Symptoms of Sexual Dysfunction in Patients Treated for Major Depressive Disorder: A Meta-Analysis Comparing Selegiline Transdermal System and Placebo Using a Patient-Rated Scale

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Objective: Spontaneous reports of sexual side effects were infrequent during placebo-controlled clinical trials of selegiline transdermal system (STS). The objective of this study was to examine the impact of STS 6 mg/24 hours on various domains of sexual function in patients with major depressive disorder (MDD), using a patient-rated questionnaire.

Method: Data from 4 short-term (6 to 8 weeks), randomized, double-blind, placebo-controlled trials of STS in patients with MDD (DSM-IV criteria) were included in the meta-analysis (STS, N = 389; placebo, N = 400). The Medex Sexual Dysfunction Subscale was used to assess sexual interest, arousal, maintenance of interest, orgasm, and satisfaction. Estimates of the average effect of study drug on each item of sexual function and 95% confidence intervals were calculated using a fixed-effects model due to homogeneity of study means. The direct effect of STS versus placebo was estimated using multivariate regression models, with baseline item score as a covariate and controlling for improvement in depression. Analyses were performed on the total population and by gender. Data were collected between January 1997 and April 2000.

Results: Estimates of difference between STS and placebo demonstrated a nonsignificant trend toward a positive treatment effect of STS on most sexual function items and significant improvement in sexual satisfaction. For women, there was a significant positive effect on interest, maintaining interest during sex, and satisfaction. The direct effect of STS on changes in individual item scores was minimal in men and showed a trend for improvement in women.

Conclusion: This meta-analysis suggests that short-term therapy with STS 6 mg/24 hours does not impair any aspect of sexual function in MDD patients as measured using a patient-rated questionnaire.

(J Clin Psychiatry 2007;68:1860–1866)

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The data in this article were derived from research studies sponsored and funded by Somerset Pharmaceuticals, Inc. Funding for assistance with manuscript editing by IneXel Medical Strategy & Communications was provided by Bristol-Myers Squibb.

Financial disclosure appears at the end of this article.

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The effectiveness of an antidepressant is determined by both its efficacy and tolerability. As a result, current guidelines for the treatment of major depressive disorder (MDD) include the recommendation that patient acceptability and side effects be considered as important factors in the selection of initial antidepressant therapy.[1] In a recent study, psychiatrists acknowledged that the wish to avoid a specific side effect influenced their choice of which antidepressant to prescribe nearly 50% of the time, with sexual dysfunction cited as the side effect of greatest concern.[2] When patients with MDD were surveyed, 97% maintained that sexual functioning was at least somewhat important to their quality of life: 27% considered it extremely important, 35% very important, 24% important, and 12% somewhat important.[3]

Unfortunately, sexual dysfunction is now recognized as a frequent side effect of many currently available antidepressants. In contrast to the relatively low incidence of spontaneously reported sexual side effects (i.e., < 15%) described in the product labeling, recent studies of anti-

depressant-associated sexual side effects using patient-completed or clinician-administered questionnaires have found rates ranging from 22% to 73%.[3–5] In particular, serotonin reuptake inhibitors (SRIs) produce higher rates of sexual dysfunction compared with agents in other antidepressant drug classes (e.g., bupropion, mirtazapine, and nefazodone).[3–5] Moreover, even when patients do not experience clinically significant global impairment in sexual function (as reflected by the total score on a standard questionnaire), dysfunction limited to 1 or more phases of the sexual response cycle is exceedingly common.[6] Clayton et al.[6] found that impairment in at least 1 phase of sexual functioning was experienced by 98% of men and 96% of women receiving SRI monotherapy who did not meet criteria for global impairment.

Given the importance of sexual functioning to overall quality of life and the frequency with which sexual dysfunction occurs during antidepressant treatment, it is not surprising that this side effect often leads to treatment discontinuation.[7] In a survey of patients newly treated with SRIs, those experiencing 1 or more side effects during the first 3 months of treatment rated sexual dysfunction as the most bothersome.[8] Similarly, Montejo et al.[5] used a questionnaire to examine the incidence and tolerability of antidepressant-related sexual dysfunction in 1022 outpatients. Thirty-eight percent of patients with sexual dysfunction deemed this side effect intolerable, leading the patients to contemplate discontinuing the treatment. Considering the importance of adherence to prescribed medication during all 3 phases of MDD treatment (acute, continuation, and maintenance) in reducing the risk of relapse,[9–11] additional antidepressant options with more favorable sexual side effect profiles are needed to diminish the likelihood of premature treatment discontinuation.

