Selegiline Transdermal System for the Treatment of Major Depressive Disorder: An 8-Week, Double-Blind, Placebo-Controlled, Flexible-Dose Titration Trial

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Objective: This study investigated the efficacy, safety, and tolerability of the selegiline transdermal system (STS) administered in a dose range of 6 mg/24 hours to 12 mg/24 hours for treating major depressive disorder (MDD).

Method: Patients meeting DSM-IV criteria for MDD (N = 265) were randomly assigned to blinded treatment with STS or a matching placebo patch for 8 weeks. Patients failing to meet or maintain protocol-defined therapeutic response criteria at predetermined time points had their STS (or placebo) dose increased. Assessments were conducted at weeks 1, 2, 3, 5, 6, and 8. Patients were not required to follow a tyramine-restricted diet. The study ran from September 2001 through August 2002.

Results: Selegiline transdermal system treatment resulted in significantly greater improvement ($p \leq .05$) compared with placebo treatment on the 3 depression rating scales: the 28-item Hamilton Rating Scale for Depression ($HAM\text{-}D_{28}$) (primary outcome measure), the Montgomery-Asberg Depression Rating Scale, and the Inventory for Depressive Symptomatology-Self Rated. The treatment effect measured by the $HAM\text{-}D_{28}$ was modest, primarily due to insomnia side effects. The antidepressant efficacy of STS was substantiated further by the significantly greater improvement in core depression symptoms (HAM-D Bech-6 subscale). The side effects of highest incidence were application-site reactions and insomnia. There were no safety concerns based on routine clinical laboratory and electrocardiogram monitoring, and there were no occurrences of hypertensive crisis.

Conclusion: Results of this double-blind, placebo-controlled, dose titration trial provide evidence of short-term efficacy, safety, and tolerability of STS in the dose range of 6 mg/24 hours to 12 mg/24 hours for treatment of MDD. Selegiline transdermal system has an improved margin of safety compared with oral monoamine oxidase inhibitors and represents a useful addition to the existing array of antidepressants.

(J Clin Psychiatry 2006;67:1354–1361)

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This research was supported by a grant from Somerset Pharmaceuticals, Inc., Tampa, Fla. Funding for assistance with manuscript editing was provided by Bristol-Myers Squibb.

Individual financial disclosure appears at the end of this article.

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Although antidepressants provide relief for many patients suffering major depressive disorder (MDD), approximately one half of patients who begin therapy with a given antidepressant may not respond to initial treatment, and a substantial number fail to respond to a series of treatments.[1] Even with numerous available antidepressants, up to two thirds of patients discontinue therapy as a result of intolerable side effects such as fatigue, sleep problems, anxiety, hyperphagia, and weight gain.[2] Drug-induced sexual dysfunction is a common reason for treatment nonadherence and can lead to a relapse of depression.[3] Clearly, a need persists for innovative antidepressant drugs with improved efficacy and tolerability.

Monoamine oxidase inhibitors (MAOIs), the first of the antidepressant drugs, have an established reputation of efficacy with recognized utility for atypical and treatment-resistant depressions.[4,5] These medications are posited to work by inhibiting monoamine oxidase-A (MAO-A) and monoamine oxidase-B (MAO-B) enzymes in monoaminergic neurons in the brain, resulting in increased activity of key neurotransmitters involved in depression, i.e., serotonin, norepinephrine, and dopamine.[6] However, orally ingested MAOIs must transit the gastrointestinal tract and liver prior to becoming systemically available and crossing the blood-brain barrier to exert

antidepressant effects. As a result, significant inhibition of MAO occurs in peripheral tissues. Specifically, substantial MAO-A inhibition in the gastrointestinal tract permits dietary tyramine, a vasopressive amine found in certain foods such as aged cheese and meat, to enter the systemic circulation intact. High levels of circulating tyramine can facilitate release of norepinephrine from adrenergic nerve terminals, resulting in a sudden, dramatic increase in blood pressure referred to as hypertensive crisis.[7,8] Until now, the only way to minimize the risk of this serious interaction with irreversible MAOI antidepressants has been to require tyramine dietary restrictions.[9]

The selegiline transdermal system (STS) was formulated to maintain the gastrointestinal barrier to ingested tyramine while gaining therapeutic effect at central nervous system target sites. By delivery of selegiline through the skin directly into the systemic circulation, transit through the gastrointestinal tract and first-pass hepatic metabolism are circumvented. With this innovative delivery system, selegiline concentrations are sufficient to inhibit both MAO-A and MAO-B in the brain, producing antidepressant effects[10] while reducing exposure of the gastrointestinal tract to the drug. Animal studies have demonstrated that transdermally delivered selegiline exhibits organ selectivity, such that even with greater than 90% inhibition of MAO in brain tissues, MAO-A of the intestinal mucosa remains functionally intact to inactivate ingested tyramine and diminish the risk of hypertensive crisis.[11,12]

The efficacy, safety, and tolerability of STS at a 6 mg/24-hour fixed dose have been shown for acute treatment and prevention of relapse of MDD in 6-week,[13] 8-week,[14] and 52-week (data on file, Somerset Pharmaceuticals, Inc., Tampa, Fla.) placebo-controlled clinical trials. In the absence of dietary restrictions in the 8-week and 52-week trials, no hypertensive crises resulted. The present 8-week trial in MDD assessed the therapeutic benefit and safety of STS in a dose range of 6 mg/24 hours to 12 mg/24 hours using a randomized, double-blind, placebo-controlled, flexible-dose study design without tyramine dietary restrictions.

