Sexual Function and Satisfaction in the Treatment of Chronic Major Depression With Nefazodone, Psychotherapy, and Their Combination

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Background: Changes in sexual interest/satisfaction and function are frequently associated with major depression and the use of some antidepressant treatments. This study compares the effects of antidepressant medication, psychotherapy, and combined treatment on sexual interest/satisfaction and function in patients with chronic major depression.

Method: Outpatients with chronic forms of DSM-IV major depressive disorder (N = 681) were randomly assigned to 12 weeks of nefazodone, Cognitive Behavioral Analysis System of Psychotherapy (CBASP), or combined nefazodone/CBASP. The Modified Rush Sexual Inventory was used to assess sexual functioning, and the 24-item Hamilton Rating Scale for Depression was used to assess depressive symptoms.

Results: At baseline, 65% of men and 48% of women reported some sexual dysfunction. Statistically significant linear improvement in sexual interest/satisfaction was noted across all 3 treatment groups ($p < .001$). Additionally, significant improvement in sexual function was observed across all 3 treatment groups on a composite measure of female sexual function ($p < .001$). Controlling for depressive symptoms and gender, combined treatment produced greater improvement in total sexual interest/satisfaction than CBASP alone ($p = .007$), but was not significantly different from nefazodone alone. Improvement in depressive symptoms was associated with improved sexual interest/satisfaction for men and women and, for men, improved sexual functioning.

Conclusion: Chronic depression is associated with high rates of sexual dysfunction. Treatment with nefazodone, CBASP, and combined treatment improved sexual interest/satisfaction, with greatest improvement observed with combined treatment.

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High rates of sexual dysfunction have been found in the general population.[1] Studies suggest that depression increases the risk for sexual dysfunction even when controlling for age, health, medication, and other variables.[1–5]

Complicating the link between depression and sexual function is the potential for many antidepressant modalities to be associated with impaired sexual function. Tricyclic antidepressants and monoamine oxidase inhibitors are associated with sexual side effects that potentially affect all phases of sexuality, including interest, arousal, and orgasm.[6] Selective serotonin reuptake inhibitors (SSRIs) are associated with relatively high rates of orgasm-related side effects in both sexes, frequently persisting during continuation and maintenance treatment,[7,8]

although some reports suggest improvement in sexual interest and functioning in women.[9,10] Nefazodone, bupropion, and mirtazapine have demonstrated similar efficacy to other conventional antidepressants such as the SSRIs,[11–13] but with a more favorable sexual side effect profile.[11,14,15]

There is a paucity of data on baseline rates of sexual function in major depression, including among depressive subtypes such as chronic depression. Also, little is known about differentiating treatment effects from illness effects on sexual interest/satisfaction and function in depressed patients, including patients with chronic depression treated with psychotherapy or pharmacotherapy. One uncontrolled study found improved sexual satisfaction in men who remit from major depressive disorder after cognitive-behavioral psychotherapy.[16] Change in sexual functioning during the treatment of chronic forms of depression is a particularly important clinical issue, since such depressions often necessitate continuation and maintenance treatment, during which adherence issues may arise if treatment-related sexual side effects emerge.

This study systematically assessed sexual interest/satisfaction and function at baseline and during treatment in patients with chronic major depression who received 12 weeks of (1) nefazodone, (2) a psychotherapy tailored to chronic depression (Cognitive Behavioral Analysis System of Psychotherapy [CBASP]),[17] or (3) the combination of nefazodone and CBASP. The primary efficacy and safety data from the acute treatment phase of this study have already been reported.[18] Combined treatment resulted in significantly higher response rates (73% of patients in the intent-to-treat group) than either CBASP alone (48%) or nefazodone alone (48%).

