The Effects of Antidepressants on Sexual Functioning in Depressed Patients: A Review

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Sexual dysfunction has long been noted as both a symptom of depressive illness and as a side effect of many of the medications used to treat depression. Although most people suffering from a major depressive illness would like to be sexually active, half experience a decrease in desire or sexual performance. Antidepressant medications often interfere with several parts of the sexual response. This review compares data from different types of research into the effect of antidepressant medications on the sexual response: case reports, chart reviews, and single- and double-blind studies with and without active control medications. From this review, it is clear that antidepressants of most classes interfere with human sexual functioning, with the notable exceptions of bupropion and nefazodone.

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Impairment of sexual functioning has long been noted as a correlate of clinical depression. Although it has been considered one of the symptoms of depression since Freud and Janet, the systematic inquiry into sexual dysfunction in patients suffering from depression began when the Hamilton Rating Scale for Depression (HAM-D),[1] developed by Max Hamilton, and the Feighner Research Diagnostic Criteria[2] were introduced into clinical research. Sexual dysfunction, as defined loosely as a reduction in sexual desire; diminished arousal; lost, delayed, or altered orgasm in men and women; and lack of satisfaction, has been noted in a number of studies of psychiatric patients that included a variety of population samples.

Some type of sexual dysfunction has been found in 50% to 90% of depressed patients with or without treatment.[2–4] Much of the information gathered on the incidence of sexual dysfunction was collected in a course of investigations not primarily designed to assess sexual dysfunction. A recent systematic study by Kennedy and others,[5] which included 134 consecutive patients referred to their clinic from community psychiatrists and general practitioners, confirmed this overall impression. Patients who met DSM-IV criteria for depression (confirmed by the Structured Clinical Interview for DSM-IV disorders) did not have concurrent medical illness, were antidepressant-free for the previous 2 weeks (5 for fluoxetine), and scored at least 16 on the HAM-D were given the Sexual Function Questionnaire (SFQ), a questionnaire designed to assess domains of sexual functioning, comprising desire, arousal, and orgasm. Kennedy and colleagues constructed 2 subscales, one combining desire and drive and the other combining arousal and orgasm (Table 1), and found that only 50% of depressed women and 75% of depressed men reported sexual activity in the preceding month. Over 40% of men and 50% of women reported decreased sexual interest. Approximately 50% of men and women reported reduced levels of arousal compared with approximately 20% who reported difficulty experiencing an orgasm or difficulty with ejaculation. The authors make the point that this nonmedicated sample of systematically diagnosed and investigated individuals provides a baseline from which to measure the positive and negative effects of treatment, particularly the effects of medical treatment of depression on sexual functioning.

Although depression itself predisposes to anhedonia in all domains of functioning, clinicians increasingly have become aware over the last 10 years that the antidepressant medications they prescribe often contribute to or increase the unwanted sexual impairment caused by depression. Far from being only of academic interest, an opinion poll conducted by Baldwin et al.[6] in the United Kingdom found that despite an increase in sexual dysfunction in patients with depression, this population still identifies sexuality as important. In this survey, over 6000 individuals were interviewed in their homes (Table 2). Over 1000, or 17%, had a current or lifetime history of depression. When asked to rate the importance of a good sex life, 70% of the total sample rated it as fairly or very important. For those

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Table 1. Item Endorsement Frequency of Sexual Dysfunction in Depressed Men and Women[a]

	Men (N = 55)		Women (N = 79)	
Item	N	%	N	%
Drive/Desire				
Decrease in sexual drive	23	41.8	38	50.0
Decrease in interest in sexually explicit material	20	36.4	30	38.0
Reduction in fantasizing about sex	23	41.8	28	35.4
Reduction in masturbation	22	40.0	24	30.4
Arousal/Orgasm				
Men (N = 41)				
Less vigorous erections	14	34.1		
Inability to sustain an erection	19	46.3		
Fewer spontaneous erections	9	22.0		
More difficulty with premature ejaculation	5	12.2		
More problems with delayed ejaculation	9	22.0		
Women (N = 40)				
Less sexual arousal			20	50.0
Difficulty obtaining vaginal lubrication			16	40.0
Difficulty having orgasm			6	15.5

[a]Reprinted, with permission, from Kennedy et al.[5]

Table 2. Attitudes Toward Sexuality Among Depressed Individuals[a]

Opinion Poll Item	Total Population (N = 6143)	Subpopulation Depressed (N = 1140)
Having a good sex life is fairly or very important	70%	75%
Loss of sexual interest would prompt visit to treating physician	3%	2%

[a]Attitudes were assessed in an opinion poll conducted in the United Kingdom by Baldwin et al.[6]

who had suffered depression, the proportion (75%) was slightly higher than for the total sample. Of the 466 subjects in the survey who had been prescribed antidepressant drugs, 51% reported feeling better after treatment; however, only 1% said that their sexual interest had increased during the antidepressant treatment.

Over the past 40 years, a large number of reports in the medical literature have linked sexual dysfunction and medications. Most of the initial reports concerned antipsychotic medications. Case reports and small clinical series expanded this literature to include tricyclic antidepressants and monoamine oxidase inhibitors.[7–11]

The first systematic attempt to study the effect of antidepressant medication on sexual dysfunction was conducted by Harrison and colleagues in 1986.[12] They compared the effects of imipramine, phenelzine, and placebo in specific aspects of sexual functioning in depressed outpatients before and after 6 weeks of treatment. Using a version of the SFQ, which they developed, they followed patients who met Research Diagnostic Criteria for major, minor, or intermittent depressive disorder. One hundred initial patients completed the SFQ and mood rating scales, and 82 completed pretreatment and posttreatment sexual function questionnaires. In a flexible dosing regimen, the patients were taking between 60 and 90 mg/day of phenelzine and between 200 and 300 mg/day of imipramine or placebo for 6 weeks. The questionnaire was administered prior to and at the end of treatment to both male and female subjects.

In this study,[12] delayed orgasm was noted in 21% of the men taking imipramine and 30% of the men taking phenelzine. No delay was noted with placebo. Orgasmic delay was noted in 11% of women taking imipramine and 36% of women taking phenelzine. Of the 7 items rated by both male and female patients, 5 items showed statistically significant treatment-related decreases in sexual function. A main effect of treatment was found for thinking about sex with interest or desire, enjoyment of sex, ability to achieve orgasm with intercourse or masturbation, and frequency of masturbation. In all cases, patients receiving active drug showed more impairment after treatment than patients taking placebo. The overall percentage of patients showing a decrease in sexual functioning was 30% with imipramine, 40% with phenelzine, and 6% with placebo (Table 3). There was no significant effect of either drug on ability to become sexually aroused. The study demonstrated a dose-related effect of serum tricyclic levels in those who developed sexual dysfunction. The nonresponders to treatment showed a tendency toward greater impairment than responders with respect to enjoyment, arousal, achievement of orgasm with either intercourse or masturbation, frequency of intercourse, and ejaculation difficulties. Changes in adverse sexual function secondary to treatment with both antidepressants occurred frequently in women, although men reported a higher incidence and more kinds of problems.

