Substitution of an SSRI With Bupropion Sustained Release Following SSRI-Induced Sexual Dysfunction

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Background: We examine changes in sexual functioning and depressive symptoms in patients' transition from a selective serotonin reuptake inhibitor (SSRI), which induced both a therapeutic response and sexual dysfunction, to bupropion sustained release (SR) over the course of an 8-week trial.

Method: The study included 11 adults (8 women and 3 men) who had a DSM-IV diagnosis of major depressive disorder in remission (Hamilton Rating Scale for Depression [HAM-D] score < 11) and were receiving an SSRI. Depression (using the HAM-D) and sexual dysfunction (using the Changes in Sexual Functioning Questionnaire) were assessed at baseline, 2 weeks after bupropion SR was added to the current antidepressant (combined treatment), 2 weeks after taper of the SSRI was initiated and completed, and after 4 weeks of bupropion SR monotherapy. T tests were performed to assess changes in depression and sexual function.

Results: Patient participation dropped from the initial group of 11 at week 2 to 9 at week 4 and to 6 by week 8. Sexual functioning improved from week 0 (baseline) to week 2 and from week 2 to week 4. The patients showed no significant change in mean HAM-D scores in weekly comparisons during the study period; 55% of patients completed the substitution without significant adverse events or recurrence of depressive symptoms.

Conclusion: Bupropion SR as a treatment for depression also alleviates sexual dysfunction due to SSRI treatment. Results show that sexual functioning improves after the addition of bupropion SR to SSRI treatment and continues to improve, after discontinuation of the SSRI, with bupropion SR treatment alone.

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Both depression and the pharmacologic treatment of depression are associated with sexual dysfunction. Approximately 70% of individuals with major depression experience decreased libido, and those with more severe symptoms of depression show the greatest decrease in sexual desire.[1] In addition, depressed men report less sexual satisfaction than control subjects.[2] Selective serotonin reuptake inhibitors (SSRIs) affect orgasm, desire, and, to a lesser degree, arousal in 30% to 50% of those treated and may lead to medication noncompliance.[3–6] Strategies to manage SSRI-induced sexual dysfunction include drug holidays,[7] addition of antidotes,[8–14] and substitution with antidepressants with minimal effects on sexual functioning, including bupropion sustained release (SR),[15,16] nefazodone,[5,17] and mirtazapine.[17] Drug substitution simplifies the medication regimen with a single agent, but the patient who has experienced a therapeutic response to an SSRI may be fearful of relapse if the SSRI is discontinued and a new antidepressant medication is initiated. To this point, and in spite of the high incidence of SSRI-induced sexual problems, only a few studies have addressed substituting an SSRI with an antidepressant with a low incidence of sexual dysfunction.[16–18]

In this feasibility study, we examine the transition from an SSRI, which induced both a therapeutic response and sexual dysfunction, to bupropion SR. The hypotheses tested were as follows: (1) bupropion SR will be an effective antidote for SSRI-induced sexual dysfunction as measured by the Changes in Sexual Functioning Questionnaire (CSFQ),[19–21] (2) bupropion SR will be as effective as an SSRI for treatment of depression as measured by the Hamilton Rating Scale for Depression (HAM-D),[22] and (3) the transition from an SSRI to bupropion SR will be well tolerated.

METHOD

Screening

Subjects were recruited either through newspaper or radio advertising or through physician referral.

Inclusion criteria. Subjects included in the study were 18 to 52 years of age, met DSM-IV criteria for single or recurrent nonpsychotic major depressive episode(s), had been receiving treatment with an SSRI for at least

2 months, demonstrated a therapeutic response to SSRI treatment, and presented with sexual dysfunction or sexual problems that worsened with SSRI treatment. To simplify drug classification, the serotonin-norepinephrine reuptake inhibitor venlafaxine has been included with the SSRIs in this study.

