A Placebo-Controlled, Randomized, Double-Blind Study of Adjunctive Bupropion Sustained Release in the Treatment of SSRI-Induced Sexual Dysfunction

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Background: Sexual side effects are among the common reasons patients discontinue selective serotonin reuptake inhibitors (SSRIs). While many antidotes have been proposed, few have been subjected to double-blind trials. Some evidence has suggested that bupropion may be an effective antidote for SSRI-induced sexual dysfunction. In this double-blind trial, the efficacy of a standard dose of bupropion sustained release (SR) is evaluated in the treatment of SSRI-induced sexual dysfunction.

Method: Patients with a history of SSRI-induced sexual side effects were randomly assigned to adjunctive treatment with either bupropion SR 150 mg daily or placebo for 6 weeks. Assessments of sexual function and interest included the Arizona Sexual Experiences Scale (ASEX), Brief Index of Sexual Functioning, and a 10-point visual analogue scale. Efficacy was defined as a 50% improvement on the ASEX at the end of 6 weeks. Data were collected from January 1999 to March 2001.

Results: Forty-one patients entered the study and completed the 6-week trial. No significant differences were seen between placebo and bupropion SR on the ASEX or on any measure of sexual functioning at the end of the trial.

Conclusion: A fixed dose of 150 mg/day of bupropion SR taken in the morning does not appear to be effective in the treatment of SSRI-induced sexual dysfunction. Additional trials will be required to define what role, if any, bupropion might have in the treatment of SSRI-induced sexual side effects.

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Selective serotonin reuptake inhibitors (SSRIs) are associated with high rates of sexual dysfunction. Recent estimates on the rates of sexual side effects associated with the SSRIs have ranged from 30% to more than 70%.[1,2] Sexual side effects have included decreased libido; delayed, reduced, or absent orgasm; diminished arousal; and erectile dysfunction. Sexual side effects are among the most common reasons that patients discontinue antidepressants despite their being effective.[3]

Many antidotes have been proposed for SSRI-induced sexual side effects in the past 10 years. Serotonin (5-HT) antagonists and partial agonists have been used with moderate success. Cyproheptadine, which is a general 5-HT antagonist, has been reported helpful in anecdotal reports.[4] Unfortunately, it has also been associated with reversal of antidepressant and antiobsessive properties of the SSRIs.[5] In addition, cyproheptadine is quite sedating and is sometimes poorly tolerated in regular use.

Buspirone, a partial agonist of the 5-HT_{1A} receptor, has also been proposed as an antidote for SSRI-induced sexual side effects. One of the few double-blind trials of an antidote for SSRI-induced sexual dysfunction has reported an advantage of buspirone over placebo.[6] However, another randomized trial failed to show benefits of buspirone over placebo.[7]

The use of noradrenergic agents for SSRI-induced sexual side effects has had its proponents over the years.

Yohimbine has been reported to reverse SSRI-induced sexual side effects in some cases.[8] Unfortunately, yohimbine is also anxiogenic and may be associated with treatment-emergent anxiety and agitation.

Sildenafil has more recently been reported to help SSRI sexual side effects in a number of case reports.[9–12] The benefits are not necessarily limited to improvement in erectile dysfunction: benefits have also been noted in libido and orgasm function. In addition, women were noted to have significant benefits in a case series of 9 patients taking SSRIs.[13] However, large case series or double-blind trials have yet to be published.

Among the more common antidotes for SSRI-induced sexual dysfunction are dopaminergic agents. Intermittent amantadine[14] and amphetamines[15] have been reported as helpful in reversing SSRI-induced sexual side effects in case reports.