In their discussion, Harrison and colleagues[12] raised the question of medication compliance in patients treated with antidepressant medication, even successfully, at the cost of a decrease in sexual functioning. At the time, this study was unique in the literature for using baseline measurement, a placebo control group, and a patient rating scale to assess orgasmic difficulties.

Since this landmark article, a large number of reports of sexual side effects of antidepressant medications have been published, particularly subsequent to the introduction of the selective serotonin reuptake inhibitors (SSRIs). The incidence of reported side effects reflects increasing awareness of sexual difficulties caused by antidepressant medications among clinicians and researchers as well. For example, the incidence of side effects reported for fluoxetine has changed dramatically from 1.9% when it was first released to 75% in the most recent survey.[13] The earliest data were flawed by the lack of systematic inquiry during the course of the clinical trials and the lack of baseline assessment of sexual dysfunction. Underreporting of sexual side effects has probably occurred in most clinical trials, almost all of which have relied on spontaneous, unprompted re-

Table 3. Mean Sexual Function Questionnaire (SFQ) Item Scores Adjusted for Baseline Score[a]

SFQ Item	Men			Women			F	p Value	Contrast
	Placebo	Phenelzine	Imipramine	Placebo	Phenelzine	Imipramine			
Thinking about sex with interest/desire	2.28	3.27	2.68	2.65	3.27	2.40	3.99	.02	Phenelzine > imipramine Phenelzine > placebo
Enjoyment of sex	2.07	3.33	2.01	2.52	2.83	1.98	3.68	.03	Phenelzine > imipramine Phenelzine > placebo
Ability to become sexually aroused	2.02	2.57	2.44	2.38	2.46	2.01	0.71	.49	NS
Ability to have an orgasm during sexual intercourse	1.61	3.67	2.30	2.22	3.20	2.10	9.55	.00	Phenelzine > imipramine Phenelzine > placebo

[a]Adapted, with permission, from Harrison et al.[12] Higher scores signify decreased sexual function.

porting of these side effects. The probable reluctance of many patients and their physicians to discuss sexual matters openly has contributed to this underreporting. Few clinical trials of SSRIs include systematic assessment of sexual functioning. In particular, in the absence of specific questioning, the incidence of anorgasmia in women may be especially underestimated. Direct questioning and the use of systematic questionnaires and structured clinical interviews invariably elicit a much higher incidence of this dysfunction, particularly in female patients.[11,12,14,15] This anecdotal literature has extended to include all of the contemporary antidepressants, with a general impression that the lowest incidence of reported sexual side effects is seen in patients treated with nefazodone, bupropion, and mirtazapine.

STUDIES WITH NONCONTROLLED PATIENT SAMPLES

A number of studies lacking placebo controls have looked at the incidence of sexual side effects of SSRIs in attempts to compare various medications. These studies include retrospective chart reviews, cross-sectional surveys, and prospective open-label studies, using standardized questionnaires to collect data. In an early cross-sectional study, Balon et al.[16] interviewed a "convenience" sample of 60 outpatients (22 men, 38 women) who had been evaluated by experienced psychiatrists and given a DSM-III-R diagnosis of mood or anxiety disorder. They developed their own questionnaire based on the Couper-Smartt and Rodham Questionnaire, which included questions about libido, time to reach orgasm, difficulty reaching orgasm, painful orgasm, difficulty getting erection, difficulty keeping an erection, erections unrelated to sexual activity, and painful erections unrelated to sexual activity.

The patient cohort in this study included 29 patients treated with imipramine (range, 20–300 mg), 14 treated with fluoxetine (range, 20–60 mg), 5 treated with trazodone (range, 75–200 mg), 4 treated with desipramine (range, 60–150 mg), 3 treated with nortriptyline (range, 60–125 mg), 3 treated with doxepin (range, 20–50 mg), and 2 treated with clomipramine (range, 150–275 mg). Forty-three percent (N = 26) of their patients reported some sexual dysfunction during the treatment (Table 4). No difference was found in the incidence of sexual dysfunction between patients with anxiety and mood disorders. Curiously, there was a significant negative correlation between weight gain and increased libido and a positive correlation between weight gain and decreased time to reach orgasm. A total of 16.6% percent of patients (7 women and 3 men) reported increased libido during treatment while taking imipramine, desipramine, fluoxetine, or doxepin.

Table 4. Sexual Dysfunction Associated With Antidepressants in 15 Women and 11 Men[a]

Drug	Patients Treated, N	Patients With Dysfunctions, N
Imipramine	29 (16 F, 13 M)	16 (8 F, 8 M)
Fluoxetine	14 (9 F, 5 M)	6 (5 F, 1 M)
Clomipramine	2 F	1 F
Nortriptyline	3 (2 F, 1 M)	1 M
Doxepin	3 (1 F, 2 M)	1 M
Desipramine	4 (3 F, 1 M)	1 F
Trazodone	5 F	0

[a]Adapted, with permission, from Balon et al.[16] Abbreviations: F = female, M = male. Some patients reported more than one specific dysfunction.

This cross-sectional study, although interesting, had a number of important limitations. No attempt was made to obtain baseline data for sexual dysfunction prospectively. There was no ability to control for or assess confounding levels of depression on anxiety. The study used an unvalidated questionnaire, the sample size was small, blood levels of antidepressants were not obtained, the source of patients was not specified, and no control group was included. Despite these limitations, the data strongly support the concept that antidepressant medications affect several aspects of sexual functioning. The overall importance of this early study lay in that it emphasized the need for systematic questioning about the specific components of generalized effects of antidepressants on sexual functioning.

In a retrospective, nonrandomized comparison of 596 psychiatric outpatients (167 men, 429 women) treated for at least 6 months with an SSRI for depression, Ashton et al.[17] found that symptoms of sexual dysfunction were

Table 5. Scores on the Arizona Sexual Experience Scale at Baseline and After 6 Weeks of Treatment With Selective Serotonin Reuptake Inhibitors for Chronically Depressed Men and Women[a]

Arizona Sexual Experience Scale Item	Men (N = 11)						Women (N = 14)					
	Baseline		6 Weeks		Treatment Analysis[b]		Baseline		6 Weeks		Treatment Analysis[b]	
	Mean	SD	Mean	SD	z	p	Mean	SD	Mean	SD	z	p
Sex drive	0.82	1.17	1.54	0.93	–1.72	.08	2.43	1.09	1.36	1.39	–2.32	.02
Psychological arousal	1.00	1.18	1.55	0.82	–1.29	.20	1.93	1.00	1.00	1.04	–2.08	.04
Physiologic arousal	0.73	1.10	1.27	1.00	–1.66	.10	1.50	1.34	0.93	0.92	–1.48	.14
Ease of orgasm	0.55	0.69	1.18	0.87	–1.93	.05	1.79	1.37	1.71	1.64	–0.33	.74
Orgasm satisfaction	0.55	0.69	1.18	0.87	–1.93	.05	1.79	1.37	1.71	1.64	–0.33	.74
Total	3.64	4.36	7.27	3.35	–2.30	.02	9.71	4.63	6.79	4.30	–2.00	.05

[a]Adapted, with permission, from Piazza et al.[19] Higher score indicates greater degree of sexual impairment.
[b]Wilcoxon test.

spontaneously reported by approximately 20% of patients. They were more common in men (23.4%) and in married individuals (22.3%) than in women and singles. The rates of dysfunction for each SSRI were as follows: sertraline, 16%; paroxetine, 22%; fluoxetine, 20%; and venlafaxine, 38%. The most common sexual problems reported in the survey were orgasmic delay or anorgasmia, decreased desire, and difficulty with sexual arousal.

