A Double-Blind, Placebo-Controlled Trial of the Safety and Efficacy of Selegiline Transdermal System Without Dietary Restrictions in Patients With Major Depressive Disorder

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Background: The monoamine oxidase (MAO) inhibitor selegiline has demonstrated antidepressant efficacy superior to placebo. A selegiline transdermal system (STS) has been developed with unique pharmacokinetic and pharmacodynamic properties that allow inhibition of central nervous system MAO-A and MAO-B enzymes while substantially avoiding inhibition of intestinal and liver MAO-A enzyme. This novel transdermal system provides targeted MAO inhibition without clinically significant increases in sensitivity to dietary tyramine. We investigated the safety and efficacy of STS in patients with major depressive disorder.

Method: 365 outpatients 18 to 65 years old with a DSM-IV diagnosis of major depressive disorder were enrolled at 16 sites. A 17-item Hamilton Rating Scale for Depression (HAM-D-17) score of ≥ 20 was required for entry. Patients were randomly assigned to receive either STS, 20 mg/20 cm^2, daily or placebo patch for up to 8 weeks. A tyramine-restricted diet was neither required nor advised. Efficacy, safety, and vital sign measures were obtained regularly.

Results: 289 patients were randomly assigned to treatment and received at least 1 on-therapy evaluation (STS, N = 145; placebo, N = 144). Although the effect size was modest, at endpoint, STS was statistically superior to placebo on the MADRS (p = .001) and HAM-D-28 (p = .039) ratings and showed a nonsignificant superiority on the HAM-D-17 (p = .069) and Clinical Global Impressions-Severity ratings (p < .055). Side effect profiles were similar for STS and placebo with the exception of application-site reaction, which was observed in 31.5% of STS patients and 15.1% of placebo-treated patients (p = .001). No significant differences were observed in blood pressure measures between treatment groups.

Conclusion: Results from this double-blind, placebo-controlled clinical trial demonstrate that STS may have a modest, but statistically significant, antidepressant benefit compared with placebo and a similar safety profile compared with placebo in the absence of a tyramine-restricted diet.

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Antidepressant activity of monoamine oxidase inhibitors (MAOIs) was initially observed in the early 1950s.[1,2] By the early 1960s, MAOIs had become a mainstay of antidepressant therapy.[3] The emergence of the biogenic amine hypothesis of depression[4] and the ease of treating depression with an oral medication led to early enthusiasm for these compounds. However, reports of serious untoward events, such as acute hypertensive reactions following ingestion of certain foods and beverages,[5] contemporaneous with the introduction of the tricyclic antidepressants, led to a decline in the use of MAOIs.

Initially, there was widespread enthusiasm for the more recently introduced selective serotonin reuptake inhibitors as broad-based antidepressant medication. However, many clinicians are now reconsidering this view and are refocusing their attention on the clinical utility of MAOIs.[6] Several studies have demonstrated that MAOIs may be broad-spectrum antidepressants and are effective in treating patients with mixed depression and anxiety,[7,8] major depression with melancholic features,[9,10] major depression with "atypical" features,[11,12] and treatment-resistant depression.[13–15] However, despite recognition of the efficacy of MAOIs for the treatment of various types of major depression, the necessity of dietary restrictions remains a stumbling block to the widespread utility of these medications.

Recently, several placebo-controlled clinical trials have demonstrated antidepressant efficacy of selegiline ([R]-[–]-N, 2-dimethyl-N-2-propynylphenethylamine

HCl).[16–18] A selegiline transdermal patch has been developed with unique pharmacokinetic and pharmacodynamic properties that allow inhibition of central nervous system (CNS) MAO-A and MAO-B enzymes while substantially avoiding inhibition of intestinal mucosa and hepatic MAO-A enzyme.[19,20] Thus, the selegiline transdermal system (STS) provides a targeted inhibition of brain MAO-A and MAO-B enzyme activity without significantly increasing sensitivity to dietary tyramine, thus eliminating the need for a tyramine-restricted diet.[21,22]

The present report describes the safety and efficacy findings of STS, 20 mg /20 cm^2, in a multicenter, double-blind, placebo-controlled, 8-week clinical trial in outpatients with moderate-to-severe major depressive disorder.

