Bupropion as an Antidote for Serotonin Reuptake Inhibitor–Induced Sexual Dysfunction

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Background: Serotonin reuptake inhibiting antidepressants (SRIs) are reported to cause sexual dysfunctions, including reduction in desire, arousal, and orgasm. This study evaluates the efficacy of bupropion in ameliorating sexual dysfunctions in patients receiving SRIs.

Method: Forty-seven patients in an outpatient psychiatric practice who complained of SRI-induced sexual dysfunction accepted a trial of bupropion as an adjunct to their SRI, either as a p.r.n. or as a fixed-dose scheduled medicine. Patients received 75 mg or 150 mg of bupropion 1 to 2 hours before sexual activity. If this was insufficient to reduce their complaints, dose was increased gradually to 75 mg t.i.d. and sustained for 2 weeks. This regimen was then continued if successful.

Results: Bupropion successfully reversed a variety of sexual dysfunctions caused by SRIs in 31 (66%) of 47 patients. Fifty-two (69%) of 75 sexual complaints improved with bupropion treatment. The p.r.n. use of bupropion assisted 18 (38%) of 47 patients. Side effects of anxiety and tremor led to discontinuation of bupropion in 7 (15%) of 47 patients. Otherwise, bupropion was well tolerated.

Conclusion: Bupropion administration may be a safe and effective method of treating SRI-induced sexual dysfunction. Placebo-controlled, double-blind studies are needed.

(J Clin Psychiatry 1998;59:112–115)

Received April 24, 1997; accepted Aug. 7, 1997. From the State University of New York at Buffalo, School of Medicine (Dr. Ashton), and the University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, Piscataway (Dr. Rosen).

Supported by a Clinical Research Grant from Glaxo Wellcome. Presented at the 22nd annual meeting of the Society of Sex Therapy and Research, March 15, 1997, Chicago, Ill.

We thank Noel Gendrano III and Irena Esterlis for assistance in data collection and analysis.

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Clinicians are increasingly aware that antidepressants which inhibit serotonin reuptake (SRIs) may cause sexual dysfunction in a substantial number of patients.[1–6] Many augmentation strategies, including cyproheptadine,[6–8] yohimbine,[6,9,10] amantadine,[6,11,12] methylphenidate,[13] buspirone,[14] as well as bupropion,[5,15] have been proposed to alleviate SRI-induced sexual dysfunction. Drug holiday also has been recommended as a potential management strategy.[16]

Bupropion is an aminoketone antidepressant that is thought to have less adverse effect on sexual functioning than other antidepressants available in the United States.[17] It has been used to maintain antidepressant efficacy in patients who were stabilized with other antidepressants but complained of sexual dysfunction.[17,18] Bupropion has also been shown in a single case report,[15] as well as a small retrospective study,[5] to be useful in treating SRI-induced sexual dysfunction.

To date, no study has reported how often various sexual dysfunctions are treated successfully with bupropion or what dose might be necessary to achieve success with this strategy. We report on 47 patients in an outpatient psychiatric practice who complained of SRI-induced sexual dysfunction and accepted a trial of bupropion as an adjunct to their SRI. The SRIs evaluated included specific serotonin reuptake inhibitors (paroxetine, fluoxetine, sertraline, fluvoxamine) and the serotonin reuptake and norepinephrine reuptake inhibitor venlafaxine.

METHOD

Psychiatric patients at a private practice in Williamsville, N.Y., who were being treated with SRIs for affective or anxiety disorders were asked about changes in sexual functioning since the initiation of treatment. Inquiry was conducted by the treating psychiatrist (A.K.A.) as part of the clinical interview. The patients were asked if any noticeable changes had occurred in sexual desire, arousal, or orgasm since starting SRI therapy. The type of dysfunction was recorded, although there was no discrimination between delayed orgasm and anorgasmia. Those patients who reported a worsening of sexual performance since onset of treatment were offered a trial of bupropion in conjunction with SRI therapy. The risks and benefits were

explained, and consent was obtained. The same psychiatrist treated all patients included in this outpatient study.

Patients who accepted a bupropion trial were instructed to take 75 mg 1 to 2 hours before anticipated sexual activity. If patients, by way of direct interview, reported a lack of efficacy, they were then instructed to take 150 mg 1 to 2 hours before the next anticipated sexual activity. If response was still insufficient, they were instructed to titrate gradually to 75 mg t.i.d.: patients were told to take 75 mg q.d. for 3 days, then 75 mg b.i.d. for 3 days, and then 75 mg t.i.d. and to remain at that dose for 2 additional weeks. This time frame was selected based upon the treating psychiatrist's (A.K.A.) observation that patients taking scheduled-dose antidotes often described response within 2 weeks of reaching a therapeutic dose. Those patients who continued to acknowledge unacceptable sexual dysfunction after 2 weeks were labeled as treatment failures with bupropion. Those reporting a reduction of sexual dysfunction were categorized as responders to bupropion augmentation. Responders were then kept on bupropion treatment in addition to their SRI for an extended period of time, the longest of which was 9 months, at which time charts were reviewed and results statistically analyzed.