Selegiline transdermal system (STS) is a dermally administered monoamine oxidase inhibitor (MAOI) that has been approved recently by the U.S. Food and Drug Administration for the treatment of MDD. Placebo-controlled trials have demonstrated the efficacy, safety, and tolerability of STS for acute (6 mg/24 hours to 12 mg/24 hours)[12–14] and continuation (6 mg/24 hours)[15] treatment. In these trials, the incidence of spontaneously reported sexual side effects in STS-treated patients was low and similar to that reported during placebo treatment.[12–16] However, evaluation of sexual dysfunction by spontaneous report could underestimate the actual incidence due to patient or physician reluctance to broach the subject.[17,18] Direct patient questioning (using a clinician-administered or patient-completed questionnaire) is a more reliable method to ascertain changes in sexual function during clinical trials.[5,19–21] The objective of this post hoc analysis was to examine the impact of STS 6 mg/24 hours on aspects of sexual function in male and female patients with MDD, using a patient-rated scale.

METHOD

Study Design

Data from 4 short-term (one 6-week, three 8-week), randomized, double-blind, placebo-controlled trials conducted during clinical development of STS for MDD were used for this meta-analysis. All 4 trials employed fixed doses of STS 6 mg/24 hours. One trial also included a dosing arm of STS 3 mg/24 hours; however, since this dose is below the recommended therapeutic dose, it was excluded from the analysis. Two of these trials (E106 and P9804) have been reported previously.[12,13] The study designs for the other 2 trials (E113 and E114) were similar to study P9804.[13] Patients received a complete description of the study and provided written informed consent prior to study enrollment. Study protocols were approved by the institutional review board at each participating study site. Data were collected between January 1997 and April 2000.

Patients

Men and women, 18 to 65 years old, were included in the studies. Patients were required to meet DSM-IV criteria for MDD, single episode or recurrent episode, with a minimum baseline score of 20 or higher on the 17-item Hamilton Rating Scale for Depression ($HAM\text{-}D_{17}$).[22]

Pregnant and lactating women were excluded from the studies; all women of childbearing potential were required to have a negative pregnancy test and agree to use a medically acceptable method of birth control during study treatment. Patients were prohibited from concomitant use of psychoactive medications that might interfere with efficacy assessments or medications that might interact with selegiline (e.g., antidepressants, antipsychotics, mood stabilizers, stimulants, dextromethorphan, meperidine, and other opioids). Patients were to have been free of these medications for at least 5 half-lives or 2 weeks (whichever was longer) prior to the first dose of study medication. With the exception of study E106, patients were not advised to follow a tyramine-restricted diet.

Assessments

Efficacy. Efficacy scales included the 28-item Hamilton Rating Scale for Depression ($HAM\text{-}D_{28}$),[22,23] the Montgomery-Asberg Depression Rating Scale (MADRS),[24] and the Clinical Global Impressions-Severity of Illness and -Improvement scales.[25]

Sexual function. The Medex Depression Evaluation Scale (MED-D), created for the STS clinical development program, is a 12-item, self-report instrument measuring depressive symptoms, somatic symptoms, and sexual dysfunction (data on file; Somerset Pharmaceuticals, Inc., Tampa, Fla.). The MED-D sexual dysfunction subscale (MED-D-SD) used for this analysis was designed to assess dysfunction in the sexual response cycle (e.g., desire, arousal, and orgasm)[26] and satisfaction. Specifically, the

Table 1. Medex Depression Evaluation Scale 5-Item Subscale for Sexual Dysfunction

Please grade all items below as they describe your feelings and activities during the past week: 1 = not at all 2 = barely 3 = mild 4 = moderate 5 = severe
1. Experiencing a decreased interest in sex?
2. Having problems getting aroused during sex?
3. Having problems maintaining interest during sex?
4. Having problems achieving climax?
5. Having problems deriving satisfaction from sexual activity?

MED-D-SD consists of 5 questions evaluating problems with interest in sex, arousal during sex, maintenance of interest during sex, achieving climax, and satisfaction with sexual activity (Table 1). Each item was rated, from 1 (not at all) to 5 (severe) or 6 (not applicable [N/A]). Ratings of 6 were not included in total or change scores. Higher scores reflect poorer sexual functioning. Patients completed the questionnaire at baseline and at the last study visit.

