A Placebo-Controlled Trial of Bupropion SR as an Antidote for Selective Serotonin Reuptake Inhibitor–Induced Sexual Dysfunction

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Objective: This study reports the results of a placebo-controlled, double-blind comparison of bupropion sustained release (SR) as an antidote for sexual dysfunction versus placebo in 42 patients with selective serotonin reuptake inhibitor (SSRI)–induced sexual dysfunction. Exploratory analyses of the association of testosterone and sexual functioning in women in the study were also performed.

Method: Patients with DSM-IV major depression who experienced a therapeutic response to any SSRI and were experiencing medication-induced global or phase-specific sexual dysfunction, as measured by the Changes in Sexual Functioning Questionnaire (CSFQ), were randomly assigned to receive either bupropion SR 150 mg b.i.d. or placebo for 4 weeks in addition to the SSRI. Total testosterone levels were assessed at baseline and week 4.

Results: The difference in global sexual functioning, based on the total CSFQ score, was not statistically significant between the 2 groups at week 4, nor were differences in orgasm, desire/interest as measured by sexual thoughts, or self-reported arousal. There was a statistically significant difference between the 2 groups at week 4 in desire as measured by self-report feelings of desire and frequency of sexual activity. Desire/frequency showed a significantly greater improvement among those patients receiving bupropion SR compared with placebo (Wilk's $F = 5.47$, $df = 1$, $p = .024$). Frequency was significantly correlated to total testosterone level at baseline ($r = 0.36$, $p = .027$) and at week 4 ($r = 0.41$, $p = .025$).

Conclusions: Bupropion SR, as an effective antidote to SSRI-induced sexual dysfunction, produced an increase in desire to engage in sexual activity and frequency of engaging in sexual activity compared with placebo. A larger study is needed to further investigate this finding.

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Impairment of sexual functioning is frequently associated with major depression and anxiety disorders. Physicians are increasingly aware that antidepressant medications often contribute to or increase the unwanted sexual impairment caused by psychiatric disorders.[1] In particular, the selective serotonin reuptake inhibitors (SSRIs), venlafaxine, and clomipramine are the antidepressants most commonly associated with the adverse effect of sexual dysfunction.[2] Depending on how it is defined, sexual dysfunction may be present in up to 90% of patients with concomitant psychiatric and medical disorders.[3] Sexual dysfunction negatively impacts patients' quality of life. In turn, patients are less likely to comply with their antidepressant therapy. Sexual dysfunction is noted to be among the most common and cumbersome adverse events precipitating the discontinuation of antidepressant treatment.[4]

Sexual dysfunctions can be divided into phases reflecting disruption in the sequential aspects of the normal sexual response cycle of sexual interest and desire, physiologic arousal (including clitoral engorgement and lubrication in women and erectile function in men), and or-

gasms.[5] The SSRIs have negative effects on all 3 phases of sexual function, although delay of orgasm and anorgasmia are most noted.[6] Even though the SSRIs differ in chemical structure, they all induce similar sexual side effects.[7] These sexual side effects have been attributed to inhibition of the serotonin (5-HT) transporter and to a subsequent increase in the synaptic concentrations of serotonin,[8] particularly at the 5-HT_2 and 5-HT_3 receptors.[9] Of note, differences in frequency and intensity of sexual dysfunction between men and women have been found. One recent study[2] found that men experienced a greater incidence of sexual dysfunction (62.4%) compared with women (56.9%) on serotonergic antidepressant treatment. However, this finding was not supported in a large-scale prevalence study when a gender-specific instrument, the Changes in Sexual Functioning Questionnaire, was utilized.[7]

Several authors have discussed general guidelines for managing antidepressant-induced sexual dysfunction. Besides choosing an antidepressant at the initiation of treatment with a favorable side effect profile, reducing the antidepressant to the minimal effective dose, waiting for adaptation to occur, or switching to another antidepressant, the clinician may decide to add a pharmacologic antidote to the medication that has induced the sexual dysfunction.[10–12]

