Reemergence of Sexual Dysfunction in Patients With Major Depressive Disorder: Double-Blind Comparison of Nefazodone and Sertraline

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Background: Several different classes of antidepressants have been associated with sexual adverse effects. This double-blind, randomized trial compared the effects of nefazodone and sertraline on reemergence of sexual dysfunction in depressed patients who had experienced sexual dysfunction as a result of sertraline treatment. Depressive symptoms were also monitored.

Method: One hundred five patients with DSM-III-R major depressive episode who were experiencing sexual dysfunction attributable to sertraline (100 mg/day) were screened for entry. Eligible patients entered a 1-week washout period that was followed by a 7- to 10-day single-blind placebo phase. Patients without symptoms of sexual dysfunction at the end of the single-blind placebo phase were randomly assigned to receive double-blind treatment with either nefazodone (400 mg/day) or sertraline (100 mg/day) for 8 weeks.

Results: Nearly 3 times more sertraline-treated patients (76%; 25/33) experienced reemergence of sexual dysfunction (ejaculatory and/or orgasmic difficulty) than did nefazodone-treated patients (26%; 10/39) ($p < .001$). In addition, patients treated with nefazodone were more satisfied with their sexual functioning than were patients treated with sertraline. Both treatment groups demonstrated a similar and sustained improvement in depressive symptoms. Both drugs were well tolerated, and the overall incidence of adverse reactions was similar for both treatment groups; however, 9 sertraline-treated patients (26%) discontinued because of adverse events compared with 5 nefazodone-treated patients (12%). Of the patients discontinuing therapy for adverse events, 5 of the sertraline-treated patients did so because of sexual dysfunction reported as an adverse event, whereas only 1 of the nefazodone-treated patients discontinued therapy secondary to sexual dysfunction.

Conclusion: In this sample of patients with major depression who had recovered from sexual dysfunction induced by treatment with sertraline, nefazodone treatment resulted in significantly less reemergence of sexual dysfunction than did renewed treatment with sertraline and provided continued antidepressant activity.

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Several classes of pharmacologic agents, including opiates, alcohol, stimulants, and antihypertensives (e.g., β-blockers, clonidine, diuretics), have been reported to disrupt normal sexual function. Psychotropic medications, such as antidepressants, have also been associated with sexual adverse effects.[1] Patients treated with tricyclic and tetracyclic antidepressants, venlafaxine, and monoamine oxidase inhibitors (MAOIs) have reported orgasmic dysfunction, ejaculatory disturbances, and changes in libido.[1–3] Similar adverse effects have been associated with the selective serotonin reuptake inhibitors (SSRIs) (e.g., fluoxetine, sertraline, paroxetine).[1] In fact, it has been estimated that the overall incidence of sexual dysfunction during antidepressant therapy is 20% to 40% or greater.[4] While in the past, the risk of sexual dysfunction was usually not a consideration in the selection of a first-line antidepressant, recent data have suggested that this risk should be considered more seriously. The emergence of symptoms of sexual dysfunction can result in significant problems, especially in long-term treatment. Sexual dysfunction can result in the need to switch antidepressants and in the premature discontinuation of therapy. It is now well recognized that one of the leading contributors to recurrence and relapse of depression is poor patient compliance,[5] and one of the leading reasons for poor compliance is sexual dysfunction.[6]

Although the mechanism of antidepressant-associated sexual dysfunction has not been clearly established, activation of the serotonergic system has been suggested.[7] Stimulation of serotonin-2 ($5\text{-}HT_2$) receptors may be one of the reasons that sexual dysfunction occurs with serotonin-active agents. Increases in central nervous system (CNS) serotonin levels caused by neuronal 5-HT re-

uptake blockade or potentiation of peripheral nervous system adrenergic activity have been implicated as causes of sexual dysfunction. Treatment with drugs that interact with specific 5-HT and norepinephrine receptors has been shown to reverse the sexual dysfunction caused by antidepressants. For example, fluoxetine-induced sexual dysfunction has been reversed with the administration of cyproheptadine, a drug with antiserotonergic properties[7–9]; buspirone, a 5-HT_{1A} partial agonist[10]; and yohimbine, an α-adrenergic antagonist.[11] Dopamine agonists, such as amantadine, have also been found to ameliorate SSRI-related sexual dysfunction.[12]

The multicenter trial described in this report was designed to compare the effects of nefazodone and sertraline on reemergence rates of sexual dysfunction in depressed patients who had previously experienced sexual dysfunction during treatment with sertraline. This study was primarily designed to investigate specified type(s) of substance-induced sexual dysfunction including difficulty in achieving/maintaining an erection, delayed or lack of ejaculation, delayed orgasm or anorgasmia, and inadequate lubrication or swelling. In addition, the effects of these treatments on improvement and maintenance in antidepressant efficacy were monitored.