Statistical Analyses

All statistical analyses were conducted by means of the SPSS software system (Statistical Package for the Social Sciences, Release 6.0, Chicago, Ill.: SPSS; 1993). Means, medians, and standard deviations for each variable were computed by treatment group. Additionally, cross-tabulations and chi-square tests of association were conducted to assess the statistical relationship between predictor and outcome variables. Nonparametric tests were used for these analyses due to the limited sample size and categorical nature of the dependent variables.

RESULTS

Fifty-two patients were offered a trial of bupropion after reporting SRI-induced sexual dysfunction. Twenty-one men with a mean age of 46.3 years; (range, 25–70) and 31 women with a mean age of 41.9 years (range, 23–61) were included in the study. Several patients had a history of failure with other antidotes prior to a bupropion trial, but this did not predict failure with bupropion. Five (10%) of 52 patients failed to use bupropion on at least one occasion despite specific requests for therapeutic intervention. These patients were not included in further analysis. Table 1 shows the sexual dysfunction complaints of and the SRIs used by the 47 patients included in our analysis.

The p.r.n. dosing of 75 mg or 150 mg of bupropion was effective in 18 of 47 (38%) patients, while scheduled dosing was effective in 13 (57%) of 23 patients, all of whom failed a trial of p.r.n. dosing. Six (13%) of 47 patients did not respond to p.r.n. dosing and declined to use bupropion on a scheduled basis. When the groups were combined, however, 31 (66%) of 47 patients responded favorably to bupropion augmentation. As noted in Table 2, most patients receiving fluoxetine (N = 17) or paroxetine (N = 15) showed improvements in sexual function during bupropion augmentation. Fewer patients receiving sertraline, venlafaxine, or fluvoxamine improved. Although this difference was not statistically significant ($\chi^2 = 2.32$, p = .13), there was a trend of greater bupropion efficacy when it was added to paroxetine or fluoxetine than when it was added to the other medications.

Gender did not predict response to bupropion, although there was a nonsignificant trend for women to respond more often than men ($\chi^2 = 3.24$, p = .07). As seen in Table 3, 22 (76%) of 29 women responded to bupropion, compared with 9 (50%) of 18 men.

The gender difference was most obvious in patients taking paroxetine. In women, 10 (91%) of 11 responded to bupropion augmentation, as opposed to 2 (50%) of 4

Table 1. Sexual Dysfunction and SRI Use in 47 Patients

Variable	Male (N = 18)	Female (N = 29)
Sexual dysfunction, N[a]		
Desire	9	14
Arousal	7	3
Orgasm	14	28
SRI used, N		
Paroxetine	4	11
Fluoxetine	8	9
Sertraline	1	3
Venlafaxine	4	4
Fluvoxamine	1	2

[a]The number of sexual complaints exceeds the number of patients because several patients had more than one dysfunction.

Table 2. Efficacy of Bupropion Administration by Dosage, SRI Treatment, and Specific Sexual Complaint

Variable	N	Outcome Rating: No Improvement	Outcome Rating: Improvement
Bupropion dosage			
75 mg prn	47	38 (81%)	9 (19%)
150 mg prn	35	26 (74%)	9 (26%)
75 mg tid	23	10 (43%)	13 (57%)
Final results	**47**	**16 (34%)**	**31 (66%)**
SRI treatment			
Paroxetine	15	3 (20%)	12 (80%)
Fluoxetine	17	6 (35%)	11 (65%)
Other			
Sertraline	4	2 (50%)	2 (50%)
Venlafaxine	8	3 (38%)	5 (63%)
Fluvoxamine	3	2 (67%)	1 (33%)
Subtotal	15	7 (47%)	8 (53%)
Total	**47**	**16 (34%)**	**31 (66%)**
Sexual complaint[a]			
Desire	23	7 (30%)	16 (70%)
Arousal	10	4 (40%)	6 (60%)
Orgasm	42	12 (29%)	30 (71%)
Total	**75**	**23 (31%)**	**52 (69%)**

[a]Ns are for number of complaints

Table 3. Efficacy of Bupropion Augmentation by SRI and Gender

SRI	N	Outcome Rating	
		No Improvement	Improvement
Paroxetine			
Male	4	2	2
Female	11	1	10
Fluoxetine			
Male	8	4	4
Female	9	2	7
Venlafaxine			
Male	4	2	2
Female	4	1	3
Sertraline			
Male	1	1	0
Female	3	1	2
Fluvoxamine			
Male	1	0	1
Female	2	2	0
Total	**47**	**16**	**31**

men. Again, this trend did not reach statistical significance ($\chi^2 = 2.86$, $p = .09$).

