Prevalence of Sexual Dysfunction Among Newer Antidepressants

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Background: Sexual dysfunction commonly occurs during antidepressant treatment. However, the reported rates of sexual dysfunction vary across antidepressants and are typically underreported in product literature. The objectives of this study were (1) to estimate the prevalence of sexual dysfunction among patients taking newer antidepressants (bupropion immediate release [IR], bupropion sustained release [SR], citalopram, fluoxetine, mirtazapine, nefazodone, paroxetine, sertraline, venlafaxine, and venlafaxine extended release [XR]) and (2) to compare physician-perceived with patient-reported prevalence rates of antidepressant-associated sexual dysfunction.

Method: This cross-sectional, observational study was conducted in 1101 U.S. primary care clinics. Adult outpatients (4534 women and 1763 men) receiving antidepressant monotherapy were enrolled. The prevalence of sexual dysfunction was measured using the Changes in Sexual Functioning Questionnaire.

Results: In the overall population, bupropion IR (22%) and SR (25%) and nefazodone (28%) were associated with the lowest risk for sexual dysfunction, whereas selective serotonin reuptake inhibitor (SSRI) antidepressants, mirtazapine, and venlafaxine XR were associated with higher rates (36%–43%). In a prospectively defined subpopulation unlikely to have predisposing factors for sexual dysfunction, the prevalence of sexual dysfunction ranged from 7% to 30%, with the odds of having sexual dysfunction 4 to 6 times greater with SSRIs or venlafaxine XR than with bupropion SR. Physicians consistently underestimated the prevalence of antidepressant-associated sexual dysfunction.

Conclusion: Ours is the first study to assess sexual dysfunction across the newer antidepressants using consistent methodology and a validated rating scale. Overall, SSRIs and venlafaxine XR were associated with higher rates of sexual dysfunction than bupropion or nefazodone. Because antidepressant-associated sexual dysfunction is considerably underestimated by physicians, greater recognition and education are imperative when prescribing antidepressant treatment.

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The treatment of depression has been advanced in recent years by the introduction of several newer antidepressants. Among these are selective serotonin reuptake inhibitors (SSRIs; e.g., citalopram, fluoxetine, paroxetine, and sertraline), drugs that affect both serotonin and norepinephrine reuptake (e.g., mirtazapine, nefazodone, and venlafaxine), and bupropion, which enhances dopamine and norepinephrine neurotransmission. These newer medications have comparable efficacy to tricyclic antidepressants and monoamine oxidase inhibitors, but offer significant improvements in ease of dosing, overall side effect profiles, and reduced risk of acute toxicity. Current treatment guidelines indicate that the effectiveness of antidepressant medications is generally comparable; therefore, one of the primary factors that should be considered when selecting an antidepressant is the constellation of anticipated side effects of the drug.[1–3]

Although spontaneous reports of sexual dysfunction listed in product labeling for these newer antidepressants

indicate a relatively low incidence of sexual side effects (i.e., < 15%), sexual dysfunction has been reported in up to 70% of patients when direct inquiry regarding sexual functioning occurs.[4] Specifically, several studies have demonstrated that SSRI antidepressants are associated with higher rates of sexual dysfunction than their product labeling indicates.[5–8] However, because of the differing methodologies used to collect sexual functioning data, it is often difficult to compare rates of sexual dysfunction across studies. The rates of sexual dysfunction reported with SSRIs range from 34% to 70% of patients across studies in which patients were questioned directly about their sexual functioning.[5–11] Despite this variation across studies, rates of sexual dysfunction between different SSRIs within studies tend to be quite similar, underscoring both the impact of methodological differences on estimates of incidence and the similarity in rates of sexual dysfunction among SSRIs.

The importance of recognizing sexual dysfunction is 2-fold. First, sexual dysfunction is a common cause of noncompliance with antidepressant treatment regimens, which can lead to relapse of depression.[3,12,13] Second, the impact of unrecognized antidepressant-induced sexual dysfunction not only affects patients' quality of life (e.g., in interpersonal relationships, self-esteem), but may actually interfere with recovery from a depressive episode.

Lack of recognition of sexual dysfunction occurs commonly in clinical settings. Despite the importance of sexual functioning in patients' lives, many physicians are reluctant to specifically address sexual functioning with their patients. Physician assessment of sexual dysfunction is hampered by a number of factors, including social barriers, lack of knowledge about sexual functioning, inadequate training for obtaining a sexual history, lack of knowledge about how to treat sexual dysfunction, and fear of their questioning being misinterpreted or considered inappropriate.[14] Yet, more than 90% of patients believe that having physicians collect information on sexual history has considerable benefit.[15]

The current 6000+-patient, cross-sectional, observational study was conducted in over 1000 U.S. primary care clinics. It was designed to measure sexual functioning associated with all of the newer antidepressants using consistent methodology and a single, validated rating scale. As such, the study allows comparison of the rates of sexual dysfunction to be made across these antidepressants. A secondary objective of the study was to examine physician-perceived and patient-reported prevalence of sexual dysfunction in a primary care setting.

METHOD

Study Design

This multicenter, cross-sectional, observational study was conducted at 1101 primary care clinics throughout the United States. The protocol was approved by an appropriately constituted Institutional Review Board, and written informed consent was obtained from each patient prior to enrollment. Prior to receiving detailed information about the study, participating primary care physicians completed a Physician Antidepressant Experience Questionnaire (available from the authors on request). This questionnaire collected the demographic characteristics, medical background (medical specialty, number of years in practice, type of practice), and antidepressant prescribing experience of the primary care physicians, as well as their experience and perception of the prevalence of sexual dysfunction associated with antidepressant treatment in their clinical practice over the past year.