Statistical Methods

Analyses were performed on pooled data from 4 randomized, placebo-controlled studies of STS. Patients who had baseline and last-visit scores for at least 1 MED-D-SD item were included in the analysis.

Each item was analyzed separately. Inclusion in an individual item analysis was dependent upon availability of baseline and endpoint MED-D-SD data. A patient could be included in one item analysis but excluded in another due to missing data or an N/A rating. This approach was taken to maximize the number of patients available for each individual item analysis.

For the computation of pooled effects, each study was assigned a weight consisting of the reciprocal of its variance. The variance for each study was calculated separately by computing the standard deviation of the differences between paired observations for the change in STS and placebo treatment arms; the standard error of the differences was then calculated. A χ^2 test was used to test homogeneity among studies and no significant interstudy variation was found.

The estimate of the principal effect was defined as the mean difference between the change in score for patients receiving STS (last visit value minus baseline value) and the change in score for patients receiving placebo (last visit value minus baseline value). This difference equals the net change. Estimates of the average effect of the study drug on each item of sexual function and 95% confidence intervals (CIs) were calculated using a fixed-effects model due to homogeneity of study means.[27] Data were also analyzed separately for male and female patients using the same model.

Treatment might influence sexual function by (1) acting as a mediator, whereby improvement in depressive symptoms in turn produces changes in sexual function, or (2) exerting a direct effect upon sexual function. Multivariate regression of the change in sexual function on trial indicator, treatment, baseline sexual function, and the change in MADRS (the causal intermediate) was used to estimate the direct effect of STS on each MED-D-SD item, by gender. The bootstrapping method[28] was used to calculate the 95% CI. Treatment effect was considered significant if the upper limit of the 95% CI was less than zero. Statistical corrections for multiple comparisons were not considered in this exploratory analysis.

The differences between baseline and last-visit MADRS scores for the 2 treatment groups were compared using the t test. A p value < .05 is considered to be statistically significant.

Table 2. Medex Depression Evaluation Scale Sexual Dysfunction Subscale Individual Item Baseline Scores, by Gender

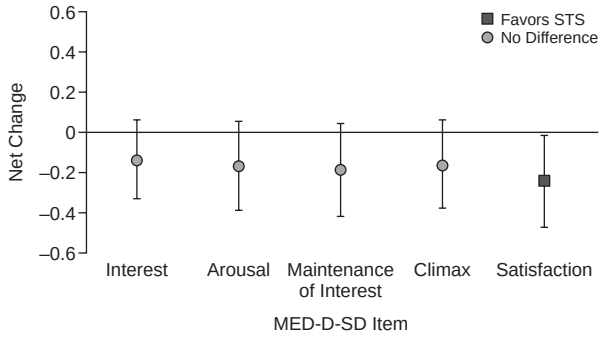
Item	STS (N = 389), Mean Score (SD)	Placebo (N = 400), Mean Score (SD)
1. Interest		
Women	3.6 (1.38)	3.6 (1.42)
Men	2.8 (1.41)	2.9 (1.43)
2. Arousal		
Women	3.4 (1.49)	3.4 (1.45)
Men	2.3 (1.40)	2.5 (1.45)
3. Maintenance of interest		
Women	3.3 (1.50)	3.4 (1.44)
Men	2.3 (1.41)	2.5 (1.56)
4. Climax		
Women	3.4 (1.55)	3.4 (1.50)
Men	2.2 (1.37)	2.2 (1.34)
5. Satisfaction		
Women	3.4 (1.48)	3.3 (1.45)
Men	2.5 (1.38)	2.5 (1.37)

Abbreviation: STS = selegiline transdermal system.