The antidepressant effects of bupropion are not mediated via the serotonin system and have been demonstrated to provide improvement in a variety of patients with SSRI-induced sexual side effects. Ashton and Rosen[13] conducted an open-label study of bupropion as an antidote in patients with SSRI-induced sexual dysfunction. They found an increase in sexual desire in 70% (16/23) of patients, an increase in sexual arousal in 60% (6/10) of patients, and an improvement in reaching orgasm in 71% (30/42) of patients. One of the frequent limitations of studies attempting to assess antidotes in the treatment of SSRI-induced sexual dysfunction is the lack of a placebo control group. One placebo-controlled study of bupropion sustained release (SR) as an antidote for SSRI-induced sexual dysfunction failed to demonstrate any significant difference between the 2 groups.[14] However, the dose of bupropion SR was low at 150 mg/day, and the instrument used to assess sexual dysfunction may not have the sensitivity to measure changes in sexual functioning in a research setting.

The purpose of this study was to assess the efficacy of 300 mg/day of bupropion SR compared with placebo as an antidote to sexual dysfunction induced by SSRIs in a sample of depressed patients. Further, an exploratory investigation of the association of testosterone to sexual functioning among women on medication for depression was conducted. Studies have reported correlations between free testosterone and erectile and orgasmic function among men,[15] between changes in testosterone level and increased sexual interest and activity among adolescent girls,[16] with testosterone deficiencies in women observed to cause problems with response to sexual stimulation.[17] Little is known about the association among testosterone and sexual interest and desire, frequency of sexual activity, and orgasms among women who are being treated for depression with medications that are also associated with sexual dysfunction.

METHOD

The study design was approved by the local human investigation committee at 3 study sites in the United States and was prepared in accordance with the ethical standards laid down in the Declaration of Helsinki. Subjects at 2 university sites in Virginia and 1 in Oklahoma were invited to participate. After a complete description of the study was given to interested patients who met the inclusion criteria, written informed consent was obtained.

Measures

The Changes in Sexual Functioning Questionnaire (CSFQ), a validated instrument that provides norms for various clinical and nonclinical samples, was used to measure sexual functioning in the subjects.[18–20] The CSFQ is a 14-item, self-report instrument designed to measure global sexual dysfunction as well as dysfunction associated with each phase of the sexual response cycle. It was originally designed to be used to assess sexual dysfunction associated with illness and treatment. Validation studies have established a range of scores from a low of 14 to a high of 70, with higher scores associated with better functioning. The CSFQ provides subscales, which correspond to the phases of the sexual response cycle and can be scored separately, to permit a content-specific assessment of function. These include (1) desire indicated by interest in sexual thoughts and fantasies (e.g., "How frequently do you engage in sexual thoughts [thinking about sex, sexual fantasies] now?"); (2) desire indicated by frequency of sexual activity (e.g., "How frequently do you engage in sexual activity [sexual intercourse, masturbation] now?" "How often do you desire to engage in sexual activity?"); (3) physiologic evidence of arousal (e.g., "Do you get an erection easily?" [men], "Do you have adequate lubrication during sexual activity?" [women]); (4) ability to experience an orgasm (e.g., "Are you able to ejaculate when you want to?" [men], "How often do you experience an orgasm?" [women]; and (5) satisfaction with the sexual experience. Subthreshold total CSFQ scores indicate global sexual dysfunction, and subthreshold subscale scores define areas of sexual complaint.

The Hamilton Rating Scale for Depression (HAM-D),[21] a 17-item instrument that is commonly used in clini-

cal trials to assess DSM-IV–defined depression, was used to measure change in this area.

Certain screening laboratory studies were also included to rule out the possibility of sexual dysfunction caused by other conditions. These included thyroid function tests, free and total testosterone levels, and beta–human chorionic gonadotropin (in females).