Patients were not randomly assigned to any one treatment group. Rather, eligible patients entered the study already receiving antidepressant treatment. To avoid selection bias, each participating primary care physician was asked to sequentially enroll the first 5 eligible patients who came into the clinic for a scheduled visit for any reason. Demographic information for potentially eligible patients was recorded on an enrollment log. For those patients who chose not to participate in the study, the reason for not enrolling was also recorded on the log.

Inclusion criteria required patients to be receiving antidepressant monotherapy for depression (e.g., taking an antidepressant plus trazodone for insomnia was not allowed) using one of the newer antidepressant medications (bupropion immediate release [IR], bupropion sustained release [SR], citalopram, fluoxetine, mirtazapine, nefazodone, paroxetine, sertraline, venlafaxine, or venlafaxine extended release [XR]). In addition, patients had to be at least 18 years of age, have been sexually active (defined as having experienced sexual intercourse, masturbation, sexual fantasies, or other sexual activity) at some time during the prior 12 months, be willing to discuss his or her sexual functioning with the physician, and give informed consent. Patients were excluded from participation if they were taking an antidepressant for the treatment of an illness other than depression.

Patients meeting enrollment criteria were asked to complete a written questionnaire regarding their demographic characteristics, antidepressant use, and sexual activity as well as the Changes in Sexual Functioning Questionnaire (CSFQ).[16,17] The CSFQ was designed to measure illness- and medication-related changes in sexual functioning. The validated, 14-item, gender-specific versions were used, which included all of the scored items from the original interview version. The questionnaire can be scored to examine global sexual functioning (total score) and each of the 5 domains that correspond to the phases of the sexual response cycle plus satisfaction: sexual pleasure, desire/frequency, desire/interest, arousal, and orgasm. Threshold scores to define sexual dysfunction are based on results reported in an article by Clayton et al.,[17] which presents

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the mean total CSFQ scores and CSFQ subscale scores, standard deviations, and 95% confidence intervals (CIs) for normal subjects compared with untreated depressed subjects.

The primary care physician reviewed the questionnaire, tallied the CSFQ score, and discussed the findings with the patient. When reviewing the subscores and the total score with the patient, the physician probed the patient about potential etiology, duration, and nature of the dysfunction. The primary care physician also recorded the length of time the patient had been seen in the practice, current medical conditions and concomitant medications, maximum severity and length of the current depressive episode, and total daily dose and length of treatment with the current antidepressant. Each patient completed the study during a single clinic visit.

Because patients may be affected by other factors that may be associated with sexual dysfunction in addition to antidepressant use, a target population (TP) subgroup was prospectively identified to assess the prevalence of sexual dysfunction among patients free of other probable causes of sexual dysfunction. Based on the existing literature, parameters were established to maximize the likelihood that patients in the TP were free of possible age-associated sexual dysfunction (e.g., male age-associated erectile dysfunction),[18,19] comorbid illnesses that may affect sexual functioning (e.g., diabetes),[20] and concomitant medications (e.g., β-blockers)[21,22] that could potentially cause sexual dysfunction. In addition, TP patients had a sufficient length of treatment (at least 3 months) with their current antidepressant, reducing the likelihood that any sexual dysfunction reported was secondary to their depression or previous antidepressant therapy.[23] The TP was therefore prospectively defined as (1) being 18 to 40 years of age, (2) reporting either no sexual side effects from any previous antidepressants taken or having no previous antidepressant use, (3) having been treated for at least 3 months with the current antidepressant, (4) taking no concomitant medications that would be expected to affect sexual functioning, (5) having no comorbid illnesses that would be expected to affect sexual functioning, and (6) having a patient-reported history of at least "some" sexual enjoyment.[24]

Statistical Methodology

The sample size for this study was calculated such that, on average, a 2-tailed 95% CI for the prevalence of sexual dysfunction for a given medication would have a maximum error boundary of 3.5 percentage points. Because it was expected that the distribution of patients across antidepressants would not be equal, it was anticipated that the error bounds for the prevalence of sexual dysfunction would range from 9 percentage points for a sample of 120 patients to 2.5 percentage points for a sample of 1537 patients for a given antidepressant medication.

Two populations of patients were prospectively identified for analysis: the overall clinical population (OCP), which comprised all patients enrolled in the study, and a TP subgroup made up of only patients free of other identified probable causes of sexual dysfunction.

The prevalence of sexual dysfunction was determined for each of the 10 antidepressant formulations (bupropion IR and SR, citalopram, fluoxetine, mirtazapine, nefazodone, paroxetine, sertraline, venlafaxine, and venlafaxine XR). Sexual dysfunction is defined as a total CSFQ score at or below the established gender-specific threshold score of 41 for women and 47 for men.[17] Two-tailed 95% CIs were calculated for all sexual dysfunction prevalence rates averaged across all medications and for each medication under study. Statistically significant differences were determined by nonoverlapping CIs for the groups being compared. Antidepressant groups with a prevalence rate associated with a CI range exceeding 30 percentage points (because of small sample size) are not presented here. The Physician Antidepressant Experience Questionnaire, which was completed prior to study training, included 8 antidepressants (bupropion SR, citalopram, fluoxetine, mirtazapine, nefazodone, paroxetine, sertraline, and venlafaxine).