The current report examines baseline data on sexual interest/satisfaction and function and the effect of the 3 treatments, controlling for some of the methodological weaknesses of previous studies. Our hypotheses were that changes in sexual interest/satisfaction would be associated with changes in depressive symptoms and that combined treatment would yield greater improvements in sexual interest/satisfaction than CBASP or nefazodone alone, even when controlling for changes in depressive symptoms. On the basis of previous literature concerning nefazodone, sexual function was not expected to worsen,[11] and no differences in changes over time among the 3 treatment differences were expected. Limited data in the literature were available to guide specific hypotheses about gender. Changes in sexual function and gender effects were therefore examined on an exploratory basis.

METHOD

Patient Population

Patients (N = 681) were recruited from 12 university-based treatment centers. Patients met criteria for either chronic major depressive disorder, current major depressive disorder superimposed on antecedent dysthymic disorder, or recurrent major depressive disorder with incomplete interepisode recovery. Diagnoses were based on the Structured Clinical Interview for DSM-IV Axis I Disorders.[19] Men and women between the ages of 18 and 75 years who scored ≥ 20 on the 24-item Hamilton Rating Scale for Depression (HAM-D)[20] at both screening and baseline following a 2-week drug-free period (4 weeks in the case of monoamine oxidase inhibitors and fluoxetine) were eligible.

Exclusion criteria included high risk for suicide; history of psychotic symptoms or schizophrenia; bipolar disorder, eating disorder (if not in remission for ≥ 1 year), obsessive-compulsive disorder, or dementia; antisocial, schizotypal, or severe borderline personality disorder; principal diagnosis of panic, generalized anxiety, social anxiety, or posttraumatic stress disorder; any substance-related abuse or dependence disorder (except nicotine) within 6 months prior to study entry; or any unstable medical condition. Written informed consent was obtained after a complete description of the study.

As described previously,[18] the group of patients randomized (N = 681) had a mean ± SD age of 43 ± 11 years and was 65% female, 90.5% white, and 42.7% married/cohabiting.

Study Design

Patients eligible at the end of the evaluation period were randomly assigned in equal ratios to nefazodone, CBASP, or combined treatment. Nefazodone was initiated at 200 mg/day (in 2 divided doses) during the first week and increased to 300 mg/day during week 2. Dose adjustments were made thereafter, in weekly increments of 100 mg/day up to 600 mg/day, on the basis of clinical response and tolerability. To remain in the study, patients needed to achieve a minimum dose of 300 mg/day by the end of week 3.

CBASP followed a manual.[21] This psychotherapy was specifically developed for chronic depression and draws on techniques from behavioral, cognitive, and interpersonal forms of psychotherapy. Patients are taught to focus on the consequences of their thoughts and behavior and to use a social problem-solving algorithm to address problematic interpersonal difficulties. Psychotherapy sessions (50 min) were held twice weekly during weeks 1 through 4 and weekly thereafter until week 12. Twice-weekly sessions could be extended through week 8 if a patient had not mastered the social problem-solving procedure, allowing a maximum of 20 sessions.

Measures

The 24-item HAM-D was used to assess depressive symptoms at baseline and at each clinic visit. Clinical response on the HAM-D was defined as at least a 50%

decrease from baseline to endpoint plus a score ≤ 15 at weeks 10 and 12 (or at endpoint for those who discontinued early).

Sexual interest/satisfaction and function were assessed using the Modified Rush Sexual Inventory (MRSI), a self-report questionnaire designed to measure baseline and historical sexual history information and changes in sexual interest/satisfaction and function,[22] with scores obtained at baseline and at weeks 4, 8, and 12. The MRSI is similar to the original Rush Sexual Inventory, with the exception that some items that were found to be of little utility were deleted. Sexual interest/satisfaction over the previous month was evaluated using 5 visual analogue items (rated 0–100): (1) frequency of pleasurable sexual thoughts, (2) ability to become sexually excited, (3) desire to initiate sexual activity, (4) frequency of initiating sexual activity, and (5) overall degree of sexual satisfaction. A total sexual interest/satisfaction score was created by summing scores on the 5 items. In the current study, this total score yielded high internal consistency reliability (Cronbach alpha of .90 at baseline), with corrected item-total correlations ranging from 0.63 to 0.83. The MRSI also includes assessment of specific domains of sexual function during the previous month, with 7 (yes/no) items for men and 5 items for women (specific items listed in Tables 1A and 1B). The presence or absence of any sexual dysfunction across the 7 items for men or 5 items for women was used as a primary outcome measure. In addition, each of the specific sexual functions for men and women was separately analyzed by assessment of discontinuation due to sexual adverse events.

