

# Incidence of Sexual Dysfunction Associated With Antidepressant Agents: A Prospective Multicenter Study of 1022 Outpatients

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**Background:** Antidepressants, especially selective serotonin reuptake inhibitors (SSRIs), venlafaxine, and clomipramine, are frequently associated with sexual dysfunction. Other antidepressants (nefazodone, mirtazapine, bupropion, amineptine, and moclobemide) with different mechanisms of action seem to have fewer sexual side effects. The incidence of sexual dysfunction is underestimated, and the use of a specific questionnaire is needed. **Method:** The authors analyzed the incidence of antidepressant-related sexual dysfunction in a multicenter, prospective, open-label study carried out by the Spanish Working Group for the Study of Psychotropic-Related Sexual Dysfunction. The group collected data from April 1995 to February 2000 on patients with previously normal sexual function who were being treated with antidepressants alone or antidepressants plus benzodiazepines. One thousand twenty-two outpatients (610 women, 412 men; mean age = 39.8 ± 11.3 years) were interviewed using the Psychotropic-Related Sexual Dysfunction Questionnaire, which includes questions about libido, orgasm, ejaculation, erectile function, and general sexual satisfaction. **Results:** The overall incidence of sexual dysfunction was 59.1% (604/1022) when all antidepressants were considered as a whole. There were relevant differences when the incidence of any type of sexual dysfunction was compared among different drugs: fluoxetine, 57.7% (161/279); sertraline, 62.9% (100/159); fluvoxamine, 62.3% (48/77); paroxetine, 70.7% (147/208); citalopram, 72.7% (48/66); venlafaxine, 67.3% (37/55); mirtazapine, 24.4% (12/49); nefazodone, 8% (4/50); amineptine, 6.9% (2/29); and moclobemide, 3.9% (1/26). Men had a higher frequency of sexual dysfunction (62.4%) than women (56.9%), although women had higher severity. About 40% of patients showed low tolerance of their sexual dysfunction. **Conclusion:** The incidence of sexual dysfunction with SSRIs and venlafaxine is high, ranging from 58% to 73%, as compared with serotonin-2 (5-HT<sub>2</sub>) blockers (nefazodone and mirtazapine), moclobemide, and amineptine.

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Impairment of sexual function in patients with psychiatric disorders is very common. It is difficult to accurately estimate its incidence, owing to factors such as the disease itself, the deterioration of social and interpersonal relationships, the effect of the medication, the difficulties the patient has with communicating the adverse effects, and the variability in assessment of these changes by the physician. Approximately 40% of men and 50% of women with major depression report a decrease in libido and problems regarding sexual arousal when questionnaires are used to investigate sexual activity during the month prior to diagnosis; however, orgasm problems occur in a lower percentage (15%–20%) prior to taking the antidepressant drug.<sup>1</sup>

Sexual side effects are frequently underestimated by physicians. Fortunately, in recent years, more attention has been paid to sexual dysfunction provoked by psychotropic agents, giving rise to the publication of more than 400 articles on the subject during the last decade.<sup>2,3</sup> Sexual dys-

function (in different degrees and with different presentation forms) is the most frequent adverse effect of certain antidepressant drugs (selective serotonin reuptake inhibitors [SSRIs], venlafaxine, and clomipramine). This problem affects the patient's quality of life and can lead to therapeutic noncompliance in long-term treatments. Although no reliable data are currently available, it is estimated that a significant proportion of patients who suffer severe sexual dysfunction after beginning antidepressant treatment discontinue the treatment because of that dysfunction. In a recent survey of 3516 members of patient advocate groups, sexual dysfunction was cited among the most common (50.8%) side effects leading to treatment dropout.<sup>4</sup>

The incidence of sexual dysfunction seems to differ according to the antidepressant used. A higher incidence is found with monoamine oxidase inhibitors (MAOIs), SSRIs, venlafaxine, and tricyclic agents (above all, those that have a high profile of serotonin reuptake blockade, such as clomipramine).<sup>5</sup> Drugs that predominantly affect norepinephrine (desipramine, nortriptyline) or dopamine (amineptine, bupropion), the serotonin-2 (5-HT<sub>2</sub>) receptor blockers (nefazodone, mirtazapine), and tianeptine may affect sexual function to a much lesser degree.<sup>6</sup> In randomized double-blind studies, sexual dysfunction values for bupropion have been lower than those for sertraline and comparable to those for placebo, demonstrating that bupropion preserves patients' sexual function.<sup>7,8</sup> In comparison with the classical MAOIs, moclobemide seems to provoke fewer sexual side effects, owing to its special pharmacodynamics.<sup>9</sup> There are still no reliable data for reboxetine regarding its ability to provoke sexual dysfunction, although it seems to be less than with the SSRIs.<sup>10</sup>

Antidepressant drugs can impair sexual activity and therefore provoke other alterations that can affect all phases of sexual activity: desire, arousal, orgasm, and ejaculation. Anecdotal reports have described some less frequent side effects of antidepressants, such as penile<sup>11</sup> or clitoral anesthesia,<sup>12</sup> painful orgasm,<sup>13</sup> orgasm associated with yawning,<sup>14,15</sup> priapism (associated with paroxetine<sup>16</sup> and trazodone<sup>17</sup>), increased libido,<sup>18</sup> spontaneous orgasm,<sup>19</sup> and decreased ejaculation volume.<sup>20</sup>

Although the data sheet reports for antidepressant drugs refer to a very low frequency of sexual dysfunction (2%–16%), the actual occurrence is often unreported if the clinical interview is not directed toward examining this adverse effect. Spontaneous reports from patients are infrequent, even though sexual side effects can considerably affect drug compliance. Although the specificity of spontaneous communication of adverse effects is very high, it has the disadvantage of low sensitivity. As an example, in studies in which patients were directly questioned about sexual alterations after beginning a treatment, only 14% reported them spontaneously and the others denied changes even though they suspected the changes could be due to the

medication.<sup>21</sup> A recent survey has shown that the general population is reluctant to speak with a physician about their sexual problems because they are afraid of finding themselves in an embarrassing situation, and they expect little help from their doctors in this regard.<sup>22</sup>

Since SSRIs were introduced into the drug market at the end of the 1980s, reports of secondary sexual dysfunction have significantly increased. Studies comparing placebo-treated patients or healthy volunteers with antidepressant-treated patients have demonstrated a close relationship between the use of antidepressants and the appearance of sexual dysfunction. Clinicians should be alert to the appearance of these undesirable side effects in order to adopt the best strategy to manage sexual dysfunction together with the patient and thus avoid deterioration of the patient's quality of life and possible withdrawal from the treatment.