Exclusion criteria. Exclusion criteria included presence of another current primary psychiatric diagnosis such as bipolar disorder, schizophrenia, generalized anxiety disorder, or substance abuse; existence of a determined physiologic cause for sexual dysfunction, including cardiovascular, endocrine, neurologic, structural or (non-SSRI) medication-induced impairment; history of psychotic illness, seizure disorder, head injury, eating disorder, structural neurologic impairment or other serious uncontrolled medical condition; for women, current pregnancy, lactation, or at perimenopause or postmenopause; current use of the following medications: coumadin, digitoxin, amantadine, yohimbine, buspirone, oral steroids, lithium carbonate, carbamazepine, valproate, neuroleptics, cyproheptadine, methylphenidate, dextroamphetamine, tryptophan, or sedative-hypnotics (except chloral hydrate); active suicidality; or known sensitivity to bupropion SR.

Measures

Sexual functioning. The interview version of the CSFQ[19] was used to assess level of sexual functioning. The CSFQ is a validated measure of sexual functioning with established reliability. CSFQ scores are based on self-report information provided by the patient to the clinician in a clinical interview setting. The questionnaire was developed and validated by the lead author (A.H.C.) in previous studies,[19–21] with normative information on various clinical and nonclinical populations, and has been found to have sound psychometric properties. It was designed to be a global measure of current sexual functioning and is not necessarily confined to intercourse or other sexual acts with a partner; it is also meant to include masturbation and other activities without a partner.

The CSFQ identifies and differentiates between individuals who have lifelong poor psychosexual adjustment and those who have acquired sexual dysfunction after prior normal functioning. The CSFQ also captures different aspects of sexual functioning: (1) sexual desire as expressed in the frequency of sexual activity, (2) sexual desire as expressed in the frequency of sexual thoughts or fantasies and enjoyment of erotica, (3) degree of sexual pleasure experienced, (4) ability to achieve and sustain sexual arousal (for women, having adequate vaginal lubrication and, for men, being able to achieve and sustain an erection), and (5) ability to attain completion through orgasm (in the case of men, also being able to ejaculate). A global measure of sexual functioning is based on summing scores on 14 items from the CSFQ that relate to current sexual activity and functioning. Global scores potentially range from 14 to 70, with higher scores representing better functioning. Based on a previous study[21] of patients with either major depressive disorder or dysthymia, scores at or below 47 for men and scores at or below 41 for women were indicative of poorer sexual functioning. Cutoff scores also exist for the subscales.*

Depression. The HAM-D[22] is a 17-item, observer-rated instrument designed to assess the severity of symptoms associated with depression as defined by the DSM-IV.

Study Trial Protocol

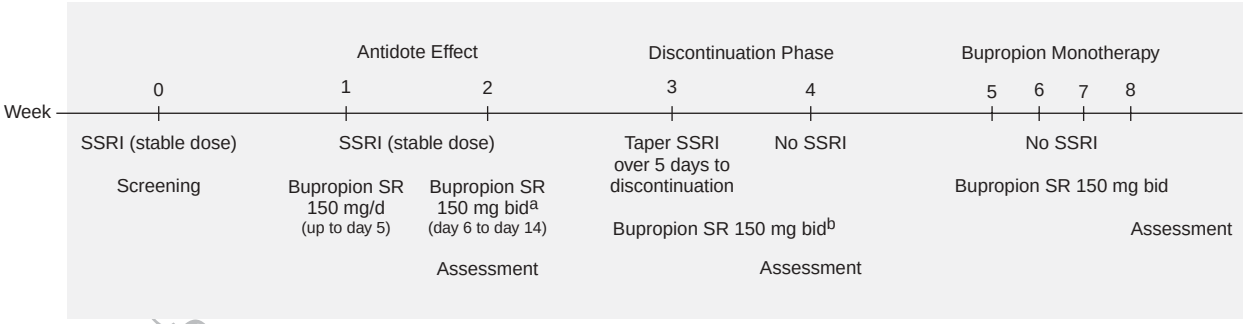
Screening visit (week 0). This study was approved by the Human Investigation Committee of the University of Virginia Health System. Informed consent forms were reviewed and signed by patients before any study procedures were performed. The screening visit entailed an in-depth assessment of the patients' sexual functioning using the CSFQ. Any present symptoms of depression or recurrence of depression was assessed using the HAM-D. A detailed intake interview was conducted by the study physician (A.H.C. or A.I.A.), and the following blood tests were performed: thyroid function tests (thyrotropin-stimulating hormone, thyroxine, and T_3 resin uptake), prolactin levels, free and total testosterone levels (for men only), and β-human chorionic gonadotropin levels (for women only). Concomitant medications, vital signs, and weight were recorded.