The patient-specific total daily doses for each antidepressant were divided into 2 groups: "higher" and "lower" doses. The division of total daily doses assigned to each group was based on the median dose. However, because the median dose was also the modal dose for a number of medications, a given dose level could not be split between the groups and thus was assigned to a single group ("higher" or "lower") to reach as close to a 50/50 split as was feasible. The placement of a specific total daily dose in either of these categories did not reflect whether the dose is considered high or low in relation to the recommended daily dose.

Logistic regression was used to identify risk factors for sexual dysfunction in the OCP. A model including potential patient characteristic risk factors was used to determine the increase in the odds of having sexual dysfunction relative to a reference group within each classification. Statistically significant differences in the odds of developing sexual dysfunction based on these risk factors were identified by 95% CI ranges not overlapping 1.0.

RESULTS

Patient Demographics

Figure 1 summarizes patient disposition in the current study. Approximately three fourths of potentially eligible patients who were approached about participation enrolled and completed the study. There were no clinically relevant differences with regard to gender, age, or antidepressant treatment between those patients who enrolled and those who did not.

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Figure 1. Patient Disposition (from enrollment logs): Flow Chart Representing Status of Potentially Eligible Patients Approached to Participate in the Study

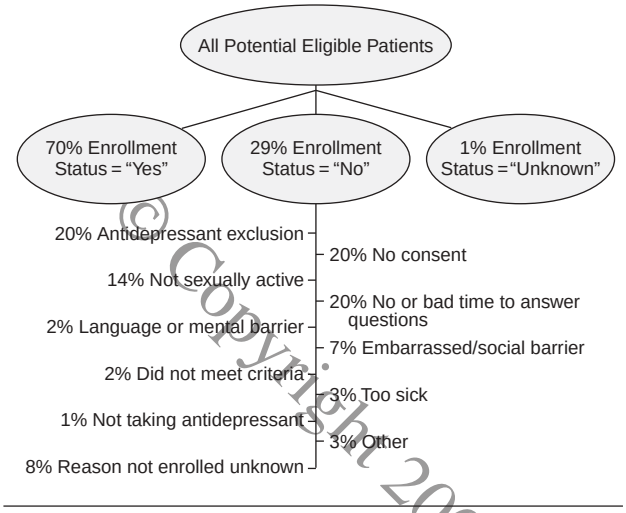

Table 1. Demographic Characteristics (from data collection forms)

Characteristic	Overall Clinical Population (N = 6297)	Target Population (N = 802)
Age, mean (SD), y	42.7 (11.32)	32.0 (5.8)
Sex, N (%)		
Female	4534 (72.0)	619 (77.2)
Male	1763 (28.0)	183 (22.8)
Race, N (%)		
White	5888 (93.5)	747 (93.1)
Black	171 (2.7)	16 (2.0)
Asian	30 (0.5)	5 (0.6)
Hispanic	169 (2.7)	30 (3.7)
Other	37 (0.6)	4 (0.5)
Data missing	2 (< 0.1)	0 (0)
Marital status, N (%)		
Married	4380 (69.6)	499 (62.2)
Single	824 (13.1)	187 (23.3)
Separated	186 (3.0)	26 (3.2)
Divorced	813 (12.9)	88 (11.0)
Widowed	92 (1.5)	2 (0.2)
Data missing	2 (< 0.1)	0 (0)
Employment status, N (%)		
Employed, full time	4014 (63.7)	548 (68.3)
Employed, part time	670 (10.6)	89 (11.1)
Full-time homemaker	559 (8.9)	84 (10.5)
Not currently employed	329 (5.2)	33 (4.1)
Volunteer work	28 (0.4)	0 (0)
Retired	357 (5.7)	0 (0)
Student	112 (1.8)	34 (4.2)
Other	224 (3.6)	13 (1.6)
Data missing	4 (0.1)	1 (0.1)
Highest educational level, N (%)		
None	1 (< 0.1)	0 (0)
Grade school (or less)	137 (2.2)	8 (1.0)
High school	1655 (26.3)	216 (26.9)
Some college/ technical school	2613 (41.5)	334 (41.6)
College graduate	1290 (20.5)	186 (23.2)
Postgraduate	596 (9.5)	56 (7.0)
Data missing	5 (0.1)	2 (0.2)
Tobacco use, N (%)		
Yes	1843 (29.3)	253 (31.5)
No	4445 (70.6)	548 (68.3)
Data missing	9 (0.1)	1 (0.1)

A total of 6297 patients were enrolled at 1101 primary care clinics throughout the United States; their demographic characteristics and those for the TP are listed in Table 1. Of these patients, 6268 (99.5%) completed all items on the CSFQ and were included in the sexual functioning analyses. Of these 6268 patients, 798 met the criteria for inclusion in the TP (4 others did not answer all CSFQ questions but did meet all inclusion criteria and completed the demographic information, for a total N of 802). The numbers of patients in the OCP and the TP taking each antidepressant under study are listed in Table 2.

The proportional rate of antidepressant use in this study resembles U.S. primary care physician antidepressant prescribing practices (Physician Drug & Diagnosis Audits [PDDAs] for November 1996–September 2000, Scott-Levin, a division of PMSI Scott-Levin, Inc., Newtown, Pa.). Length of treatment with the antidepressant varied: 1% of patients, < 1 week; 24%, > 1 week but < 3 months; 17%, 3 to 6 months; 17%, > 6 months but < 12 months; 28%, 1 to 3 years; and 12% had been treated with the current antidepressant for more than 3 years. The maximum severity of the current episode of depression was "moderate" in approximately half of the patients (mean = 52%; range across individual antidepressants = 48%–59%). Eighty-six percent of enrolled patients (N = 5401) reported being currently involved in sexual activity with a partner, and 35% (N = 2187) reported being currently involved in sexual activity without a partner. When asked about the importance of sexual functioning, 85% of patients (N = 5356) reported that sexual functioning was either extremely important (27%, N = 1677), very important (35%, N = 2199), or important (24%, N = 1480), while 12% (N = 746) reported that it was somewhat important and only 3% (N = 171) felt that it was not important. When sexual pleasure was assessed, 91% of all patients stated that they had had "much" or "great" pleasure at some point in their lifetime.