The physiologic mechanism of normal sexual response includes a combination of neurogenic, psychogenic, vascular, and hormonal factors that are coordinated by the hypothalamus, limbic system, and cerebral cortex centers. Nowadays, it is accepted that human sexual function is influenced by the intervention of many neurotransmitters, and an attempt has been made to describe their mechanism of action as accurately as possible.<sup>23</sup> These neurotransmitters include dopamine, serotonin, norepinephrine, acetylcholine,  $\gamma$ -aminobutyric acid (GABA), oxytocin, arginine-vasopressin, angiotensin II, growth hormone-releasing hormone, substance P, neuropeptide Y, and cholecystokinin-8, among others.

Dopamine enhances sexual function. In contrast, serotonin stimulation inhibits sexual desire, ejaculation, and orgasm.<sup>24–27</sup> In animal models, this inhibitory action is mediated by the postsynaptic 5-HT<sub>2</sub> receptors, although 5-HT<sub>2C</sub> subtype agonists such as *m*-chlorophenylpiperazine (*m*-CPP) provoke sexual excitement in experimental animals. Interestingly, not only does *m*-CPP (a common metabolite of nefazodone and trazodone) not provoke sexual dysfunction, but it has also been reported that nefazodone can reverse SSRI-induced anorgasmia associated with previous treatment.<sup>28</sup> It has been shown that SSRIs provoke a high incidence of sexual dysfunction in sexually active patients.<sup>29</sup>

Although its role in sexual intercourse is unclear, noradrenergic activity seems to have a close relationship to the onset and maintenance of copulatory behavior in male rats.<sup>30</sup> Blockage of the peripheral  $\alpha$ -adrenergic and cholinergic receptors in the genitourinary tract impairs sexual function.<sup>31</sup> Drugs with potent anticholinergic and/or  $\alpha$ -receptor blocking action (such as antidepressants and antipsychotic agents) can greatly alter the sexual arousal process.<sup>32</sup>

Nitric oxide (NO) activity has been linked to sexual dysfunction secondary to antidepressant agents.<sup>33</sup> Sildenafil, which stimulates NO action, has demonstrated great usefulness in erection problems that have different etiologies.

Sexual dysfunction has also been linked to other pharmacologic groups such as cardiovascular agents, antihypertensive drugs, anti-H<sub>2</sub> agents, digoxin, hormones, and antineoplastic and hypolipidemic agents, although these are rarely reported to national pharmacovigilance systems, and when they are reported, it is almost always by manufacturers.<sup>34</sup> The antihypertensive agents<sup>35,36</sup> methyldopa, reserpine, clonidine, and propranolol have demonstrated a relative incidence of erectile dysfunction and/or ejaculatory problems, possibly due to adrenergic inhibition.<sup>37</sup> Although the pathogeny is unclear, there is no evidence that they affect the neuroendocrine system because their use does not modify testosterone, estradiol, or luteinizing hormone (LH) levels.<sup>38</sup> The neuroendocrine changes induced by dopaminergic inhibition are surely of great importance in sexual dysfunction in schizophrenic patients receiving chronic treatment.<sup>39</sup> These changes affect prolactin, testosterone, LH, and follicle-stimulating hormone blood levels.

The aims of this study were (1) to prospectively assess the incidence of sexual dysfunction secondary to antidepressant therapy by administering a sexual dysfunction questionnaire to patients who had had normal sexual function before antidepressant treatment and (2) to compare the frequency, intensity, and outcome of such dysfunction in patients receiving 10 antidepressants.

## METHOD

### Administration of the PRSexDQ

The Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ) (Appendix 1) was prepared for use with a prospective, observational, open, multicenter study. It was administered to 1022 outpatients who met the inclusion criteria (610 women and 412 men; mean age = 39.8 ± 11.3 years) in a clinical interview held when they visited an outpatient clinic. The study was carried out from April 1995 to February 2000 by the Spanish Working Group for the Study of Psychotropic-Related Sexual Dysfunction. This group of psychiatrists from several Spanish hospitals and mental health services was previously trained to apply the questionnaire correctly. Patients were interviewed naturalistically with the questionnaire every time they went to the clinic. Special attention was given to each patient's sexual function before starting antidepressant treatment and to the subsequent onset of sexual dysfunction. A form was used to collect demographic data (name, age, marital status, sex, etc.) and clinical data (diagnoses using DSM-IV criteria, including personality disorders, months from the beginning of treatment, associated medications, and other clinical evaluation variables), which were entered into the database by the study coordinator.

The PRSexDQ consists of 7 items pertaining to sexual dysfunction. The first item is a screening item to assess whether the patient has any sort of sexual dysfunction. The second item assesses whether the patient has reported any

sexual dysfunction to his or her physician. The next items (items 3–7) assess 5 dimensions of sexual dysfunction according to severity or frequency: loss of libido (0 = nil, 1 = mild, 2 = moderate, 3 = severe), delayed orgasm or ejaculation (0 = nil, 1 = mild, 2 = moderate, 3 = severe), absence of orgasm or ejaculation (0 = never, 1 = occasionally, 2 = often, 3 = always), erectile dysfunction in men/vaginal lubrication dysfunction in women (0 = never, 1 = occasionally, 2 = often, 3 = always), and patient's tolerance of the sexual dysfunction (1 = good, 2 = fair, 3 = poor). *Good tolerance* is defined by a patient's lack of concern even though some type of sexual dysfunction is present. The term *fair* is used when the sexual dysfunction provokes concern or distress in the patient and/or his or her partner, although the patient does not intend to discontinue treatment because of it. The term *poor tolerance* is applied when the patient is very concerned by the adverse effect(s) and seriously considers discontinuing treatment.

