Brief Report

Sustained-Release Bupropion for Selective Serotonin Reuptake Inhibitor-Induced Sexual Dysfunction: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study

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Objective: The authors compared low-dose sustained-release bupropion with placebo for sexual dysfunction induced by selective serotonin reuptake inhibitors (SSRIs).

Method: Thirty adults who had received SSRIs for at least 6 weeks, who were euthymic, and who had sexual dysfunction as determined by a total score greater than 19 out of a possible 30 on the Arizona Sexual Experience Scale were randomly assigned to receive either 150 mg/day of sustained-release bupropion or placebo at 6:00 p.m. for 3 weeks.

Results: There were no significant differences between the sustained-release bupropion and placebo groups as measured by change in Arizona Sexual Experiences Scale or Hamilton Depression Rating Scale scores or side effects.

Conclusions: Future studies should compare higher doses of bupropion for treating sexual dysfunction and should include a greater number of subjects.

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Selective serotonin reuptake inhibitors (SSRIs) are widely used to treat mood, anxiety, and premenstrual disorders (1). Side effects of the SSRIs include gastrointestinal disturbances and sexual dysfunction (1). Persistent sexual dysfunction may affect compliance and patient satisfaction. Previous treatments for SSRI-induced sexual dysfunction have included adjunctive treatment with yohimbine (2), amantadine (3), cyproheptadine (4), bupropion (5), nefazodone (6), buspirone (7), granisetron (8), and sildenafil (9). Other strategies have included drug holidays (10), dose decreases (11), waiting for tolerance to develop (12), and switching to another antidepressant or another class of drug that is known to cause lower rates of sexual dysfunction (13).

On the basis of our previous experience with open-label bupropion, we designed the present double-blind, placebo-controlled study to determine if adjunctive low-dose sustained-release bupropion would improve sexual dysfunction significantly in patients treated with SSRIs.

Method

Thirty-nine patients who had received SSRI therapy for at least 6 weeks, who were euthymic as measured by a score of less than 10 on the 21-item Hamilton Depression Rating Scale, and who had sexual dysfunction as measured by a total score of 19 or higher on the Arizona Sexual Experiences Scale (14) or any individual item score greater than 5 or any three individual item scores equal to 4 were enrolled in the study. We screened the patients for causes of sexual dysfunction other than SSRI use, including medical conditions, previous diagnosis of a sexual disorder, and major disruptions in relationships.

Demographic data, including marital status, age, and gender, were obtained at baseline. Written informed consent was obtained from all participating subjects. The study was approved by the institutional review board at the State University of New York Health Science Center at Syracuse.

Eight patients dropped out of the study without receiving any study drug. The remaining 31 patients were randomly assigned to receive 150 mg/day of sustained-release bupropion or placebo at 6:00 p.m. for 3 weeks after they were asked if they were likely to engage in sexual activity in the evening. One patient dropped out after taking two doses of the study drug (active sustained-release bupropion) because of insomnia. Thirty patients completed the study.

During the 3-week trial, subjects were rated on the Arizona Sexual Experiences Scale, Hamilton depression scale, and Udvalg for Kliniske Undersøgelser Side Effect Rating Scale (15) each week. Patients were strongly encouraged to be sexually active during the study. Improvement in sexual dysfunction was defined as a decrease of 50% or more in total Arizona Sexual Experiences Scale scores; individual items of the Arizona Sexual Experiences Scale were also analyzed.

Categorical baseline characteristics were analyzed by using Pearson's chi-square test, and continuous variables were compared by using the t test. The percentage improvement in total and individual Arizona Sexual Experiences Scale scores between patients receiving active drug and those receiving placebo was also evaluated by using Pearson's test, although Fisher's exact test was used for comparisons where 25% of the expected cell counts were less than 5. The t test was used to analyze the differences in Arizona Sexual Experiences Scale scores from baseline to each successive week between the patients receiving active drug and those receiving placebo.

The response profile over time was analyzed by using a repeated measures analysis of variance procedure. A multivariate approach to this analysis was used to account for the "compound symmetry" assumption violation. This assumption was tested by using Maulchy's criterion applied to a set of orthogonal components. SAS software (Cary, N.C.) was used for all analyses described above.