Agren and colleagues[18] collected spontaneous reports of sexual dysfunction from 353 depressed outpatients participating in a clinical trial comparing paroxetine and sertraline. They found that women prescribed paroxetine experienced a significant decrease in sexual desire (9%) compared with those receiving sertraline (2%) (p = .02). Orgasmic problems in women and men were reported more frequently in the paroxetine group (6% and 14%) than in the sertraline group (1% and 5%). When Agren and colleagues asked the same patient sample about sexual dysfunction directly using questions from the UKU Side Effect Rating Scale, the incidence of reported sexual side effects was higher. For sertraline-treated patients, the incidence of decreased sexual desire at week 24 was 10%; of orgasmic dysfunction, 19%; and of male ejaculatory delay, 20%. In paroxetine-treated patients, the incidences were higher: 17% for decreased sexual desire, 27% for orgasmic dysfunction, and 32% for male ejaculatory delay.

These 3 noncontrolled studies have a common theme: sexual dysfunction often occurs when antidepressants are prescribed. It may occur at different rates in patients treated with different medications, and the rates vary widely depending on the way the data are collected.

PROSPECTIVE OPEN-LABEL STUDIES

In a study of 344 patients with mixed psychiatric diagnoses, Montejo-Gonzalez and associates[15] found an overall incidence of sexual dysfunction of 58% in patients who had a history of normal sexual functioning before SSRI treatment. Information about sexual dysfunction and side effects of the antidepressant medications was obtained by systematic physician inquiry using the Rush Sexual Inventory. This study included patients with mixed psychiatric disorders receiving monotherapy with fluoxetine, fluvoxamine, paroxetine, or sertraline at therapeutic doses. Patients had a history of sexual dysfunction prior to their being prescribed medication. Patients with a major medical illness or other medical reason for sexual dysfunction were excluded from the study. The frequency of adverse sexual effects was highest (65%) for paroxetine and was 59% for fluvoxamine, 56% for sertraline, and 54% for fluoxetine. The incidence of sexual side effects was found to be roughly dose related.

Piazza and colleagues[19] conducted a prospective study of sexual functioning in men and women diagnosed with a chronic depressive disorder before and after a 6-week course of sertraline or paroxetine. After receiving a diagnosis of chronic major depression, double depression, or dysthymia (DSM-III-R) and having a HAM-D score of at least 12, patients were randomly assigned to receive 6 weeks of treatment with sertraline or paroxetine with standard clinical management at 2-week intervals. Patients with confounding medical histories and a history of drug or alcohol abuse were excluded from the study. Although not mentioned, it is presumed that organic sexual dysfunction present prior to a patient's becoming depressed was an exclusion criterion. The measure of sexual dysfunction was the Arizona Sexual Experience Scale, which measures 5 areas of sexual functioning: sex drive, psychological arousal, physiologic arousal, ease of orgasm, and orgasm satisfaction, along with a total score. Each item was measured on a 5-point Likert scale. At the time of entry, there was significantly greater impairment for women in all items except for physiologic arousal.

After 6 weeks of treatment with an SSRI, sex drive and psychological arousal improved significantly in women, despite no change in physiologic arousal, ease of orgasm, or orgasm satisfaction (Table 5). In men, ease of orgasm and orgasm satisfaction significantly worsened, and there was a trend toward worsening sex drive. No change was found in psychological arousal or physiologic arousal (erection). The global measure of sexual functioning improved significantly in women and worsened sig-

Table 6. Improvement of Sexual Function/Satisfaction Separated by Gender and Treatment Group[a]

Study Drug	Men	Women
Fluoxetine	Increased frequency of desires to initiate sexual activity*	Increased frequency of pleasurable sexual thoughts*
	Increased frequency of initiating sexual activity*	Increased frequency of desire to initiate sexual activity*
	Increased overall degree of sexual satisfaction attained*	Increased ability to achieve an orgasm*
	Gained waking from sleep with an erection†	
	Decreased requiring more stimuli than usual to achieve an erection†	
	Experienced loss of delayed orgasm†	
	Experienced loss of premature ejaculation†	
Paroxetine	Increased ability of get an erection when sexually stimulated†	
	Gained waking from sleep with an erection†	
Sertraline	Gained waking from sleep with an erection†	Increased ability to achieve an orgasm†

[a]Reprinted from Zajecka et al.[14]
*$p \leq .05$.
†Trend toward significance.

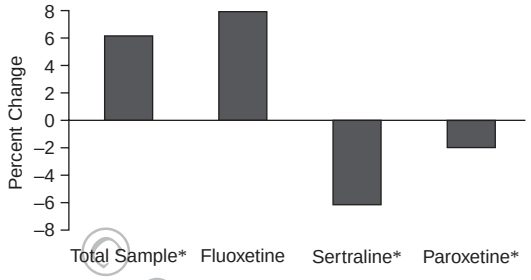
nificantly in men. Although the women were slightly more depressed than the men at baseline and endpoint (for women, mean ± SD HAM-D score = 23.6 ± 5.9 at baseline, 9.1 ± 7.1 posttreatment; for men, mean HAM-D score = 21.1 ± 6.3 at baseline, 7.6 ± 6.9 posttreatment), these differences are insufficient to explain these findings. After 6 weeks of treatment, 64% of women and 73% of men met response criteria with a HAM-D score of less than 10 and more than a 50% improvement from baseline. The sample size was too small to detect differences between treatment groups on any measures.

The study by Piazza et al.[19] is an interesting early open-label study and one of the few to show a measure of improvement in sex drive in women treated with an SSRI. As a pilot study, it suffers from a small sample size (25 subjects, 11 men and 14 women) who finished the trial, its open-label design, lack of control for the length of time or severity of depression of the patients, and relatively low doses of drug (sertraline: 60 mg q.d. for women, 66.7 mg q.d. for men; paroxetine: 25 mg q.d. for women, 20 mg q.d. for men), and despite treatment at no cost, the study had a requirement that the patients purchase their medication, which may have engendered cognitive dissonance in some of the participants. In the methodology, it is not clear that the person initially interviewing the patient and making the diagnosis, along with administering the Arizona Sexual Experience Scale, was the same person readministering the scale after 6 weeks of treatment. It would have been interesting to know if any differences in outcome existed between same- and different-sex pairing of patients and raters.