The first 2 items are answered on a scale with 2 response options; items 3 to 6, on a scale with 4 response options; and item 7, on a scale with 3 response options. In addition to scores for each item, a total score may be obtained as a sum of items 3 to 7.

### Psychometric Properties of the PRSexDQ

This questionnaire has been shown to have adequate feasibility and psychometric properties to be used in a recent clinical study.<sup>40</sup> Feasibility was assessed by analyzing the percentage of patients with missing responses. Reliability was assessed by calculating Cronbach  $\alpha$ . Construct validity was assessed by correlating PRSexDQ scores with Clinical Global Impression on Sexual Dysfunction and Hamilton Rating Scale for Depression (HAM-D)<sup>41</sup> scores and by comparing groups of naive patients with groups of patients pretreated with antidepressants. Finally, sensitivity to change was assessed with the paired Wilcoxon test, and the standardized effect size (SES) was calculated.

The PRSexDQ has shown excellent feasibility, with patients registering missing responses for only items 1 and 2 (1.7% and 15.5% of patients with missing response, respectively). Cronbach  $\alpha$  value was 0.93, which indicates adequate reliability. The PRSexDQ has also shown adequate construct validity. As may be expected, the PRSexDQ showed a high correlation with Clinical Global Impression scores on Sexual Dysfunction ( $r = 0.79$ ) and a moderate correlation with HAM-D scores ( $r = 0.63$ ). PRSexDQ scores also showed good discrimination between naive and pretreated depressed or dysthymic patients, with statistically significant differences found between those groups of patients (Mann-Whitney U test,  $p < .05$ ). The PRSexDQ also showed sensitivity for detecting clinical changes in sexual dysfunction. Statistically significant changes in PRSexDQ scores before and after treatment in patients taking nefazodone were found

Table 1. Diagnosis Distribution (N = 1022)

Diagnosis <sup>a</sup>	N	Women/ Men	Patients With Sexual Dysfunction	
			N	%
Major depression	614	349/265	346	56.3
Dysthymic disorder	177	119/58	97	54.8
Panic disorder	124	92/32	74	59.6
Obsessive-compulsive disorder	60	24/36	36	60.0
Others <sup>b</sup>	38	26/12	22	58.3

<sup>a</sup>Some patients had more than one diagnosis.

<sup>b</sup>Others include personality disorder, bipolar disorder, anorexia/bulimia, phobias, etc.

for all items and overall scores. Greater changes were found in patients previously treated with antidepressants who were switched to nefazodone than in naive patients (SES = -3.77 in patients switching to nefazodone, SES = -0.64 in naive patients).

### Entry Criteria

Criteria for inclusion were (1) normal sexual function prior to taking antidepressants, (2) treatment with an antidepressant alone or combined with a benzodiazepine, (3) previous regular and satisfactory sexual practices, and (4) occurrence of sexual dysfunction within the 2 months after the introduction of an antidepressant.

Criteria for exclusion were (1) prior sexual dysfunction, (2) combination antidepressant and neuroleptic treatment, (3) treatment with hormones or any other drug capable of interfering with sexual intercourse, (4) significant intercurrent diseases affecting sexual function, and (5) substance abuse (alcohol or illicit drugs).

### Statistical Analysis

Variables among the drug groups were compared, assuming a 95% probability for rejecting the null hypothesis. A parametric statistic (analysis of variance) was used to compare continuous variables (age, time taking an antidepressant, and dosage of treatment), and a nonparametric statistic (chi-square test) was used to compare categorical data (sexual function).

## RESULTS

Analysis according to DSM-IV diagnosis shows a predominance of mood disorders (Table 1). Patient age ranged from 16 to 78 years. Compared with the patients diagnosed with dysthymic disorder, the patients diagnosed with obsessive-compulsive disorder showed slightly higher sexual dysfunction values that could be due to the fact that the obsessive-compulsive group received larger doses of antidepressants.

In agreement with previous works, a substantial increase in the incidence of sexual dysfunction (59.1%) was found when patients were examined by asking them direct

Table 2. Incidence of Sexual Dysfunction With Antidepressants Assessed by the Psychotropic-Related Sexual Dysfunction Questionnaire (N = 1022)<sup>a</sup>

Drug <sup>a</sup>	N	Women/ Men	Mean Dose, mg	Patients With Sexual Dysfunction	
				N	%
Citalopram	66	36/30	28.7	48	72.7
Paroxetine	208	137/71	23.4	147	70.7
Venlafaxine	55	30/25	159.5	37	67.3
Sertraline	159	96/63	90.4	100	62.9
Fluvoxamine	77	33/44	115.7	48	62.3
Fluoxetine	279	166/113	24.5	161	57.7
Mirtazapine	49	28/21	37.7	12	24.4
Nefazodone	50	35/15	324.6	4	8.0
Amineptine	29	17/12	187.2	2	6.9
Moclobemide	26	16/10	265.6	1	3.9

<sup>a</sup>Other groups (N = 24): clomipramine (N = 10), imipramine (N = 8), maprotiline (N = 4), phenelzine (N = 2), trazodone (N = 1).

questions using the sexual dysfunction protocol designed by our working group. Only 20.2% of the patients reported their sexual dysfunction spontaneously, and the remaining 79.8% would have gone undiagnosed if a questionnaire measuring sexual response had not been used.

Table 2 shows the overall frequency of sexual dysfunction for each of the antidepressants analyzed. Of the 1022 patients, 604 (59.1%) experienced some type of sexual dysfunction. Citalopram, paroxetine, and venlafaxine had the highest incidence values. Citalopram doses were comparatively higher than the doses for the rest of the antidepressants; however, there must be other, more complex contributing factors. Coinciding with these results, the number of reports of masculine sexual dysfunction received by the British Committee on Safety of Medicines during the first 2 years that SSRIs were on the market in Great Britain is 10 times greater for paroxetine than for the remaining SSRIs (fluvoxamine, fluoxetine, sertraline, and citalopram).<sup>42</sup> In addition, greater frequency of sexual dysfunction and sedation has been reported with paroxetine than with other SSRIs when a meta-analysis is used.<sup>42</sup> Until now, few data have been published on the capacity of citalopram to affect sexual function; however, these reports<sup>43</sup> have shown a high rate of sexual dysfunction, which may be due to the fact that citalopram and paroxetine are the most potent serotonin uptake inhibitors compared with other SSRIs. In our group of patients, fluoxetine had a slightly lower incidence of sexual dysfunction compared with the other SSRIs. This finding could be explained by the recent discovery that fluoxetine has certain postsynaptic 5-HT<sub>2A</sub> receptor blocking activity (data on file, Eli Lilly and Company, Indianapolis, Ind.).