The 5-HT_3 antagonist granisetron was reported to have some utility in SSRI-induced sexual dysfunction. However, both double-blind studies of granisetron in SSRI-induced sexual dysfunction failed to show any benefit over placebo.[16,17]

Bupropion, an antidepressant with both noradrenergic and dopaminergic properties, has been associated with a significant improvement in sexual side effects when patients are switched from SSRIs to bupropion.[18] A number of case reports also suggest a role of adding bupropion to an SSRI to reverse sexual side effects.[19] Open-label trials have also suggested that bupropion may reverse SSRI sexual side effects. Labbate and colleagues[20] reported that the addition of 75 mg/day of bupropion to an SSRI significantly improved sexual side effects in 4 of 8 patients treated openly. In a larger open trial of 47 patients, intermittent or daily dosing of bupropion in doses of 75 mg p.r.n. to 225 mg/day led to a complete reversal of sexual side effects in 66% of patients and to improvement in 69% of patients.[21]

Two double-blind trials using a fixed dose of bupropion have been published.[22,23] One study[22] failed to find a difference between placebo and bupropion 150 mg given in the evening. Limitations of this study included a short duration of treatment (3 weeks) and a small sample size (N = 30). In addition, the authors speculated that the evening dose of the drug might not have provided an optimal peak serum level to exert the maximum benefits on sexual dysfunction. In the second study, Clayton and colleagues[23] studied 42 patients with SSRI-induced sexual dysfunction who were treated with bupropion sustained release (SR) given b.i.d. Using the Changes in Sexual Functioning Questionnaire, they found improvement in desire and frequency of sexual functioning. However, there were no differences in orgasm or arousal between the 2 groups.

In the present double-blind trial, the utility of improving SSRI-induced sexual side effects with a fixed morning dose of adjunctive bupropion SR over 6 weeks is examined.

METHOD

Subjects were recruited from clinic populations and by advertisement. The Stanford University Institutional Review Board approved the study, and patients signed an informed consent. Data were collected from January 1999 to March 2001.

Subjects were required to be between the ages of 18 and 60 years old and to have been taking a fixed, therapeutic dose of fluoxetine, paroxetine, citalopram, or sertraline for at least 6 weeks. A therapeutic dose was defined as at least 20 mg/day of citalopram, fluoxetine, or paroxetine, or 50 mg/day of sertraline. In addition, patients had to endorse complaints of sexual side effects, such as lowered libido or delayed, diminished, or absent orgasm, which they believed to be temporally related to their antidepressant use. Arizona Sexual Experiences Scale (ASEX)[24] scores of at least 15 out of 30 were required for participation. Subjects with a preexisting history of sexual dysfunction or those patients with a preexisting medical condition known to be associated with sexual dysfunction, including peripheral vascular disease and diabetes, were excluded from participation. In addition, patients who were taking other medications that could be contributing to their sexual dysfunction including cardiac glycosides, antihypertensives, and anti-Parkinson's drugs were also excluded.

Subjects were randomly assigned to either placebo or bupropion SR added to their current SSRI for the 6-week trial duration. The bupropion SR was initiated and maintained at a fixed dose of 150 mg/day dosed in the morning. Subjects were seen weekly for the first 2 weeks of the study and then every 2 weeks for the remaining 4 weeks.

Sexual function was assessed by a variety of self-assessment scales. These included the ASEX (male and female),[24] the Brief Index of Sexual Functioning (BISF),[25] and a 10-point visual analogue scale that assessed interest ("How would you rate your sexual interest?") and satisfaction ("How would you rate your overall level of sexual satisfaction?") for both the previous week and prior to taking an SSRI. Secondary measures included a Hamilton Rating Scale for Depression (HAM-D),[26] a Beck Depression Inventory (BDI),[27] and a clinician Clinical Global Impressions-Improvement scale (CGI)[28] focusing on sexual dysfunction.

RESULTS

Forty-one patients (24 women, 17 men) entered the study, and all completed the 6-week trial. The mean age of the participants was 46 years, with a standard deviation of 10.79. Treatment group and SSRI data are presented

Table 1. Subjects Enrolled in a 6-Week Randomized, Double-Blind Trial of Adjunctive Bupropion SR vs. Placebo for SSRI-Induced Sexual Dysfunction (by sex)

Medication Status	Female	Male
Received bupropion SR	14	6
Received placebo	10	11

Abbreviations: SR = sustained release, SSRI = selective serotonin reuptake inhibitor.