Subjects had to have a HAM-D score < 11 and either a total CSFQ score < 47.0 for men or < 41.0 for women, an orgasm subscale score < 13.0 for men or < 11.0 for women, or a desire/interest subscale score < 11.0 for men or < 9.0 for women.

Treatment protocol. If patients met criteria for inclusion, bupropion SR was added to the current antidepressant medication at a starting dose of 150 mg/day and, if tolerated, increased after 5 days to 150 mg twice daily. The dosage of the SSRI remained stable throughout the first 2 weeks of treatment with bupropion SR. The HAM-D and CSFQ were administered, and concomitant medications, vital signs, and weight were assessed at week 2 of combined treatment. This 2-week phase examined the antidote/adjunctive effect. If the HAM-D score remained less than 11 at week 2, taper of the SSRI was initiated and completed as tolerated over the next 14 days. Patients were instructed to take half the dose of the SSRI for 5 days and then discontinue the SSRI. This 2-week period monitored the effect of SSRI discontinuation. By week 4, the patient was completely off the SSRI and continued on bupropion SR monotherapy until week 8. The assessments were repeated

*Cutoff scores are based on the upper limit of the 95% confidence interval for the mean score on the CSFQ and its subscales from a sample of patients (19 women and 13 men) diagnosed with major depressive or dysthymic disorder. Scores for men and women were computed separately.

Figure 1. Weekly Dosages of Selective Serotonin Reuptake Inhibitors (SSRIs) and Bupropion Sustained Release (SR) From Baseline to Week 8



[a]If tolerated.
[b]If there was a 25% increase in Hamilton Rating Scale for Depression scores between week 2 and week 4, dosing of bupropion was increased by 100 mg up to 400 mg/day.

at weeks 4 and 8. At week 4, if the change in HAM-D score from week 2 to week 4 increased by more than 25% or if the absolute HAM-D score was greater than 14, bupropion SR was increased by 100 mg to a maximum of 200 mg twice daily (Figure 1).

Statistical Analysis

Paired sample (single-tailed) t tests were conducted to test for improvement in sexual functioning as assessed by the CSFQ from week 0 to week 2, week 2 to week 4, and week 4 to week 8. Additional contrasts were done to compare mean scores between week 0 and week 4 and between week 0 and week 8. Pairwise comparisons (week to week) were used to accommodate missing data. Improvement in global level of sexual functioning, as well as specific aspects of improvement such as desire/interest and ability to achieve orgasm, was analyzed. Multiple t tests were also performed to assess for changes in depression as determined by HAM-D scores.

RESULTS

Final Sample

Eleven patients (8 women and 3 men) were enrolled and 6 (4 women and 2 men) completed the study. One patient withdrew during the first phase of the study secondary to adverse events. Four patients withdrew from the study after week 2 due to adverse events. Since the small sample size does not permit analysis by gender, scores from men and women were combined.

Demographics. Patients ranged from 22 to 52 years of age, and all were non-Hispanic white. Five patients were married, 4 patients were single, and 2 patients were divorced. All but 2 patients had completed college, and these 2 had attended some college. All but 2 patients were currently involved in a sexual relationship; 1 woman had just ended a relationship, and another woman described herself as being in a dating relationship with little sexual intimacy or activity. All but 1 described their sexual activity as at least "somewhat (important) of an issue" in their marital or dating relationship.