CSFQ Results: Sexual Dysfunction in the OCP and TP

The prevalence of sexual dysfunction in the OCP, based on CSFQ total scores for all antidepressants combined, was 37% (95% CI = 36% to 38%) and ranged from 22% to 43% across antidepressants. The lowest rates of sexual dysfunction were in the bupropion groups (22% and 25% for bupropion IR and SR, respectively) and the nefazodone group (28%), while the highest rates were in the paroxetine and mirtazapine groups (43% and 41%, respectively). Figure 2 displays the overall prevalence of sexual dysfunction by antidepressant for

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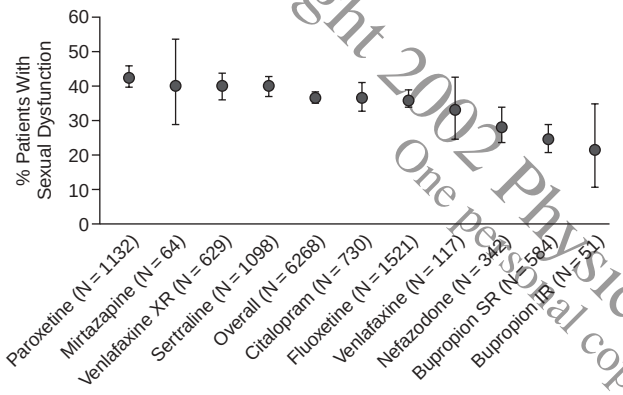
Table 2. Numbers of Patients Taking Newer Antidepressants

	Overall Clinical Population (N = 6297)		Target Population (N = 798)	
Antidepressant	N	%	N	%
Bupropion IR	52	0.8	2	0.3
Bupropion SR	584	9.3	45	5.6
Citalopram	734	11.7	83	10.4
Fluoxetine	1531	24.3	245	30.7
Mirtazapine	65	1.0	2	0.3
Nefazodone	343	5.4	21	2.6
Paroxetine	1136	18.0	159	19.9
Sertraline	1104	17.5	161	20.2
Venlafaxine	117	1.9	10	1.3
Venlafaxine XR	631	10.0	70	8.8

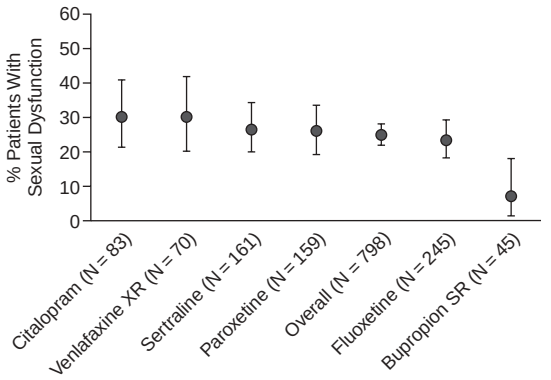
Figure 2. Prevalence of Sexual Dysfunction: Overall Clinical Population[a]



[a]Sexual dysfunction is defined as a Changes in Sexual Functioning Questionnaire score at or below the gender-specific threshold total score. Bars represent the 95% confidence interval. Abbreviations: IR = immediate release, SR = sustained release, XR = extended release.

the OCP. Patients taking either bupropion SR or nefazodone had a statistically significantly lower prevalence of sexual dysfunction than did patients taking fluoxetine, paroxetine, sertraline, or venlafaxine XR. In addition, patients taking bupropion SR had a significantly lower prevalence of sexual dysfunction than did patients taking citalopram or mirtazapine. Patients taking bupropion IR had a significantly lower prevalence of sexual dysfunction than did patients who were taking paroxetine, sertraline, or venlafaxine XR. Patients taking fluoxetine had a lower prevalence of sexual dysfunction than did patients taking paroxetine. No other differences between antidepressants in the prevalence of sexual dysfunction were statistically significant. Two thousand three hundred fourteen patients were identified as having sexual dysfunction on the basis of their subthreshold total CSFQ score, indicative of global sexual dysfunction. Within each of the domains of sexual functioning, similar proportions of patients exhibited subthreshold scores across each of the antidepressants.

Figure 3. Prevalence of Sexual Dysfunction: Subpopulation of Patients Without Other Probable Causes of Sexual Dysfunction (target population)[a]



[a]Sexual dysfunction is defined as a Changes in Sexual Functioning Questionnaire score at or below the gender-specific threshold total score. Bars represent the 95% confidence interval (CI). Data were included only for antidepressant groups with a CI range less than 30 percentage points. Abbreviations: SR = sustained release, XR = extended release.

Within the TP, the overall prevalence of sexual dysfunction on the basis of CSFQ total scores averaged 24% [95% CI = 22% to 28%] for all antidepressants combined and ranged from 7% (bupropion SR) to 30% (citalopram and venlafaxine XR) across antidepressants. Figure 3 displays the prevalence of sexual dysfunction by antidepressant for the TP. Although included in the total sample, 4 medications (bupropion IR, mirtazapine, nefazodone, and venlafaxine) are not reported in the TP analyses due to small sample sizes. Relative to bupropion SR, the odds of developing sexual dysfunction were 6 times greater with citalopram and venlafaxine XR, 5 times greater with paroxetine and sertraline, and 4 times greater with fluoxetine. Patients taking bupropion SR had a significantly lower prevalence of sexual dysfunction than did patients taking citalopram, paroxetine, sertraline, or venlafaxine XR; there were no other statistically significant differences between antidepressants in the prevalence of sexual dysfunction among patients in the TP.