Inclusion Criteria

Subjects between the ages of 18 and 45 years were eligible to participate in the study if they (1) met DSM-IV criteria for single or recurrent nonpsychotic major depressive episode, (2) experienced a therapeutic response to their present SSRI treatment (with a sustained remission for at least 3 months), and (3) demonstrated either global or phase-specific SSRI-induced sexual dysfunction, as indicated by self-report and by the CSFQ.[18] Based on results from an earlier nonrandomized study of bupropion and SSRIs using the same instrument,[22] significant improvement in global sexual functioning, sexual desire/interest, and orgasm was found. As such, subjects with either an orgasm subscale score on the CSFQ of ≤ 13 for men and ≤ 11 for women or a desire/interest subscale score on the CSFQ of ≤ 11 for men and ≤ 9 for women were also eligible for inclusion even if the total CSFQ score was slightly above threshold for dysfunction.[19] At baseline, the subjects were required to have a 21-item HAM-D[21] score of ≤ 7, indicating remission of depressive symptoms on SSRI treatment.

Exclusion Criteria

Subjects were excluded from the study if they had another primary psychiatric diagnosis, had another determined physiologic cause for sexual dysfunction (other than secondary to the SSRI), or had a history of seizure disorder, head injury, or serious uncontrolled medical condition. Other exclusions were pregnant or menopausal females, active suicidal ideation, or known sensitivity to bupropion. Current use of yohimbine, bupropion, warfarin, digitoxin, amantadine, methylphenidate, dextroamphetamine, lithium carbonate, carbamazepine, valproate, antipsychotics, cyproheptadine, sedative-hypnotics, buspirone, oral steroids, and tryptophan was prohibited.

Study Protocol

Following screening laboratory tests, eligible subjects' depressive symptoms and sexual functioning were assessed at baseline and at weeks 2 and 4 with the HAM-D and the CSFQ, respectively. At baseline, the patient was randomly assigned to either bupropion SR 150 mg/b.i.d. or placebo in a double-blind fashion. The initial dose of bupropion was 150 mg/day for 3 days. If tolerated and clinically indicated, the dose of bupropion SR (or placebo) was increased to 150 mg twice daily (1 pill b.i.d.) after day 3, i.e., 300 mg/day.

Statistical Analyses

Pearson chi-square tests were used to compare categorical variables between the groups (placebo vs. bupropion). A series of 2 group (bupropion and placebo) repeated-measures analyses of variance (ANOVAs) were run separately for HAM-D, total CSFQ, and each of the 5 CSFQ subscale scores. An exploratory analysis of the patterns of association between testosterone and sexual functioning was conducted by calculating Pearson correlation coefficients.

RESULTS

Sample

A total of 55 adults (48 women, 7 men) were enrolled in the study from the 3 sites. Thirteen subjects either did not complete the study, did not follow the treatment regimen, provided incomplete data, or had anomalous CSFQ scores. Three subjects terminated the study by week 4 due to mild adverse events. One of these subjects had been assigned to placebo and complained of a range of symptoms including palpitations, tightness in the chest, pain in the big toes, and insomnia that led to early withdrawal. The other 2 subjects were on bupropion therapy and withdrew from the study due to complaints of dry mouth. Of these, one also complained of nervousness, and the other of itching/hives. The final sample included 42 subjects (37 women, 5 men) who completed the study to week 4 and provided reliable data.

Demographics

Ages of the subjects in the study ranged from 22 to 45 years old, with an average age of 39 (mean = 38.45 years, SD = 5.73). Three subjects were American Indian, 1 was Hispanic, 1 was African American, and the remainder (N = 37) were non-Hispanic white. Most subjects (66.7%) were married: 28 were married, 6 were single, and 8 were divorced or separated. There were no statistically significant gender ($\chi^2 = 1.12$, df = 1, p = .289) or age ($\chi^2 = 6.7$, df = 1, p = .654) differences among subjects in the placebo compared with the bupropion SR group.

Antidepressant History/Chief Complaints

At the time of the study, all subjects were being treated with an SSRI. Seventeen were taking sertraline, 10 were taking paroxetine, 11 were taking fluoxetine, and 4 were taking citalopram. All patients had been taking antidepressants for at least 3 months prior to participation. The chief sexual dysfunction complaints of the patients included reduced sexual desire/libido and problems with orgasm and/or ejaculation, as well as problems with arousal including erectile dysfunction or inadequate vaginal lubrication concurrent with either decreased libido and/or orgasmic dysfunction.