Table 2. Mean Dose and Duration of SSRI Treatment Prior to Participation in a 6-Week Randomized, Double-Blind Trial of Adjunctive Bupropion SR vs. Placebo for SSRI-Induced Sexual Dysfunction

SSRI	N	Mean Dose, mg	Mean Duration of Use Prior to Participation, wk
Citalopram	1	20	6
Fluoxetine	16	31	34
Paroxetine	12	25	25
Sertraline	12	96	15

Abbreviations: SR = sustained release, SSRI = selective serotonin reuptake inhibitor.

in Tables 1 and 2, respectively, and baseline measures of depression and sexual function are presented in Table 3.

To assess sexual functioning, both total ASEX scores and individual items were assessed. Significant improvement was defined as a 50% reduction in total ASEX score. In addition, a total of 36 items were treated as separate dependent variables: the 3 CGI items worded with regard to sexual dysfunction, the 6 distinct items across the 2 versions (male and female) of the ASEX, 21 of the items on the BISF, item number 14 from the HAM-D, and item number 22 from the BDI. Finally, total HAM-D and BDI scores were assessed over time.

A limited number of items from the BISF were chosen for analysis a priori, based on previous research on SSRI-induced sexual dysfunction. Items taken from the BISF can be grouped into 3 categories: those asked of men only, those asked of women only, and those asked of both men and women. Items for men only included level of arousal during masturbation, insertion of penis, and thrusting of penis; frequency of nocturnal erections; frequency of ejaculation during sleep and intercourse; and frequency of difficulty with ejaculation during masturbation and intercourse. Items for women only included frequency of desire to engage in masturbation or intercourse; frequency of arousal during masturbation or intercourse; frequency of orgasm during masturbation, sleep, and intercourse; frequency of lack of vaginal lubrication; and frequency of difficulty reaching orgasm. For both men and women, items included frequency of masturbation and intercourse and level of pleasure from sexual experience.

Two-way repeated-measures analyses of variance were conducted on these variables, with treatment group and time as factors and p = .05 corrected for familywise error

Table 3. Baseline ASEX, HAM-D, and BDI Scores of Subjects Enrolled in a 6-Week Randomized, Double-Blind Trial of Adjunctive Bupropion SR vs. Placebo for SSRI-Induced Sexual Dysfunction

Measure	Mean Score[a]	Standard Deviation
ASEX (total)[b]	22	4
HAM-D[c]	11	6
BDI[d]	10	6

[a]Higher scores indicate more dysfunction for all 3 scales.
[b]Scores can range from 5 through 30.
[c]Scores can range from 0 through 75.
[d]Scores can range from 0 through 63.
Abbreviations: ASEX = Arizona Sexual Experiences Scale, BDI = Beck Depression Inventory, HAM-D = Hamilton Rating Scale for Depression, SR = sustained release, SSRI = selective serotonin reuptake inhibitor.

Table 4. Response at Endpoint of a 6-Week Randomized, Double-Blind Trial of Adjunctive Bupropion SR vs. Placebo for SSRI-Induced Sexual Dysfunction as Measured by 25% or More Improvement on the Total ASEX

Medication Status	Responders	Nonresponders
Received bupropion SR	5	15
Received placebo	6	15

Abbreviations: ASEX = Arizona Sexual Experiences Scale, SR = sustained release, SSRI = selective serotonin reuptake inhibitor.

with a stepwise Bonferroni procedure. Of all assessments of sexual functioning, none were found to be significantly different over time as a function of treatment group. That is, any changes over time were similar for the subjects who received placebo and those who received bupropion SR (Tables 4 and 5). There was no difference in placebo- and bupropion-treated patients in total ASEX improvement, and few patients from either group showed significant improvement.