Antidepressant history/chief complaints. Among the 11 patients, 4 were taking paroxetine (mean dose = 35 mg/day), 4 were taking sertraline (mean dose = 94 mg/day), 2 were taking fluoxetine (mean dose = 12.5 mg/day), and 1 was taking venlafaxine (mean dose = 225 mg/day). Patients reported taking their current antidepressant for as long as 46 months or as short as 2 months. The most commonly reported sexual complaints at baseline assessment were problems with reduced sexual desire or libido (reported by 9 patients) and problems with orgasm and/or ejaculation (reported by 10 patients). Six patients also reported problems with ability to achieve or sustain arousal, ranging from erectile difficulties (for men) to inadequate vaginal lubrication (for women). The mean dose of bupropion SR at study termination was 345 mg/day.

Changes in Sexual Functioning

Global CSFQ scores. Single-tailed paired t tests revealed significant improvement in global CSFQ scores from week 0 to week 2 and from week 2 to week 4 (Table 1). Each of the mean scores at weeks 2, 4, and 8 were significantly greater than the mean score at week 0, thus indicating improvement in global sexual functioning after starting bupropion SR.

Sexual desire/interest. The mean scores at weeks 4 and 8 were both significantly greater than the mean score at baseline, which indicates greater improvement in desire/interest subscale scores while patients were receiving bupropion SR alone (see Table 1).

Orgasm. Likewise, scores on the orgasm subscale showed a significant increase from week 0 to week 4 and from week 0 to week 8. Thus, both desire/interest and orgasm subscale scores showed significant improvement

Table 1. Change in Sexual Functioning Across Each Treatment Period and From Baseline[a]

	Global CSFQ Score				Sexual Desire/Interest Subscale Score				Orgasm Subscale Score			
Comparison	Mean	SD	t	p	Mean	SD	t	p	Mean	SD	t	p
Week 0 (N = 11)	39.44	8.31	–1.81	< .05	7.36	2.06	NS	NS	7.73	1.95	NS	NS
Week 2 (N = 11)	43.55	12.82			8.18	3.57			7.82	4.26		
Week 2 (N = 9)	43.67	12.21	–2.28	< .05	8.33	3.57	NS	NS	7.89	4.20	NS	NS
Week 4 (N = 9)	50.89	12.11			9.78	2.44			10.33	3.67		
Week 4 (N = 6)	54.00	10.26	NS	NS	10.83	1.94	NS	NS	11.00	2.97	NS	NS
Week 8 (N = 6)	57.00	6.00			11.00	2.45			11.83	2.32		
Week 0 (N = 9)	40.67	8.25	–3.94	< .05	7.44	2.24	–2.99	< .05	8.00	2.06	–2.14	< .05
Week 4 (N = 9)	50.89	12.11			9.78	2.44			10.33	3.67		
Week 0 (N = 6)	42.67	8.09	–6.80	< .05	7.67	2.07	–2.91	< .05	8.67	2.25	–4.50	< .05
Week 8 (N = 6)	57.00	6.00			11.00	2.45			11.83	2.32		

[a]Abbreviations: CSFQ = Changes in Sexual Functioning Questionnaire, NS = not significant.

Table 2. Hamilton Rating Scale for Depression Scores at Weeks 0, 2, 4, and 8

	Mean	SD	Minimum	Maximum
Week 0 (N = 11)	6.45	2.88	3	11
Week 2 (N = 11)	7.16	4.12	4	16
Week 4 (N = 9)	9.33	6.80	3	21
Week 8 (N = 6)	3.50	1.18	0	8

during the period after SSRI discontinuation, with bupropion SR alone (see Table 1).

Severity of Depression

Mean scores on the HAM-D at week 0 and at other weeks were not statistically different, suggesting depression did not worsen with discontinuation of SSRI treatment (Table 2).