Odds Ratios of Risk Factors for Sexual Dysfunction

Table 3 presents the odds ratios for sexual dysfunction by each risk factor in the OCP. Of the potential risk factors analyzed, gender, race, and duration of current antidepressant treatment did not predict risk for sexual dysfunction.

The odds of having sexual dysfunction tend to increase as patients get older. Those who were 40 years of age or older (and statistically significantly for those aged 50–59) had higher odds of having sexual dysfunction, compared with the reference age group of 20- to 29-year-old patients, while the 18- and 19-year-old and 30- to 39-year-old

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Table 3. Odds Ratios of Sexual Dysfunction by Risk Factor in the Overall Clinical Population[a]

Risk Factor	Odds Ratio	N	95% CI
Age, y			
20–29	1.00	769	
18–19	0.54	46	0.24 to 1.14
30–39	0.84	1627	0.69 to 1.04
40–49	1.02	2141	0.83 to 1.25
50–59	1.42	1226	1.14 to 1.79[b]
60–69	1.31	348	0.94 to 1.82
≥ 70	1.63	97	0.93 to 2.88
Gender			
Male	1.00	1746	
Female	0.94	4510	0.82 to 1.08
Race			
White	1.00	5849	
Black	1.10	170	0.77 to 1.54
Asian	0.89	29	0.35 to 2.06
Hispanic	1.37	169	0.97 to 1.91
Other	1.30	37	0.62 to 2.66
Marital status			
Married	1.00	4353	
Single	0.76	815	0.63 to 0.92[b]
Separated	0.66	184	0.46 to 0.93[b]
Divorced	0.80	810	0.67 to 0.95[b]
Widowed	0.63	92	0.38 to 1.03
Highest educational level			
High school	1.00	1646	
Grade school (or less)	1.12	136	0.76 to 1.67
Some college/technical school	0.95	2592	0.83 to 1.10
College graduate	0.79	1282	0.66 to 0.93[b]
Postgraduate	0.65	595	0.52 to 0.82[b]
Employment status			
Employed, full time	1.00	3984	
Employed, part time	1.27	668	1.06 to 1.53[b]
Full-time homemaker	1.32	555	1.07 to 1.62[b]
Not currently employed	1.56	327	1.21 to 2.01[b]
Volunteer work	1.07	28	0.43 to 2.54
Retired	1.67	355	1.24 to 2.24[b]
Student	1.35	112	0.86 to 2.10
Other	1.41	223	1.04 to 1.90[b]
Tobacco use			
None	1.00	4413	
1–5 times/d	0.76	393	0.59 to 0.97[b]
6–20 times/d	1.18	1183	1.02 to 1.38[b]
> 20 times/d	1.31	241	0.98 to 1.75
Previous use of another antidepressant			
None	1.00	2959	
Yes, reported no sexual side effects	0.88	1409	0.76 to 1.02
Yes, reported sexual side effects	1.67	1888	1.46 to 1.91[b]
Duration of antidepressant treatment			
≥ 3 mo	1.00	4673	
< 3 mo	1.04	1583	0.91 to 1.19
Comorbid illness			
None	1.00	1442	
Yes (none known to affect sexual functioning)	1.02	2790	0.87 to 1.20
Yes (at least 1 known to affect sexual functioning)	1.24	2024	1.03 to 1.49[b]
Concomitant medications			
None	1.00	1387	
Yes (none known to affect sexual functioning)	1.26	2869	1.07 to 1.49[b]
Yes (at least 1 known to affect sexual functioning)	1.25	2000	1.03 to 1.50[b]
Total daily dose			
Lower	1.00	3738	
Higher	1.26	2518	1.11 to 1.43[b]
History of sexual enjoyment			
At least "some"	1.00	6155	
"Little" or "no"	5.35	92	3.05 to 9.83[b]
Importance of sexual functioning			
Important, very important, or extremely important	1.00	5329	
Somewhat important	3.60	746	3.04 to 4.28[b]
Not important	15.19	169	9.16 to 26.95[b]
Antidepressant			
Bupropion SR	1.00	583	
Bupropion IR	0.86	51	0.39 to 1.75
Citalopram	2.22	726	1.70 to 2.90[b]
Fluoxetine	2.23	1519	1.75 to 2.87[b]
Mirtazapine	1.66	64	0.92 to 2.95
Nefazodone	1.26	342	0.91 to 1.74
Paroxetine	2.89	1130	2.24 to 3.73[b]
Sertraline	2.49	1096	1.94 to 3.20[b]
Venlafaxine	1.46	117	0.90 to 2.32
Venlafaxine XR	2.36	628	1.80 to 3.09[b]

[a]Abbreviations: CI = confidence interval, IR = immediate release, SR = sustained release, XR = extended release.
[b]95% CI ranges did not cross 1.0.