Our results indicate that the incidence of sexual dysfunction with mirtazapine is much less than that with the SSRIs, although, surprisingly, it is greater than that expected according to the values in the medical data sheet and its theoretical pharmacodynamic profile. This unexpected higher incidence could be related to blockage activ-

Table 3. Observed Frequency of Sexual Dysfunction by Drug Groups (N = 1022)<sup>a</sup>

Event	Fluoxetine N = 279	Paroxetine N = 208	Fluvoxamine N = 77	Sertraline N = 159	Citalopram N = 66	Venlafaxine N = 55	Mirtazapine N = 49	Nefazodone N = 50
Decreased libido	50.2	63.9	48.1	54.7	62.1	60.0	20.4	6.0
Delayed orgasm/ejaculation	49.5	63.9	54.5	56.6	63.6	61.9	18.4	2.0
Anorgasmia/no ejaculation	39.1	52.8	37.6	47.1	51.5	41.8	8.2	2.0
Erectile dysfunction/ decreased vaginal lubrication	21.8	41.4 <sup>b</sup>	20.8	28.9	34.8	40.0	14.2	0.0

<sup>a</sup>All values represent percentage of total N.

<sup>b</sup>Significantly different from other antidepressants,  $p < .005$ .

Table 4. Intensity of Sexual Dysfunction<sup>a,b</sup>

Event	Paroxetine	Fluoxetine	Fluvoxamine	Sertraline	Citalopram	Venlafaxine	Mirtazapine
Delayed orgasm/ejaculation	2.33*	2.03	2.15	2.22	2.04	2.14	1.25*
Anorgasmia/no ejaculation	1.63	1.39	1.31	1.54	1.40	1.30	0.58**
Erectile dysfunction/ decreased vaginal lubrication	1.13***	0.63	0.65	0.83	0.94	1.11	0.92

<sup>a</sup>Severity scale: 0 = nil, 1 = mild, 2 = moderate, 3 = severe.

<sup>b</sup>Nefazodone, amineptine, and moclobemide are excluded because they have fewer sexual side effects.

\*Paroxetine versus fluoxetine, mirtazapine versus other antidepressants,  $p < .05$ .

\*\*Mirtazapine versus other antidepressants,  $p < .05$ .

\*\*\*Paroxetine versus fluoxetine, fluvoxamine, and sertraline,  $p < .05$ .

ity on the 5-HT<sub>2</sub> and postsynaptic receptors because 5-HT<sub>2C</sub> plays a role in enhancing sexual activity. On the other hand, the incidence can partially be explained by mirtazapine's activity on other cholinergic neurotransmitter systems (slight anticholinergic effect). Its stimulation of the adrenergic system could be responsible for the stimulation of peripheral postsynaptic  $\alpha_1$  receptors that are related to the emptying of the corpora cavernosa, provoking erectile dysfunction. Although its capacity is unknown at present, mirtazapine may influence NO levels in the genitourinary tract, as occurs with paroxetine. A combination of these factors could play some role, although limited, in the presence of sexual dysfunction (mainly erectile dysfunction, with a limited effect on libido and orgasmic function).

We found that nefazodone has very few sexual side effects, possibly owing to 2 factors: on the one hand, it has blocking properties on the postsynaptic 5-HT<sub>2</sub> receptors (whose stimulation provokes alterations in ejaculation and orgasm), and on the other hand, its *m*-CPP metabolite is a stimulant of the serotonin 5-HT<sub>2C</sub> receptor subtype, which seems to enhance sexual function. Amineptine and moclobemide also have very little effect on sexual function, very possibly owing to their stimulation of dopaminergic activity and lack of serotonergic effect.

Table 3 shows the incidence of each of the adverse effects observed: decreased libido, orgasm/ejaculation delay, anorgasmia, and erectile dysfunction/decreased vaginal lubrication. Amineptine and moclobemide are not represented because they have almost no effect on sexual function. In 50 patients taking nefazodone, the incidence of sexual side effects ranged from 0% for erectile dysfunction to 6% for decreased libido. Decreased libido and delayed orgasm make up the most frequent sexual effects of

SSRIs and venlafaxine. Erectile dysfunction is significantly less frequent than orgasm problems, suggesting a different action mechanism for erectile dysfunction that is not related to serotonin but rather to the peripheral adrenergic and cholinergic pathways in combination with other factors. The differences among paroxetine, citalopram, and venlafaxine in erectile dysfunction incidence are significant because the erectile dysfunction values approach 30% to 40%. Paroxetine showed a significantly greater incidence of erectile dysfunction in men and decreased vaginal lubrication in women compared with the other drugs analyzed ( $p < .05$ ). The decrease in sexual activity produced by paroxetine and by the other SSRIs has been taken advantage of in clinical use because it seems to be useful in patients with excessive sexual libido, premature ejaculation, or paraphilias.<sup>44-46</sup>

The intensity of the sexual dysfunction caused by each drug was measured for each group of symptoms (Table 4). No differences were found between the SSRIs and venlafaxine in regard to intensity of decreased libido, but there were differences in the remaining sexual function items. Paroxetine showed significantly greater erectile dysfunction intensity (1.13) compared with fluoxetine (0.63), fluvoxamine (0.65), and sertraline (0.83) ( $p < .05$ ). This result can be explained by the greater capacity of paroxetine to bind to the cholinergic receptors, as it is 5 to 160 times more potent in its cholinergic blocker capacity than the remaining SSRIs. On the other hand, it has been recently found that paroxetine is a potent inhibitor of NO (as it inhibits oxide-nitric-synthetase) both in vitro as well as in vivo,<sup>47</sup> which could explain the data found by our group regarding its greater capacity to provoke erectile dysfunction compared with the other SSRIs.