RESULTS

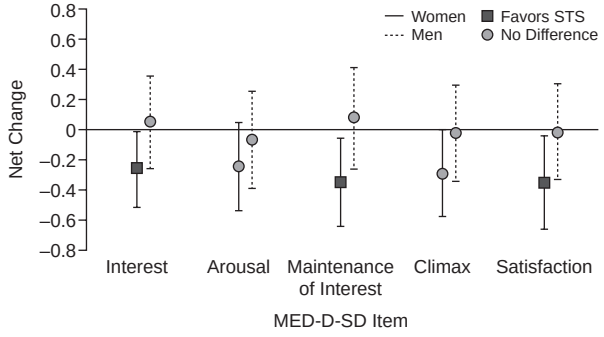
A total of 789 patients (STS, N = 389; placebo, N = 400) were included in these analyses. For item 1 of the MED-D-SD, 772 patients were included (STS, N = 384; placebo, N = 388). Item 2 analyses included 532 patients (STS, N = 265; placebo, N = 267); item 3 included 529 patients (STS, N = 262; placebo, N = 267); item 4 included 530 patients (STS, N = 267; placebo, N = 263); and item 5 included 536 patients (STS, N = 269; placebo, N = 267). In the total population, the STS and placebo groups were similar with respect to demographic and clinical characteristics. Mean patient age was 42 years, and a majority of patients were female (62%). Of the 420 patients for whom baseline data on episode were available, 53% had recurrent depression. Baseline MED-D-SD scores by gender (Table 2) did not differ significantly between treatment arms (STS vs. placebo). However, women tended to have higher baseline scores for each item compared with men.

Figure 1. Estimates of Net Change Between Selegiline Transdermal System (STS) and Placebo (± 95% CI)



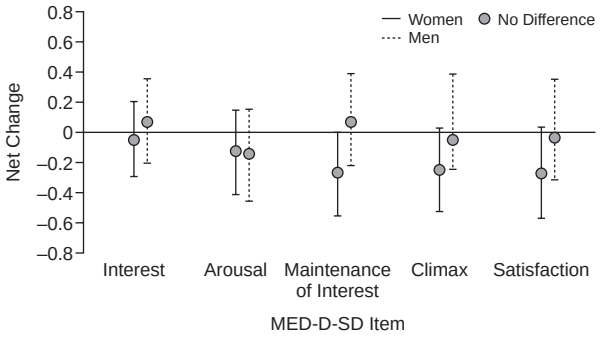
Abbreviation: MED-D-SD = Medex Depression Evaluation Scale sexual dysfunction subscale.

Figure 2. Estimates of Net Change Between Selegiline Transdermal System (STS) and Placebo, by Gender (± 95% CI)



Abbreviation: MED-D-SD = Medex Depression Evaluation Scale sexual dysfunction subscale.

Figure 3. Estimated Direct Effect of Selegiline Transdermal System Treatment on Change in Sexual Function, by Gender (± 95% CI)



Abbreviation: MED-D-SD = Medex Depression Evaluation Scale sexual dysfunction subscale.

Improvement in Depression

In the total population, treatment with STS resulted in statistically significant improvement in depression compared with placebo treatment, based on the mean change from baseline to endpoint on the MADRS. The mean score change was –8.02 (SD = 10.47) for placebo and –9.82 (SD = 10.50) for STS (p = .016).

Sexual Function Item Analysis

Estimates of difference between STS and placebo demonstrated a nonsignificant trend toward a positive treatment effect (net change was less than zero) for STS on 4 of 5 MED-D-SD items and a statistically significant difference on the sexual satisfaction item (upper limit of 95% CI was less than zero) (Figure 1).

Sexual Function Item Analysis by Gender

For women, estimates of difference between STS and placebo demonstrated a nonsignificant trend toward a positive treatment effect (net change was less than zero) for STS on 2 of 5 items of the MED-D-SD, and a statistically significant improvement in interest, maintaining interest during sex, and satisfaction (upper limit of 95% CI was less than zero) (Figure 2). For men, there were no differences between STS and placebo on sexual dysfunction items (Figure 2).

Analysis of Direct Effect of STS on Sexual Function

To differentiate a direct effect of STS treatment on sexual function from an indirect effect mediated through depressive symptom improvement, a multivariate regression analysis was conducted (see Statistical Methods). Differences between STS and placebo were not significant in this analysis (95% CI included zero), indicating that STS treatment did not worsen any domain of sexual function in either women or men after controlling for improvement in depression. In women there was a nonsignificant trend toward improvement (net change was less than zero) for maintenance of interest, climax, and satisfaction attributable to a direct effect of STS on sexual functioning (Figure 3).

DISCUSSION

This meta-analysis specifically examines the effects of STS treatment on various domains of sexual function in patients with MDD, using data obtained from a patient-rated questionnaire. The results confirm the low frequency of spontaneously reported sexual side effects observed during the STS clinical trial program.[16] The current analysis is important because empirical evidence substantiates the superiority of direct inquiry (using a clinician-administered or patient-completed questionnaire) compared with spontaneous reporting of sexual adverse events during antidepressant treatment.[5,20,21] As much as 80% of antidepressant-related sexual dysfunction may go

unrecognized when relying on spontaneous reports.[5] Specifically, Montejo et al.[5] found that 59% of patients acknowledged sexual dysfunction on direct questioning, whereas only 20% of these patients spontaneously reported their sexual dysfunction.