Statistical Methods

The treatment groups were compared on sexual medical information at baseline using the Cochran-Mantel-Haenszel test for categorical variables, with site as the stratification variable.

The primary analysis for examining change over time was a longitudinal analysis that included all available data between baseline and week 12 using the MRSI total sexual interest/satisfaction score. A random coefficient model was implemented with random intercept and random slope terms that allowed each patient's intercept and slope to deviate from the population-averaged intercept and slope. The model included main effect terms for treatment, gender, site, and time, plus interaction terms for treatment-by-site, treatment-by-gender, treatment-by-time, gender-by-time, and treatment-by-time-by-gender. The model also included HAM-D total score as a time-varying covariate, the interaction of HAM-D score and treatment group, the interaction of HAM-D score and time, and the 3-way interaction of HAM-D score–by-treatment-by-time. The treatment-by-site and treatment-by-time-by-site interactions were not significant ($p > .10$) and were not included in the final models. The treatment-by-time interaction is the test for differential rate of change from baseline to week 12 for the 3 treatment groups. Contrasts of the rate of change for the 3 treatment conditions were made. An unstructured error covariance structure was specified. A simpler analysis that included HAM-D response status as term, rather than continuous HAM-D scores at each assessment as a time-varying covariate, was also performed; results were largely similar and therefore only the more powerful time-varying covariate analysis is presented. However, for descriptive purposes, changes in sexual interest/satisfaction and functioning are displayed by responder status and by treatment group.

For each of the dichotomous (presence/absence) overall and individual sexual function items, a generalized linear mixed model was implemented using the SAS GLIMMIX macro (SAS 8.0, SAS Institute, Cary, N.C.) that implements the Wolfinger-O'Connell procedure.[23] Terms in the model were the same as those described for the random coefficients models, except that these analyses were performed separately for men and women.

To understand the impact of depressive symptoms on sexual interest/satisfaction and function, Pearson correlation coefficients were calculated between the sexual interest/satisfaction/function scores and the HAM-D total score at each point in time for each treatment group.

All statistical tests were 2-tailed; significance was declared at the .05 level for analyses of the total sexual interest/satisfaction score and the total sexual function scores for men and women; for the individual sexual function items, a Bonferroni-corrected alpha of .005 (.05/10) was employed because 10 separate dysfunctions were examined.

RESULTS

Sexual Function and Medical Information at Baseline

Sexual history data were available at baseline for 658 patients (227 men and 431 women). Sixteen percent of the study group had experienced sexual dysfunction while taking medication in the past. Baseline sexual dysfunction data were available for 669 patients (230 men and 439 women). Sixty-five percent (149/230) of men reported at least 1 sexual dysfunction symptom at baseline (Tables 1A and 1B). The incidence and type of dysfunction in men included the following: 19% (44/230), difficulty achieving an erection when sexually stimulated; 37% (84/230), delay in achieving orgasm/ejaculation; 13% (30/230), inability to achieve orgasm/ejaculation; and 22% (50/230), premature orgasm/ejaculation.