TABLE 1. Difference in Response to 3 Weeks of Treatment for Selective Serotonin Reuptake Inhibitor-Induced Sexual Dysfunction Between Patients Receiving Sustained-Release Bupropion (N=15) and Patients Receiving Placebo (N=15)

Arizona Sexual Experiences Scale Item	Baseline–Week 1 t (df=28)	p	Baseline–Week 2 t (df=28)	p	Baseline–Week 3 t (df=28)	p
Sex drive	–0.80	0.43	–1.50	0.15	–0.87	0.40
Arousal	–0.49	0.63	–0.94	0.36	0.58	0.57
Vaginal lubrication/erection	–1.80	0.09	–2.20	0.04	–1.49	0.15
Orgasm	0.00	1.00	–0.33	0.75	–0.72	0.48
Orgasm satisfaction	0.82	0.43	–1.15	0.27	–1.58	0.13
Total	–0.77	0.45	–1.64	0.14	–0.98	0.34

Results

There were no differences in demographic variables between the 15 patients in the sustained-release bupropion group and the 15 patients in the placebo group. One of the patients in the placebo group and none of those in the bupropion group had a decrease of 50% or more in total Arizona Sexual Experiences Scale score from baseline to week 3 (p=1.00, Fisher's exact test). In the bupropion group, the decrease in total Arizona Sexual Experiences Scale score from baseline to week 3 for four patients was from –25% to –1%, for nine patients the decrease was from 0% to 24%, and for two patients the decrease was from 25% to 49%. In the placebo group, however, the decrease in total Arizona Sexual Experiences Scale score from baseline to week 3 for two patients was from –25% to –1%, for 11 patients the decrease was from 0% to 24%, and for one patient the decrease was from 25% to 49%. This did not reveal any significant differences between treatment groups when the total Arizona Sexual Experiences Scale was divided into four categories (p=0.62, Fisher's exact test).

Although the response profiles did not differ over time between the bupropion and placebo groups, significant improvement was seen for the group as a whole in total Arizona Sexual Experiences Scale score ($F=3.69$, df=3, 26, $p=0.03$), sexual arousal ($F=3.07$, df=3, 26, $p=0.05$), and vaginal lubrication/erection ($F=4.28$, df=3, 26, $p=0.02$). Marginal improvement was seen for sex drive ($F=2.96$, df=3, 26, $p=0.06$). When differences between baseline and week 1, week 2, and week 3 were compared between the two treatment groups, no significant improvements were seen except for vaginal lubrication/erection from baseline to week 2 (Table 1); this improvement was marginal and favored the placebo group (Table 1).

Bupropion was well tolerated. Side effects included concentration difficulties, reduced duration of sleep, and tremor. There were no significant differences between the groups in side effects.

Discussion

There were no differences between adjunctive low-dose sustained-release bupropion and placebo for the treatment of SSRI-induced sexual dysfunction. Side effects were similar in the bupropion and placebo groups.

To our knowledge, there are only two other double-blind, placebo-controlled studies of augmentation therapy to treat SSRI-induced sexual dysfunction. Michelson et al. (16) randomly assigned 61 women with 17-item Hamilton depression scale scores less than 10 who reported impaired orgasm or sexual arousal while taking fluoxetine (mean dose 28.5 mg/day) to amantadine (up to 50 mg b.i.d.), buspirone (up to 15 mg b.i.d.), or placebo for 8 weeks. Overall, sexual function improved significantly (25%–29%) in each group, but there were no statistically significant differences between treatments. Amantadine patients reported statistically significant increases in energy level compared with patients taking placebo.

Landen et al. (17) treated 47 patients who had failed to respond to an SSRI and who also had sexual dysfunction with either buspirone (at endpoint, mean dose=48.5/day) or placebo for a period of 4 weeks. Sexual dysfunction was evaluated with a structured interview. During the 4 weeks of treatment, approximately 58% of the subjects treated with buspirone reported an improvement with respect to sexual function, compared with a response rate of 30% in the patients receiving placebo. The difference between the two treatment groups was not statistically significant at week 4 (p=0.07). In contrast to our study, the patients in the study by Landen et al. were depressed before they were randomly assigned to receive buspirone or placebo, which confounds the results.

A meta-analysis of 136 men with erectile dysfunction and depression (unpublished 1998 paper by T. Hargreave) found sildenafil to be superior to placebo in improving erections, measured by using the International Index of Erectile Function and a global efficacy measure.

Limitations in our current study included a low dose of sustained-release bupropion; timing of the dose at 6:00 p.m., which may have resulted in peak blood levels occurring before or after sexual activity; and lack of quantification and documentation of frequency of sexual activity before baseline and during the study. The frequency of sexual activity may have been low before baseline and during the study, resulting in Arizona Sexual Experiences Scale scores that remained static.

The power of this study to detect a difference is another major limitation. Supposing a large effect size (shift of 0.8 of a standard deviation), this study had a chance to detect an effect of approximately 0.59. Furthermore, the number of subjects in this study resulted in only about a one-in-four chance (power=0.28) of finding a moderate effect size (Cohen's d=0.5). Further double-blind, placebo-controlled studies of longer duration using therapeutic doses of sustained-release bupropion are warranted to determine the

effect of this antidepressant on SSRI-induced sexual dysfunction.

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