Adverse Events With Combination Treatment

Eight (73%) of 11 patients reported some adverse experiences while receiving combined treatment, and 9 (82%) of 11 reported either an onset or continuation of adverse experiences after discontinuation of the SSRI. Table 3 shows the percentage of patients reporting adverse experiences. Some patients reported multiple adverse events. Of the 45% who discontinued participation in the study, most reported symptoms associated with SSRI discontinuation syndrome[23] including agitation, nausea, sweating, flushing, headache, tinnitus, dizziness, and depressed mood beginning 3 days after discontinuation of the SSRI. Four of the patients with early termination from the study were taking SSRIs with short half-lives (2 receiving sertraline and 2 receiving paroxetine). After these 4 subjects withdrew from the study, they were treated clinically by restarting the SSRI at the baseline dose. The adverse events abated within 24 hours of taking a full dose of the SSRI, supporting the clinical diagnosis of SSRI discontinuation syndrome. The 2 patients receiving paroxetine who withdrew from the study (18% of the study sample) also experienced a recurrence of depressive symptoms after discontinuation of the SSRI. The single patient receiving venlafaxine

Table 3. Patients Reporting Adverse Events at Weeks 2, 4, and 8

	Week 2[a] (N = 11)		Week 4[b] (N = 9)		Week 8[c] (N = 6)	
Adverse Event	N	%	N	%	N	%
Nausea	2	18	4	44	1	17
Constipation	3	27	2	22	1	17
Mood swings	2	18	2	22	0	0
Agitation	2	18	2	22	2	33
Sweating	2	18	2	22	1	17
Sleep disturbance	2	18	1	11	0	0
Vertigo	1	9	3	33	0	0
Headache	2	18	5	56	1	17
Flushing	1	9	0	0	1	17
Tinnitis	1	9	0	0	0	0

[a]Selective serotonin reuptake inhibitor (SSRI) + bupropion sustained release (SR) (antidote phase).
[b]SSRI discontinuation + bupropion SR.
[c]Bupropion SR monotherapy.

discontinued participation in the study after 2 weeks of combined treatment, complaining of dizziness, nausea, and headache.

DISCUSSION

This study indicates that bupropion SR as a treatment for depression also alleviates sexual dysfunction due to SSRI treatment. Sexual functioning improved with both the addition of bupropion SR and substitution of bupropion SR for the SSRI. Improvement in sexual functioning occurred within 2 weeks of beginning bupropion SR during SSRI treatment, and sexual functioning continued to improve during the weeks following SSRI discontinuation. This improvement was statistically significantly different from baseline at each visit for global measures of sexual functioning. Sexual desire/interest and orgasmic function (week 4) showed statistically significant improvement over baseline only after discontinuation of the SSRI. This lack of statistically measurable effect might be explained by increased levels of some of the SSRIs in the blood during combined treatment secondary to the cytochrome P450 2D6 (CYP2D6) inhibitory effects of

bupropion SR.[24] Theoretically, then, reduction in the dose of the SSRI, once combined treatment is initiated, may allow for improved sexual functioning while maintaining remission of depressive symptoms.

A random-effects analysis indicated that subjects with higher levels of sexual functioning at week 0 were somewhat more likely to drop out of the study by week 8 (see Table 1). This trend, while not statistically significant, is particularly apparent from weeks 4 to 8. Global CSFQ scores (mean = 54.00) at week 4 were noticeably higher for 6 participants who finished the study than week 4 global scores (mean = 50.89) for the 5 participants who did not finish the study.