METHOD

Patients

Men and women, 18 years and older, meeting DSM-IV criteria for MDD, single episode or recurrent, moderate to severe, were eligible for enrollment in this study, which ran from September 2001 through August 2002. A diagnosis of MDD was made after psychiatric interview by an experienced clinician and use of the semi-structured Mini-International Neuropsychiatric Interview. Scores of ≥ 20 on the 17-item Hamilton Rating Scale for Depression ($HAM\text{-}D_{17}$)[15] and ≥ 4 (moderately ill) on the 7-point Clinical Global Impressions-Severity (CGI-S)[16] scale were required during screening and at the baseline visit. Duration of the index depressive episode must have been at least 2 months but not exceeding 2 years.

Patients were excluded from the trial for presence of a DSM-IV Axis I disorder other than MDD (except for dysthymia) or an Axis II disorder that made it unlikely that the patient would be compliant or treatment-responsive. Pregnant and lactating women were excluded, and all women of childbearing age agreed to use a medically acceptable method of birth control during study treatment. Other exclusion criteria included unstable psychosocial situations or recent Axis IV stressors; investigational drug use within 60 days; nonresponse to a previous trial of an MAOI; known or suspected hypersensitivity to selegiline; and a clinically significant medical condition that might affect protocol implementation, including skin abnormalities, serious central nervous system disorders (e.g., Alzheimer's disease, Parkinson's disease, or epilepsy), and significant cardiovascular disease (i.e., unstable angina, congestive heart failure, poorly regulated hypertension [diastolic blood pressure > 100 mm Hg]).

Concomitant use of medications that could interact with selegiline or alter mood and depressive symptoms (e.g., meperidine, dextromethorphan, other opioids, sympathomimetic agents, antidepressants, antipsychotics, mood stabilizers) was prohibited. Patients were required to be free of psychoactive medications for at least 5 half-lives, usually 1 week (longer for fluoxetine), before starting study medication. Zolpidem and chloral hydrate were allowed for sleep, as were chlorpheniramine, diphenhydramine, loratadine, and fexofenadine.

Patients were not advised to follow a tyramine-restricted diet.

Selegiline Transdermal System Patches

Selegiline transdermal system patches contain 1 mg of selegiline per cm^2 and deliver approximately 0.3 mg of selegiline per cm^2 over 24 hours. The 3 sizes of STS patches used in this study (20 mg/20 cm^2, 30 mg/30 cm^2, and 40 mg/40 cm^2) deliver, on average, doses of 6 mg/24 hours, 9 mg/24 hours, or 12 mg/24 hours, respectively.

Study Design

All patients received a complete description of the study and provided written informed consent prior to enrollment. The study protocol was reviewed and approved by the institutional review board at each of the 3 study sites.

After completing screening procedures during a variable screening period of up to 28 days, baseline safety and efficacy data were collected and patients were randomly assigned to treatment with STS 6 mg/24 hours or to matching placebo patch. Site personnel assisted patients in identifying several potential application sites (i.e., torso, upper thigh, or upper arm) and then applied the first

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patch to demonstrate proper patch application. Between visits, patients applied the patch to a different application site once daily (i.e., every 24 hours). The time for study drug application on each day of treatment remained consistent (± 1 hour) for each patient during the course of his/her participation in the study (except on the day of a clinic visit, when the patient left the patch on until seen in the clinic). Efficacy, safety, and tolerability were assessed at weeks 1, 2, 3, 5, and 8. Patients requiring a dose increase at the week 5 visit returned for a week 6 assessment.

After 2 weeks, patients experiencing definite improvement (defined by protocol as a Clinical Global Impressions-Change (CGI-C)[16] rating of 1 [very much improved] or 2 [much improved]) continued treatment unchanged at 6 mg/24 hours of STS or matching placebo. For all other patients, the dose was increased to STS 9 mg/24 hours or matching placebo. After 3 weeks of treatment, any patient on STS 6 mg/24 hours (or placebo) who did not maintain a CGI-C rating of 1 or 2 had their dose increased to STS 9 mg/24 hours (or placebo). After 5 weeks of treatment, patients with a CGI-C rating of 1 or 2 remained at their current dose; those with a CGI-C rating ≥ 3 had their dose increased, i.e., from STS 6 mg/24 hours to 9 mg/24 hours (or matching placebo) or from STS 9 mg/24 hours to 12 mg/24 hours (or matching placebo) and returned for an additional evaluation at week 6. Patients who experienced an adverse event due to a dose increase could have their dose decreased by 1 level at any time.