Zajecka and colleagues[14] conducted a similar open-label study in 42 outpatients (22 women, 20 men) diagnosed with depression with or without comorbid obsessive-compulsive disorder. After baseline assessment, patients were followed for 8 weeks of treatment with an SSRI: fluoxetine, 20 to 60 mg q.d.; sertraline, 50 to 200 mg q.d.; or paroxetine, 20 mg q.d. Patients with concurrent interfering medication or medical conditions and preexisting (prior to depression) organic sexual dysfunction were excluded. In this systematic study, the Rush Sexual Inventory was used to assess sexual excitement, frequency of desires to initiate sexual activity, frequency of initiating sexual activity, overall degree of sexual satisfaction, and frequency of pleasurable sexual thoughts. Within the total population and across treatments, treatment-emergent sexual dysfunction was similar for men and women (60% and 57%, respectively). Despite a decrement in some areas of sexual functioning (Table 6), there was improvement in both men and women in other areas. On visual analogue scale measures, differences in the percent change from baseline, both negative and positive, were noted for frequency of pleasurable sexual thoughts, ability to be sexually excited, frequency of desires to initiate sexual activity, frequency of initiating sexual activity, and overall degree of sexual satisfaction. It is of note that the areas of negative impact on sexual functioning were largely related to ejaculation/orgasm/maintenance of erection in men and loss of orgasm or decreased sensitivity in genitals in women rather than the psychological aspects of desire and arousal. This is one of the few studies to find differences (not statistically significant) between a number of SSRIs. The study is limited by its open-label design, the lack of indication of why patients were randomly assigned to one treatment or another, and the lack of indication of level of depression (Figures 1–5).

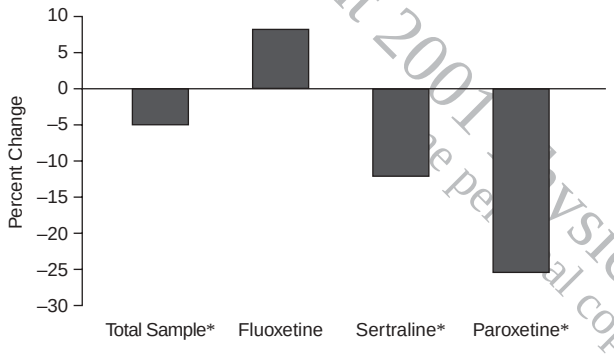
These 3 representative prospective, baseline-controlled open-label studies present convincing evidence that in a significant percentage of depressed patients, treatment with an SSRI antidepressant is followed by sexual dysfunction. The studies are small, and although a significant degree of dysfunction is described, it is difficult to say definitively if one or another antidepressant causes more of this type of dysfunction. The Montejo-Gonzalez et al.[15] and Zajecka et al.[14] articles concur in presenting the impression that of the SSRIs, paroxetine may cause more interference with sexual performance than the other antidepressants of this class. The type of interference with sexual functioning is more commonly in the domain of the organic symptoms concerned with arousal and orgasm than in that of desire or libidinal drive. Piazza et al.[19] and Zajecka et al.[14] found some positive changes, particularly in women, in drive and desire.

Figure 1. Percent Change in Frequency of Pleasurable Sexual Thoughts From Baseline to Endpoint (week 8)[a]



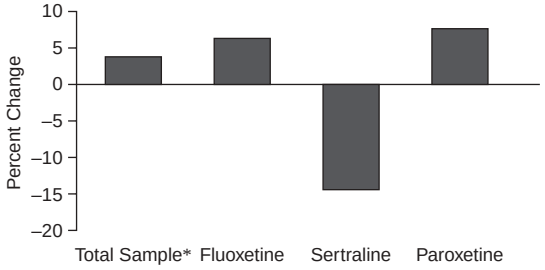
[a]Reprinted from Zajecka et al.[14]
*p < .05.

Figure 2. Percent Change in Ability to Become Sexually Excited From Baseline to Endpoint (week 8)[a]



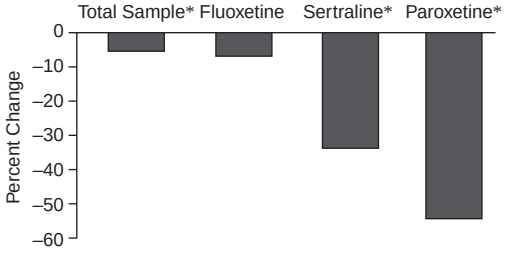
[a]Reprinted from Zajecka et al.[14]
*p < .05.

Figure 3. Percent Change in Frequency of Desires to Initiate Sexual Activity From Baseline to Endpoint (week 8)[a]



[a]Reprinted from Zajecka et al.[14]
*p < .05.

Figure 4. Percent Change in Frequency of Initiating Sexual Activity From Baseline to Endpoint (week 8)[a]



[a]Reprinted from Zajecka et al.[14]
*p < .05.

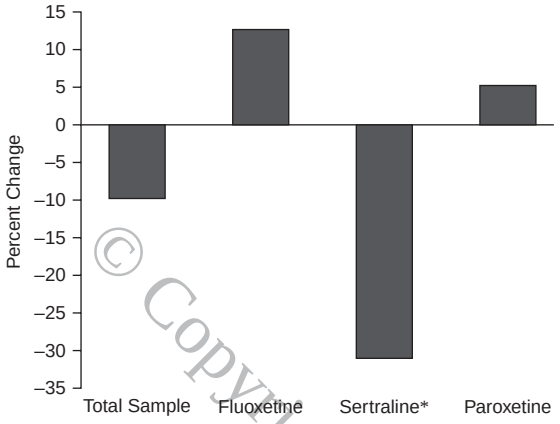
OPEN-LABEL REVERSAL OF DRUG-INDUCED SEXUAL DYSFUNCTION

Walker et al.[20] conducted a systematic open-label study of patients who had been carefully characterized as having developed sexual dysfunction during the course of treatment with fluoxetine for a depressive disorder. In this 3-center clinical study of 31 patients, the inclusion criteria included the development of orgasmic failure or delay while taking fluoxetine that was not present prior to starting fluoxetine. The patients had to have a willingness to discuss sexual functioning with the investigator, a stable sexual relationship, and sexual activity at least once every 2 weeks prior to the current depressive disorder. Patients were excluded if they had preexisting sexual dysfunction, an etiology other than fluoxetine treatment, or intercurrent medical or psychiatric illness that would prohibit participation. Patients were recruited by advertisement.

After complete psychiatric and psychosexual evaluations, patients were instructed to discontinue fluoxetine and return to the clinic in 2 weeks (fluoxetine dose not reported; time from discontinuation 1–3 weeks prior to screening). After at least a 2-week drug-free interval, patients were assigned to receive bupropion at an initial dose of 75 mg b.i.d., which was increased, if clinically indicated, to a maximum of 150 mg t.i.d.