Forty-eight percent of women (210/439) reported at least 1 sexual dysfunction symptom at baseline. The incidence and type of dysfunction in women included the

Table 1A. Male Patients With Sexual Dysfunctions at Baseline and Weeks 4, 8, and 12[a]

	Treatment Group							
	Nefazodone		CBASP		Combined		Total	
Type of Sexual Dysfunction	N/Total N	%	N/Total N	%	N/Total N	%	N/Total N	%
Any dysfunction								
Baseline	52/79	66	51/84	61	46/67	69	149/230	65
Week 4	36/64	56	40/65	62	26/55	47	102/184	55
Week 8	33/62	53	23/55	42	27/55	49	83/172	48
Week 12	37/59	63	35/61	57	30/57	53	102/177	58
Difficulty getting an erection when sexually stimulated								
Baseline	15/79	19	16/84	19	13/67	19	44/230	19
Week 4	11/64	17	10/65	15	8/55	15	29/184	16
Week 8	10/62	16	5/55	9	9/55	16	24/172	14
Week 12	13/59	22	8/61	13	12/57	21	33/177	19
Difficulty maintaining an erection to complete sexual act								
Baseline	19/79	24	17/84	20	18/67	27	51/230	22
Week 4	10/64	16	12/65	18	11/55	20	33/184	18
Week 8	9/62	15	7/55	13	14/55	25	30/172	17
Week 12	14/59	24	10/61	16	17/57	30	41/177	23
Decreased sensitivity of genitals upon physical stimulation								
Baseline	17/79	22	14/84	17	10/67	15	41/230	18
Week 4	9/64	14	9/95	9	9/55	16	27/184	15
Week 8	12/62	19	11/55	20	9/55	16	32/172	19
Week 12	8/59	14	5/61	8	5/57	9	18/177	10
Delay in achieving orgasm/ejaculation								
Baseline	24/79	30	34/84	40	26/67	39	84/230	37
Week 4	21/64	33	15/65	23	19/55	35	55/184	30
Week 8	23/62	37	8/55	15	15/55	27	46/172	27
Week 12	24/59	41	15/61	25	17/57	30	56/177	32
Inability to achieve orgasm/ejaculation								
Baseline	8/79	10	8/84	10	14/67	21	30/230	13
Week 4	7/64	11	4/65	6	9/55	16	20/184	11
Week 8	6/62	10	5/55	9	10/55	18	21/172	12
Week 12	6/59	10	7/61	12	10/57	18	23/177	13
Orgasm/ejaculation occurring earlier than desired								
Baseline	13/79	16	23/84	27	14/67	21	50/230	22
Week 4	8/64	12	15/65	23	6/55	11	29/184	16
Week 8	7/62	11	8/55	15	5/55	9	20/172	12
Week 12	8/59	14	11/61	18	9/57	16	28/177	16
Generally decreased intensity of orgasm								
Baseline	25/79	32	27/84	32	24/67	36	76/230	33
Week 4	20/64	31	22/65	34	10/55	18	52/184	28
Week 8	18/62	29	13/55	24	13/55	24	44/172	26
Week 12	17/59	29	17/61	28	13/57	23	47/177	27

[a]Abbreviation: CBASP = Cognitive Behavioral Analysis System of Psychotherapy.

following: 21% (92/439), inability to achieve orgasm; 19% (83/439), decreased intensity of orgasm; and 18% (81/439), inadequate swelling or vaginal lubrication during sexual arousal.

Study Treatment

For randomized patients that received study treatment, the mean ± SD final daily dose of nefazodone was 466 ± 144 mg in the nefazodone-alone group (N = 216) and 460 ± 139 mg in the combined treatment group (N = 221 for whom data were available). The mean ± SD number of CBASP treatment sessions was 16.0 ± 4.7 (N = 216) for the CBASP-alone group and 16.2 ± 4.8 (N = 226) for the combined treatment group.

Discontinuations Due to Treatment-Emergent Sexual Adverse Events

No patient discontinued treatment solely because of treatment-emergent sexual adverse events, although 2 patients taking nefazodone discontinued treatment between day 1 and day 8 postrandomization as a result of multiple adverse events, including sexual dysfunction.