Assessments

The protocol-defined primary endpoint for efficacy was mean change from baseline on the 28-item version of the Hamilton Rating Scale for Depression (HAM-D_{28}).[15] Two additional depression rating scales were employed, the Montgomery-Asberg Depression Rating Scale (MADRS)[17] and the Inventory for Depressive Symptomatology-Self Rated (IDS-SR).[18] Other secondary efficacy measures were mean change from baseline on the HAM-D_{17} and the core depression symptom subscale (HAM-D Bech-6: item 1—depressed mood, item 2—feelings of guilt, item 7—work and activities, item 8—retardation, item 10—psychic anxiety, item 13—general somatic symptoms). Changes in the distribution of responses on HAM-D depressed mood (item 1), CGI-C, and response rate (50% decrease in HAM-D_{28}) were also assessed.

Drug safety was assessed by adverse event (AE) incidence, vital signs, clinical laboratory tests (hematology, chemistry, urinalysis), physical examination (including application sites), and 12-lead electrocardiogram.

Statistical Methods

A sample size of 250 patients (125 per group) was calculated to provide 80% power to detect a between-group difference of approximately 3.5 units in mean change from baseline in HAM-D_{28} scores. Efficacy analyses utilized the modified intent-to-treat patient sample, defined as all randomly assigned patients who received study drug and had a postbaseline HAM-D_{28} evaluation. Results were considered statistically significant when the appropriately calculated 2-sided p value was ≤ .05. All statistical analyses utilized SAS software, Version 6.12 (SAS Institute Inc., Cary, N.C.).

For the primary efficacy analysis, a 2-way analysis of variance (ANOVA) model was fitted using the last-observation-carried-forward (LOCF) HAM-D_{28} change from baseline as the response, treatment group and center as main effects, and baseline score as covariate. Treatment-by-center interaction was not statistically significant ($p > .10$) and thus was not included in the model. For other efficacy continuous variables, the same approach applied. For categorical variables, a Cochran-Mantel-Haenszel (CMH) type 2 (ANOVA mean score) statistic using center as stratum was used for ordinal variables (e.g., CGI-S, HAM-D item 1), and a CMH type 1 statistic was used for nominal variables (e.g., response rates).

The safety patient sample included all patients randomly assigned to treatment who applied study medication. Safety analyses were performed by treatment group and summarized using descriptive statistics for continuous variables and frequency distributions for categorical variables. Adverse events were summarized using Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) preferred terms.

RESULTS

Two hundred sixty-five patients were randomly assigned to STS (N = 132) or placebo (N = 133). Fifty-nine patients (STS 32, placebo 27) prematurely discontinued treatment, and 206 patients (STS 100, placebo 106) completed the study. The most frequent reasons for discontinuation were "lost to follow-up" (N = 16) and "adverse event" (N = 12).

Patient Demographics

The mean age of both STS and placebo patients was 42 years. Patients were predominantly women (STS 61%, placebo 53%), white (STS 80%, placebo 81%), and had recurrent major depression (STS 70%, placebo 76%). Mean baseline HAM-D_{28} scores were 28.3 (SD = 3.7) and 28.6 (SD = 4.0) for STS and placebo patients, respectively. Pretreatment CGI-S scores were either 4 (moderately ill) or 5 (markedly ill) for all but 1 patient (CGI-S = 6, severely ill).

A small number of patients reported antidepressant use within 90 days of enrollment (STS 17%, placebo 10%). Prior to randomization, hypnotic/sedative use was 6% for STS patients and 1% for placebo patients.

Table 1. Comparison of Baseline Scores With Week 5 and Week 8 Scores for Efficacy Measures (modified ITT population, LOCF analysis)

	STS (N = 129)		Placebo (N = 128)		
Efficacy Measure	Mean (SD)	Mean Change (SD)	Mean (SD)	Mean Change (SD)	p Value
HAM-D (28-item)					
Baseline	28.3 (3.7)		28.6 (4.0)		.61
Week 5	19.1 (8.4)	–9.2 (8.1)	21.5 (7.7)	–7.1 (7.1)	.03[a]
Week 8	17.2 (8.6)	–11.1 (8.6)	19.8 (9.2)	–8.9 (9.1)	.03[a]
MADRS					
Baseline	29.3 (4.2)		29.3 (4.2)		.83
Week 5	20.3 (9.5)	–9.0 (9.3)	23.0 (8.9)	–6.3 (8.3)	.02[a]
Week 8	17.8 (9.9)	–11.6 (9.8)	20.7 (10.7)	–8.6 (10.3)	.02[a]
IDS-SR[b]					
Baseline	37.3 (8.8)		37.6 (9.4)		.75
Week 5	25.8 (11.2)	–11.5 (10.7)	28.4 (13.1)	–9.1 (10.8)	.07
Week 8	23.3 (11.4)	–13.9 (12.1)	26.7 (14.4)	–10.6 (12.5)	.03[a]
HAM-D (17-item)					
Baseline	23.4 (2.5)		23.7 (2.7)		.53
Week 5	16.2 (6.9)	–7.3 (6.5)	17.6 (6.1)	–6.1 (5.7)	.11
Week 8	14.7 (7.2)	–8.7 (7.0)	16.2 (7.5)	–7.4 (7.4)	.13
HAM-D (6-item Bech)					
Baseline	12.4 (1.3)		12.6 (1.3)		.40
Week 5	8.0 (3.8)	–4.4 (3.8)	9.4 (3.5)	–3.2 (3.3)	< .01[a]
Week 8	6.9 (4.3)	–5.5 (4.3)	8.5 (4.3)	–4.1 (4.2)	< .01[a]

[a]Represents a significant ($p \leq .05$) between-group difference.
[b]N = 123 for STS, N = 124 for placebo.
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, IDS-SR = Inventory for Depressive Symptomatology-Self Rated, ITT = intent to treat, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, STS = selegiline transdermal system.