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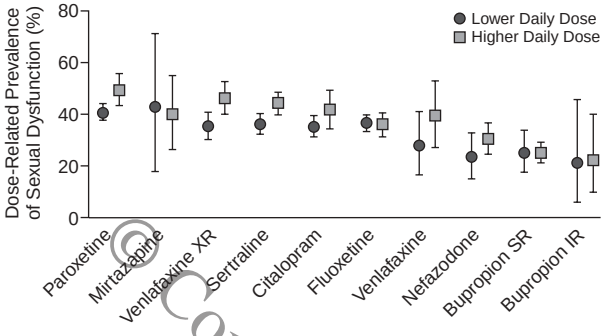
patients had lower odds. Compared with married people, all other marital groups had lower odds of sexual dysfunction, and for those who were single, separated, or divorced, these odds were statistically significant. Patients with some college, technical school, or graduate school education had lower odds of having sexual dysfunction compared with those with a high school education only; that difference became statistically significant for those with a graduate or postgraduate degree. For those with grade school or less education, the odds were higher compared with the reference group. Compared with patients working full time, the odds of reporting sexual dysfunction were higher for all other employment categories and were statistically significantly higher for all categories except for students or volunteers. Interestingly, patients who reported using tobacco 1 to 5 times per day reported statistically significantly less sexual dysfunction than those who did not use tobacco, although those using tobacco 6 to 20 times per day reported statistically significantly more sexual dysfunction than non–tobacco users. Those using tobacco more than 20 times per day had even higher odds of having sexual dysfunction than those using it 6 to 20 times per day, but the odds were not statistically significant (most likely because of the smaller sample size) compared with nonusers.

Patients taking concomitant medications (regardless of whether the medication was known to affect sexual functioning) had statistically significantly higher odds of having sexual dysfunction than did patients taking no concomitant medications. Those who had a comorbid illness

Figure 4. Prevalence of Sexual Dysfunction by Lower and Higher Doses of Antidepressant[a]



[a]The dose-related rate of sexual dysfunction is plotted for both the lower and higher total daily dose groups of patients taking each antidepressant. Bars represent the 95% confidence interval. Abbreviations: IR = immediate release, SR = sustained release, XR = extended release.

had higher odds of reporting sexual dysfunction, although the odds were statistically significant only for patients with a comorbid illness that affects sexual functioning. Those who had experienced sexual dysfunction while taking a previous antidepressant had statistically significantly higher odds of sexual dysfunction than those who had never taken another antidepressant, and the odds were also higher than for those who had taken another antidepressant and did not have sexual dysfunction. The odds of sexual dysfunction were statistically significantly higher in patients who reported that sexual functioning was either not or only somewhat important compared with those for whom sexual functioning had more importance. Moreover, patients with a history of little or no sexual enjoyment reported statistically significantly higher odds of having sexual dysfunction than those with at least some history of sexual enjoyment.

Patients taking any of the antidepressants except for bupropion IR had greater odds of reporting sexual dysfunction than patients taking bupropion SR. For patients taking citalopram, fluoxetine, paroxetine, sertraline, and venlafaxine XR, these odds were statistically significant. Figure 4 presents the prevalence rates for the "higher" and "lower" total daily dose categories. Across all antidepressants combined, patients taking higher total daily doses had statistically significantly greater odds of developing sexual dysfunction than those taking lower doses (Table 3). Given that the study was not powered to detect differences for each of the individual antidepressants, the difference in prevalence rates of sexual dysfunction for the higher and lower total daily dose groups was not statistically significant for each of the individual medications. Data for the paroxetine, venlafaxine, sertraline, citalopram, and nefazodone treatment groups showed a trend toward dose-related increases in sexual dysfunction.

Table 4. Antidepressant Total Daily Doses (TDD)[a]

Antidepressant	Total Range of Doses	Lower TDD Range	Higher TDD Range	Mean TDD	Median TDD	Modal TDD
Bupropion IR	75–450	≤ 200	≥ 300	255.0	300	300
Bupropion SR	100–600	≤ 250	≥ 300	273.7	300	300
Citalopram	10–75	≤ 25	≥ 30	24.9	20	20
Fluoxetine	5–120	≤ 20	≥ 30	25.5	20	20
Mirtazapine	7.5–60	≤ 15	≥ 30	28.6	30	30
Nefazodone	50–600	≤ 275	≥ 300	293.2	300	300
Paroxetine	5–300	≤ 20	≥ 30	23.3	20	20
Sertraline	5–400	≤ 50	≥ 75	81.4	50	50
Venlafaxine	20–300	≤ 75	≥ 112.5	124.9	112.5	75
Venlafaxine XR	20–450	≤ 75	≥ 100	114.9	75	75

[a]All doses are in mg/day. Abbreviations: IR = immediate release, SR = sustained release, XR = extended release.

The trend was not observed in the mirtazapine, fluoxetine, and bupropion treatment groups. The dose ranges for lower and higher doses and the mean, median, and modal doses for each antidepressant are shown in Table 4.

Physician-Perceived and Patient-Reported Prevalence of Sexual Dysfunction

Analyses of physician-perceived and patient-reported prevalence of sexual dysfunction revealed that physicians consistently underestimated the prevalence of sexual dysfunction. Prior to study participation, physicians estimated a 20% prevalence rate of sexual dysfunction across antidepressants in the overall population, whereas 37% of patients were found to have sexual dysfunction as measured by the CSFQ total score. The magnitude of underestimation (difference between physician-perceived and patient-reported prevalence rates) ranged from 10% to 32% across the individual antidepressants.

DISCUSSION

This study is the first to assess the rate of sexual dysfunction in all of the newer antidepressants by using a validated rating scale. The results of this study demonstrate that sexual dysfunction is a widespread problem associated with certain newer antidepressants. Overall, SSRIs and venlafaxine XR are associated with higher rates of sexual dysfunction than bupropion SR or nefazodone. Furthermore, the rate of sexual dysfunction is considerably underestimated by physicians. Patients are concerned about the impact of sexual side effects on their quality of life and want treatment alternatives when such side effects do occur.