Overall Improvement and Treatment Differences

Taking into account all of the data across 12 weeks of treatment, a significant linear improvement over time ($F = 49.5$, $df = 1,658$; $p < .001$) was found for the MRSI total sexual interest/satisfaction score across all treatment groups (Table 2). In addition, a significant treatment-by-

Table 1B. Female Patients With Sexual Dysfunctions at Baseline and Weeks 4, 8, and 12[a]

	Treatment Group							
	Nefazodone		CBASP		Combined		Total	
Type of Sexual Dysfunction	N/Total N	%	N/Total N	%	N/Total N	%	N/Total N	%
Any dysfunction								
Baseline	75/144	52	63/140	45	72/155	46	210/439	48
Week 4	51/115	44	42/111	38	55/138	40	148/364	41
Week 8	33/94	35	33/100	33	62/128	48	128/322	40
Week 12	39/97	40	26/100	26	43/112	38	108/309	35
Decreased sensitivity in genitals upon physical contact								
Baseline	17/144	12	13/140	9	15/155	10	45/439	10
Week 4	8/115	7	9/111	8	9/138	7	6/364	7
Week 8	8/94	9	2/100	2	12/128	9	22/322	7
Week 12	8/97	8	2/100	2	5/112	4	15/309	5
Inadequate swelling or vaginal lubrication during sexual arousal								
Baseline	28/144	19	21/140	15	32/155	21	81/439	18
Week 4	19/115	17	17/111	15	16/138	12	52/364	14
Week 8	10/94	11	8/100	8	20/128	16	38/322	12
Week 12	12/97	12	6/100	6	16/112	14	34/309	11
Difficulty achieving orgasm								
Baseline	51/144	35	40/140	29	41/155	26	132/439	30
Week 4	34/115	30	27/111	24	34/138	25	95/364	26
Week 8	23/94	24	23/100	23	37/128	29	83/322	26
Week 12	27/97	28	19/100	19	26/112	23	72/309	23
Inability to achieve orgasm								
Baseline	32/144	22	28/140	20	32/155	21	92/439	21
Week 4	17/115	15	10/111	9	19/138	14	46/364	13
Week 8	15/94	16	10/100	10	17/128	13	42/322	13
Week 12	18/97	19	4/100	4	14/112	12	36/309	12
Decreased intensity of orgasm								
Baseline	31/144	22	23/140	16	29/155	19	83/439	19
Week 4	19/115	17	15/111	14	23/138	17	57/364	16
Week 8	14/94	15	9/100	9	21/128	16	44/322	14
Week 12	16/97	16	9/100	9	20/112	18	45/309	15

[a]Abbreviation: CBASP = Cognitive Behavioral Analysis System of Psychotherapy.

time interaction was found for the MRSI total sexual interest/satisfaction score ($F = 3.6$, $df = 1,658$; $p = .03$). Pairwise comparisons revealed that combined treatment showed greater improvement than CBASP ($F = 7.2$, $df = 1,658$; $p = .007$), but combined treatment was not superior to nefazodone alone ($F = 1.5$, $df = 1,658$; $p = .22$), and nefazodone alone and CBASP alone were not significantly different from each other ($F = 2.1$, $df = 1,658$; $p = .15$) (Table 2). The slope coefficients were 7.6 for combined treatment, 6.5 for nefazodone, and 5.2 for CBASP.

Female sexual dysfunction also showed significant improvement over time ($F = 11.9$, $df = 1,426$; $p < .001$). Forty-eight percent of women at baseline, and 35% at week 12, reported at least 1 dysfunction symptom (Tables 1A and 1B). No specific female sexual dysfunction symptoms improved significantly over time using the Bonferroni-corrected alpha of .005.

There was no significant improvement in sexual dysfunction over time in men. However, delay of achieving orgasm/ejaculation in men did show a significant treatment-by-time interaction ($F = 6.1$, $df = 2,218$; $p = .003$) (Tables 1A and 1B). Pairwise comparison revealed that delay in achieving orgasm/ejaculation improved significantly more for patients treated with CBASP than those treated with nefazodone ($F = 12.2$, $df = 1,218$; $p = .001$), but there was no significant difference between CBASP and combined treatment ($F = 3.2$, $df = 1,218$; $p = .08$) or between nefazodone and combined treatment ($F = 2.9$, $df = 1,218$; $p = .09$). The percentage of patients with this symptom of dysfunction decreased for CBASP (41% at baseline to 25% at week 12) and combined treatment (39% to 30%), but increased for nefazodone (30% to 41%).