METHOD

Patients

Three hundred sixty-five outpatients aged 18 to 65 years were screened at 16 investigative sites. All patients had a primary diagnosis of major depressive disorder, single or recurrent episode, as defined by DSM-IV criteria.[23] A score ≥ 20 on the Hamilton Rating Scale for Depression (HAM-D)[24] was required at intake; subjects showing a decrease ≥ 20% or a fall below a total score of 20 during the placebo run-in period were dropped from the trial to eliminate early placebo responders. Of the 365 patients, 301 were enrolled into double-blind treatment and 289 had at least 1 on-therapy evaluation. Diagnostic assessments were performed prior to enrollment in the study using a semistructured version of the Structured Clinical Interview for DSM-IV.[25] Patients with a primary DSM-IV Axis I or Axis II diagnosis other than major depressive disorder and patients with a history of manic or hypomanic episode or psychosis, or a history of substance abuse within 6 months were excluded from the trial.

All patients had a physical examination and laboratory evaluation including a complete blood count, blood chemistry profile, thyroid function tests, urinalysis, pregnancy test (in women of childbearing potential), and electrocardiogram (ECG).

The presence of a current medical illness with the potential to compromise subject safety or interfere with implementation of the protocol or interpretation of results was used as an exclusion criterion. Other exclusion criteria included the presence of any significant cardiac disease or conduction abnormalities, hypertension (diastolic blood pressure [BP] >95 mm Hg; systolic BP >160 mm Hg), thyroid disease of less than 6 months' stability, insulin-dependent diabetes mellitus, malignancy or chemotherapy within 2 years, allergy with dermal manifestation, laboratory indicators of hepatic or renal disease, or history within 2 years of head trauma, CNS surgery, or CNS disorder. Pregnant or breastfeeding women were not included; women of childbearing age were required to comply with a medically acceptable method of birth control. Patients were required to be free of any psychoactive medications, including herbal preparations with purported CNS activity, for 5 elimination half-lives or 2 weeks prior to study initiation, whichever was longer. Prior use of MAOIs was not allowed within 2 months of study onset.

Procedures

After receiving a complete description of the study, all patients provided signed informed consent before enrollment, in accordance with the ethical standards and guidelines of the respective Institutional Review Board at their study site.

Following a 1-week, single-blind placebo lead-in period, 301 patients were randomly assigned to receive STS, 20 mg/20 cm^2, (N = 149) or placebo patch (N = 152) daily for 8 weeks under double-blind conditions. Patches were applied to skin areas on the upper torso and extremities in a rotating fashion such that individual patch sites were alternated. Each patch was worn continuously for a 24-hour period. Removal during showering, bathing, and athletic activities was not necessary. Patients were instructed not to remove or change their patch on the day of study appointments, so that the occurrence and severity of any application-site reactions could be assessed. Medication compliance was documented at each visit by a count of returned patches. Examinations for treatment-emergent spontaneous patient-reported and physician-elicited adverse events, efficacy, vital signs, and body weight were conducted at study visits for screening enrollment, baseline randomization, and treatment weeks 1, 2, 3, 4, 6, and 8.

Patients were *not* required or specifically instructed to follow a tyramine-restricted diet. They were, however, not allowed to take "over-the-counter" (OTC) nonprescription cold preparations, narcotic or non-narcotic analgesics, antihypertensives, antihistamines, sedatives, tranquilizers, tryptophan, melatonin, other proprietary pharmaceutical or herbal (e.g., St. John's wort) antidepressants, or any prescription medication without first consulting the study physician.

To monitor patients for possible acute, dietary-induced hypertensive reactions, investigators instructed patients to promptly report the sudden onset of headache or other unusual symptoms such as palpitations, tachycardia, a sense of constriction in the throat or chest, sweating, dizziness, neck stiffness, nausea, or vomiting.

Assessments

Efficacy was assessed using the total Montgomery-Asberg Depression Rating Scale (MADRS),[26] HAM-D-28, and HAM-D-17 scores. Other outcome measures included the Clinical Global Impressions-Severity of

Illness (CGI-S) and CGI-Change (CGI-C)[27] scores, the change in distribution of HAM-D item 1 ("depressed mood"), the change in distribution of HAM-D item 3 ("suicide"), and the percentage of patients with a ≥ 50% reduction in baseline HAM-D-28 and HAM-D-17 scores.