Table 5. Gender Differences (N = 604)

Variable	Women N = 347	Men N = 257	p Value
Sexual dysfunction, %	56.9	62.4	
Decreased libido <sup>a</sup>	2.13	1.57	.0001
Delayed orgasm/ejaculation <sup>a</sup>	2.21	2.06	.07
Anorgasmia/no ejaculation <sup>a</sup>	1.69	1.13	.0001
Erectile dysfunction/decreased vaginal lubrication <sup>a</sup>	0.87	0.86	NS
Tolerance <sup>b</sup>	1.11	1.08	NS
Dose, mean, mg/d	49.7	62.6	.008
Months elapsed, mean	7.2	6.5	NS
Age, mean, y	37.4	45.4	.001

<sup>a</sup>Intensity scale: 0 = nil, 1 = mild, 2 = moderate, 3 = severe.

<sup>b</sup>Tolerance scale: 1 = good, 2 = fair, 3 = poor.

Our study found that sexual dysfunction is caused much less frequently (24.4%) by mirtazapine than by SSRIs and venlafaxine, and when mirtazapine does provoke it, the intensity is significantly lower (delayed orgasm and milder anorgasmia,  $p < .05$ ). However, erectile dysfunction occurs with the same intensity as with the other drugs, owing to the different mechanisms involved in orgasmic and erectile function. As expected, nefazodone demonstrated a very low incidence of sexual dysfunction (8%) and was the most tolerated drug in regard to sexual function among those having serotonergic activity. This explains why it is a first-choice alternative in patients with sexual dysfunction secondary to antidepressants.

### Gender Differences

Differences in frequency and intensity of sexual dysfunction between sexes were found (Table 5). Men experienced a greater incidence of sexual dysfunction (62.4%) compared with women (56.9%); however, women experienced greater intensity of decreased libido, delayed orgasm, and anorgasmia ( $p < .05$ ). The dose used was lower in women, and mean age was also significantly lower (37.4 years) than that of the men (45.4 years). Because women are generally more reluctant than men to report sexual side effects, it is especially important to ask women about their sexual function after initiating antidepressant drug treatment.

### Relationship Between Age and Length of Treatment

A positive correlation between patient age and a lower tolerance of sexual dysfunction was found ( $r^2 = 0.025$ ;  $p < .05$ ), suggesting that age makes patients more concerned about the onset of sexual problems. There is also a positive correlation between the severity of difficulty in maintaining sexual arousal and the number of months elapsed since treatment began ( $p < .01$ ). This result suggests that treatment length may be an important variable in the occurrence of this dysfunction and that the presence of impotence could be secondary to libido, orgasm, and ejaculation disorders that have lasted for months.

Table 6. Spontaneous Remission of Sexual Dysfunction

Time Elapsed	Partial Remission		Total Remission		Global Improvement	
	N	%	N	%	N	%
> 6 months (N = 143)	14	11.2	16	9.7	30	21.0
3–6 months (N = 131)	10	7.6	5	3.8	15	11.4
< 3 months (N = 78)	9	11.5	1	1.7	10	12.8

### Acceptance of the Sexual Dysfunction by Patients and/or Their Partners

A total of 27.2% of the patients showed good tolerance of their sexual dysfunction, 34.5% accepted it with some objection (fair tolerance), and 38.3% considered it unacceptable with a serious risk of noncompliance with the treatment (poor tolerance). The worst results of drug tolerance observed in patients with sexual dysfunction was with paroxetine when compared with fluoxetine ( $p < .05$ ). As was mentioned previously, data for surveys performed in large series of patients demonstrated that between 41.7% and 50.8% of the total withdrawals were due to adverse effects, showing that poor tolerance has a close relationship to treatment withdrawal. Thus, the use of alternative treatments that can decrease the frequency or intensity of sexual dysfunction in patients with poor tolerance and in whom the probability of discontinuing treatment is significantly increased must be considered.

### Spontaneous Remission of Sexual Dysfunction

Some patients may experience partial or total improvement of their dysfunction either immediately or after weeks or months of treatment.<sup>48</sup> However, until now, specific data on the mean time required for sexual side effects to disappear or on the probability of a spontaneous remission were unknown. The present study measured the presence of spontaneous improvement at 3 points in time: (1) prior to 3 months, (2) between months 3 and 6, and (3) after 6 months of treatment as long as the initial drug dose had remained stable in order to assess whether the patients adapted to the sexual dysfunction over the course of time. The results are shown in Table 6.

Only 9.7% of the patients showed a total improvement or spontaneous remission at the end of 6 months of treatment, 11.2% showed partial improvement, and 79.1% showed no improvement. The percentages of adaptation prior to 6 months are less than those previously mentioned, so, although some patients benefit from this "spontaneous remission" mechanism, it does not seem to be practical to take a wait-and-see attitude for this to occur as a first therapeutic alternative in patients who are very affected by their sexual dysfunction. Although it could be expected that a greater number of patients would have shown improvement at 12 months, many of them remained in treatment for a shorter period, making it difficult to obtain consistent data on this point. The data from

our study suggest that at least 15.6% of patients (55/352) would have experienced spontaneous improvement sometime after the onset of treatment.

The physiopathologic mechanisms of this adaptation are still unknown, although the intervention of several interrelated factors could be hypothesized: individual susceptibility, enzyme autoinduction mechanisms with a consequent decrease in plasma levels, the presence of mildly intense sexual dysfunction from the onset, decrease in compliance over time, or even improvement in mood after treatment, which would include an improvement in the relationship of the couple.

## DISCUSSION

### Clinical Management of Sexual Dysfunction: Switching Strategies

Our results were accompanied by commentary in the previous section. The following is a brief discussion of our experience in managing this troublesome side effect, which focuses on switching strategies. Considering that the correct duration of treatment for a depressive episode is at least 6 months and that this time is extended for years and even for a lifetime in some cases, therapeutic alternatives must be found to treat sexual dysfunction when it is not tolerated by the patient.