Two measures showed an increase over time without regard to treatment group: question 1 from the ASEX (with men and women combined), "How strong is your sex drive?" ($F = 11.81$, $df = 3$, $p < .0001$); and question 2 from the ASEX, "How easily are you sexually aroused (turned on)?" ($F = 4.241$, $df = 3$, $p < .007$).

CONCLUSION

This study failed to demonstrate a consistent improvement in SSRI-induced sexual dysfunction related to the addition of a fixed morning dose of bupropion SR. There may be a number of reasons for this. One is that the dose of bupropion SR used in the study was too low. Some of the beneficial effects of bupropion on sexual dysfunction may be related to its dopamine reuptake effects. However, these dopamine effects are typically not seen except at the higher doses.[29] Thus, this is the second study to show that a fixed dose of 150 mg/was ineffective,[22] while 300 mg/day has shown some benefit.[23]

Table 5. Response at Endpoint of a 6-Week Randomized, Double-Blind Trial of Adjunctive Bupropion SR vs. Placebo for SSRI-Induced Sexual Dysfunction as Measured by 50% or More Improvement on the Total ASEX

Medication Status	Responders	Nonresponders
Received bupropion SR	1	19
Received placebo	1	20

Abbreviations: ASEX = Arizona Sexual Experiences Scale, SR = sustained release. SSRI = selective serotonin reuptake inhibitor.

Another factor may have been the timing of the dose of bupropion. Some reports have suggested using bupropion in close proximity to sexual activity. The present study used a fixed morning dose. Perhaps an evening dose might be more temporally related to sexual activity. However, the Masand et al.[22] study found no more utility to dosing the drug in the evening than we found in the morning.

Another problem may have been the sustained-released preparation. Virtually all of the reports suggesting a benefit of bupropion in SSRI-induced sexual dysfunction have used an immediate-release preparation. However, these reports were case reports or open-label studies from which few conclusions could be drawn. The immediate-release preparation of bupropion results in higher serum levels. These higher serum levels may be more problematic in their association with adverse effects including seizures.[30] However, it is also conceivable that higher peak serum levels might be required to improve some sexual side effects.

Subjects entered the trial with low HAM-D and BDI scores (Table 3). Thus, their depression was well controlled with the SSRI. In this sample of patients with well-controlled depression, the addition of bupropion might be less beneficial if bupropion improves sexual dysfunction by indirectly improving depression via augmentation of the SSRI. However, bupropion augmentation of an SSRI, while commonly used in clinical practice, has only been evaluated in small open trials,[31] and no double-blind trials currently exist to support the use of this practice.

There are also significant limitations in the study design. For example, a sample size of 41 is underpowered to evaluate a small effect size of the active drug. Perhaps there are consistent but more modest effects of bupropion on SSRI-induced sexual dysfunction. It is also possible that the instruments used, the ASEX and BISF, are not sensitive enough to pick up changes in SSRI-induced sexual dysfunction. However, at least the ASEX has been used in the assessment of SSRI-induced sexual dysfunction and appears to be useful.[32,33] In addition, the frequency of visits and the use of the same assessments at every visit might have contributed to a higher placebo response rate.

An improvement in sex drive and arousal was seen in both the active drug and placebo-treated groups. Since the vast majority of the literature on the treatment of SSRI-induced sexual dysfunction is anecdotal, it is probable that some of the beneficial effects of the many proposed antidotes are placebo induced.

Bupropion is a well-tolerated adjunctive agent to SSRIs. Bupropion may have benefits, including antidepressant augmentation, beyond any suggested benefits in the treatment of SSRI-induced sexual dysfunction. A much larger study with higher dosing may be needed to fully assess the role of bupropion SR in the treatment of SSRI-associated sexual dysfunction.

Drug names: amantadine (Symmetrel and others), bromocriptine (Parlodel and others), bupropion (Wellbutrin and others), buspirone (BuSpar and others), citalopram (Celexa and others), fluoxetine (Prozac and others), granisetron (Kytril), paroxetine (Paxil and others), sertraline (Zoloft), sildenafil (Viagra).

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