Supine and standing systolic and diastolic BP and pulse rate measurements were obtained at each study visit using a manual sphygmomanometer. Measurements were obtained with the patient in the supine position after approximately 15 minutes of rest and repeated after the patient stood quietly for 1 and for 3 minutes. All measurements were obtained as part of routine clinical monitoring, and no intersite reliability or validity measurements were obtained. Oral temperature and body weight were also measured at each study visit.

Adverse events were assessed at each study visit and summarized using COSTART body systems and COSTART preferred terms within each treatment group. Any untoward, unexpected, or intercurrent event was recorded without attribution to causal relationship. Particular attention was paid to the number, nature, and severity of patch application-site reactions. Treatment-emergent changes in laboratory measurements (including hematology, blood chemistry, urinalysis, and ECG) were determined, as were any changes in findings of physical examination or vital signs.

The Medex Depression Evaluation Scale (MED-D; unpublished; available from the author on request), a patient self-assessment scale, was used to assess sexual function during treatment. Specific symptoms assessed were (1) decreased sexual interest, (2) sexual arousal problems, (3) problems maintaining interest in sex, (4) problems achieving orgasm, and (5) diminished sexual satisfaction. At baseline and week 8, patients were asked to assess their feelings and activities over the preceding 7- to 10-day period using a 6-point scale ranging from 1 (not at all) to 5 (severe) or 6 (not applicable).

Concomitant Medications

The following medications were not permitted during the study: other psychotropic medications, centrally active anticholinergics, anticonvulsants, antiparkinsonian agents, nootropics, vasodilators, reserpine, sedatives, sympathomimetic drugs (i.e., amphetamines, epinephrine, OTC nasal decongestants, appetite suppressants), L-tyrosine, L-tryptophan, metoclopramide, ergot preparations, meperidine, opiates, dextromethorphan, serotonin receptor agonists or antagonists (i.e., sumatriptan, zolmitriptan, cyproheptadine, methysergide), St. John's wort, yohimbine, or *Ginkgo biloba*.

Chloral hydrate, 500 to 1000 mg, or zolpidem, 5 to 20 mg, at bedtime was permitted up to twice weekly for insomnia, but not the night before a study visit. Loratadine, 10 mg/day, was permitted for treatment of cold symptoms or allergies.

Statistical Analyses

A sample size of 250 (125 per group) was calculated to provide an 80% power to detect a treatment group difference of 2.5 points in mean total HAM-D-17 scores by week 8 of treatment. The determination of drug efficacy was assessed by change in total MADRS, HAM-D-28, and HAM-D-17 scores from baseline to week 8 (or endpoint) of treatment. Efficacy analyses were performed on intent-to-treat data using a last-observation-carried-forward analysis on patients who received double-blind therapy and had at least 1 on-therapy evaluation. Continuous data for the MADRS, total HAM-D-28, and total HAM-D-17 scores were analyzed using a 2-way analysis of variance (ANOVA). If a statistically significant difference was found between the 2 treatment groups for a baseline variable ($p \leq .10$), the variable was incorporated into the efficacy analysis as a covariate. Qualitative data were analyzed using the Cochran-Mantel-Haenszel procedure.

Total scores obtained at baseline from the MADRS, HAM-D-28, and HAM-D-17 were summarized as means per treatment group, and changes from baseline were analyzed using a 2-way ANOVA that accounted for study site and treatment group. Pretreatment HAM-D item 1, HAM-D item 3, and CGI-S scores were summarized using frequency distributions and analyzed with a center stratified Cochran-Mantel-Haenszel sum test using mean rank scores.

Safety analyses included all patients who received at least 1 dose of study drug. The Fisher exact test was used to detect differences between treatment groups in the proportion of patients with each adverse event. Changes in physical examination, ECG results, BP, and pulse rate were assessed using a general linear model that considered study site and treatment group. Clinical laboratory results were summarized using descriptive statistics.

Results were considered statistically significant when the appropriately calculated 2-sided p value was ≤ .05. Statistical analyses were performed using SAS, Version 6.12, software (SAS Institute Inc., Cary, N.C.).

RESULTS

Demographics

No statistically significant differences between study groups in baseline clinical or demographic characteristics were noted (Table 1). Patients were predominantly white women diagnosed with recurrent major depressive disorder. Compliance with study medication use was > 98% in both treatment groups. Forty-one patients from each group discontinued from the study; the majority were lost to follow-up (STS, 18; placebo, 10) or discontinued due to an adverse event (STS, 10; placebo, 8), including application-site reactions, depression, agitation, sinusitis, and headache.