Several methods (reviewed by Zajecka<sup>76</sup> in this supplement) have been proposed to improve sexual dysfunction secondary to the use of antidepressants. These methods include waiting for spontaneous remission over time, decreasing the dose or discontinuing the treatment, weekend drug holidays,<sup>49</sup> adding adjunctive drugs or drugs with an "antidote" effect, as well as switching to a drug with a different pharmacologic profile (mainly bupropion, moclobemide, amineptine, mirtazapine, or nefazodone).<sup>50</sup>

Many substances with an antidote effect that can counteract the physiopathologic mechanisms that are caused by sexual dysfunction have been described; currently, however, none of them are exempt from inconveniences.<sup>51-53</sup> The efficacy of sildenafil has been demonstrated in erectile dysfunction with psychogenic and organic etiologies and also in dysfunction secondary to psychotropic agents. At present, it is known that NO plays an important role in the facilitatory mechanisms of erection, but it is not very clear what action it has, if any, on sexual desire and orgasm. Preliminary studies suggest that sexual dysfunction could have a common NO-mediated production mechanism<sup>54</sup> and that this mechanism could function as a mediator in all of the sexual activation processes, from the appearance of desire to successful orgasm. These encouraging data are being studied in greater depth in a multicenter, placebo-controlled study designed in Spain by our working group. The study is being conducted to verify the usefulness of sildenafil in patients with sexual dysfunction secondary to antidepressants.

Table 7. Improvement in Sexual Side Effects With Switching to Other Drug

Drug	N	Total		Partial Improvement		No Improvement		Dropouts	Global Improvement	
		N	%	N	%	N	%			
Nefazodone <sup>a</sup>	41	31	75.6	1	2.4	0	0	9	22.0	78.0
Mirtazapine <sup>b</sup>	17	8	47.1	3	17.6	3	17.6	3	17.6	64.7
Amineptine <sup>c</sup>	47	22	46.8	9	19.4	7	14.9	9	19.4	65.9
Moclobemide <sup>d</sup>	15	11	73.3	1	6.7	0	0	3	20.0	80.0
Paroxetine <sup>d</sup>	38	2	5.3	2	5.3	25	65.8	9	23.7	10.5

<sup>a</sup>Data from Montejo et al.<sup>64</sup>

<sup>b</sup>Data from Montejo et al.<sup>74</sup>

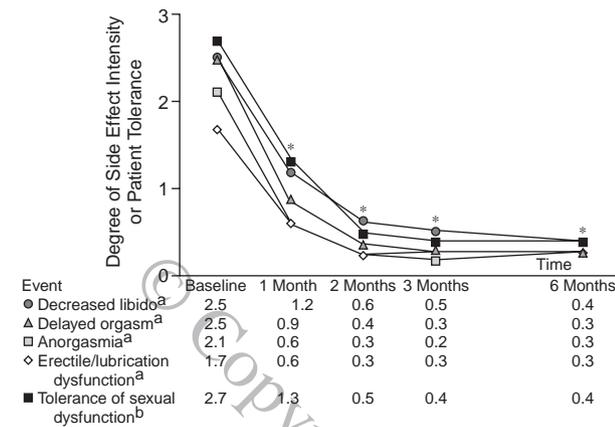
<sup>c</sup>Data from Montejo et al.<sup>63</sup>

<sup>d</sup>Data from Montejo et al.<sup>21</sup>

Switching strategies have a relatively user-friendly approach. The drug that patients are switched to could be more acceptable and/or less costly to patients than multi-drug treatment and might enhance patient compliance. The objective of antidepressant drug substitution is to find a drug whose mechanism of action is different from those that are causing the sexual dysfunction but which can maintain the therapeutic efficacy of the substituted drug.<sup>55</sup> The dose equivalence and the appearance of possible discontinuation symptoms must be carefully considered, a washout period must be established to avoid summation of initial adverse effects, the efficacy of the new drug to prevent relapses must be assessed, and the possible adverse effects of the new drug must be weighed when considering the change. At present, data indicate that the problems of patients with SSRI-induced sexual dysfunction do not improve when they are changed to a different SSRI, because the SSRIs have a similar mechanism of action.

Moclobemide, a reversible monoamine oxidase A inhibitor with a low incidence of sexual dysfunction,<sup>56,57</sup> was used by our group as a substitute treatment in 15 patients.<sup>21</sup> When a dose of 450 to 600 mg/day was administered, sexual dysfunction completely disappeared in 11 patients (73.3%) (Table 7). The incidence of sexual dysfunction with moclobemide is much lower than that observed with other antidepressants and, according to our data, does not exceed 4%. These results have been replicated with 5 patients treated with fluoxetine who completely improved when switched to moclobemide.<sup>58</sup> The improvement in this group of patients who were switched to moclobemide suggests that the different action mechanism of moclobemide could explain the lower incidence of sexual dysfunction due to monoamine oxidase inhibition activity as opposed to serotonergic receptor activity. It even seems to have a stimulating effect on sexual function.<sup>59</sup> In contrast, the nonreversible classic MAOIs (such as phenelzine) produce a high rate of sexual dysfunction,<sup>60</sup> which can be improved with cyproheptadine, thus suggesting that these drugs have a serotonergic stimulation action.<sup>61</sup> In a controlled study with placebo, moclobemide demonstrated an incidence of

Figure 1. Improvement of Sexual Side Effects Over 6 Months in Patients Switched to Nefazodone



\* $p < .05$ .

<sup>a</sup>Intensity scale: 0 = nil, 1 = mild, 2 = moderate, 3 = severe.

<sup>b</sup>Tolerance scale: 1 = good, 2 = fair, 3 = poor.

decreased libido and delayed ejaculation similar to that of placebo, whereas the phenelzine values were 28.6% for decreased libido and 42.8% for delayed ejaculation.<sup>62</sup> In routine clinical practice in Spain, psychiatrists' use of moclobemide has been limited because of certain doubts about its long-term usefulness, the hypothetical need to increase the dose over time, and doubts about its efficacy in severe depressions. Finally, patients with sexual dysfunction who are diagnosed with pathologies other than depression (panic disorder, obsessive disorder, agoraphobia, etc.) would not benefit from the use of moclobemide because it has not been approved for these indications.