In the OCP, the prevalence of sexual dysfunction was similar among SSRIs (citalopram, fluoxetine, paroxetine, and sertraline), ranging from 36% to 43%. With the exception of patients taking fluoxetine having a lower prevalence of sexual dysfunction than patients taking paroxetine in the OCP, no statistically significant differences in the prevalence of sexual dysfunction were noted among the

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SSRIs in either the OCP or the TP. These data indicate that the differences between the SSRIs are not clinically significant with regard to sexual dysfunction. In addition, the similarity in the rate of sexual dysfunction associated with SSRI therapy and the comparatively lower rates associated with bupropion and nefazodone treatment suggest that sexual dysfunction is an effect of treatment with the SSRI class of antidepressants.

The prospectively defined target population analysis was performed to better determine the rate of sexual dysfunction in patients free of other possible causes of sexual dysfunction. In this subpopulation, the odds of having sexual dysfunction with an SSRI or venlafaxine XR were 4 to 6 times greater than with bupropion SR. Unfortunately, the TP sample size was too small to determine the relative odds of sexual dysfunction with bupropion IR, mirtazapine, nefazodone, or venlafaxine treatment.

No other study has been conducted to assess the relative prevalence of sexual dysfunction associated with all of the newer antidepressant treatments in such a large patient sample and with the same rating scale. Nonetheless, the rates of sexual dysfunction associated with antidepressant therapy in this study are similar to those of Balon et al.[9] In contrast, the rates of sexual dysfunction found in this study are somewhat lower than those reported by Montejo-Gonzalez et al.[11] In that study, 58% of 344 patients taking SSRIs reported sexual dysfunction. The difference in sexual dysfunction rates between the current study and the Montejo-Gonzalez study is quite likely explained by the fact that Montejo-Gonzalez et al. did not use a validated scale for assessing the presence of sexual dysfunction and used generous clinical cutoff scores for defining sexual dysfunction. Furthermore, in our study, physicians may have considered sexual dysfunction when choosing a specific antidepressant prior to participation in the study, and patients presenting with sexual dysfunction early in treatment may have already had their antidepressant changed before enrolling in this study, thus lowering the sexual dysfunction prevalence rate observed in the OCP. In earlier reports,[25,26] mirtazapine was associated with lower rates of sexual dysfunction than our finding of a 40.6% prevalence rate of sexual dysfunction. In the current study, 80% of patients treated with mirtazapine, compared with 53% of patients across antidepressants, had been treated previously with an antidepressant. These data may suggest that more mirtazapine patients were treatment refractory or treatment intolerant, resulting in a possibly higher than expected rate of sexual dysfunction for that antidepressant group. In addition, the small sample size for patients treated with mirtazapine makes interpretation of the mirtazapine results more difficult.

Sexual dysfunction may be due to impairment in multiple phases of the sexual cycle (desire, arousal, or orgasm) as other studies[1] point out and as this study supports. Two thousand three hundred fourteen patients were identified as having sexual dysfunction on the basis of their subthreshold total CSFQ score, indicative of global sexual dysfunction. Within each of the domains of sexual functioning, similar proportions of patients exhibited subthreshold scores across each of the antidepressants. Prospective clinical studies have focused on orgasm dysfunction as the most commonly recognized type of antidepressant-associated sexual dysfunction,[5,6,8] whereas the current study indicates that antidepressant treatment is associated with global sexual dysfunction across the phases of the cycle when total CSFQ score is used to define sexual dysfunction.

Our study included a representative sample of primary care patients. Because the physicians were asked to enroll the first 5 patients that met selection criteria, it is not surprising that the proportional rate of antidepressant use in the study resembles U.S. primary care physician antidepressant prescribing practices (PDDAs for November 1996–September 2000, Scott-Levin, a division of PMSI Scott-Levin, Inc., Newtown, Pa.). Almost 70% of potentially eligible patients given the opportunity to enroll in the study chose to participate. Only 6% of those who declined participation in the study did so due to embarrassment or unwillingness to discuss sexual functioning. An additional 20% of patients declined to participate, but did not cite a specific reason; it is likely that some of these patients did so because they were uncomfortable with the subject matter. Nonetheless, the vast majority of patients were willing to discuss sexual functioning with their primary care physician, as evidenced by consenting to participate in this study.

Certain patient characteristics increased the risk for sexual dysfunction. Risk factors for sexual dysfunction included increasing age, higher daily antidepressant dose, being married, having less than a college education, employment status other than full time, having a comorbid illness associated with sexual dysfunction, or taking any concomitant medication. The influence of age on sexual functioning increased significantly at age 50, and the odds of developing sexual dysfunction remained high at older ages. Decreasing the antidepressant dose has long been an initial strategy in the management of sexual dysfunction, and the data from this study appear to support that approach. The increased risk for sexual dysfunction associated with being married may have been due to the influence of the depressive illness on the marital relationship, independent of the effect of antidepressant therapy, and married patients were older than single patients. Patients who did not have a history of sexual enjoyment, for whom sexual functioning had little importance, or who had a history of sexual dysfunction with previous antidepressant therapy were also at greater risk for sexual dysfunction. Finally, sexual dysfunction was associated with higher levels of tobacco use, reaching statistical significance in those who smoked 6 to 20 cigarettes per day. Interestingly,

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gender, race, and length of antidepressant treatment did not predict risk for sexual dysfunction.