Table 1. Demographics and Patient Characteristics, All Randomized Patients

Characteristic	Selegiline (N = 149)	Placebo (N = 152)	p Value[a]
Age, y			
Mean ± SD	41.2 ± 11.6	43.5 ± 10.0	.073
Range	19–64	19–65	
Sex, N (%)			
Women	94 (63.1)	99 (65.1)	.664
Men	55 (36.9)	53 (34.9)	
Race, N (%)			
White	114 (76.5)	134 (88.2)	.326
Black	20 (13.4)	8 (5.3)	
Hispanic	13 (8.7)	8 (5.3)	
Asian	1 (0.7)	1 (0.7)	
Other	1 (0.7)	1 (0.7)	
Weight, kg			
Mean ± SD	81.8 ± 21.9	84.7 ± 27.2	.277
Range	43.3–181.4	46.3–223.8	
Major depressive episode type, N (%)			
Single	32 (36.0)	26 (29.6)	.288
Recurrent	57 (64.0)	62 (70.5)	
HAM-D-17 baseline score			
Mean ± SD	22.8 ± 3.0	22.9 ± 3.0	.604
Range	16.0–34.0	17.0–32.0	

[a]Reflects between–treatment group comparisons.
Abbreviation: HAM-D-17 = 17-item Hamilton Rating Scale for Depression.

Table 2. Comparison of Baseline and Week 8 Values in Efficacy Parameters (ITT efficacy population, LOCF analysis)

Assessment	Selegiline (N = 145)	Placebo (N = 144)	p Value[a]
MADRS score, mean ± SD			
Baseline	28.26 ± 6.14	28.47 ± 6.02	.741
Week 1	24.09 ± 8.07	24.57 ± 8.17	.827
Week 2	21.66 ± 8.80	22.55 ± 8.74	.312
Week 4	19.37 ± 9.35	21.68 ± 8.86	.024
Week 6	19.22 ± 9.67	21.61 ± 8.91	.027
Week 8	18.05 ± 10.06	21.75 ± 9.93	.001
Response at week 8 (≥ 50% reduction in MADRS total score), N (%)	48 (33.1)	30 (20.8)	.031
HAM-D-28 score, mean ± SD			
Baseline	28.95 ± 4.45	29.79 ± 5.00	.120
Week 1	23.59 ± 7.35	24.48 ± 7.38	.840
Week 2	21.85 ± 7.99	22.35 ± 8.17	.951
Week 4	20.19 ± 8.72	21.45 ± 8.52	.425
Week 6	19.51 ± 8.85	21.15 ± 8.46	.237
Week 8	18.67 ± 9.41	21.26 ± 9.37	.039
HAM-D-17 score, mean ± SD			
Baseline	22.79 ± 2.92	22.99 ± 3.04	.604
Week 1	18.46 ± 4.93	19.00 ± 5.34	.544
Week 2	17.05 ± 5.67	17.31 ± 6.32	.742
Week 4	15.77 ± 6.60	16.56 ± 6.32	.356
Week 6	15.23 ± 6.87	16.25 ± 6.47	.247
Week 8	14.71 ± 7.29	16.32 ± 7.15	.069
HAM-D item 1 (depressed mood), N (%)			
Score "0" at baseline	0 (0.0)	1 (0.7)	.215
Score "0" at endpoint	26 (17.9)	14 (9.7)	.062
HAM-D item 3 (suicide), N (%)			
Score "0" at baseline	53 (36.6)	44 (30.6)	.174
Score "0" at endpoint	99 (68.3)	88 (61.1)	.021

[a]Reflects between–treatment group comparisons.
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, ITT = intent to treat, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale.

Efficacy

At baseline, there was no significant difference between treatment groups in mean total MADRS, total HAM-D-28, total HAM-D-17, HAM-D item 1, or HAM-D item 3 scores (Table 2). Additionally, no significant differences were noted in CGI-C or CGI-S distributions (Table 3).

STS was superior to placebo on the MADRS at week 4 ($p = .024$), week 6 ($p = .027$), and week 8 ($p = .001$) of treatment and at week 8 of treatment on the HAM-D-28 ($p = .039$). STS did not demonstrate statistical superiority over placebo on the HAM-D-17 at any timepoint examined (Table 2).