Treatment Compliance

Treatment compliance was assessed based on the number of patches distributed and returned during the study. All unreturned patches were assumed to have been used by the patient. Patients were considered to be compliant if they used at least 80% but no more than 120% of patches; 127 of 132 (96%) STS patients and 119 of 133 (89%) placebo patients were compliant with study treatment.

Distribution of Doses

Of the 265 patients participating in the study, 230 (87%) had their starting doses increased, with similar percentages of patients in the STS (116/132, 88%) and placebo groups (114/133, 86%) having their doses titrated to STS 9 mg/24 hours or the equivalent-sized placebo patch. While, overall, 147 of 265 patients (55%) had their doses increased further to STS 12 mg/24 hours (or placebo), this occurred less frequently for patients receiving STS (63/132, 48%) than for those receiving placebo (84/133, 63%) treatment. Twelve patients underwent dose reduction due to an adverse event. Six patients had doses decreased from 9 mg/24 hours to 6 mg/24 hours (4 STS, 2 placebo), and 6 patients had doses reduced from 12 mg/24 hours to 9 mg/24 hours (3 STS, 3 placebo).

Efficacy

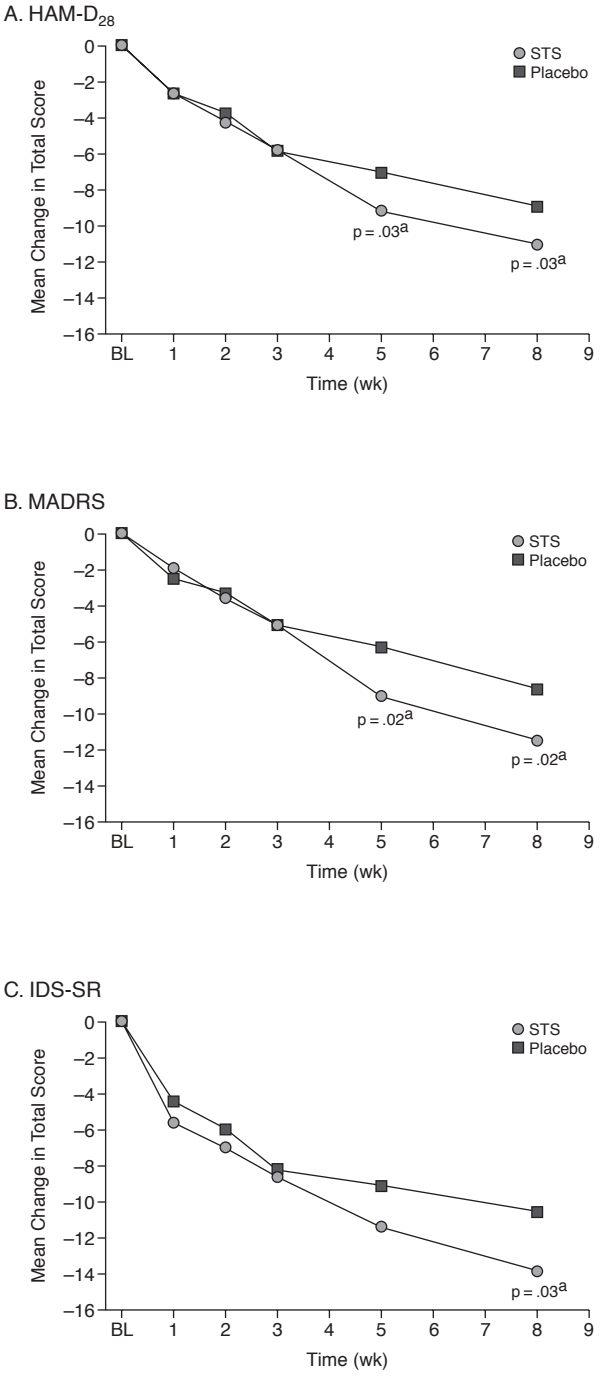
Selegiline transdermal system treatment produced significantly greater improvement compared with placebo treatment in the HAM-D_{28} ($p = .03$) (primary measure), the MADRS ($p = .02$), and the IDS-SR ($p = .03$) depression rating scales (Table 1 and Figure 1). Mean improvement in HAM-D_{17} score was greater with STS treatment (–8.7) than with placebo treatment (–7.4), but the between-group differences were not statistically significant. Improvement at week 5 in HAM-D_{28} and MADRS scores (Figure 1) was also significantly greater ($p \leq .05$) with STS than placebo treatment, at which time all STS patients were receiving either 6 mg/24 hours or 9 mg/24 hours. On other secondary outcome measures, end-of-treatment improvement in HAM-D Bech-6 ($p < .01$), HAM-D depressed mood ($p < .01$), and CGI-C ($p = .04$) ratings were superior with STS compared with placebo treatment. Response rates based on the number of patients with ≥ 50% improvement in HAM-D_{28} scores also favored STS (40%) compared with placebo (30%), but the difference was not significant.