Impact of Depressive Symptoms

A significant ($F = 109.8$, $df = 1,658$; $p < .001$) relationship between the HAM-D total score as a time-varying covariate and the MRSI total sexual interest/satisfaction score was apparent, indicating that these 2 measures were significantly correlated. This relationship did not vary by treatment group, but did vary by time (time-by–HAM-D score interaction, $F = 50.2$, $df = 1,658$; $p < .001$) due to increasing correlations of HAM-D and MRSI total sexual interest/satisfaction scores over time. For nefazodone, the correlations of total sexual interest/

Table 2. Total Sexual Interest/Satisfaction Scores (mean ± SD) on the Modified Rush Sexual Inventory at Baseline and Weeks 4, 8, and 12[a]

	Treatment Group							
	Nefazodone		CBASP		Nefazodone + CBASP		Overall	
Visit	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N
Baseline								
Women	123 ± 110	144	130 ± 113	157	126 ± 101	139	127 ± 108	440
Men	235 ± 118	80	231 ± 123	68	255 ± 106	84	241 ± 115	232
All	163 ± 125	224	175 ± 120	225	160 ± 125	223	166 ± 123	672
Week 4								
Women	122 ± 112	115	133 ± 112	138	104 ± 105	111	121 ± 111	364
Men	233 ± 113	65	211 ± 115	55	214 ± 109	65	220 ± 112	185
All	162 ± 125	180	144 ± 119	193	156 ± 118	176	154 ± 121	549
Week 8								
Women	135 ± 124	94	157 ± 120	127	99 ± 92	100	132 ± 115	321
Men	248 ± 122	62	235 ± 113	54	238 ± 97	57	241 ± 111	173
All	180 ± 135	156	149 ± 115	157	180 ± 123	181	170 ± 125	494
Week 12								
Women	152 ± 127	98	207 ± 122	113	139 ± 112	101	167 ± 124	312
Men	279 ± 111	59	272 ± 106	57	267 ± 99	61	273 ± 105	177
All	200 ± 137	157	187 ± 123	162	229 ± 120	170	206 ± 128	489

[a]Abbreviation: CBASP = Cognitive Behavioral Analysis System of Psychotherapy. Values are the sums of scores on 5 visual analogue scales scored from 0 to 100. Higher scores indicate greater sexual interest/satisfaction.

satisfaction score and HAM-D score ranged from –0.09 (N = 224; p < .16) at baseline to –0.30 (N = 146; p = .0003) at week 12; the same correlations ranged from –0.15 (N = 223; p = .02) to –0.18 (N = 147; p = .03) for CBASP, and from –0.28 (N = 225; p < .0001) to –0.34 (N = 161; p < .0001) for combined treatment. Increases in the size of these correlations over time were most likely a result of increased variability in HAM-D scores over time (HAM-D SD = 5 at baseline and 9 at week 12). This increase in correlations over time did not vary significantly by treatment group.

There was no significant relationship between HAM-D total scores and occurrence of female sexual dysfunction (F = 0.30, df = 1,426; p = .59), nor did this relationship vary significantly by treatment group, time, or treatment-by-time. In contrast, there was a highly significant relationship between HAM-D total scores and occurrence of male sexual dysfunction (F = 15.6, df = 1,218; p < .001), with greater severity of depressive symptoms associated with more male sexual dysfunction. This relationship did not vary significantly by treatment, time, or treatment-by-time. There were no significant differences in rates of any sexual dysfunction at baseline between responders and nonresponders for men or women.