Sexual dysfunction was rated on a 7-point Likert scale from 1 (very much improved) through 7 (very much worse) at all visits. Ratings were conducted at the time of screen, day 0, day 14, day 28, day 42, and day 56. Three domains were queried using the Likert scale: orgasmic functioning, sexual satisfaction, and libido or sex drive. At day 0, patients were also asked to describe the nature of their orgasm function or dysfunction. At the end of study day 56, the investigator rated global changes in the patients' orgasm functioning satisfaction, sexual function, and libido over the entire study using the set of questions similar to those used to evaluate sexual functioning during the 2-week intervals between clinic visits. In addition, the patients' mood disorders were monitored using the 28-item HAM-D, the Clinical Global Impression-Severity of Illness scale (CGI-S), and the CGI-Improvement scale (CGI-I). The investigators determined a priori that patients had to receive 225 mg q.d. of bupropion to be evaluable. Of the 44 patients beginning the trial, 39 entered the treatment phase, and 31 received the minimum dose of bupropion, 225 mg q.d., for at least 4 weeks. Fifty-six percent of

Figure 5. Percent Change in Overall Degree of Sexual Satisfaction From Baseline to Endpoint (week 8)[a]



[a]Reprinted from Zajecka et al.[14]
*p < .05.

the patients were female. The average patient was 45 years of age and received fluoxetine for 17 months at a mean dose of 25 mg q.d. Patients reported that they developed an orgasmic disturbance within 2 months of starting fluoxetine that, on average, lasted 15 months.

By definition, all patients reported orgasmic dysfunction at screen that had manifested itself during the initiation of fluoxetine treatment. By the end of 2 weeks during the washout phase (day 0), 13% of patients had returned to normal functioning. At the end of the bupropion treatment phase, orgasmic functioning returned to normal in 26 (84%) of the 31 patients. At screen, all 31 patients were dissatisfied (by definition) with their sexual functioning, and 84% reported decreased libido while taking fluoxetine. Improvement was found in all 3 sexual functioning domains measured—orgasm function, satisfaction with sexual function, and libido—after 2 weeks of bupropion treatment (4 weeks without fluoxetine). Similar results were observed when the investigators rated global improvement, measuring the 3 sexual functioning parameters over the entire length of the study. Of the 31 patients, 94% had complete or partial resolution of their orgasm dysfunction at the completion of the bupropion treatment. At the end of bupropion treatment, 100% of male patients (N = 15) and 88% of female patients (14/16) reported partial or complete resolution of fluoxetine-associated orgasmic dysfunction. Two patients (6%) had no improvement; none reported a worsening. For patients included in the sexual functioning analysis, little difference was found between male and female patients with respect to the level of sexual functioning at screen, baseline, and study discontinuation. The mean HAM-D score decreased during bupropion treatment from 16.6 at baseline to 8.4 at study discontinuation.

Although the data acquired in this study show a very clear return of sexual functioning, the study has several methodological drawbacks: the history of adequate sexual functioning and the diagnosis of depression were obtained from retrospective information, the use of fluoxetine was variable with the duration of use and dose not specified, the washout period between treatments was only 2 weeks with the possibility that the response seen was due to the clearance of fluoxetine rather than the effect of bupropion, a limited nonstandard sexual dysfunction rating scale was used, and no placebo control or comparator was included.

DOUBLE-BLIND COMPARATIVE STUDIES WITHOUT PLACEBO CONTROL

Feiger and colleagues[21] compared the effects of nefazodone and sertraline in patients with major depressive disorder, looking at both measures of antidepressant efficacy and sexual function and satisfaction. They enrolled 160 patients at 4 research sites in a clinical trial using DSM-III-R criteria for recurrent moderate or severe nonpsychotic major depressive disorder with a rating on the 17-item HAM-D of 20 or more. Patients met standard inclusion and exclusion criteria. They could not have used sertraline within the previous year or any other antidepressant within 3 weeks before the baseline phase of the study. Patients had a 1- to 4-week baseline during which they received no medication prior to being randomly assigned into the 6-week double-blind treatment phase of the study. At the beginning of this screening period, demographic, medical, and psychiatric information was obtained, and patients' sexual functioning was assessed using a series of questions requiring a specific "yes" or "no" response or ratings on a scale of 1 through 4 if a patient had been sexually active during the previous week. The questionnaire was completed at the beginning and end of the baseline evaluation and at the weekly evaluations during the 6-week acute treatment period. In the questionnaire, women were asked to rate their ability to achieve orgasm and their satisfaction with orgasms, and men were asked to evaluate their ability to maintain an erection and describe difficulties related to ejaculation. Both men and women were asked to rate their ability to enjoy sex and their overall satisfaction with sexual functioning.

Patients were considered evaluable for analysis if they had been assigned to receive treatment, received a dose of study medication, were sexually active, and had responded to the questionnaires during treatment. The term *endpoint* on the sexual dysfunction questionnaire referred to the responses obtained during the last week in which the patients were sexually active.

Sertraline and nefazodone were given in a double-dummy fashion. The initial dose of nefazodone was 100 mg q.d. for days 1 to 3; at day 3, the dosage could be increased by 100 mg in the absence of clinical improvement with a target dosage of 400 mg, or 4 tablets, q.d., at the

end of week 2. At the end of week 4 or any time thereafter, the dose could be increased to 600 mg. The initial dose for the sertraline group was 50 mg for the first week. During the next 2 weeks, the dose could be increased by 50-mg increments if there was no significant clinical improvement. The dose titration to a maximum level of 200 mg could occur any time during weeks 5 and 6. Weekly study assessments were made for safety, efficacy, and sexual functioning.

With 2 exceptions, baseline demographic information was comparable in the 2 groups. A greater percentage of patients in the nefazodone group had a history of recurrent depression compared with patients in the sertraline group (73% vs. 57%, p = .01), and patients who received nefazodone had on average more pretreatment episodes of depression than those treated with sertraline (4.1 vs. 2.1, p = .03). The mean daily dose of medication at week 6 was 456 mg of nefazodone or 148 mg of sertraline. One hundred twenty-one patients (76%) completed the entire 6 weeks of treatment. Twenty patients in the sertraline group and 19 in the nefazodone group discontinued treatment.

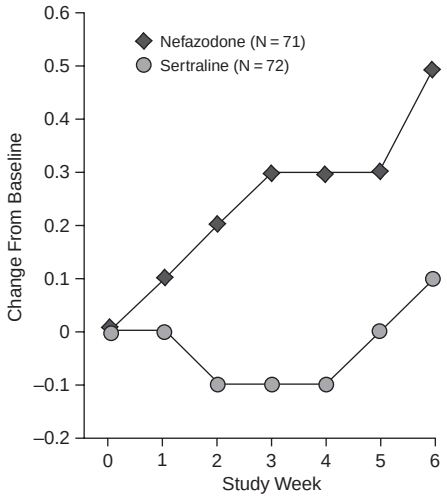
No differences were seen between the 2 groups in efficacy as measured by the HAM-D or the CGI.