Safety and Tolerability

The extent of exposure (days of treatment) varied by dose but not by treatment group. Patients receiving STS treatment compared with those receiving placebo treatment spent a mean of 17.7 (SD = 10.0) days and 17.4 (SD = 9.4) days at 6 mg/24 hours of STS or placebo; 26.8 (SD = 11.1) days and 24.9 (SD = 9.3) days at 9 mg/24 hours of STS or placebo; and 19.6 (SD = 4.6) days and 20.5 (SD = 4.4) days at 12 mg/24 hours of STS or placebo, respectively.

There were no occurrences of hypertensive crisis. Clinically significant postbaseline blood pressure elevations were noted in 2 patients in the STS group and 3 pa-

Figure 1. Mean Change From Baseline at Specified Study Visits for Efficacy Measures (modified ITT population, LOCF analysis)



[a]Represents a significant ($p \leq .05$) between-group difference.
Abbreviations: BL = baseline, HAM-D = Hamilton Rating Scale for Depression, IDS-SR = Inventory for Depressive Symptomatology-Self Rated, ITT = intent to treat, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, STS = selegiline transdermal system.

Table 2. Treatment-Emergent Adverse Events Occurring in ≥ 10% of STS-Treated Patients and More Frequently Than With Placebo (all randomized patients)

Adverse Event[a]	STS (N = 132), N (%)	Placebo (N = 133), N (%)
Overall	105 (80)	98 (74)
Application-site reaction	53 (40)	27 (20)
Insomnia	40 (30)	19 (14)
Infection	18 (14)	17 (13)
Dizziness	17 (13)	9 (7)
Dry mouth	16 (12)	10 (8)
Nervousness	13 (10)	8 (6)
Diarrhea	13 (10)	5 (4)

[a]Adverse events are summarized by the Coding Symbols for a Thesaurus of Adverse Reactions Terms (COSTART) preferred terms within each treatment group.
Abbreviation: STS = selegiline transdermal system.

tients in the placebo group. Postbaseline orthostatic hypotension (defined as a decrease ≥ 10 mm Hg in mean arterial pressure on change from sitting to standing position) was recorded in 9 STS patients and 9 placebo patients. No clinically meaningful trends were observed during study treatment for routine clinical laboratory or electrocardiogram monitoring.

Treatment with STS was generally well tolerated. The treatment-emergent AEs with ≥ 10% incidence and greater frequency in the STS treatment group were application-site reaction, insomnia, infection, dizziness, dry mouth, nervousness, and diarrhea (Table 2). The most frequent AEs were application-site reactions (40% vs. 20%) and insomnia (30% vs. 14%) for STS and placebo, respectively. Concomitant use of sedatives/hypnotics occurred in 14% of patients on STS compared with 8% of patients in the placebo group.

The incidence of AEs associated with sexual dysfunction was low and was similar for STS (0.8%) and placebo (1.5%) treatment. No patients developed excessive weight gain. At the end of treatment, patients in the STS group had a mean weight change of –0.7 (SD = 2.6) kg; there was no change in mean weight for placebo patients.

Most AEs were rated either mild or moderate in intensity. Nine patients in the STS group and 3 patients in the placebo group discontinued treatment due to AEs. Application-site reactions rated as severe occurred in 4 STS patients, 2 of whom prematurely terminated from the study. Other AEs contributing to premature discontinuation for more than a single patient were insomnia (1 STS, 1 placebo), dizziness (2 placebo), and nervousness (1 STS, 1 placebo).

During study treatment, there were no deaths and only a few (4/265) serious adverse events (SAEs). One placebo patient sustained a lower abdominal infection considered unrelated to study drug, and 1 STS patient received treatment for an ovarian cyst considered unrelated to study drug. One STS patient attempted suicide and survived; in this case, the investigator judged the SAE to be remotely

related to study drug because the patient had a history of psychiatric hospitalization for suicide gesture, and, although STS 6 mg/24 hours was dispensed at the baseline visit, application of study drug could not be confirmed because the patient prematurely discontinued due to the SAE before postbaseline assessment. One STS patient had a series of protocol violations not disclosed until he entered open-label extension treatment after completing double-blind treatment (maximum dose STS 12 mg/24 hours). On the third day of extension treatment with STS 12 mg/24 hours, the patient was hospitalized for overdose of diet pills (containing ephedrine) and nortriptyline (eight 50-mg capsules) while concurrently wearing 2 STS patches (12 mg/24 hours each). He was also noted to have in his possession a prescription for bupropion. The patient required intensive care, including endotracheal intubation, for treatment of serotonin syndrome secondary to multiple drug-drug interactions. The patient responded and was discharged after 10 days to outpatient follow-up care. When the study site learned of this event, it was further documented that the patient had 2 prior unreported drug overdoses during double-blind STS treatment and was taking bupropion 100 mg t.i.d.