The analysis of MED-D-SD individual items suggests that STS does not induce dysfunction in any phase of the sexual response cycle or satisfaction in either male or female patients with MDD. This meta-analysis confirms single-study results demonstrating a lack of sexual dysfunction with STS treatment as measured by the change in total MED-D-SD score.[12,13] Furthermore, the data from this pooled population of patients suggest that STS may improve sexual functioning, in particular satisfaction. This positive treatment effect is primarily attributable to the statistically significant improvement of interest, maintaining interest, and satisfaction in female patients. The finding of higher baseline scores in women is consistent with previous reports demonstrating more severe impairment in sexual function among women with untreated MDD compared with men.[29,30]

Differentiating the direct effects of antidepressant treatment on sexual function from dysfunction preceding or consequent to depressive illness is challenging. Nearly 50% of individuals with untreated MDD report decreased sexual interest.[20,31] In addition, 40% to 50% of depressed women may experience diminished arousal and decreased lubrication.[31] Ejaculatory and orgasmic difficulties are least likely to be associated with MDD.[32] When these dysfunctions occur in the context of antidepressant treatment, it is highly probable that they are the result of a direct drug effect.[32] Several recent placebo-controlled trials have compared bupropion sustained release or bupropion extended release with sertraline, fluoxetine, or escitalopram. These studies found a 30% or greater incidence of new-onset orgasm dysfunction with the SRIs compared to 15% or less with bupropion and 11% or less with placebo.[33–35] The Arizona Sexual Experience Scale[36] was used in 4 acute-phase MDD placebo- and paroxetine-controlled trials of duloxetine.[37] Patients receiving duloxetine or paroxetine had significantly greater impairment in ease of reaching orgasm compared with placebo-treated patients. The data were also examined by gender. Men had significant impairment in ease of orgasm in both active treatment arms and in satisfaction from orgasm in the duloxetine group. Women receiving duloxetine or paroxetine did not differ from placebo.[37] In our analyses, no individual item, including climax, worsened with STS treatment compared with placebo, even when controlling for improvement in depressive symptoms. In fact, the data suggest that for women, there may be a direct positive effect of STS treatment on sexual function as evidenced by a nonsignificant trend toward improvement in maintenance of interest, climax, and satisfaction (Figure 3).

The mechanism of action of an antidepressant may play a key role in the induction of sexual dysfunction during therapy. Sexual function in humans relies upon a complex interplay between central nervous system and peripheral factors, including gonadal (and other) hormones and neurotransmitters.[38] Dopamine, a mediator of motivation and pleasure pathways,[39–41] appears to facilitate various aspects of sexual behavior, including desire, arousal, and orgasm.[42–45] Noradrenergic factors may also facilitate arousal and orgasm, centrally and peripherally.[35,38] Conversely, inhibitory effects of serotonin on desire, arousal, and orgasm are most likely mediated by postsynaptic 5-HT_2 receptors and may involve inhibition of mesolimbic dopamine activity.[44] Selective SRIs (SSRIs) and other antidepressant agents with serotonin reuptake inhibition appear most likely to increase the risk for sexual dysfunction.[3,5,46] Those agents that do not directly bind to the serotonin transporter (e.g., bupropion) or those agents with 5-HT_2 antagonistic properties (e.g., nefazodone and mirtazapine) may have a lower risk for sexual side effects.[3,5,46] Moreover, recent evidence suggests that patients with a functional polymorphism of the 5-HT_{2A} receptor may be particularly vulnerable to SSRI-induced sexual dysfunction.[47] Individual differences in sexual behavior, such as desire, arousal, and orgasmic function, may be attributable to polymorphisms of the dopamine D4 receptor gene.[45]

MAOIs are unique among antidepressants because they impede the catabolism of all 3 neurotransmitters implicated in the pathophysiology of MDD: serotonin, norepinephrine, and dopamine.[48] Selegiline may be further distinguished from other MAOIs by its high affinity for MAO-B, yielding a distinctive therapeutic profile resulting from enhanced dopaminergic transmission.[49,50] In the current analysis, a contribution from the prodopaminergic effects of STS is suggested by the positive treatment effect on satisfaction (total population and women), interest (women), and maintenance of interest (women). In addition, the pharmacodynamics of delivering an irreversible MAOI transdermally may contribute to the preservation of sexual function. Evidence suggests that an additional mechanism by which SSRIs and orally administered MAOIs contribute to sexual dysfunction is through their peripheral effects.[38] As the vast majority of serotonin receptors are in the periphery,[38] an antidepressant that can preferentially enhance central serotonergic neurotransmission could be advantageous. Hence, the relative selectivity of STS for central nervous system target sites (vs. peripheral tissues)[51,52] may be particularly relevant to effects on sexual function.