Although most patients (about 73%) experienced some early adverse effects following the addition of bupropion SR, in only 1 case did it result in early termination soon after starting the combined treatment with the SSRI. These adverse events may have been related to an increase in available venlafaxine due to the inhibitory effects of bupropion SR on the CYP2D6 system or due to combined effects of venlafaxine and bupropion SR on norepinephrine reuptake. The combination of SSRI and bupropion SR was relatively well tolerated. In 2 cases (18% of the study sample), patients withdrew due to SSRI discontinuation symptoms with a recurrence of depressive symptoms (perhaps part of the discontinuation syndrome). This should be reassuring to patients wishing to substitute a second antidepressant when an SSRI has induced sexual dysfunction. The outcome in this study does not differ significantly from the study by Walker et al.[16] in which subjects were off fluoxetine treatment for 2 weeks before beginning bupropion SR.[16] In 2 cases (18% of the study sample), patients discontinued early from the study due to experiencing SSRI withdrawal without depressed mood. This appears to be secondary to the rapid discontinuation of the SSRI over 5 days and could possibly be prevented with a prolonged taper, especially for SSRIs with short half-lives such as paroxetine and sertraline since withdrawal reactions have been described even after a 2-week taper.[25] Superimposition of common side effects of bupropion SR with SSRI discontinuation symptoms is also a possibility. In conclusion, 55% of the patients completed the substitution without adverse events or recurrence of depressive symptoms. Thus, patients contemplating substitution of an SSRI with bupropion SR could expect at least a 55% chance of success, with 18% experiencing recurrence of depressive symptoms. This rate of sustained remission of depressive symptoms is similar to the rates of remission achieved with initial treatment with a single antidepressant.

Limitations of this study include its small sample size. In addition, the CSFQ, although a valid and reliable instrument, may have limitations in sensitivity to detect change in subscale scores as compared to the global CSFQ score. With the possibility of self-selection, those who did not improve on bupropion SR treatment were more likely to withdraw from the study early. In addition, the discontinuation of the SSRI contributed to the dropout rate. The design of the study could not have included a placebo-control group because randomly assigning patients to placebo who had previously responded well to treatment with an SSRI, except for the development of sexual side effects, raises ethical questions regarding relapse of depression. Enrollment was limited because some patients were fearful of switching antidepressants once their depression was in remission, even if they experienced SSRI-induced sexual dysfunction. Therefore, enrollment was stopped early, and a new study design was planned that allows evaluation of bupropion SR versus placebo as an antidote/adjunctive therapy in patients with SSRI-induced sexual dysfunction. Although adjunctive strategies may impact patient compliance, they do offer patients a potential antidote for SSRI-induced sexual dysfunction and potential additional improvement in depressive symptoms, as were found in this study. Finally, with adjunctive strategies, lower doses of bupropion SR may be required and the adverse events associated with SSRI discontinuation are avoided. Still, this study demonstrates improvement in desire, orgasmic function, and overall sexual functioning, without recurrence of depressive symptoms in more than 50% of the subjects, with substitution of bupropion SR for SSRIs that induced sexual dysfunction.

Drug names: amantadine (Symmetrel and others), bupropion (Wellbutrin), buspirone (BuSpar), carbamazepine (Tegretol and others), cyproheptadine (Periactin), dextroamphetamine (Dexedrine and others), fluoxetine (Prozac), methylphenidate (Ritalin and others), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor), yohimbine (Aphrodyne and others).

REFERENCES

1. Casper RC, Redmond DE Jr, Katz NM, et al. Somatic symptoms in primary affective disorder: presence and relationship to the classification of depression. Arch Gen Psychiatry 1985;42:1098–1104
2. Nofzinger EA, Thase ME, Reynolds CF, et al. Sexual function in depressed men: assessment by self-report, behavioral, and nocturnal penile tumescence measures before and after treatment with cognitive behavioral therapy. Arch Gen Psychiatry 1993;50:24–30
3. Segraves RT. Overview of sexual dysfunction complicating the treatment of depression. J Clin Psychiatry Monograph 1992;10(2):4–10
4. Balon R, Yeragani VK, Pohl R, et al. Sexual dysfunction during antidepressant treatment. J Clin Psychiatry 1993;54:209–212
5. Feiger A, Kiev A, Shrivastava RK, et al. Nefazodone versus sertraline in outpatients with major depression: focus on efficacy, tolerability, and effects on sexual function and satisfaction. J Clin Psychiatry 1996;57 (suppl 2):53–62
6. Montejo-Gonzales AL, Llorca G, Izquierdo JA. SSRI-induced sexual dysfunction: fluoxetine, paroxetine, sertraline, and fluvoxamine in a prospective multicenter and descriptive clinical study of 344 patients. J Sex Marital Ther 1997;23:176–194
7. Rothschild AJ. Selective serotonin reuptake inhibitor–induced sexual dysfunction: efficacy of a drug holiday. Am J Psychiatry 1995;152: 1514–1516
8. Ashton AK, Rosen RC. Bupropion as an antidote for serotonin reuptake inhibitor–induced sexual dysfunction. J Clin Psychiatry 1998;59:112–115
9. Balogh S, Hendricks SE, Kang J. Treatment of fluoxetine-induced anorgasmia with amantadine [letter]. J Clin Psychiatry 1992;53:212–213

