, or an unrelated factor contributed to the death. In the present analysis, 1 case of serotonin syndrome was reported, but it was not confirmed because no further information was available. Two cases of serotonin syndrome, reported as SAEs, occurred with STS treatment in previous MDD RCTs.[3–5] Among the 13 drug interaction cases in the present postmarketing safety analysis, 4 had reports of altered consciousness; 2 of these cases involved alcohol, 1 case involved amphetamine and clomipramine combination, and 1 subject was on treatment with the scopolamine patch. None of the 4 cases involving altered consciousness were diagnosed as serotonin syndrome. However, clinicians are reminded that concomitant use of most antidepressants is contraindicated with STS due to risk of serotonin syndrome. Hence, a minimum washout period from existing antidepressants (equivalent to 4–5 half-lives [1 week for most antidepressants, 4 weeks for fluoxetine]) should be followed before starting STS treatment. Additionally, a minimum 2-week washout period is required when switching from STS to other antidepressants to allow time for the MAO enzyme to regenerate.[15–17]

The FDA has issued a boxed warning concerning increased suicidal ideation and behavior associated with antidepressant drug treatment in children and adolescents, although it is still controversial whether antidepressant agents actually increase the risk of completed suicides in children or adults.[15–17] According to data from the Centers for Disease Control and Prevention, 11% to 17% of all

MDD patients eventually commit suicide.[18,19] The overall rate in the United States was 11.3 suicide deaths per 100,000 people in 2007.[18,19] Four completed suicides were reported out of 29,141 patients exposed to STS in the present postmarketing safety analysis.

Little official postmarketing safety analysis of MAOIs has been conducted. However, according to a postmarketing safety analysis of moclobemide[20] involving 780,000 subjects, AEs had been reported by less than 0.2% of users. The most frequently reported AEs were psychiatric, neurologic, and gastrointestinal disorders. In the analysis, hepatobiliary and cardiovascular AEs were rare.[20] This safety profile was largely unchanged from those observed at 1 and 2 years postlaunch.[20] In addition, there was no evidence of an increased risk of suicidal behavior in users of moclobemide.[20] Overall, such a safety and tolerability profile of moclobemide was in line with our present analysis of STS.

Although we utilized the company's Adverse Event Reporting System, these systems cannot completely determine the incidence of an event, because adverse reaction reporting is prone to significant underreporting, differential reporting, and uneven quality of data.[9,21] Also, the company's reporting system cannot adequately address relative safety or risks between medications under investigation. The reports of AEs are complicated by many clinical factors, such as time since medication launch, market share, the unexpectedness of AEs, market trends, physician variability in reporting, and other public issues.[22–24] Epidemiologic studies, including case series, secular trends, and case-control and cohort studies, may be necessary to supplement investigations based on data from adverse event reporting systems in order to detect a safety signal for currently marketed medicines.[21,24,25] Further, patient privacy laws may make it difficult to track and follow up on reported information. Additionally, the data we used were not compared to data yielded by the FDA's postmarketing surveillance system. Finally, given the relatively modest exposure numbers (N = 29,141), continued safety monitoring of the use of STS in routine clinical practice is clearly needed.

The AE profile for STS from reported postmarketing adverse events appears to be consistent with safety and tolerability data of STS derived from the randomized, placebo-controlled efficacy trials. The reports of serious adverse events such as hypertensive crisis and serotonin syndrome were very low. Therefore, on the basis of the reported data, therapeutic doses of STS appear to be tolerable in routine clinical practice.

Drug names: albuterol (Proventil, Ventolin, and others), bupropion (Wellbutrin, Aplenzin, and others), clomipramine (Anafranil and others), clonazepam (Klonopin and others), cyclobenzaprine (Amrix, Flexeril, and others), diazepam (Diastat, Valium, and others), eletriptan (Relpax), esomeprazole (Nexium), fluticasone/salmeterol (Advair), fluoxetine (Prozac and others), lamotrigine (Lamictal and others), lithium (Lithobid and others), methylphenidate (Focalin, Daytrana, and others), modafinil (Provigil), montelukast (Singulair), phenelzine (Nardil and others), pramipexole (Mirapex and others), propranolol (Inderal, InnoPran, and others), quetiapine (Seroquel), scopolamine patch (Transderm Scop), selegiline transdermal system (EMSAM), sulindac (Clinoril and others), tamsulosin (Flomax and others), topiramate (Topamax and others), tranylcypromine (Parnate and others), trazodone (Oleptro and others), triazolam (Halcion and others), valacyclovir (Valtrex and others), verapamil (Verelan, Isoptin, and others), ziprasidone (Geodon), zolpidem (Ambien, Edluar, and others).

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