METHOD

Study Population

A total of 105 patients, aged between 18 and 65 years, were screened for entry into this multicenter study. All patients had a DSM-III-R diagnosis of moderate or severe major depressive episode with or without melancholia (but without psychotic features), were receiving sertraline therapy (100 mg/day), and were experiencing sexual dysfunction attributable to sertraline therapy (difficulty with ejaculation or orgasm in men; orgasm difficulties or inadequate lubrication or swelling in women). At the time of entry into the study, all patients were judged to be clinically stable and appropriate candidates for discontinuation of sertraline therapy for 2 weeks. All patients were required to sign informed consent forms prior to entering the study.

Women were excluded from the study if they were pregnant, lactating, or of childbearing potential and not using an adequate method of contraception. Also excluded were patients who had any of the following: a diagnosis of treatment-resistant depression, dysthymia, organic mood syndrome with depression, dementia with depression, or any concurrent DSM-III-R Axis I disorder; a history of sexual dysfunction resulting from any organic disorder (either before receiving any antidepressant medications or related to the depressive illness); the inability to discontinue current psychotropic medications or the likelihood of requiring treatment with a prohibited concomitant therapy such as investigational or psychotropic medications (except for infrequent use of chloral hydrate, 0.5 g to 1.5 g, or diphenhydramine for insomnia as required); known allergy or hypersensitivity to trazodone, etoperidone, *m*-chlorophenylpiperazine, or sertraline; use of concomitant medication that could cause sexual dysfunction; a significant risk of committing suicide; or a positive urine drug screen. Patients were not selected if they had any significant or uncontrolled medical condition(s) that could confound the interpretation of the safety and efficacy data or had implanted penile prosthetic devices. Other reasons for exclusion were use of an investigational drug within 30 days of entering the study, receipt of electroconvulsive therapy treatments within 3 months of the start of the study, or participation in a previous nefazodone clinical trial.

Study Design

During the screening phase of the study, patients were evaluated to preliminarily determine that the sexual dysfunction they were experiencing was related to current treatment with sertraline, 100 mg/day. While no minimum duration of sertraline treatment was required, patients were to receive sufficient treatment with sertraline in order for the investigator to assess whether their complaints of sexual dysfunction were due to sertraline treatment. Sexual dysfunction was documented using a patient self-rating scale and a physician-rated sexual dysfunction scale (see Assessments). In addition, the following information was collected: demographic and historical data, psychiatric evaluation, physical evaluation, vital sign measurements, electrocardiographs (ECGs), and clinical laboratory tests (including a serum pregnancy test for women of childbearing potential). After a 1-week washout period during which sertraline treatment was suspended, patients entered a 7- to 10-day single-blind lead-in phase during which they received placebo only. This phase of the study was designed to establish that the sexual dysfunction was the result of sertraline treatment. All symptoms of substance-induced sexual dysfunction were required to be absent for the patient to be randomly assigned to treatment. Although symptoms of substance-induced sexual dysfunction resulted in exclusion from the study, subjective complaints of sexual dysfunction (i.e., diminished libido) were allowed. These subjective symptoms are often associated with depressive illness.[13] After the single-blind placebo phase, patients who were no longer experiencing substance-induced sexual dysfunction were randomly assigned to receive double-blind therapy with either nefazodone or sertraline for 8 weeks, with stratification of treatment groups to ensure a similar representation of gender in each. Dosage was initiated as nefazodone, 200 mg daily (one 100-mg nefazodone capsule in the morning and one in the evening), or sertraline, 50 mg daily (one 50-mg sertraline capsule in the morning and one placebo capsule in the evening). Beginning on day 8, dosages were doubled

to nefazodone, 400 mg daily (two 100-mg nefazodone capsules in the morning and two in the evening), and sertraline, 100 mg daily (two 50-mg capsules in the morning and two placebo capsules in the evening), for the remaining 7 weeks.