10. Bartlik BD, Kaplan P, Kaplan HS. Psychostimulants apparently reversed sexual dysfunction secondary to selective serotonin reuptake inhibitors. J Sex Marital Ther 1995;4:264–271
11. Jacobsen FM. Fluoxetine-induced sexual dysfunction and an open trial of yohimbine. J Clin Psychiatry 1992;53:119–122
12. Hollander E, McCarley A. Yohimbine treatment of sexual side effects induced by serotonin reuptake blockers. J Clin Psychiatry 1992;53:207–209
13. Norden MJ. Buspirone treatment of sexual dysfunction associated with selective serotonin re-uptake inhibitors. Depression 1995;2:109–112
14. Fava M, Rankin MA, Alpert JE, et al. An open trial of oral sildenafil in antidepressant-induced sexual dysfunction. Psychother Psychosom 1998; 67:328–331
15. Kavoussi RJ, Segraves RT, Hughes AR, et al. Double-blind comparison of bupropion sustained release and sertraline in depressed outpatients. J Clin Psychiatry 1997;58:532–537
16. Walker PW, Cole JO, Gardner EA, et al. Improvement in fluoxetine-associated sexual dysfunction in patients switched to bupropion SR. J Clin Psychiatry 1993;54:459–465
17. Ferguson JM, Shrivastava RK, Stahl SM, et al. Effects of double-blind treatment with nefazodone or sertraline on re-emergence of sexual dysfunction in depressed patients. In: New Research Program and Abstracts of the 149th Annual Meeting of the American Psychiatric Association; May 7, 1996; New York, N.Y. Abstract NR358:164
18. Gelenberg AJ, Laukes C, McGahey C, et al. Mirtazapine substitution in SSRI-induced sexual dysfunction. Presented at the 38th annual meeting of the New Clinical Drug Evaluation Unit; June 10–11, 1998; Boca Raton, Fla
19. Clayton AH, Owens JE, McGarvey EL. Assessment of paroxetine-induced sexual dysfunction using the Changes in Sexual Functioning Questionnaire. Psychopharmacol Bull 1995;31:397–413
20. Clayton AH, McGarvey EL, Clavet GJ. The Changes in Sexual Functioning Questionnaire (CSFQ): development, reliability, and validity. Psychopharmacol Bull 1997;33:731–745
21. Clayton AH, McGarvey EL, Clavet GJ, et al. Comparison of sexual functioning in clinical and non-clinical populations using the Changes in Sexual Functioning Questionnaire (CSFQ). Psychopharmacol Bull 1997; 33:747–753
22. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
23. Rosenbaum JF, Fava M, Hoog SL, et al. Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. Biol Psychiatry 1998;44:77–87
24. Benazzi F. Venlafaxine-fluoxetine interaction. J Clin Psychopharmacol 1999;19:96–98
25. Fava M, Mulroy R, Alpert J, et al. Emergence of adverse events following discontinuation of treatment with extended-release venlafaxine. Am J Psychiatry 1997;154:1760–1762