There was no difference between the 2 treatment groups in baseline sexual activity. Of the 46 women who were sexually active at baseline and responded to the questionnaire during treatment, 38 were sexually active and answered at baseline. Of the 54 men who were sexually active at baseline and answered the questionnaire, 46 were sexually active and responded at baseline. No demographic differences or differences in HAM-D or CGI-S scores were found between groups. In women, nefazodone was significantly superior to sertraline on measures of patients' ease of achieving orgasm (p = .03) and satisfaction with the ability to achieve orgasm (p = .04). The mean endpoint score for sertraline was worse than the baseline score for both of these measures.

For men, significant differences between treatments were seen in 5 of 9 questions. During the last treatment week in which they were sexually active, nefazodone-treated men enjoyed sex more than sertraline-treated men (p < .01), with 100% of the nefazodone-treated men responding that they fully enjoyed or sometimes enjoyed sex compared with 57% of the sertraline-treated men. Overall satisfaction with sexual functioning in men was significantly greater for men treated with nefazodone (89%, p = .01) compared with 50% of sertraline-treated men. Sixty-seven percent of sertraline-treated men reported difficulty with ejaculation (vs. 18% at baseline) compared with 19% of nefazodone-treated men (13% at baseline).

Item 14 of the HAM-D asks about "genital symptoms such as loss of libido and menstrual difficulties." The response to this item is scored on a scale of 0 to 2, where 0 = none, 1 = mild, 2 = severe. When the change in the score for this item over the 6-week time course of this study is analyzed for the 2 treatment groups, a statistically significant difference (p = .01) is seen after 2 weeks of double-blind treatment (Figure 6) that persists through the final week of treatment.[22]

Figure 6. Improvement in Hamilton Rating Scale for Depression Item 14: Libido[a]



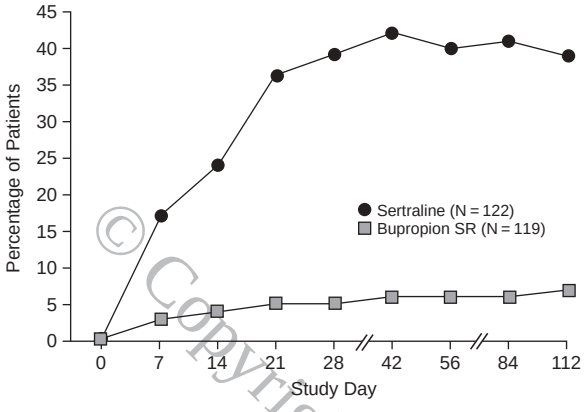
[a]Data from Feiger et al.[22]

Both nefazodone and sertraline were well-tolerated and had excellent safety profiles. The efficacy of the 2 compounds was almost identical. Treatment discontinuation attributable to adverse events occurred similarly in both groups, 19% with nefazodone and 12% with sertraline. Two patients in the sertraline group and no patients in the nefazodone group discontinued owing to sexual dysfunction.

Kavoussi et al.[23] conducted a non–placebo-controlled comparison of bupropion sustained release (SR) and sertraline in 248 depressed outpatients. The selection criteria included moderate-to-severe depression (DSM-IV criteria), with no concomitant medical or psychiatric illness. The patients could have single- or multiple-episode depression, with the current episode ≥ 4 weeks and ≤ 24 months. To participate, patients had to be in a stable relationship, be sexually active, and have "normal sexual functioning." Patient inclusion in the study was stratified by gender to ensure a uniform sample.

Subsequent to a screening period, patients were titrated to an effective dose of medication. The daily dosage of bupropion SR was 100 mg for the first 3 days, was increased to 200 for days 4 through 7, and after that, if indicated, was increased to 300 mg. Sertraline treatment was begun at a daily dose of 50 mg for the first 7 days, was increased to 100 mg for days 8 through 14, and after that could be increased if clinically indicated by 50 mg per week to 200 mg. The mean final doses were 238 mg/day for bupropion SR and 114 mg/day for sertraline.

Figure 7. Percentage of Patients Experiencing Orgasm Failure and/or Delay During Treatment With Bupropion SR or Sertraline for 16 Weeks[a]



[a]Reprinted, with permission, from Kavoussi et al.[23] Abbreviation: SR = sustained release.

Patients were seen at screen and baseline and at weeks 1, 2, 3, 4, 6, 8, 12, and 16. At each visit, they were administered the HAM-D, the Hamilton Rating Scale for Anxiety (HAM-A), and the CGI, and the investigator asked about orgasmic functioning using a structured interview based on questions from the Kinsey Institute Interviewer Ratings of Sexual Functioning.

The samples were matched for demographic and depressive characteristics. The initial study cohort was 248 patients. Of the 122 patients in the bupropion SR group, 119 were included in the sexual functioning analyses and 87 completed the trial. Of 126 sertraline-treated patients, 122 were included in analyses and 83 completed the trial. It is of note that among those dropping out of the study, 17 (13%) of the sertraline-treated patients and 4 (3%) of the bupropion SR–treated patients dropped out because of sexual side effects of the drug.

There was no difference in efficacy on any of the measures of depression in time to effect or effect size. An effect on orgasmic functioning was seen after 7 days of double-blind (randomized) treatment (Figure 7). This difference was significant at the $p = .001$ level throughout the study. There were gender differences in response between the 2 groups. Among men, orgasmic dysfunction reported at any time during the 16-week trial was 10% for the bupropion SR–treated group compared with 61% in the sertraline-treated group ($p = .001$). Among women, orgasmic dysfunction was reported by 7% of the bupropion-treated group compared with 41% of those receiving sertraline ($p = .001$)

In this study, patients were enrolled who had experienced an episode of depression that had lasted less than 2 years, who were moderately to severely depressed, and who reported normal sexual functioning as defined by responses elicited by a skilled interviewer to questions about orgasmic dysfunction. Like the Feiger et al.[21] study, this clinical trial is prospective and baseline controlled, but lacks a placebo group and is limited to questions about orgasmic functioning.