Table 1. HAM-D and CSFQ Subscale Scores at Baseline, Week 2, and Week 4 for the Bupropion SR (N = 20) and Placebo (N = 22) Groups

Scale and Clinical Cutoff Scores for Females/Males	Baseline		Week 2		Week 4	
	Mean	SD	Mean	SD	Mean	SD
HAM-D ≤ 7/7						
Bupropion SR group	5.74	4.33	5.55	3.70	4.20	3.50
Placebo group	6.59	4.12	5.36	3.30	4.82	3.12
CSFQ						
Desire/interest ≤ 9/11						
Bupropion SR group	7.35	2.39	8.85	2.28	8.85	2.70
Placebo group	7.45	2.67	8.32	2.71	7.91	2.33
Desire/frequency ≤ 6/8						
Bupropion SR group	5.45[a]	1.10	6.45	1.05	6.65[a]	1.57
Placebo group	5.27	1.16	5.82	1.30	5.77	1.15
Arousal/excitement ≤ 12/13						
Bupropion SR group	8.85	2.43	10.65	2.03	10.50	2.80
Placebo group	8.23	2.09	9.23	2.41	9.27	2.55
Completion/orgasm ≤ 11/13						
Bupropion SR group	8.65	1.98	9.75	2.77	10.05	2.80
Placebo group	7.68	2.68	8.45	3.33	8.91	3.16
Total CSFQ ≤ 41/47						
Bupropion SR group	40.80	5.93	46.95	7.59	48.00	9.83
Placebo group	38.82	6.97	42.77	8.25	43.50	7.74

[a]Bupropion SR group showed a significant improvement over placebo group, $p < .05$.
Abbreviations: CSFQ = Changes in Sexual Functioning Questionnaire, HAM-D = Hamilton Rating Scale for Depression, SR = sustained release.

Changes in Sexual Functioning

Table 1 shows changes in depression and sexual functioning over the study period for the subjects in the placebo group compared with the drug group. Repeated-measures ANOVA indicated a significant increase in desire/frequency raw score among all patients from baseline to week 2 and baseline to week 4. The mean desire/frequency score from baseline to week 4 showed a greater improvement for the drug group than for the placebo group (Wilk's $F = 5.47$, $df = 1$, $p = .024$). The differences between the bupropion SR and placebo group in orgasm, interest as measured by sexual thoughts, self-reported arousal, and global sexual functioning were not significant. However, both groups reported scores above threshold for total CSFQ score at week 4.

For descriptive purposes, Table 2 shows changes in CSFQ clinical status (low or normal functioning) for women from baseline to week 4 by placebo and bupropion SR group. The last score available for patients who dropped out of the study in either week 2 or week 4 was carried forward to show data for all study participants. Most women in the study fell below the threshold score for normal sexual function in desire/frequency (score < 10) at baseline. Women in the bupropion SR group (6 of 17, 35.3%) were more than twice as likely to show a clinical improvement as those in the placebo group (3 of 20, 15.0%). The percentage of women who fell below the clinical cutoff for sexual dysfunction at baseline who improved to normal function by week 4 was higher for the bupropion SR group than for the placebo group for desire/interest and total CSFQ although not for completion/orgasm. There was no statistical difference in response to intervention between the different antidepressant medications (citalopram, fluoxetine, paroxetine, sertraline).

Depressive Symptoms

Repeated-measures ANOVAs indicated a significant drop in HAM-D scores for patients on both drug and placebo, from baseline (mean HAM-D score = 6.9) to week 2 (mean HAM-D score = 5.7, $F = 6.347$, $df = 1,42$; $p < .05$), and from baseline (mean HAM-D score = 6.8) to week 4 (mean HAM-D score = 4.6, $F = 7.322$, $df = 1,38$; $p < .01$), indicating fewer symptoms of depression over time. The decrease in symptom scores was not significantly different for the drug and placebo groups from baseline to week 4, $F = 0.061$, $df = 1,38$; $p = .807$ (see Table 1).