The percentage of patients with a final HAM-D item 3 score of "0" (absent) in the STS treatment group was significantly greater than in the placebo treatment group ($p = .021$); a non-significant trend ($p < .07$) favoring STS treatment in attainment of a final HAM-D item 1 score of "0" (depressed mood absent) was also observed (Table 2). Similarly, the percentage of patients with a CGI-S classification of "normal, not at all ill" at 8 weeks was higher among STS-treated patients versus placebo-treated patients, demonstrating a trend toward significance ($p = .005$; Table 3).

The percentage of patients experiencing ≥ 50% reduction in baseline MADRS scores was significantly greater among STS-treated patients (Table 2). Although a higher percentage of STS-treated patients achieved a ≥ 50% reduction in baseline total HAM-D-28 (STS, 32.4%; placebo, 29.2%; $p = .589$) and HAM-D-17 (STS, 32.4%; placebo, 27.8%; $p = .471$) scores, these differences did not achieve statistical significance.

Safety

In general, the STS and placebo treatment conditions were well tolerated. Table 4 displays reported side effects in both treatment groups that occurred with a frequency ≥ 3%. Ten STS-treated patients (6.7%) and 8 placebo-treated patients (5.3%) discontinued treatment due to adverse events.

The only significant difference between the groups in adverse event reporting was observed in the frequency of patch application-site reactions, which were described as rash, itching, erythema, redness, irritation, swelling, or urticarial lesion. More STS-treated patients (31.5%) than placebo-treated patients (15.1%) ($p = .001$) experienced application-site reactions. The severity of skin reactions was generally judged as "mild" or "moderate" and related to patch application. Five STS-treated patients and no

Table 3. Comparison of Baseline and Week 8 Values in CGI Parameters (ITT efficacy population, LOCF analysis)[a]

Assessment	Selegiline (N = 145)	Placebo (N = 144)	p Value[b]
CGI-S			
Baseline rating			.225
Mildly ill	5 (3.4)	5 (3.5)	
Moderately ill	111 (76.6)	101 (70.1)	
Markedly ill	29 (20.0)	37 (25.7)	
Severely ill	0 (0.0)	1 (0.7)	
Rating at week 8			.055
Normal, not at all ill	12 (8.3)	5 (3.5)	
Borderline ill	26 (17.9)	23 (16.0)	
Mildly ill	37 (25.5)	26 (18.1)	
Moderately ill	55 (37.9)	66 (45.8)	
Markedly ill	14 (9.7)	24 (16.7)	
Severely ill	1 (0.7)	0 (0.0)	
CGI-C rating at week 8			.157
Very much improved	22 (15.2)	13 (9.0	
Much improved	40 (27.6)	33 (22.9)	
Minimally improved	41 (28.3)	40 (27.8)	
Unchanged	35 (24.1)	45 (31.3)	
Minimally worse	6 (4.1)	11 (7.6)	
Much worse	1 (0.7)	2 (1.4)	

[a]All values shown as N (%).
[b]Reflects between–treatment group comparisons.
Abbreviations: CGI-C = Clinical Global Impressions-Change, CGI-S = Clinical Global Impressions-Severity of Illness, ITT = intent to treat, LOCF = last observation carried forward.

Table 4. Adverse Experiences Reported by ≥ 3% of Patients During Double-Blind Treatment Periods (safety population)[a]

Body System and COSTART Term	Selegiline (N = 149)	Placebo (N = 152)	p Value[b]
Any adverse event	93 (62.4)	76 (50.0)	.037
Body as a whole	25 (16.8)	34 (22.4)	.247
Asthenia	5 (3.4)	5 (3.3)	1.000
Headache	17 (11.4)	19 (12.5)	.860
Pain, abdominal	1 (0.7)	6 (4.0)	.121
Cardiovascular	6 (4.0)	4 (2.6)	.539
Digestive	19 (12.8)	20 (13.2)	1.000
Diarrhea	8 (5.4)	9 (5.9)	1.000
Dyspepsia	2 (1.3)	5 (3.3)	.448
Nausea	6 (4.0)	6 (4.0)	1.000
Metabolic and nutritional	5 (3.4)	6 (4.0)	1.000
Nervous	29 (19.5)	34 (22.4)	.573
Anxiety	1 (0.7)	7 (4.6)	.067
Dizziness	6 (4.0)	4 (2.6)	.539
Dry mouth	8 (5.4)	8 (5.3)	1.000
Insomnia	11 (7.4)	6 (4.0)	.221
Somnolence	3 (2.0)	5 (3.3)	.723
Respiratory	5 (3.4)	4 (2.6)	.748
Skin	56 (37.6)	26 (17.1)	< .001
Application-site reaction	47 (31.5)	23 (15.1)	.001
Rash	5 (3.4)	1 (0.7)	.118
Special sense	9 (6.0)	6 (4.0)	.439
Urogenital	3 (2.0)	5 (3.3)	.723