DOUBLE-BLIND COMPARATIVE STUDIES WITH PLACEBO CONTROL

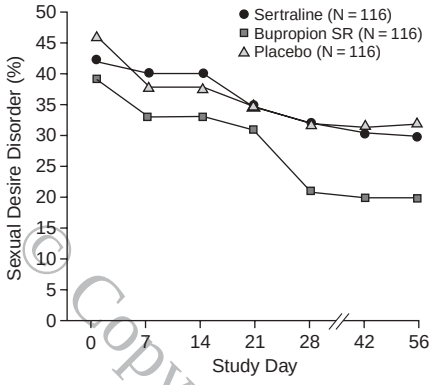
Two clinical studies prospectively looked at the effect of antidepressant medication on sexual functioning in depressed patients within the context of a placebo-controlled clinical trial. The first of these, by Harrison and colleagues,[12] was cited at the beginning of this article. In the second, Croft et al.[24] conducted an 8-center clinical trial comparing bupropion SR, sertraline, and placebo in 360 patients. In this comparative trial, moderately to severely depressed patients with depression as defined by DSM-IV and a HAM-D score (first 21 items) greater than 18 were enrolled. At the time of screening, patients were not allowed to participate if there were medical or psychiatric problems or problems that contributed to their depression or sexual functioning, medications that might interfere with sexual functioning, or other factors that might interfere with their recovery from depression or interfere with their sexual functioning. They had to be in a stable relationship, be engaged in sexual activities that could lead to orgasm at least once every 2 weeks, and have normal sexual functioning, which was defined as the absence of any history of organic sexual dysfunction. In addition, they had to be able to talk about sexual matters with the reviewing physician.

The clinical trial was 8 weeks long, during which time they were seen at screening and on study days 7, 14, 21, 28, 42, and 56. At each of these visits, depression was assessed using the HAM-D, anxiety was assessed using the HAM-A, and overall improvement with the CGI. The investigators interviewed the patients at each clinic visit to rate the following sexual functioning variables (as defined in DSM-IV): sexual desire (deficiency of sexual fantasies and desire for sexual activity), sexual arousal (lubrication and swelling in women, erectile difficulties in men), orgasmic dysfunction (orgasm delay or failure in men), and premature ejaculation. Each of these was rated as present or absent. Patient satisfaction with overall sexual functioning was rated as satisfactory or unsatisfactory by the patient during the rating interview.

At baseline, these samples were evenly matched for psychopathology and demographic factors. Patients were allowed into the study only if they had "normal sexual functioning," which was defined as the absence of organic sexual dysfunction or sexual dysfunction based on DSM-IV definitions of sexual disorders.

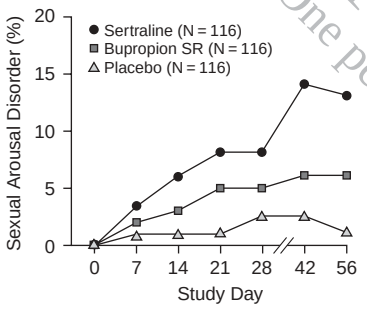
Of the 360 patients that entered the trial, two thirds in each group completed the study (71% treated with bupropion SR, 68% with sertraline, 67% with placebo). The antidepressant efficacy and time to effect were similar in

Figure 8. Change in Percentage of Patients With Sexual Desire Disorder From Baseline to Endpoint[a]



[a]Reprinted, with permission, from Croft et al.[24] Abbreviation: SR = sustained release.

Figure 9. Change in Percentage of Patients With Sexual Arousal Disorder From Baseline to Endpoint[a]

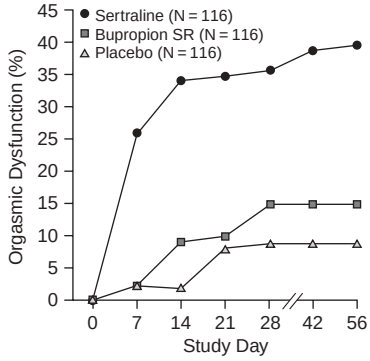


[a]Reprinted, with permission, from Croft et al.[24] Abbreviation: SR = sustained release.

both active treatment groups and significantly different from placebo by day 42 according to HAM-D ratings.

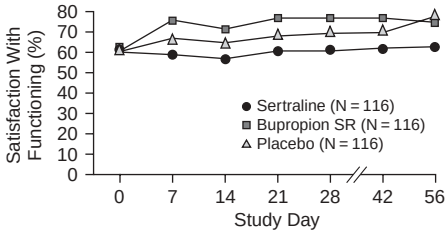
As seen in Figure 8, the percentage of patients with sexual desire disorder was significantly less by day 42 in the bupropion SR–treated group than in either the placebo or sertraline-treated group. At baseline, however, 39% of the bupropion group compared with 46% of the placebo group were diagnosed with sexual desire disorder, a non-significant but large difference. Sexual arousal disorder occurred significantly more by day 14 in patients who were receiving sertraline than placebo, reaching a significantly greater degree of impairment for bupropion than placebo by day 56 (Figure 9). Orgasmic dysfunction occurred in the sertraline-treated group by day 7, with a highly significant ($p < .001$) difference from bupropion SR and placebo. There was no statistically significant difference throughout the trial between placebo and bupropion SR (Figure 10). No men reported premature ejaculation before or during the study.

Figure 10. Change in Percentage of Patients With Orgasmic Dysfunction From Baseline to Endpoint[a]



[a]Reprinted, with permission, from Croft et al.[24] Abbreviation: SR = sustained release.

Figure 11. Change in Satisfaction With Overall Sexual Functioning From Baseline to Endpoint[a]



[a]Reprinted, with permission, from Croft et al.[24] Abbreviation: SR = sustained release.

At baseline, approximately 60% of patients in each treatment group were satisfied with their overall sexual functioning. Beginning at day 7 and continuing through the end of the study, significantly more bupropion SR–treated patients were satisfied with their sexual functioning than those in the sertraline-treated group ($p < .05$; Figure 11). By day 56, significantly more placebo-treated patients were satisfied with their sexual functioning than sertraline-treated patients.

This study of treatment-emergent sexual dysfunction used a standard clinical format, with standardized assessments of anxiety, depression, and improvement. Assessment of sexual functioning was conducted by clinician interview using the diagnostic criteria for sexual disorders found in the DSM-IV. Patients were recruited into the study having reported no sexual dysfunction and presuming no organic sexual dysfunction prior to the clinical trial with the exception of possible sexual desire disorder, which is commonly associated with depression. Treatment-emergent orgasmic dysfunction occurred after 1 week of treatment with sertraline and continued through the 8-week course of the clinical trial. The temporal relationship of

onset and persistence confirms earlier findings in the study by Kavoussi et al.[23] of sertraline-treated patients reporting a lack of recovery over 16 weeks of treatment and in the report by Feiger et al.[21] of sexual dysfunction reviewed above. The rate of reported orgasmic dysfunction is in line with earlier published reports. Approximately 60% of patients entering the clinical trial were satisfied with their overall sexual functioning at baseline. Interestingly, this percentage increased over time in the bupropion SR– and placebo-treated groups, but not in the sertraline-treated group. This finding is in line with the 16-week study by Kavoussi and colleagues described above.