DISCUSSION

This is the first report of a placebo-controlled trial employing flexible dosage of STS (6 mg/24 hours to 12 mg/24 hours) for treatment of MDD. In this trial, statistically significant improvement in mean change from baseline was observed on 3 depression rating scales: the primary scale, HAM-D_{28}, and 2 secondary scales, MADRS and IDS-SR. Significant improvement in HAM-D_{28} and MADRS ratings was observed as early as week 5 of treatment, at which time patients were receiving either STS 6 mg/24 hours or 9 mg/24 hours. The finding of STS efficacy on these 3 depression rating scales was supported by significant improvement ($p \leq .05$) compared with placebo in other secondary outcome measures, including core depression symptoms (HAM-D Bech-6), depressed mood (HAM-D item 1), and global improvement rating (CGI-C).

In this trial, the mean difference between treatments on the HAM-D_{17} score was not significant, and treatment effect measured by HAM-D_{28}, while significant, was only modest. Despite its accepted limitations for assessing efficacy of activating antidepressant drugs,[19] the HAM-D was selected as the primary efficacy measure because this trial was intended to provide pivotal evidence of drug efficacy for registrational purposes. The 28-item version was chosen because it additionally assesses effectiveness for reverse vegetative symptoms of depression, i.e., hypersomnia, hyperphagia, and weight gain. Since 3 items of the HAM-D_{17} evaluate symptoms of insomnia (early, middle, and late),[15] it is generally accepted that the HAM-D scale is a better instrument for evaluating the efficacy of sedating antidepressant drugs. Activating antidepressants may cause somatic side effects, such as insomnia, that can artificially increase HAM-D scores and obscure drug effect.[20] Post hoc analysis of the HAM-D_{17}, excluding insomnia items (4, 5, and 6), revealed a statistically significant improvement from baseline in the STS group compared with the placebo group at weeks 5 ($p = .01$) and 8 ($p = .03$). The MADRS, the second most widely employed depression rating scale, was selected for use in this efficacy trial in part because ratings are less influenced by somatic symptoms than the HAM-D scale.

While the HAM-D remains the most widely used instrument for measuring outcome in MDD efficacy trials, the multidimensionality of the HAM-D causes this scale to be relatively insensitive with respect to detecting change in core symptoms of depression.[21–23] It has been recommended that clinical trials employ several outcome measures to assess efficacy and better characterize antidepressant response.[24] In this study, it is of interest that measurement of core depression symptoms by the Bech-6 subscale of the HAM-D demonstrated a highly significant therapeutic advantage of STS over placebo ($p < .01$). A particular strength of this study is the consistency of the positive efficacy finding for STS across 3 validated and widely used depression rating scales, the HAM-D_{28}, the MADRS, and the IDS-SR, as well as the Bech-6 core symptoms measure. The magnitude of the treatment effect noted with the MADRS (mean difference = 3) is similar to that recently reported in the pivotal efficacy studies of escitalopram.[25–27]

The present trial shows significant antidepressant efficacy with good tolerability for STS within a dose range of 6 mg/24 hours to 12 mg/24 hours. The tolerability profile of STS in this dose-titration trial is consistent with that previously reported in fixed-dose trials of STS 6 mg/24 hours, with the exception that application-site reactions and insomnia were more frequent in the current study.[13,14]

Sexual dysfunction AEs had a low incidence in both treatment groups, although these symptoms were not specifically elicited. A post hoc analysis of the HAM-D libido item showed similar improvement at endpoint for STS- (–0.36) and placebo-treated (–0.28) patients. These results are consistent with previous reports suggesting STS does not induce sexual side effects.[13,14]

In spite of an absence of dietary restrictions, no tyramine-induced acute hypertensive reactions occurred during treatment at higher STS doses. However, because only 116 patients were exposed to STS 9 mg/24 hours to 12 mg/24 hours, the risk of hypertensive crisis without dietary restrictions at higher doses cannot be fully evaluated from the results of this trial. Although postural hypotension is a common side effect of MAOI antidepressants, vital sign monitoring in this study revealed a relatively low incidence of postural hypotension, with a similar

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incidence in both treatment groups. As with all MAOIs, use of STS concomitantly with certain medications affecting monoamine activity in the central nervous system should be avoided due to the potential for serotonin syndrome. This is supported by the report of a noncompliant patient who overdosed with diet pills and nortriptyline, and possibly concurrent bupropion, while using twice the maximum recommended dose of STS (2 patches, 12 mg/24 hours each).

Because of the flexible-dose design specifying dose titration, the incidence of side effects in this trial should be interpreted with caution.[28] Either or both of the aforementioned study design features (flexible dose and/or dose titration) might have contributed to a high incidence of the AE insomnia. On the other hand, inasmuch as certain side effects, especially sexual dysfunction and weight gain, commonly associated with other antidepressants, including MAOIs, have an especially negative impact on treatment adherence,[2,3] the generally low side effect burden of STS is an important feature in support of its therapeutic utility in treating depression.