Female Sexual Function and Testosterone

To investigate a possible relationship between sexual functioning and testosterone, testosterone levels were obtained from blood tests on 37 women who completed the CSFQ at baseline and week 4. The testosterone level at baseline ranged from 7 to 124 ng/dL, with a mean total level of 34.03 ng/dL (SD = 22.4) for all women. While it is difficult to determine if androgens are normal in women due to physiologic (cyclical/diurnal) variations, the normal range in our laboratory for total testosterone in women is 10 to 55 ng/dL. Upper normal ranges are reported from 50 to 100 ng/dL in some studies.[23] Levels are considered problematic or low when less than 20 ng/dL.[23] There was no statistical difference between the placebo and bupropion SR group for mean total testosterone levels at baseline and week 4. The mean total testosterone levels for the placebo group were 30.58 ng/dL (SD = 17.21) at baseline and 20.68 ng/dL (SD = 13.03) at week 4. Bupropion SR group mean levels were 37.19 ng/dL (SD = 28.35) at baseline and 30.81 ng/dL (SD = 18.05) at week 4. For both groups, the measures of serum testosterone fell in the normal range at baseline and week 4, with a statistically significant difference between the 2 timepoints ($F = 6.9$, $df = 1,33$; $p = .013$). Pearson correlation coefficients were calculated. Women with higher frequency scores tended to have higher total testosterone levels at baseline ($r = 0.36$, $p = .027$) and at week 4 ($r = 0.41$, $p = .025$).

Adverse Experiences

Very few adverse events were reported for the combination of SSRI and treatment medication. Side effects reported in 10% of patients at any visit that occurred at more than twice the rate of the comparison group were few (Table 3). In patients treated with bupropion SR, these adverse events included irritability, dry mouth, and headache. For patients receiving placebo, increased anxiety, in-

Table 2. Clinical Status of Sexual Functioning (CSFQ Total and Subscale Scores Used for Study Inclusion Criteria) From Baseline to Week 4 for the Placebo (N = 20) and Bupropion SR (N = 17) Groups

	Remained Clinically Low		Improved From Clinically Low to Normal Range		Worsened From Normal to Clinically Low		Remained in the Normal Range	
Score by Group	N	%	N	%	N	%	N	%
Desire/interest								
Buproprion SR group								
Baseline to week 4	14	70.0	5	25.0	1	5.0	0	0
Placebo group								
Baseline to week 4	16	72.7	2	9.1	2	9.1	2	9.1
Desire/frequency								
Buproprion SR group								
Baseline to week 4	13	65.0	6	30.0	0	0	1	5.0
Placebo group								
Baseline to week 4	15	68.2	3	13.7	2	9.0	2	9.0
Completion/orgasm								
Buproprion SR group								
Baseline to week 4	17	85.0	3	15.0	0	0	0	0
Placebo group								
Baseline to week 4	16	72.7	5	22.7	1	4.5	0	0
Total CSFQ								
Buproprion SR group								
Baseline to week 4	7	35.0	6	30.0	1	5.0	6	30.0
Placebo group								
Baseline to week 4	10	45.4	7	31.8	0	0	5	22.7

Abbreviation: CSFQ = Changes in Sexual Functioning Questionnaire.

Table 3. Percentage of Patients Reporting Side Effects at Weeks 2 and 4 by Bupropion SR (N = 20) versus Placebo (N = 22) Groups

	Bupropion SR Group		Placebo Group	
	Week 2	Week 4	Week 2	Week 4
Side Effect	%	%	%	%
Tinnitis	4	4	0	0
Irritability	8	12[a]	5	5
Dry mouth	12[a]	8	0	0
Nausea/vomiting	12	0	10	0
Dizziness	8	0	0	0
Headache	15[a]	8	5	0
Decreased concentration	4	4	0	0
Increased anxiety	4	4	10[a]	0
Diarrhea	4	4	5	0
Heart palpitations	0	8	5	0
Decreased energy	0	4	10[a]	0
Increased stress	0	4	14[a]	10[a]
Insomnia	0	4	5	0
Mood lability	0	0	0	10[a]

[a]Occurred at a ≥ 10% rate in week 2 or 4 and also occurred at more than twice the rate of that in the comparison group.

creased stress, decreased energy, and mood lability were reported. No other adverse experiences differed between the bupropion SR and placebo groups.