The ability of amineptine (a drug with a dopamine-stimulating action mechanism similar to bupropion) to alter patients' sexual function seems to be limited. Our group has recently evaluated whether switching to amineptine improves SSRI-provoked sexual dysfunction in a prospective, observational, open-label, multicenter study<sup>63</sup> using a dose of 200 mg/day in 111 depressed patients, with 6 months of follow-up. In the group of 47 patients who switched to amineptine, the incidence of decreased libido, delayed orgasm, anorgasmia, and erectile dysfunction decreased significantly, from almost 100% at the onset of the treatment to 42.1%, 42.1%, 34.2%, and 31.5%, respectively, at 6 months. The antidepressant effect already obtained with SSRIs was maintained. After these very recent encouraging results were reported in February 1999, amineptine was withdrawn from the drug market in Europe because of long-term dependency problems in some patients. However, it seems clear that substances with dopaminergic activity have a limited secondary sexual dysfunction profile, so it is necessary to consider these data in the investigation of new antidepressant substances in the future.

Because nefazodone accounts for one of the lowest rates of sexual dysfunction in our database, we have performed an observational, prospective study to assess the effectiveness and tolerability of switching patients with low tolerance of sexual dysfunction associated with other antidepressants to nefazodone. The preliminary results have recently been reported.<sup>64</sup> The last-observation-carried-forward data set was made up of 41 of the 44 patients recruited: 26 women and 15 men who had at least 1 postbaseline evaluation and were followed for 6 months. Significant improvement was observed in all 5 dimensions of the PRSexDQ as early as 1 month and continued until the end of the follow-up (Figure 1). At the endpoint evaluation, sexual dysfunction was rated as much or very much improved in 31 (75.6%) of 41 patients, and 33 (80.5%) of the 41 patients were satisfied or very satisfied with their treatment. Twelve (27.3%) of the 44 discontinued treatment (4 [9.1%] lost to follow-up, 4 [9.1%] owing to adverse events). Tolerability was rated as good or very good in 81.8% of the patients. Only 2 patients (4.4%) relapsed (HAM-D  $\geq 18$  in 2 consecutive visits).

Our results, together with the Ferguson et al. study,<sup>65</sup> suggest that switching to nefazodone is an efficacious and well-tolerated therapeutic alternative for treating antidepressant-induced sexual dysfunction. The mechanism that explains patients' improvement may be related to, on the one hand, nefazodone's blocking of the postsynaptic 5-HT<sub>2</sub> receptors that have been reported to be responsible for provoking sexual dysfunction, and, on the other hand, the activity of its *m*-CPP metabolite. It has been demonstrated that 5-HT<sub>2C</sub> agonists such as *m*-CPP (a common metabolite of nefazodone and trazodone) are capable of provoking sexual arousal in experimental animals. In humans, nefazodone can provoke spontaneous ejaculation<sup>66</sup>; it has also been reported to reverse SSRI-induced anorgasmia.<sup>28</sup> At therapeutic doses (400 mg/day), nefazodone could be the drug most similar to the SSRIs with the advantage of not deteriorating sexual activity. Special attention should be given to the technique of drug switching. According to our experience, drug switching should be done by slowly tapering the previous drug and slowly increasing the dose of nefazodone or by applying a washout period between the drugs. When these precautions are taken, it is possible to avoid both the appearance of symptoms added to the initial serotonergic symptoms (restlessness, nausea, sensation of dizziness, confusion, etc.) and the symptoms of the withdrawal or discontinuation syndrome (instability, restlessness, tremors, digestive symptoms, deterioration of depressive symptoms, etc.).

Mirtazapine has the mixed capacity of stimulating noradrenergic and serotonergic activity through the postsynaptic 5-HT<sub>1</sub> receptors when it selectively blocks the 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors. This drug also increases serotonergic activity by blocking the presynaptic  $\alpha_2$  autoreceptors of the serotonergic neurons.<sup>67</sup> Because of its pharmacody-

dynamic profile, it has been hypothesized that the incidence of sexual dysfunction with mirtazapine is lower than that of other antidepressants and that it could function as a therapeutic alternative for patients experiencing sexual dysfunction. Recent studies seem to suggest a lower incidence of sexual dysfunction,<sup>68</sup> and efficacy studies have even indicated that the incidence of sexual dysfunction is less than with placebo.<sup>69</sup> Currently, there are only anecdotal reports or short series on sexual problems associated with mirtazapine.<sup>70</sup> In a recent study, mirtazapine was administered to 11 patients who discontinued treatment with SSRIs because of sexual dysfunction. None of them showed sexual problems after switching.<sup>71</sup> Some reports indicate that mirtazapine reverses sexual side effects when added to SSRI treatment.<sup>72</sup> Mirtazapine also seems to improve sexual difficulties in depressed men and women.<sup>73</sup>

In the experience of our working group,<sup>74</sup> 17 depressed patients with stable clinical improvement (HAM-D < 10) and poorly tolerated sexual dysfunction secondary to antidepressant treatment were switched to mirtazapine. A prospective, observational method was used. A total of 8 patients (47.1%) completely recovered their sexual function, 3 patients (17.6%) reported partial improvement, 3 patients (17.6%) reported no improvement, and 3 other patients (17.6%) did not tolerate the change because of the appearance of other adverse effects (see Table 7).<sup>75</sup> No data on long-term antidepressant efficacy are available as of yet for these patients, and the presence of other possible adverse effects (weight increase, somnolence) must be considered. However, the global improvement found in 11 patients (64.7%) suggests that mirtazapine is a good therapeutic alternative in patients with severe sexual dysfunction secondary to other drugs, above all, in patients with orgasm problems.