Assessments

The presence of sexual dysfunction was evaluated weekly using both the physician's rating of sexual dysfunction symptoms (PRSDS) and a validated self-rating scale (modified version of the Rush-Presbyterian Sexual Function Inventory [R-SFI]).[14] The PRSDS provides a 4-point scale of 1 (normal) to 4 (severe) for specified substance-induced sexual dysfunction and for sexual dysfunction in the following domains: interest/desire, arousal, and satisfaction. To calculate the reemergence rate of substance-induced sexual dysfunction, patients were categorized as "yes" if they were rated as mild, moderate, or severe on the specified sexual dysfunction item. The sexual dysfunction category of the PRSDS was the primary variable for assessing differences between treatments in the emergence of sexual dysfunction, since all patients were required to be free of substance-induced sexual dysfunction symptoms at the point of randomization. The self-rating scale provided 100-mm visual analog scales to rate (1) frequency of sexual thought, (2) ability to become sexually excited, (3) desire to initiate sexual activity, (4) frequency of initiation of sexual activity, and (5) overall degree of sexual satisfaction achieved. Gender-specific questions on aspects of sexual functioning were also evaluated. The modified R-SFI included assessment of sexual functioning and sexual dysfunction at various sexual response cycles. Patients were asked to respond yes or no to each question.

The Clinical Global Impressions-Severity of Illness (CGI-S) and -Improvement scales (CGI-I) (including the Severity of Illness, Doctor's Opinion of Improvement, and Patient's Opinion of Improvement scales)[15] and the 17-item Hamilton Rating Scale for Depression (HAM-D-17)[16] were completed weekly and every 2 weeks, respectively, to assess changes in depressive symptoms. A responder/nonresponder categorization was used to summarize the Doctor's and Patient's Opinion of Improvement components of the CGI. Patients were categorized as responders if they were rated "much improved" or "very much improved." Otherwise, they were classified as nonresponders by this criterion.

Vital signs, reporting of concomitant medication, and adverse events were recorded at each weekly visit. Adverse events were collected on the basis of spontaneous patient reports. Laboratory evaluations were conducted at the screening visit and at the beginning and end of the 8-week double-blind treatment phase. Physical examination and 12-lead ECGs were conducted at the screening visit and at the completion of the double-blind treatment period.

Statistical Analyses

Baseline comparisons between the nefazodone and sertraline groups were made for demographic and other patient characteristics. Sexual function and antidepressant efficacy were evaluated by considering the change from baseline of the self-rated and physician-rated sexual dysfunction scales, the HAM-D-17, and the CGI ($\alpha = .05$) for both the intent-to-treat and evaluable patient samples. Analyses of the intent-to-treat sample, which included all patients who received at least one dose of study medication and had one treatment evaluation, were performed using the last observations carried forward (LOCF) as the primary data set. The analyses of the LOCF data set were corroborated by analyses of the decreasing N data set, which consisted of the actual observations at each visit for the evaluable patient sample.

Categorical data, such as CGI-I scores and the reemergence of sexual dysfunction symptoms (PRSDS) were analyzed by the Cochran-Mantel-Haenszel procedure, stratifying by study center. Analysis of variance techniques were used to analyze continuous variables, such as change from baseline in HAM-D-17 total score, severity of sexual dysfunction symptoms (PRSDS), and the visual analog scores of the self-rating inventory. Effects such as treatment, study site, and treatment-by–study site interaction were considered. Ninety-five percent confidence intervals for the difference in the treatment-group means were calculated using the standard errors from the least-square means. Confidence intervals for the difference in CGI response rates were calculated using the standard error derived from the formulas for the difference between 2 proportions. When appropriate, analysis of covariance was carried out to test the effects of baseline covariates on the results. A p value of $\leq .05$ was considered significant. For yes/no items of the patient rating scale, changes from baseline were examined by McNemar tests and compared between treatment groups by Cochran-Mantel-Haenszel tests.

All patients who received treatment were included in the safety evaluation. Laboratory data were analyzed for changes between baseline and week-8 therapy evaluations (or last evaluation) using Stuart-Maxwell and sign tests. Comparisons of the incidence of adverse event rates between treatment groups were done using the Fisher exact test.

The planned sample size of 30 evaluable patients per treatment arm (60 in total) had a power of 94% to detect a 40% difference in rates of sexual dysfunction–type adverse events between sertraline and nefazodone at the $\alpha = .05$ level.