Data for the placebo patients who reported side effects (anxiety, increased stress, decreased energy, and/or mood lability) were examined to determine if the patients were the same as those who had also reported placebo-induced improvement in sexual functioning. Among the 5 patients who received placebo and who reported side effects, 2 reported reaching normal levels of sexual function from baseline to week 4 (total CSFQ and completion/orgasm).

DISCUSSION AND CONCLUSIONS

In this placebo-controlled study, bupropion SR, as an effective antidote to SSRI-induced sexual dysfunction, produced an increase in desire to engage in sexual activity and frequency of engaging in sexual activity. Improvement over placebo was not found for global sexual functioning, sexual interest, arousal, or orgasm. This result contradicts the findings of the Masand and colleagues' study,[14] which found no significant difference in outcomes. It is possible that the higher dose of bupropion SR used in the present study (300 mg/day) and/or the use of the CSFQ, which is sensitive to phases of the sexual response cycle for women, as well as men, accounts for the difference. Further investigation would be needed to confirm the reasons for the differences.

This study is important in that it acknowledges by implication that sexual satisfaction is more than just a total score for overall or global sexual functioning, which is defined as relatively high function in all phases of the sexual response cvcle. Sexual functioning in the normal U.S. populations indicates that as many as 43% of women and 31% of men report some type of sexual dysfunction, but not necessarily global dysfunction.[24] Nevertheless, problems within any phase of the sexual response cycle can cause reduced quality of life in patients and can affect intimate relationships in those in treatment for depression with SSRIs. In our study, subjects taking SSRIs who were treated with bupropion SR as an antidote reported significant improvement over subjects on placebo in an important phase of the sexual response cycle: they both desired and participated in sexual activity more often than at baseline.

The positive correlations between testosterone and sexual desire/frequency, desire/interest, and self-reported arousal are interesting and need further investigation. Future research with a better controlled, larger sample of women representing low, mid, and high levels of testosterone are needed to further investigate the correlates of the sexual phases and global sexual functioning to level of testosterone. Further information is needed to determine whether greater improvements in desire may be seen in premenopausal women with lower testosterone levels and SSRI-induced sexual dysfunction by using bupropion SR combined with testosterone therapy.

For both the bupropion SR and placebo groups, the HAM-D score improved significantly over baseline

scores that met criteria for remission with an SSRI alone. This finding suggests the persistence of residual symptoms even in remission (HAM-D score ≤ 7), and the resolution of these symptoms with continued treatment with the SSRI. The decrease in depressive symptoms over the 4 weeks of the study may have increased the effect of the placebo on sexual functioning, as the sexual dysfunction may have represented residual symptoms of depression that improved with more time on the SSRI treatment. Also, 5% to 10% of patients with SSRI-induced sexual dysfunction may develop tolerance to the sexual dysfunction after 4 to 6 months of SSRI treatment,[2,13] the timing of which may have coincided with the 4-week study period, resulting in an increased placebo response. Greater improvement in sexual function might have occurred if the dose of the SSRI were decreased, as theoretically bupropion might increase blood levels of the SSRI, and at 300 mg/day of bupropion SR, patients were taking a therapeutic dose of antidepressant.

There were few adverse effects in either treatment group, indicating that the combination of therapeutic doses of bupropion SR and therapeutic doses of SSRI is well tolerated. Patients who received placebo reported significantly more anxiety and stress-related symptoms than those who received bupropion SR. The study subjects may have been suffering from anxiety related to expectations of receiving an unknown drug. Anxiety symptoms may have been suppressed in the active treatment group due to the antianxiety effects of bupropion.[25]

In conclusion, improvements in sexual function and residual depressive symptoms when bupropion SR is added to an SSRI may improve quality of life in patients with SSRI-induced sexual dysfunction in the desire/frequency phase and potentially enhance medication compliance.

Drug names: amantadine (Symmetrel and others), bupropion (Wellbutrin and others), buspirone (BuSpar and others), carbamazepine (Tegretol, Carbatrol, and others), citalopram (Celexa), dextroamphetamine (Dexedrine and others), fluoxetine (Prozac and others), methylphenidate (Ritalin, Concerta, and others), paroxetine (Paxil and others), sertraline (Zoloft), venlafaxine (Effexor), warfarin (Coumadin, Jantoven, and others).

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