## CONCLUSION

The incidence of sexual dysfunction secondary to the use of antidepressants is presently underestimated by clinicians and is clearly the most frequently appearing adverse effect with SSRIs and venlafaxine. Until now, psychiatrists have paid little attention to this problem owing to the combination of several factors, such as the few spontaneous reports of this adverse effect by patients, the false belief that depression was the only cause of the sexual dysfunction, and the limited experience of clinicians in the therapeutic management of these patients. It seems reasonable and even essential to obtain a psychosexual clinical history prior to initiating treatment with antidepressants in order to analyze later changes and select an individualized strategy to handle sexual dysfunction secondary to the treatment. Treatments with antidepressants, which often must be used for a long period of time or even indefinitely, must fulfill several essential requirements. On the one hand, they should be efficacious, and on

the other hand, the level of long-term tolerability should not jeopardize compliance and should help the patient and family to attain the best possible quality of life.<sup>75</sup> Direct examination of previous sexual function with specific questionnaires and contrasted validity is a decisive factor in the detection of dysfunction after treatment. Using new antidotes such as sildenafil or switching the treatment to drugs with a serotonergic profile (such as nefazodone or mirtazapine) seem to be the strategies of choice for patients who do not spontaneously adapt to sexual dysfunction. However, only controlled, prospective studies lasting at least 6 months can provide us with a sufficiently authentic assessment of these alternatives to consolidate them as definitive procedures toward improving patients' sexual function. Sexual side effects should be an important factor when selecting antidepressants.

*Drug names:* bupropion (Wellbutrin), citalopram (Celexa), clomipramine (Anafranil and others), clonidine (Catapres and others), cyproheptadine (Periactin), desipramine (Norpramin and others), digoxin (Lanoxin and others), fluoxetine (Prozac), fluvoxamine (Luvox), methylodopa (Aldomet and others), mirtazapine (Remeron), nefazodone (Serzone), nortriptyline (Pamelor and others), paroxetine (Paxil), phenelzine (Nardil), propranolol (Inderal and others), sertraline (Zoloft), sildenafil (Viagra), venlafaxine (Effexor).

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

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Editor's Note: Appendix 1 appears on p. 21.

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## Appendix 1. Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ) (Montejo AL, et al.)

**Doctor** \_\_\_\_\_ **Hospital** \_\_\_\_\_  
**Patient name (initials)** \_\_\_\_\_  
**# Reference** \_\_\_\_\_ **Age** \_\_\_\_\_ **Sex** \_\_\_\_\_ **Marital status** \_\_\_\_\_  
**Drug** \_\_\_\_\_  
**Dosage** \_\_\_\_\_ (mg/day) **Length of use** \_\_\_\_\_ (months)  
**Associated drugs** \_\_\_\_\_  
**Diagnosis** \_\_\_\_\_  
**Sexual dysfunction? (yes/no)** \_\_\_\_\_ **Spontaneous communication?** \_\_\_\_\_  
**Decreased libido** \_\_\_\_\_ (0 = nil, 1 = mild, 2 = moderate, 3 = severe)  
**Delayed orgasm/ejaculation** \_\_\_\_\_ (0 = nil, 1 = mild, 2 = moderate, 3 = severe)  
**Anorgasmia** \_\_\_\_\_ (0 = never, 1 = occasionally, 2 = frequently, 3 = always)  
**Erectile/lubrication dysfunction** \_\_\_\_\_ (0 = never, 1 = occasionally, 2 = frequently, 3 = always)  
**Previous sexual functioning** \_\_\_\_\_ (normal/abnormal)  
**Improvement with time?** \_\_\_\_\_ **Sexual dysfunction acceptance** \_\_\_\_\_ **Drop out? (yes/no)** \_\_\_\_\_  
(0 = total, 1 = medium, 2 = none) (0 = good, 1 = moderate, 2 = bad)  
**Dosage decrease? (yes/no)** \_\_\_\_\_ **New dosage** \_\_\_\_\_ (mg/day) **Improvement** \_\_\_\_\_  
(0 = total, 1 = much, 2 = moderate, 3 = poor, 4 = no)  
**Switching to another drug? (yes/no)** \_\_\_\_\_ **New drug** \_\_\_\_\_  
**Dosage** \_\_\_\_\_ (mg/day) **New drug improvement** \_\_\_\_\_ **Improvement began after** \_\_\_\_\_  
(0 = total, 1 = much, 2 = moderate, 3 = poor, 4 = no)  
**Drug holiday prior to sexual intercourse? (yes/no)** \_\_\_\_\_ **Hours?** \_\_\_\_\_  
**Improvement with drug holiday?** \_\_\_\_\_ (0 = total, 1 = much, 2 = moderate, 3 = poor, 4 = no)  
**Adjunctive treatment?** \_\_\_\_\_ **Dosage** \_\_\_\_\_ (mg/day) **Improvement?** \_\_\_\_\_  
(0 = total, 1 = much, 2 = moderate, 3 = poor, 4 = no)  
**Comments:** \_\_\_\_\_

The following questions refer to the possible appearance of sexual dysfunction after initiating treatment with psychotropic agents. It serves as a support for the physician to ask questions and fill out the attached protocol.

- Have you observed any type of change in your sexual activity (excitation, erection, ejaculation, or orgasm) since you began taking the drug treatment?  
Yes.  
No.
- Has the patient spontaneously reported this alteration, or was it necessary to expressly question him or her to discover the sexual dysfunction?  
Yes, it was spontaneously reported.  
No, it was not spontaneously reported.
- Have you observed any decrease in your desire for sexual activity or in your interest in sex?  
0. No problem.  
1. Mild decrease. Somewhat less interest.  
2. Moderate decrease. Much less interest.  
3. Severe decrease. Almost none or no interest.
- Have you observed any delay in ejaculation/orgasm?  
0. No delay.  
1. Mild delay or hardly noticeable.  
2. Moderate delay or clearly noticeable.  
3. Long delay, although ejaculation is possible.
- Have you observed that you are unable to ejaculate or have an orgasm once you begin sexual relations?  
0. No.  
1. Sometimes: less than 25% of the time.  
2. Often: 25%–75% of the time.  
3. Always or almost always: more than 75% of the time.
- Have you experienced any difficulty obtaining an erection or maintaining it once you have initiated sexual activity? (vaginal lubrication in women)  
0. Never.  
1. Sometimes: less than 25% of the time.  
2. Often: 25%–75% of the time.  
3. Always or almost always: more than 75% of the time.
- How well have you tolerated these changes in your sexual relations?  
0. Well. No problem due to this reason.  
1. Fair. The dysfunction bothers him or her although he or she has not considered discontinuing the treatment for this reason. It interferes with the couple's relationship.  
2. Poor. The dysfunction presents an important problem. He or she has considered discontinuing treatment because of it, or it seriously interferes with the couple's relationship.