A substantial portion of the OCP had at least 1 risk factor associated with sexual dysfunction. It is particularly important for physicians to identify depressed patients who have predictive risk factors for sexual dysfunction, particularly those with multiple risk factors, when considering choices for antidepressant treatment. The discrepancies between the physician-perceived and patient-reported prevalence of sexual dysfunction suggest that the sexual side effects are significantly more common than many physicians believe. On average, patients reported a prevalence of sexual dysfunction almost twice as great as that perceived by physicians. This underestimation by physicians may be related to the underreporting of sexual dysfunction in product labeling and in published studies that did not assess sexual functioning directly by either interview or questionnaire. Perhaps more importantly, physician awareness of patients' experience with sexual dysfunction is hampered by social barriers, lack of knowledge about sexual functioning, inadequate training in obtaining a sexual history, and fear of their questioning being misinterpreted or considered inappropriate. Furthermore, patients may be unlikely to spontaneously report sexual dysfunction to their physician due to embarrassment and/or lack of awareness that their antidepressant therapy may be responsible for their sexual dysfunction. Therefore, an instrument such as the CSFQ may help facilitate physician dialogue with the patient and overcome barriers in identifying sexual dysfunction.

As patients become more aware of and comfortable with discussing sexual side effects, the appropriate selection of an antidepressant will be more important than ever. Use of bupropion or nefazodone as first-line antidepressant treatment, because of the lower prevalence of sexual dysfunction relative to other currently available antidepressants, may help reduce treatment noncompliance and decrease the need for switching antidepressant medications.

Because of the point prevalence and cross-sectional design, there are inherent limitations in interpreting the results of this study. Pretreatment rates of sexual dysfunction in this population of patients were not available for comparison. Neither a literature review nor this study provides a population or control group of subjects who were not depressed and not taking antidepressants with which to compare the prevalence rates of sexual dysfunction. The study included no measure of compliance or therapeutic response to antidepressant treatment. Sample sizes for some drugs were small, even in the OCP, but the distribution across antidepressants does reflect the prescribing practices of primary care physicians in the United States (PDDAs for November 1996–September 2000, Scott-Levin, a division of PMSI Scott-Levin, Inc., Newtown, Pa.). The racial demographics of the current study (93% white) are representative of the U.S. patient population who are seen in physician offices and diagnosed with a depressive disorder.[27] The results, however, are inadequate to assess differences between racial groups, and the sexual dysfunction rates may not be generalizable across all races. In addition, U.S. validation of the CSFQ instrument was performed in a predominantly white population (73% of the nonclinical sample and 84% of the clinical sample were white).[17]

Although the TP analysis attempted to control for other possible risk factors of sexual dysfunction beyond the antidepressant, other possible causes could not be definitively ruled out. Patients who were taking a concomitant medication, even those not known to cause sexual dysfunction, did show statistical significance for sexual dysfunction compared with those taking no other medications, according to the odds ratio analyses. Therefore, taking any concomitant medication should have been an exclusion criterion for the TP. Conversely, some potential risk factors were included in the prospectively defined TP criteria that could have been excluded. For example, the odds ratio analyses indicated 1 nonsignificant risk factor category: duration of current antidepressant therapy. Furthermore, patients aged 40 to 49, who were not included in the TP analysis, did not have statistically significantly higher sexual dysfunction than the reference group of patients aged 20 to 29. Thus, the TP criteria may have been too strict and excluded patients with no other cause for their sexual dysfunction but their antidepressant, may have allowed patients with potential existing risk factors, and may not have included other unrecognized confounding risk factors for sexual dysfunction.

Finally, our findings may have been affected by the decision-making process of the physician preceding study implementation. For example, physicians may have considered the risk for sexual dysfunction when originally choosing the antidepressant or may have discontinued the patient's previous antidepressant due to sexual dysfunction prior to the patient's enrollment. A final limitation is that, in general, the prescribed total daily doses of antidepressants in a primary care setting may be lower than those prescribed by psychiatrists, resulting in lower rates of sexual dysfunction than may be seen in psychiatric practice.

CONCLUSION

The credibility and significance of the current study stand firmly on the fact that a single validated rating scale was used to measure the prevalence of sexual dysfunction in the primary care setting. Furthermore, use of this rating scale provided internal consistency in methodology across all of the newer antidepressants in the large (6000+) patient population who were enrolled within a 3-month time period. As such, it allows for comparison of the relative odds of developing sexual dysfunction associated with the newer antidepressants, which is important in guiding the selection of the most appropriate antidepressant for

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each patient. The accurate assessment of the impact of an antidepressant on sexual functioning requires direct questioning, rather than reliance on spontaneous reports. Direct assessment of sexual functioning can be accomplished quickly and easily via either a questionnaire, such as the CSFQ or Arizona Sexual Experience Scale,[28] or a brief clinical interview (e.g., the CSFQ-Clinical,[18] the clinical interview version of the CSFQ).

This study demonstrates that SSRI antidepressants and venlafaxine are associated with higher rates of sexual dysfunction than bupropion or nefazodone. Furthermore, the rate of sexual dysfunction is considerably underestimated by physicians. Further study is needed to better understand the relative risk of sexual dysfunction associated with the newer antidepressants and to measure sexual dysfunction in each phase of sexual functioning. It is hoped that increased awareness of the "real-world" risk of developing antidepressant-associated sexual dysfunction will lead to better recognition and prevention of sexual dysfunction. For patients being treated for depression, identification of sexual dysfunction may translate into increased compliance with the appropriate antidepressant, resulting in reduced risk of relapse of depression and improved quality of life.

Drug names: bupropion (Wellbutrin and others), citalopram (Celexa), fluoxetine (Prozac and others), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

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