[a]All values shown as N (%).
[b]Reflects between–treatment group comparisons.

patients in the placebo group discontinued treatment because of an application-site reaction.

The incidence of cardiovascular side effects was ≤ 4% in both treatment groups. STS-treated patients had a slightly smaller mean *decrease* in systolic BP (–0.5 ± 10.7 mm Hg) compared with placebo-treated patients (–0.8 ± 11.7 mm Hg) (p = .9684) and a smaller mean *decrease* in diastolic BP (–0.5 ± 7.7 mm Hg vs. –1.0 ± 7.5 mm Hg, respectively) (p = .1196). None of these changes was considered clinically meaningful.

ECG measures were similar between treatment groups. Reported frequencies of headaches, dizziness, lightheadedness, and other symptoms suggestive of hypertension or hypotension were similar in both treatment groups, and no acute hypertensive episodes were reported or observed.

Sexual Side Effects

Patient-rated sexual symptoms were similar in the STS-treated and placebo-treated patients at endpoint (week 8). In addition, no changes from baseline ratings were obtained for the STS or placebo groups (p = .559). Similar results were obtained when the data were analyzed by gender.

DISCUSSION

The present randomized, double-blind, placebo-controlled study has demonstrated a modest but statistically significant benefit of STS, 20 mg/20 cm^2, compared with placebo as measured by MADRS at weeks 4, 6, and 8 of treatment and by the HAM-D-28 rating at week 8 in outpatients with major depressive disorder (Table 2). Moreover, the safety profile of STS was statistically indistinguishable from that of placebo, with the exception of application-site reactions, which occurred more frequently in the STS-treated patients (Table 4). Despite the lack of a tyramine-restricted diet, no clinically significant differences in cardiac measures, systolic or diastolic BP, heart rate, or ECG parameters were noted between treatment groups, and no clinical symptoms were noted that were believed to be related to dietary tyramine–induced hypertensive episodes.

These data support findings from a previous study in 177 depressed patients treated with STS, 20 mg/20 cm^2, (N = 89) or placebo (N = 88) for 6 weeks.[28] However, in contrast to the present study, the previous 6-site, double-blind trial (which included the use of a tyramine-restricted diet) demonstrated statistically significant superiority of STS over placebo on the MADRS, HAM-D-28, HAM-D-17, and CGI scales as early as 1 to 2 weeks of treatment. Moreover, that study showed a higher percentage of STS-treated patients with moderate-to-marked improvement or remission of depression compared with placebo. Despite these differences in efficacy, both trials demonstrated no significant differences in side effect profiles between STS and placebo with the exception of a higher percentage of application-site reactions with STS. Moreover, when reported adverse events were compared between the present study (without tyramine restrictions)

and the previous study (with tyramine restrictions),[29] there were no significant differences observed in cardiovascular or hemodynamic side effects.

Irreversible nonselective MAOIs, such as tranylcypromine and phenelzine, have established efficacy in the treatment of major depression with melancholic features,[9,10] major depression with atypical features,[11,12] dysthymic disorder,[30] bipolar major depression,[31] psychotic depression,[32] mixed anxiety and depression,[7,8] and refractory depression.[13,14] However, these agents are infrequently used because of concerns over safety issues involving acute hypertensive reactions following the ingestion of dietary tyramine or OTC sympathomimetic decongestants.[33,34] Despite this potential safety issue, the American Psychiatric Association and the British Association for Psychopharmacology, in their practice guidelines,[35,36] have recently reversed their opinions regarding MAOIs and have recommended the use of these agents, with dietary restrictions, for patients with major depressive disorder with atypical features and for some patients who have failed other antidepressant medication trials.