RESULTS

Study Population

A total of 105 patients were screened for entry to the study at 9 study sites. Of the 105 patients screened, 30 pa-

Table 1. Demographic and Baseline Psychiatric Characteristics (intent-to-treat patient sample)[a]

Patient Characteristics	Nefazodone (N = 39)	Sertraline (N = 33)
Gender, N (%)		
Male	21 (54)	17 (52)
Female	18 (46)	16 (48)
Race, N (%)		
White	37 (95)	32 (97)
Black	0 (0)	1 (3)
Hispanic	2 (5)	0 (0)
Age, y, mean ± SE	43.2 ± 1.4	44.8 ± 2.0
Depression diagnosis, N (%)		
Single episode, moderate	7 (18)	10 (30)
Single episode, severe	0 (0)	1 (3)
Recurrent, moderate	32 (82)	22 (67)
Melancholia, N (%)	24 (62)	18 (55)
Baseline HAM-D-17 score, mean	11.5	10.5

[a]Abbreviation: HAM-D-17 = 17-item Hamilton Rating Scale for Depression.

Figure 1. Antidepressant Effects (intent-to-treat patient population) for Nefazodone (N = 39) and Sertraline (N = 33) as Determined by Mean Total Score (last observation carried forward) on the 17-Item Hamilton Rating Scale for Depression (HAM-D-17)

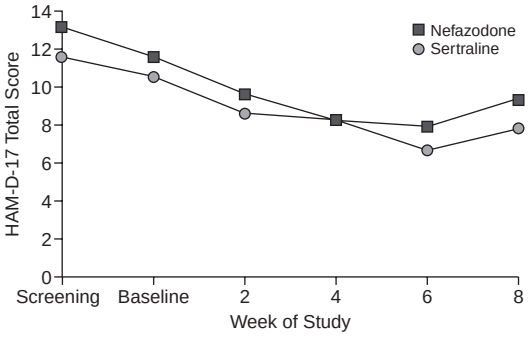
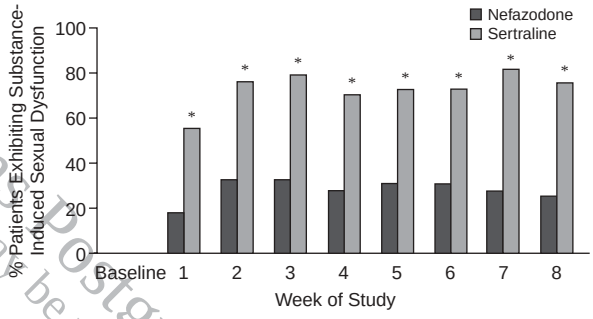


Figure 2. Percentage of Patients (intent-to-treat population, LOCF) Exhibiting Reemergence of Substance-Induced Sexual Dysfunction (as determined by the PRSDS) Following Treatment With Nefazodone (N = 39) or Sertraline (N = 33)[a]



[a]Abbreviations: LOCF = last observation carried forward, PRSDS = physician's rating of sexual dysfunction symptoms.
*p ≤ .01.

tients did not qualify for randomization, the most common disqualifier being a positive urine drug screen; only 4 patients did not qualify for randomization owing to persistence in sexual dysfunction. Three of the 75 randomized patients had major protocol violations (substance-induced sexual dysfunction at baseline [1 patient], no baseline sexual dysfunction evaluation [2 patients]) and were excluded from the sexual function and efficacy (antidepressant response) portions of the analysis. Six additional patients were excluded from the evaluable patient sample because they received study medication for less than 14 days, but they are included in the intent-to-treat sample. No significant differences were noted between the treatment groups for any baseline demographic or psychiatric characteristics, either in the evaluable patient sample or the intent-to-treat sample (Table 1).

Fifty-one patients (68%), 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 (5/41 [12%] in the nefazodone group and 9/34 [26%] in the sertraline group). Of the patients discontinuing therapy for adverse events, 5 of the sertraline-treated patients did so because of sexual dysfunction reported as an adverse event versus 1 of the nefazodone-treated patients who discontinued therapy secondary to sexual dysfunction.

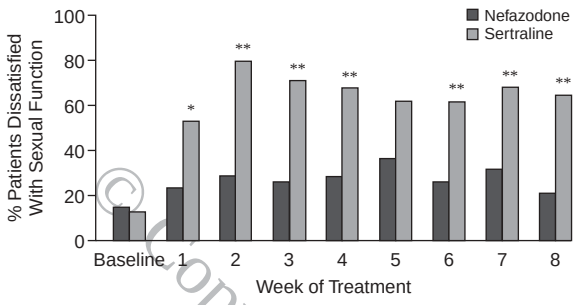
Efficacy (Antidepressant Response) and Sexual Function

Results for the evaluable patient sample and the intent-to-treat sample were similar; therefore, only the latter is presented below.