To illustrate the impact of changes in HAM-D score on changes in sexual function, Figures 1 and 2 present mean scores per assessment visit by HAM-D responder status. In all treatment groups, sexual dysfunction in men was greatest for nonresponders at week 12 (Figure 1). In contrast, for women (Figure 2), the lack of relation between the HAM-D score and sexual dysfunction described above is evident in terms of nonresponders to CBASP displaying the lowest, rather than the highest, rate of sexual dysfunction at week 12 (although the treatment differences are not significant).

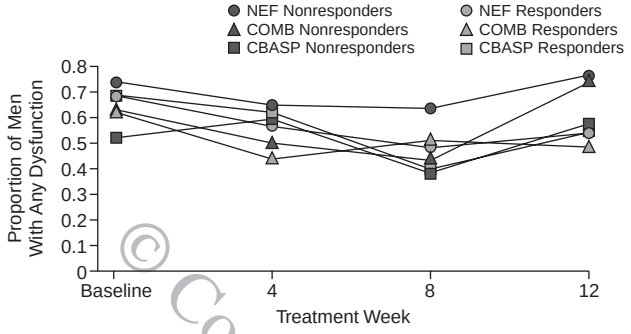
Gender Differences in Sexual Interest/Satisfaction

Baseline MRSI sexual interest/satisfaction scores were available for 672 patients (232 men and 440 women). Averaged across all assessments, men had significantly greater sexual interest/satisfaction than women (Table 2). At baseline, the mean ± SD MRSI total sexual interest/satisfaction score for men was 241 ± 115, over a standard deviation higher than that for women (mean ± SD = 127 ± 108), and this magnitude of difference did not vary significantly over time or across treatment groups. Differences between the treatment groups in rate of change over time did not vary by gender.

DISCUSSION

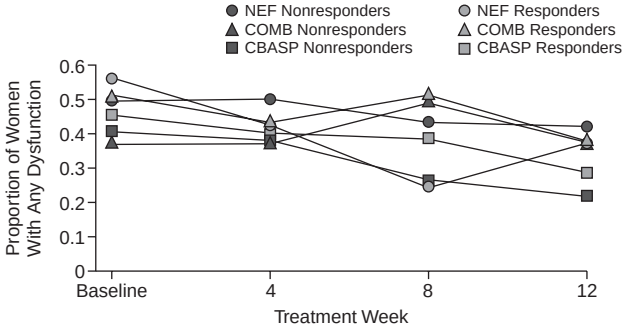
Several major findings emerged from this study. This study is the first large-scale evaluation and reporting of baseline rates of sexual interest/satisfaction and function in patients with chronic depression, providing reliable epidemiologic and phenomenological data on the extent of sexual problems associated with depression. Sixty-five percent of men and 48% of women reported some sexual dysfunction at baseline. Direct comparisons of the rate of sexual dysfunction with community samples are problematic since the exclusion criteria for this study excluded patients with significant medical conditions, concomitant medications, and other factors that impact sexual function. Direct comparisons with previous studies of sexual function and depression may also be confounded by differences in age and target diagnoses of study groups.

Figure 1. Proportion of Men With Any Sexual Dysfunction: Responders and Nonresponders[a]



[a]Abbreviations: CBASP = Cognitive Behavioral Analysis System of Psychotherapy, COMB = combination treatment, NEF = nefazodone.

Figure 2. Proportion of Women With Any Sexual Dysfunction: Responders and Nonresponders[a]



[a]Abbreviations: CBASP = Cognitive Behavioral Analysis System of Psychotherapy, COMB = combination treatment, NEF = nefazodone.

As hypothesized, change in depressive symptoms was associated with improved sexual interest/satisfaction across all 3 treatment groups and, for men, improved sexual functioning. This association between changes in depressive symptoms and sexual interest/satisfaction (for both sexes) and sexual function (for men) underscores the link between these disorders.