The fear of dietary hypertensive events in patients treated with traditional MAOIs has led clinical researchers to study the effectiveness of newer agents with selective properties for MAO-A or MAO-B inhibition in humans. These studies have suggested the requirement for MAO-A inhibition in the CNS for full antidepressant activity.[37] However, safety research in this area has shown that inhibition of MAO-A activity in peripheral structures such as gastric mucosa, liver, and sympathetic neurons also plays the central role in the expression of acute hypertension following the ingestion of dietary tyramine.[38]

Selegiline HCl is a selective MAO-B inhibitor currently approved, without dietary restrictions, at oral doses of 10 mg/day as an adjunct to levodopa in the management of late-stage Parkinson's disease. Selegiline HCl also has been shown to have antidepressant efficacy at oral doses of 30 to 60 mg/day.[16–18] However, these doses result in progressive inhibition of peripheral MAO-A activity and associated increases in cardiovascular sensitivity to tyramine, necessitating dietary restriction.[39] Accordingly, STS has been developed with a pharmacokinetic and pharmacodynamic profile distinct from that of oral selegiline. The unique pharmacologic profile of STS allows for targeted inhibition of CNS MAO-A and MAO-B while substantially avoiding inhibition of intestinal mucosa and liver MAO-A.[19,20] This CNS-weighted inhibition prevents the gastric absorption of dietary tyramine yet provides sufficient CNS MAO-A inhibition to achieve antidepressant effects. This is accomplished with STS by avoiding the extensive first-pass metabolism observed with oral selegiline in order to achieve antidepressant concentrations of selegiline in the CNS. In this regard, clinical studies in human volunteers have demonstrated a 74% bioavailability of selegiline with STS as compared with 4% with the oral formulation.[40] At the same time, STS reduces the exposure of the intestinal mucosa to the high-dose levels of orally administered selegiline that are required to produce antidepressant effects.

Several caveats should be considered in the interpretation of the present results. One methodological limitation of the present study was the use of a fixed-dose 20-mg/20-cm^2 STS patch. It is possible that a larger STS daily dosage may have resulted in a greater overall effect size compared with placebo. Although this study was not powered to detect a significant drug-placebo difference before 8 weeks using the HAM-D, there was a statistically superior benefit over placebo as early as week 4 on the MADRS. Moreover, an earlier controlled antidepressant trial conducted with STS, 20 mg/20 cm^2, demonstrated superiority over placebo as early as the first week of treatment.[29]

Finally, concerns might reasonably be raised regarding the presence of antidepressant-induced sexual side effects.[41] In the present study, STS-treated patient self-report MED-D ratings demonstrated no deterioration in sexual function at 8 weeks compared with ratings of patients using placebo. However, to fully appreciate the effect of STS on sexual function, longer duration STS treatment studies will be necessary.

In summary, STS showed a modest, but statistically significant, benefit over placebo at weeks 4 through 8 of treatment as measured by the change in total MADRS ratings and by week 8 of treatment as measured by the change in total HAM-D-28 scores in patients with major depression. In addition, STS showed a higher percentage of patients with a CGI-S classification of "normal, not at all ill" rating at week 8 compared with placebo—a difference that approached statistical significance ($p = .055$). The safety profile of STS was statistically indistinguishable from placebo, with the exception of application-site reactions. No clinically significant differences in cardiac parameters or BP with STS compared with placebo were noted despite the lack of dietary tyramine restrictions.

CONCLUSION

STS is an MAOI antidepressant with a unique pharmacologic profile that results in targeted, irreversible brain MAO-A and MAO-B inhibition without requiring a tyramine-restricted diet. The present multicenter, double-blind, placebo-controlled study extends earlier findings of antidepressant efficacy with STS and demonstrates that STS is effective and well tolerated, without the need for dietary restrictions, in patients with major depressive disorder.

Drug names: cyproheptadine (Periactin and others), loratadine (Claritin), meperidine (Demerol and others), methysergide (Sansert), metoclopramide (Reglan and others), phenelzine (Nardil), reserpine (Serpalan and others), selegiline (Eldepryl and others), sumatriptan (Imitrex), tranylcypromine (Parnate), zolmitriptan (Zomig), zolpidem (Ambien).

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