DOUBLE-BLIND COMPARATIVE RECHALLENGE STUDY

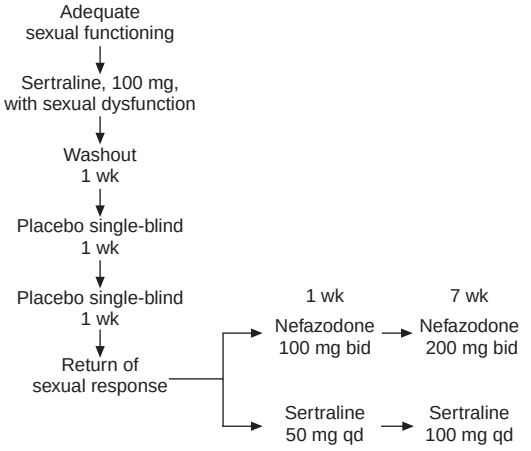
Ferguson and colleagues[25] conducted a clinical trial comparing nefazodone, sertraline, and placebo to look at the reemergence of sexual dysfunction with antidepressant treatment. Patients in the community who had been treated with 100 mg of sertraline and who reported a loss of sexual functioning coincident with that treatment were recruited for the study. They must have had, by history, adequate sexual functioning prior to their treatment with sertraline (Figure 12).

After an evaluation of their medical, psychiatric, and sexual history, and their current depression and sexual dysfunction, patients abruptly discontinued their treatment with sertraline. After a 1-week washout, they were given single-blind placebo medication for 1 week. After this 2-week interval, if there was a return of adequate sexual functioning, they were randomly assigned to receive either nefazodone, 100 mg b.i.d., or sertraline, 50 mg q.d. At week 2, nefazodone was increased to 200 mg b.i.d. and sertraline to 100 mg q.d.

The study employed a trained physician who interviewed each patient at each visit using a modification of the Rush Sexual Inventory. This rating scale asks the interviewer to make a global rating of severity of sexual dysfunction on a scale of 1 (normal) through 4 (severe) for the following 4 items: sexual interest/desire, sexual arousal, sexual satisfaction, and specific organic sexual dysfunction. At the time of screen, this specific organic or physiologic dysfunction was specifically defined in the following categories: difficulty in maintaining or achieving erection, delayed or lack of ejaculation, delayed orgasm or anorgasmia, and inadequate lubrication or swelling. Forty-four patients were enrolled in the nefazodone-treatment group and 31 in the sertraline-treatment group. Patients were matched according to age and demographics.

During the 2-week washout period, there was no sign of withdrawal from sertraline, nor was there a relapse in depression. Both treatments were equally effective for the underlying depression. Normal sexual functioning returned during the 2-week washout to everyone who continued on in the study. Fifty-one (68%) of the intent-to-treat sample, including 29 (71%) of 41 nefazodone recipients and 22 (65%) of 34 sertraline recipients, completed the 8-week double-blind treatment phase. The main reason for discontinuation was adverse events: 5 (12%) in the nefazodone group and 9 (26%) in the sertraline group. The reemergence of sexual dysfunction occurred in the first week of rechallenge with 50 mg of sertraline, a dose often considered to be below the therapeutic dose (Figure 13). Throughout the 8-week trial, the difference in the return in sexual dysfunction between the 2 treatment groups remained statistically significant, with the exception of week 5. Statistically significant differences favoring nefazodone on measures of satisfaction with sexual functioning and severity of sexual dysfunctioning were seen throughout the trial.

Figure 12. Double-Blind Comparative Rechallenge Study of Nefazodone and Sertraline in Depressed Patients[a]



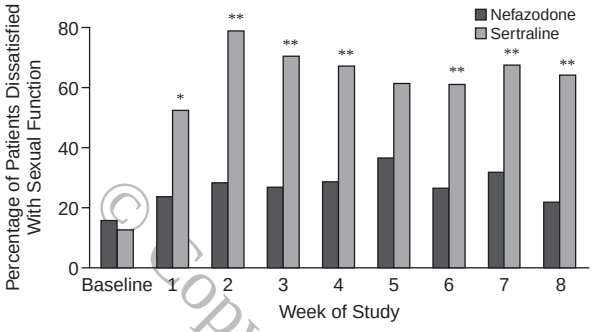
[a]Based on Ferguson et al.[25]

CONCLUSIONS

Several types of research methodology have been brought to bear on the investigation of the sexual side effects of antidepressant medications. These range from cross-sectional studies to retrospective studies to prospective nonanchored studies to comparative studies to placebo-controlled studies. The change in methodology appears to mirror the seriousness with which the psychiatric community has begun to look at sexual dysfunction in depressed patients and the possibility that sexual side effects have a potential to interfere with treatment.

Throughout the literature, both anecdotal, semicontrolled, and controlled studies point to the fact that drugs which have as a single mode of action serotonin reuptake inhibition have the potential for interfering in sexual dysfunction. This is seen with the tricyclic antidepressants (for

Figure 13. Patient Dissatisfaction With Sexual Function as Determined by Physician's Rating of Sexual Dysfunction Symptoms[a]



[a]Reprinted, with permission, from Ferguson et al.[25] Intent-to-treat, last-observation-carried-forward analysis used.
*Significantly different from nefazodone, $p \leq .05$.
**Significantly different from nefazodone, $p \leq .01$.

example, clomipramine), monoamine oxidase inhibitors, and SSRIs. Mixed compounds such as venlafaxine appear to share this liability. Anecdotally, it appears that there is a spectrum of severity ranging from the greatest effect seen with paroxetine to the least with fluoxetine; however, in the absence of controlled clinical trial comparisons, it is difficult to estimate the validity of this observation.

Two antidepressants with different mechanisms of action appear to be far less prone to cause sexual dysfunction: bupropion and nefazodone. Both have been shown in clinical trials to be highly efficacious in the treatment of depression and to be relatively sparing of sexual functioning, particularly orgasmic dysfunction. These characteristics have been shown in prospective, double-blind comparison trials compared with sertraline and, in the case of bupropion, in a placebo-controlled and comparative trial. For nefazodone, the relative lack of sexual side effect liability was shown in a double-blind rechallenge-design study.

Nefazodone and bupropion have very different mechanisms of action. Bupropion is thought to exert its effect on depression through a yet little understood dopaminergic mechanism; nefazodone works by blocking serotonin reuptake and at the same time blocking postsynaptic serotonin-2 (5-HT_2) receptors and down-regulating these 5-HT_2 receptors with chronic administration. The overall effect is to increase serotonin concentration within the synapse for binding to postsynaptic 5-HT receptors including 5-HT_{1A} receptors, while shielding the postsynaptic 5-HT_2 receptors. Nefazodone also has minor activity in inhibiting norepinephrine reuptake.

Given the importance of sexuality in depressed individuals, as pointed out by Baldwin and colleagues,[6] and the importance of patient satisfaction with compliance to medication prescription, it is incumbent on clinicians to assess the patients' overall functioning and the appearance of their sexual functioning when prescribing an antidepressant medication.

Drug names: bupropion (Wellbutrin), clomipramine (Anafranil and others), desipramine (Norpramin and others), doxepin (Sinequan and others), fluoxetine (Prozac), fluvoxamine (Luvox), mirtazapine (Remeron), nefazodone (Serzone), nortriptyline (Pamelor and others), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft), venlafaxine (Effexor).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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