There are several limitations that should be considered when interpreting the results of this post hoc analysis. Individual trials included in these analyses were not designed or powered to assess changes in sexual function. Nevertheless, pooling of data sets for meta-analysis is an

accepted method for deriving sufficient data to achieve statistical significance,[53] and given the inclusion of all patients from acute treatment trials of STS 6 mg/24 hours, the data are compelling. In addition, this analysis was not designed to assess a dose effect of STS on sexual function, as higher doses of STS were not examined. However, in a placebo-controlled, flexible-dose titration study of STS 6 mg/24 hours titrated to 12 mg/24 hours, reported sexual dysfunction was low in both STS- and placebo-treated patients. Moreover, a post hoc analysis of the HAM-D libido item demonstrated similar improvement in both groups at the end of treatment (–0.36 for STS, –0.28 for placebo).[14]

Finally, because the MED-D-SD was constructed for use in the STS clinical trial program and has not been empirically validated, direct comparison of these data with those from studies using other sexual function assessments is not possible. Furthermore, definitions of sexual dysfunction based on individual item and composite scores have not been operationalized. Therefore, conducting a subanalysis on patients without defined impairment in sexual function at baseline was not possible; however, when individual item data from patients without symptoms (score of 1) were analyzed, no differences between treatment groups were observed (data not shown). Despite these shortcomings, the MED-D-SD concisely assesses satisfaction with sexual activity and function in each phase of the sexual response cycle. In this regard, it is quite similar to the Arizona Sexual Experience Scale,[36] an instrument that is now widely accepted, but one that had not yet been validated when the STS clinical trial program was developed.

CONCLUSIONS

Meta-analysis of data from 4 placebo-controlled clinical trials indicates that short-term therapy with STS 6 mg/24 hours does not impair any aspect of sexual function in either men or women as measured by the patient-rated MED-D-SD questionnaire. STS, a transdermally administered MAOI, may offer a therapeutic option for the treatment of MDD that lacks the propensity to induce sexual side effects.

Drug names: bupropion (Wellbutrin and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), meperidine (Demerol and others), mirtazapine (Remeron and others), norepinephrine (Levophed and others), paroxetine (Paxil, Pexeva, and others), selegiline (EMSAM, Eldepryl, and others), sertraline (Zoloft and others).

Financial disclosure: **Dr. Clayton** has received grants from BioSante Pharmaceuticals, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, Forest, GlaxoSmithKline, Neuronetics, Novartis, Pfizer, sanofi-aventis, and Wyeth; has been on advisory boards and/or has served as a consultant to Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, Fabre-Kramer Pharmaceuticals, GlaxoSmithKline, Novartis, Pfizer, sanofi-aventis, Vela Pharmaceuticals, and Wyeth; and is on the speaker's bureau for Eli Lilly, GlaxoSmithKline, Palatin Technologies, Pfizer, and Wyeth. **Dr. Campbell** is an employee and stock shareholder of Bristol-Myers Squibb. **Dr. Favit** is a former employee of Bristol-Myers Squibb. **Dr. Yang** is employed by Bristol-Myers Squibb. **Dr. Moonsammy** is a former employee of Somerset Pharmaceuticals. **Dr. Piontek** was employed as a consultant to IneXel Medical Strategy & Communications. **Dr. Amsterdam** served as an investigator on STS studies E-106, 9804, and 9806 reviewed in this article; served as a scientific consultant to Somerset Pharmaceuticals and Bristol-Myers Squibb; and is on the speaker's bureau of Bristol-Myers Squibb. Partial support for Dr. Amsterdam for the writing of this article was provided by The Jack Warsaw Endowment for Research in Biological Psychiatry of the University of Pennsylvania Medical Center, National Institute of Mental Health, National Institutes of Health, Eli Lilly, Forest, Stanley Medical Research Institute, and Wyeth.

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