A similar response in depressive symptoms was found for both treatments. Mean HAM-D-17 scores at screening and baseline (baseline scores: nefazodone = 11.5, sertraline = 10.5) were similar between the 2 groups. The mean HAM-D-17 total scores did not differ significantly between the 2 groups at any time during treatment (Figure 1). Similarly, no statistically significant differences were noted between treatment groups at screening, baseline, or any week during treatment for either the CGI-S or the CGI-Doctor's Opinion of Improvement parameter.

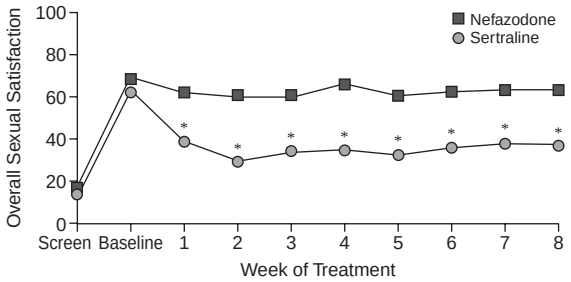
The PRSDS analysis for reemergence rates of substance-induced sexual dysfunction is presented in Figure 2. The incidence of reemergence of substance-induced sexual dysfunction was significantly greater for patients treated with sertraline than for those treated with nefazodone at all treatment weeks (see Figure 2). At week 1, 18% (7/39) of nefazodone-treated patients had experienced reemergence of sexual dysfunction, whereas 55% (18/33) of the patients receiving sertraline were reported to have significant sexual dysfunction ($p < .001$). The reemergence of substance-induced sexual dysfunction in sertraline-treated patients continued to show a marked in-

Figure 3. Percentage of Patients (intent-to-treat population, LOCF) Dissatisfied With Sexual Function (as determined by the PRSDS) Following Treatment With Nefazodone (N = 39) or Sertraline (N = 33)[a]



[a]Abbreviations: LOCF = last observation carried forward, PRSDS = physician's rating of sexual dysfunction symptoms.
*p ≤ .05.
**p ≤ .01.

Figure 4. Patient-Rated Overall Degree of Sexual Satisfaction for the Intent-to-Treat Population (last observation carried forward) Following Treatment With Nefazodone (N = 39) or Sertraline (N = 33)[a]



[a]Patients used a visual analog scale, on which 0 mm corresponded to low sexual satisfaction and 100 mm represented high sexual satisfaction.
*p ≤ .01.

crease over the course of treatment, so that at endpoint 76% (25/33) of sertraline recipients experienced reemergence of significant sexual dysfunction. In contrast, the reemergence of sexual dysfunction with nefazodone was consistently and significantly less than that with sertraline and was 26% (10/39) at endpoint ($p < .001$ vs. sertraline).

Significant differences favoring nefazodone were also found for the satisfaction, arousal, and interest/desire domains of the PRSDS. The percentage of patients who were dissatisfied with their sexual function was consistently greater in the sertraline group at all weeks, reaching statistical significance at all weeks during the course of treatment except week 5 (Figure 3). The percentage of patients reporting impairment in sexual interest/desire during the course of treatment ranged from 23% to 36% in nefazodone-treated patients, compared with 52% to 79% in sertraline-treated patients, the difference attaining statistical significance at weeks 2, 3, 4, 6, 7, and 8. The incidence of impairment in sexual arousal during the course of treatment ranged from 21% to 31% in nefazodone-treated patients, compared with 46% to 67% in sertraline-treated patients, the difference attaining statistical significance at weeks 1, 2, 3, and 4.

Nefazodone caused less sexual dysfunction based on the patient's self-rating scale, with statistical significance being attained on 3 of 5 visual analog scales: "frequency of pleasurable thoughts" at weeks 2 through 7, "ability to become sexually excited" at all treatment weeks, and "overall degree of sexual satisfaction" at all treatment weeks (Figure 4). It is interesting to note that both groups of patients reported similar improvement in these scales between screening and baseline. However, following initiation of treatment, the improvement was sustained in the nefazodone-treated patients, whereas the sertraline group reported significant worsening of scores on these rating scales. No overall significant differences were observed between the 2 treatment groups on the other 2 visual analog scales: "frequency of desires to initiate sexual activity" and "how often do you initiate sexual activity."