Sexual interest/satisfaction increased significantly from baseline to week 12 with all 3 treatments. In addition, combined treatment was superior to psychotherapy alone on change in sexual interest/satisfaction, controlling for change in depressive symptoms. This finding suggests that the determinants of acute change in sexual interest/satisfaction are complex, with both pharmacologic and psychotherapeutic interventions contributing independently. These independent effects, however, are more than just the greater efficacy of combined treatment with regard to changes in depression reported previously.[18]

The current study confirms previous reports[11,24] documenting that nefazodone has minimal negative impact on sexual interest/satisfaction and function. Women showed significant improvement in the occurrence of sexual dysfunction symptoms across all treatments. Men, however, evidenced little change in sexual dysfunction over the course of treatment. The one possible exception was delay in achieving orgasm in men, which evidenced a slight worsening for patients receiving nefazodone, but an improvement for those receiving psychotherapy alone. Combined treatment also evidenced improvement on this dysfunction, suggesting that psychotherapy might provide some additional benefit. SSRIs have also been reported to produce delay in orgasm in men.[7,8] It is possible that dose increases for nonresponders to nefazodone may have produced the increased rate of delay in achieving orgasm in men. However, the fact that the mean final dose of nefazodone was equal for the nefazodone-alone and combined treatment groups argues against increased incidence of this sexual dysfunction being secondary to dose increases. Dose increases for nonresponders were mandatory in the current study, making it impossible to disentangle the role of dose increases and clinical response in producing, or alleviating, sexual dysfunction within the groups that received nefazodone.

Finally, gender differences were apparent. Sexual dysfunction symptoms improved over 12 weeks of treatment for women. Men had higher levels of sexual interest/satisfaction at baseline and throughout the 12-week treatment period, but generally did not show improvements in sexual dysfunction symptoms. It may be that depression has a differential impact on sexual function for men compared with women. Reporting biases, with men having on average more difficulty admitting to lack of sexual interest than women, may also contribute to the difference found. Regardless of the explanation, these gender effects highlight the need to examine differences between men and women in any study of the influence of treatments on sexual interest/satisfaction and function.

Several limitations of this research deserve mention. The inclusion/exclusion criteria for this study constrain the generalizability of the results, both the baseline findings and treatment effects. In particular, the extent to which the findings hold for patients with uncomplicated dysthymia and nonchronic major depression, patients with medical illnesses or concomitant medications that influence sexual functioning, or patients outside the age range within this study needs further study. It is unknown whether the benefits of combined treatment extend to other forms of psychotherapy and other antidepressants that have minimal impact on sexual interest/satisfaction and function. Regarding the baseline levels of sexual dysfunction, the particular definitions used in the current study (any dysfunction across 5 female-specific and 7 male-specific dysfunctions) may have inflated overall rates of sexual dysfunction relative to other studies. Other limitations include the awareness of patients and treating clinicians of the type of treatment patients received

(although blinded raters administered the HAM-D) and that the study did not include a placebo control. Another issue is the inherent confounding of mood state with reports of sexual satisfaction and function. Although we addressed this issue to a degree by controlling for depressive symptoms, it is impossible to uncouple these issues using self-report assessments of sexual satisfaction and function. No partner ratings or physiologic measures of sexual dysfunction were obtained, and the MRSI has only preliminary validation data from previous studies including limited data on sensitivity to change. Because of the limited information on preexisting sexual dysfunction available, there may have been some group differences that may have affected the results. Finally, this study is limited in that only 12-week outcomes were evaluated.

Despite the improvements in sexual interest/satisfaction for both men and women, sexual dysfunctions in men did not improve significantly. Sexual functioning did improve in women, but 35% still reported some dysfunction at week 12. Therefore, further studies are needed to examine whether further improvements in sexual interest/satisfaction and function are evident over the course of continuation and maintenance treatment for responders from the acute phase. Sustained improvements in sexual interest/satisfaction and function, along with symptomatic and psychosocial (work, social) improvements, will increasingly be seen as integral to overall recovery from major depressive disorder, especially chronic forms of the illness.

Drug names: bupropion (Wellbutrin and others), fluoxetine (Prozac and others), mirtazapine (Remeron), nefazodone (Serzone).

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