The impact of bupropion treatment on specific components of sexual responses (e.g., desire, arousal, orgasm) is described in Table 2. The number of sexual complaints exceeded the number of patients because several patients had more than one dysfunction. As indicated, the largest numbers of problems were in the desire and orgasm phases of sexual response. Twenty-three (31%) of 75 complaints were of reduced desire. Forty-two (56%) of 75 complaints were of reduced ability to achieve orgasm. Improvements in sexual functioning were seen in 52 (69%) of 75 complaints. Although improvements were noted in all types of sexual dysfunction, a trend toward greater improvements was noted in desire and orgasmic difficulties ($\chi^2 = 0.06$, $p = .82$). In women, 37 (82%) of 45 complaints responded to bupropion as opposed to 15 (50%) of 30 complaints in men. This difference by gender reached statistical significance ($\chi^2 = 8.67$, $p < .01$).

The most commonly reported adverse effects of bupropion were anxiety and tremor, which led to discontinuation in 7 (15%) of 47 patients. One additional patient discontinued bupropion because of diarrhea. One patient described hypersexuality without hypomania while taking bupropion, which was perceived as pleasurable. No patients had seizures or other adverse events while taking bupropion.

DISCUSSION

Our findings indicate that bupropion augmentation appears to be an effective means of counteracting SRI-induced sexual dysfunction in patients with anxiety and depressive disorders. The effect of bupropion was somewhat more positive for sexual desire and orgasmic problems than for arousal difficulties. However, if one compares percentage of symptoms improved with percentage of patients improved, the percentages are almost identical (69% vs. 66%). Over one third of patients were able to successfully use bupropion on a p.r.n. basis. Most patients tolerated bupropion augmentation well.

There was a nonsignificant trend for female patients receiving paroxetine or fluoxetine to be especially responsive to bupropion augmentation therapy. Although this comparison did not reach statistical significance, the response was provocative. There may be several explanations for why more women responded in our study. The average age of women was younger than for men. In addition, more women were taking paroxetine, a drug associated with an increased bupropion response. Also, more women complained of orgasmic dysfunction, and fewer women complained of arousal dysfunction compared with men; these complaints in turn were associated with an enhanced bupropion response. These factors may have contributed to greater improvement in sexual function in women. Despite this gender difference, however, 50% of men did note a favorable effect from bupropion.

Despite the overall positive effects observed with bupropion treatment, there are several limitations to this study. First, the trial was not placebo controlled. Therefore, the percentage of responders demonstrating a placebo response is unknown. It is uncertain how many patients may have shown accommodation to the sexual side effects of their particular SRI over time, although this phenomenon has been previously reported to be uncommon.[5,6] Since patients were kept on scheduled bupropion treatment for only 2 weeks before abandoning this augmentation strategy, it is possible that nonresponders may have responded had they remained on bupropion treatment longer. Also, it is possible that nonresponders might have responded had the bupropion dose been increased. As noted, several patients did not follow instructions to take bupropion on a t.i.d. basis after failing p.r.n. dosing. It is possible that several, if not all, of these patients would have been converted into responders had they agreed to follow the prescribed protocol. Efficacy of bupropion continued throughout the course of treatment, which was up to 9 months. No patient noted a loss of efficacy after an effective dose of bupropion had been attained.

This study did not address the mechanism of action by which bupropion alleviated sexual symptoms in this population. In other contexts, mild dopamine agonism has been shown to enhance sexual functioning.[19,20] It is likely that dopaminergic effects of the drug were contributory in this study, since other receptor effects of bupropion appear minimal.[17]

Implications for further research include assessing response based on patient self-report using a standardized rating scale. The potential of bupropion to potentiate an antidepressant effect separate from its ability to reverse sexual dysfunction is unknown. Standardized mood rating scale assessments before and after initiation of bupropion

augmentation may more clearly define this phenomenon. Finally, it may be helpful to determine whether bupropion provides a preferential effect based on diagnosis.

CONCLUSION

A substantial number of patients taking SRIs are likely to develop sexual dysfunctions. Patient reports by way of direct interview from this study suggest that bupropion augmentation may be a valuable means by which to assist patients in overcoming these troublesome side effects. Bupropion augmentation was well tolerated, and efficacy was maintained over time in most patients. Further studies utilizing a clinical trial or randomized double-blind, placebo-controlled format are needed to more clearly delineate medication effects and optimal dosing schedule.

Drug names: amantadine (Symmetrel), bupropion (Wellbutrin), buspirone (BuSpar), cyproheptadine (Periactin and others), fluoxetine (Prozac), fluvoxamine (Luvox), methylphenidate (Ritalin), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor), yohimbine (Yocon and others).

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