Side Effects

All 41 patients (100%) who received nefazodone and 33 (97%) of the 34 patients who received sertraline reported at least one adverse event. Overall, the incidence rates for adverse events were similar in both treatment groups. However, pain and rash were reported significantly more frequently ($p \leq .05$) in the group treated with sertraline. There was a trend for more sertraline-treated patients (N = 5) to spontaneously report sexual dysfunction compared with nefazodone-treated patients (N = 1) ($p = .058$). As stated above, 5 patients (12%) in the nefazodone group and 9 patients (26%) in the sertraline group discontinued therapy prematurely because of adverse events, including all 6 patients (5 in the sertraline group and 1 in the nefazodone group) who reported sexual dysfunction as an adverse event.

DISCUSSION

This study provides further evidence that treatment with nefazodone is associated with a lower incidence of sexual dysfunction than is sertraline treatment. Patients with a history of sexual dysfunction during treatment with sertraline were approximately 3 times as likely to have reemergence of substance-induced sexual dysfunction (e.g., ejaculatory/orgasm disturbances in men, orgasm disturbances in women) when rechallenged with 100 mg/day of sertraline (76% reemergence at week 8) than when treated with 400 mg/day of nefazodone (26% reemergence at week 8). The significantly lower propensity of nefazodone to produce reemergence of substance-induced sexual

dysfunction is consistent with the very low incidence of spontaneously reported sexual dysfunction associated with nefazodone during its clinical testing.[17–19] These data indicated that the incidence of sexual dysfunction associated with nefazodone treatment was virtually indistinguishable from that associated with placebo. This reduced liability of nefazodone to produce sexual dysfunction is most likely attributable to its 5-HT_2 antagonist properties.[20]

In addition, patients treated with nefazodone were more satisfied with their sexual function than were patients treated with sertraline, on the basis of both clinician rating and self-rating using visual analog scales. Closer analysis of these latter data suggests several interesting conclusions. First, as discussed above, nefazodone showed no superiority to sertraline on the 2 visual analog questions involving initiation of sex: "frequency of desires to initiate sexual activity" and "how often do you initiate sexual activity." Rather, nefazodone appeared to result in patient-perceived differences in the pleasure derived from sexual activity. Thus, nefazodone resulted in significantly greater "frequency of pleasurable thoughts," "ability to become sexually excited," and "overall degree of sexual satisfaction" scores than did sertraline. The second interesting observation is derived from the time courses of these responses in Figure 4. Following the washout of sertraline (i.e., the time between screening and baseline values), the patient responses demonstrated significant improvement. When these patients were randomly assigned to nefazodone, the improvements in the visual analog scales were sustained. In contrast, renewed treatment with sertraline resulted in immediate impairment of these patient-rated indices of sexual function and satisfaction.

The results of the current study confirm the previous findings of Feiger et al.[21] In that study, the effects of nefazodone and sertraline on sexual function and satisfaction were compared in a multicenter, double-blind, parallel-group study in depressed patients. Nefazodone was associated with low incidence of sexual dysfunction, whereas treatment with sertraline produced significantly greater sexual dysfunction. Specifically, when compared with nefazodone, sertraline resulted in significantly less enjoyment of sex, less satisfaction with sexual functioning, and more difficulty with ejaculation in men and significantly more difficulty in achieving orgasm in women.

In the current study, no significant differences in mean HAM-D-17 total scores, CGI-S scores, and CGI responder analyses were found between nefazodone and sertraline treatment groups at any week during double-blind treatment. In addition, both drugs were well tolerated.

The current study indicates that nefazodone treatment of depressed patients with sexual dysfunction related to sertraline therapy is associated with significantly less risk of reemergence of substance-induced sexual dysfunction than renewed treatment with sertraline. These data indicate that depressed patients exhibiting antidepressant-induced sexual dysfunction can be switched to nefazodone with continuation of antidepressant response, but significantly less risk of substance-induced sexual dysfunction.

Drug names: amantadine (Symmetrel and others), buspirone (BuSpar), clonidine (Catapres and others), cyproheptadine (Periactin), diphenhydramine (Benadryl and others), fluoxetine (Prozac), nefazodone (Serzone), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor), yohimbine (Yocon and others).

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