Other strengths of this study were high rates of treatment compliance and trial completion, especially for patients receiving STS, 96% of whom complied with treatment and 76% of whom completed the trial, with only 7% withdrawing because of adverse events. Patients' adherence to established guidelines for acute, continuation, and maintenance treatment of MDD significantly reduces the likelihood of relapse or recurrence, and treatment adherence varies by choice of medication.[29] The favorable safety profile across a range of doses, coupled with excellent compliance and completion rates in this study, suggests that STS may be a therapeutic option that fosters compliance.

A flexible-dose study design has the purported advantages of a greater sensitivity for detecting between-group differences and lower placebo response rates.[30] This is particularly important as the efficacy of the newer generation of antidepressants is debated,[31] fueled, in part, by the apparent rise over the past 20 years in placebo response rates in antidepressant trials.[32] It should be emphasized that this was a flexible-dose design, not a dose-response trial that compares multiple fixed doses of drug versus placebo. The protocol-defined algorithm to increase the dose of STS (or placebo) due to insufficient therapeutic response was substantially more aggressive in rapidity of raising the dose than recommended by clinical guidelines. Typically, response to a given dose of antidepressant requires a minimum of 3 to 4 weeks at a potentially therapeutic dose.[33] In this study, because patients had to meet a rigorous response criterion at specified visits in order to remain at a given dose level, dose titration to STS 12 mg/24 hours occurred at week 5 for a majority of patients in spite of the fact that a statistically significant mean difference between STS and placebo on the HAM-D_{28} and MADRS depression rating scales was evident at this time point. The fact that most patients had their dose titrated to 9 mg/24 hours or 12 mg/24 hours cannot be interpreted as evidence that these doses are necessarily more effective than 6 mg/24 hours because the "optimal" dose for any given patient in this study may have been obscured by the rapidity of the titration over the 8-week treatment period.

CONCLUSION

Previous studies demonstrated both short-term and long-term safety and efficacy of STS at a fixed daily dose of 6 mg/24 hours. Results of this randomized, double-blind, placebo-controlled, flexible-dose titration trial provide further evidence of the efficacy of STS administered within a therapeutic dose range of 6 mg/24 hours to 12 mg/24 hours. This 8-week study is the first to demonstrate the short-term efficacy, safety, and tolerability of STS at doses of up to 12 mg/24 hours. The evidence suggests that STS is a well-tolerated antidepressant with an improved margin of safety over oral MAOIs.

Drug names: bupropion (Wellbutrin and others), chlorpheniramine (Chlor-Trimeton and others), diphenhydramine (Benadryl and others), fexofenadine (Allegra and others), fluoxetine (Prozac and others), loratadine (Alavert, Claritin, and others), meperidine (Demerol and others), nortriptyline (Aventyl, Pamelor, and others), selegiline transdermal system (EMSAM), zolpidem (Ambien).

Financial disclosure: Dr. Feiger has received grant/research support from Bristol-Myers Squibb, Organon, and Wyeth; has been a paid consultant for Bristol-Myers Squibb, Hoffman-La Roche, and Organon; and has been on the speakers or advisory boards of Bristol-Myers Squibb. Dr. Rickels has received grant/research support (issued to the University of Pennsylvania) from AstraZeneca, Bristol-Myers Squibb, Cephalon, Fabre-Kramer, Merck, National Institute of Mental Health (NIMH), Pfizer, Predix, Somerset, and Wyeth and has received honoraria from, served as a consultant for, or been on advisory boards of Cephalon, DOV, Eli Lilly, MediciNova, Merck, Novartis, Pfizer, Pharmacia, Pherin, Predix, Sanofi-Synthelabo, and Wyeth. Dr. Rynn has received grant/research support from AstraZeneca, Eli Lilly, Forest, NIMH, Organon, Pfizer, and Wyeth; has been a consultant for AstraZeneca, Eli Lilly, Pfizer, Predix, and Wyeth; and has been on the speakers or advisory boards of Eli Lilly, Pfizer, and Wyeth. Dr. Zimbroff has received grant/research support from Bristol-Myers Squibb, Cephalon, Forest, GlaxoSmithKline, Indevus, Merck, Novartis, Organon, Pfizer, Sanofi-Synthelabo, and Solvay; has been a paid consultant for Bristol-Myers Squibb; and has been on the speakers boards for Bristol-Myers Squibb, Otsuka, and Pfizer. Dr. Robinson has been a consultant for Bristol-Myers Squibb, CeNeRx, Fabre-Kramer, Genaissance, Organon, Predix, Scirex, Somerset, Takeda, and ZARS.

REFERENCES

1. Greden JF. Unmet need: what justifies the search for a new antidepressant? J Clin Psychiatry 2002;63(suppl 2):3–7
2. Lin EH, Von Korff M, Katon W, et al. The role of the primary care physician in patients' adherence to antidepressant therapy. Med Care 1995;33:67–74
3. Clayton AH, Pradko JF, Croft HA, et al. Prevalence of sexual dysfunction among newer antidepressants. J Clin Psychiatry 2002;63:357–366
4. Thase ME, Trivedi MH, Rush AJ. MAOIs in the contemporary treatment of depression. Neuropsychopharmacology 1995;12:185–219
5. Robinson DS. Monoamine oxidase inhibitors: a new generation.

Psychopharmacol Bull 2002;36:124–138
6. Stahl SM. Basic psychopharmacology of antidepressants, pt 1: antidepressants have seven distinct mechanisms of action. J Clin Psychiatry 1998;59(suppl 4):5–14
7. Blackwell B, Marley E, Price J, et al. Hypertensive interactions between monoamine oxidase inhibitors and foodstuffs. Br J Psychiatry 1967;113:349–365
8. Brown C, Taniguchi G, Yip K. The monoamine oxidase inhibitor-tyramine interaction. J Clin Pharmacol 1989;29:529–532
9. Shulman KI, Walker SE, MacKenzie S, et al. Dietary restriction, tyramine, and the use of monoamine oxidase inhibitors. J Clin Psychopharmacol 1989;9:397–402
10. Gordon MN, Muller CD, Sherman KA, et al. Oral versus transdermal selegiline: antidepressant-like activity in rats. Pharmacol Biochem Behav 1999;63:501–506
11. Mawhinney M, Cole D, Azzaro AJ. Daily transdermal administration of selegiline to guinea-pigs preferentially inhibits monoamine oxidase activity in brain when compared with intestinal and hepatic tissues. J Pharm Pharmacol 2003;55:27–34
12. Wecker L, James S, Copeland N, et al. Transdermal selegiline: targeted effects on monoamine oxidases in the brain. Biol Psychiatry 2003;54:1099–1104
13. Bodkin JA, Amsterdam JD. Transdermal selegiline in major depression: a double-blind, placebo-controlled parallel-group study in outpatients. Am J Psychiatry 2002;159:1869–1875
14. Amsterdam JD. A double-blind, placebo-controlled trial of the safety and efficacy of selegiline transdermal system without dietary restrictions in patients with major depressive disorder. J Clin Psychiatry 2003;64:208–214
15. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
16. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
17. Montgomery SA, Asberg MC. A new depression rating scale designed to be sensitive to change. Br J Psychiatry 1979;134:382–389
18. Rush AJ, Giles DE, Schlesser MA, et al. The Inventory for Depressive Symptomatology (IDS): preliminary findings. Psychiatry Res 1986;18:65–87
19. Bagby RM, Ryder AG, Schuller DR, et al. The Hamilton Depression Rating Scale: has the gold standard become a lead weight? Am J Psychiatry 2004;161:2163–2177
20. Burke WJ. Selective versus multi-transmitter antidepressants: are two mechanisms better than one? J Clin Psychiatry 2004;65(suppl 4):37–45
21. Faries D, Herrera J, Rayamajhi J, et al. The responsiveness of the Hamilton Depression Rating Scale. J Psychiatr Res 2000;34:3–10
22. Entsuah R, Shaffer M, Zhang J. A critical examination of the sensitivity of unidimensional subscales derived from the Hamilton Depression Rating Scale to antidepressant drug effects. J Psychiatr Res 2002;36:437–448
23. Bech P, Gram LF, Dein E, et al. Quantitative rating of depressive states. Acta Psychiatr Scand 1975;51:161–170
24. Gibbons RD, Clark DC, Kupfer DJ. Exactly what does the Hamilton Depression Rating Scale measure? J Psychiatr Res 1993;27:259–273
25. Wade A, Michael Lemming O, Bang Hedegaard K. Escitalopram 10 mg/day is effective and well tolerated in a placebo-controlled study in depression in primary care. Int Clin Psychopharmacol 2002;17:95–102
26. Burke WJ, Gergel I, Bose A. Fixed-dose trial of the single isomer SSRI escitalopram in depressed outpatients. J Clin Psychiatry 2002;63:331–336
27. Lepola UM, Loft H, Reines EH. Escitalopram (10–20 mg/day) is effective and well tolerated in a placebo-controlled study in depression in primary care. Int Clin Psychopharmacol 2003;18:211–217
28. Hsu PH, Laddu AR. Analysis of adverse events in a dose titration study. J Clin Pharmacol 1994;34:136–141
29. Sood N, Treglia M, Obenchain RL, et al. Determinants of antidepressant treatment outcome. Am J Manag Care 2000;6:1327–1336
30. Khan A, Khan SR, Walens G, et al. Frequency of positive studies among fixed and flexible dose antidepressant clinical trials: an analysis of the Food and Drug Administration summary basis of approval reports. Neuropsychopharmacology 2003;28:552–557
31. Kirsh I, Moore TJ, Scoboria A, et al. The emperor's new drugs: an analysis of antidepressant medication data submitted to the U.S. Food and Drug Administration. Prevention & Treatment 2002;5:article 0023a. Available at: http://www.journals.apa.org/prevention/volume5/pre0050023a.html. Accessed Oct 19, 2005
32. Walsh BT, Seidman SN, Sysko R, et al. Placebo response in studies of major depression: variable, substantial, and growing. JAMA 2002;287:1840–1847
33. Sackeim HA. The definition and meaning of treatment-resistant depression. J Clin Psychiatry 2001;62(suppl 16):10–17

