Sexual dysfunction in depressed patients undergoing treatment with antidepressants

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INTRODUCTION: To determine the incidence of treatment-induced sexual dysfunction in depressed outpatients treated with five different antidepressants.

METHODS: 100 depressed patients (ICD-10 criteria for depressive episode, recurrent depressive disorder, and dysthymia) with an active sex life were assessed by the MADS, the CGI, and the Sexual Function Questionnaire at baseline and at 1, 2, and 4 months.

RESULTS: Although the sample showed a slight improvement, generally, in sexual functioning after 4 months treatment, there were several cases of deterioration.

CONCLUSIONS: Greatest interference with sexual functioning occurs with paroxetine, venlafaxine, and clomipramine.

Keywords sexual dysfunction antidepressants depression Sexual Function Questionnaire

INTRODUCTION

Sexual behaviour in depressed patients is very frequently disturbed. The incidence of sexual problems among depressed patients is approximately twice that found in healthy controls (50% vs. 24%). In some cases this is due to the effect of the depression itself on the individual and, in others, it is a result of the deterioration of interpersonal relationships brought on by the depression.

The most frequent sexual dysfunction is the decrease in libido, to the point that it is included in the diagnostic criteria for depression in almost all international classifications. On the other hand, prior depressive episodes are very frequently reported in individuals with hypoactive and chronically inhibited sexual desire. The decrease in sexual desire is frequently attributed to these depressive episodes. It has been suggested that changes in the libido may be an indicator of depression, or of subtypes of depression, in people under 70.

Although decrease in libido is the most frequent sexual dysfunction found in depressed patients, dysfunctions of excitement and orgasm may also be present. Impotence secondary to depression has been reported in up to 25% of depressed patients. Mathew and Weinman found 35% erectile dysfunction and 47% ejaculatory delay in depressed males.

Psychopharmacological treatment can improve the sexual dysfunction associated with the psychiatric illness in many cases. However, as Angst has shown, if the incidence of sexual dysfunction is twice as high among depressed patients as in healthy controls, this figure is tripled if we consider depressed patients in treatment (63% vs. 26%). The effect of the drugs themselves, especially antidepressants and neuroleptics, on sexual functioning has been the subject of growing interest. Hypoactive sexual desire, erectile dysfunction (impotence and priapism), and orgasmic or ejaculatory dysfunction have been reported among the adverse effects of psychopharmacological treatment. In many cases, sexual functioning can be restored to its previous level by modifying the therapeutic regimen, without sacrificing efficacy in the treatment of the psychiatric illness.

The exact incidence of sexual dysfunction during antidepressant treatment is as yet unknown. The sexual side-effects of the tricyclic antidepressants have been almost totally ignored. Nevertheless, it is known that, of the tricyclics, clomipramine shows the greatest incidence of sexual dysfunction.

Selective serotonin re-uptake inhibitors (SSRIs), in particular fluoxetine and paroxetine, have been studied more closely from the point of view of sexual dysfunction. In the case of fluoxetine, there has been considerable variation in the figures from the first studies to the most recent,
ranging from 5–8% to 43%, and as high as 75%. The pattern for paroxetine has been the same. Specifically, ejaculation difficulties have been reported in 6–9% of cases, and orgasmic dysfunction in 42.3%. Although paroxetine has been associated with a slightly higher incidence of sexual side-effects, Waldinger et al find no differences between fluoxetine, paroxetine and sertraline.

Premarketing studies with venlafaxine reported 12% of cases of erectile dysfunction, 6% of abnormal ejaculation, and 2% of orgasmic difficulties in women. However, Schweizer et al and Cunningham et al found that 10% of the women treated with venlafaxine presented some kind of sexual dysfunction, especially anorgasmia. Studies with nefazodone show an incidence of sexual dysfunction similar to that with placebo and lower than that found with sertraline in a double blind study (30% vs. 71%). Finally, moclobemide appears to be the exception, since there have been no reports of sexual dysfunction associated with its use.

Our study was an attempt to determine the incidence of sexual dysfunction in depressed outpatients treated with five antidepressants.

METHOD

A 4-month longitudinal observational study was carried out.

PATIENTS

Subjects were recruited from adults who had requested help in two mental health centres in Gijón (Asturias). A total of 100 outpatients were included in the study. Inclusion criteria were: ICD-10 criteria for depressive episode, recurrent depressive disorder, or dysthymia, and with an active sexual life. Exclusion criteria were: bipolar disorder, serious organic illness, alcohol consumption greater than 30 g/day, and the use of any drug that might interfere with sexual function.

The patients were assigned to one of the following five treatment groups, based on the clinician's judgement (expectations of benefit and improvement with that treatment): 20 to clomipramine, 20 to moclobemide, 20 to nefazodone, 20 to paroxetine, and 20 to venlafaxine.

ASSESSMENT

Evaluations were made at baseline and at 1, 2, and 4 months. The Montgomery-Åsberg Depression Scale (MADS), both forms of the Clinical Global Impression (the Severity of Illness (CGI-SI) and the Improvement Scale (CGI-I)), the Sexual Function Questionnaire (SFQ), and the SF-36 were used for assessment. An ad hoc protocol which gathered sociodemographic and clinical information, and the Eysenck Personality Questionnaire (A) (EPQ-A), were also administered at baseline.

The SFQ was designed to measure treatment-emergent changes in the areas of desire, arousal, and orgasm. There are 10 items for men and eight items for women. (Seven of the items are identical for men and women). Each item is answered using a 5-point Likert scale, where 1=best possible functioning and 5=worst. It was decided to eliminate questions 6 and 7, related to masturbation, due to difficulties in obtaining this type of information from the Spanish adult population.

STATISTICAL ANALYSIS

Since the SFQ does not provide a global measurement of sexual functioning, a global variable for sexual dysfunction was created by using the sum of all the items of the SFQ, except for frequency. Those patients who presented dysfunction in at least one of the SFQ items (as employed in this study) were classified as “having sexual dysfunction”. In contrast, those patients who showed no dysfunction in any of the SFQ items were classified as “having no sexual dysfunction”. χ², Student's t-test and the ANOVA (with Duncan post-hoc analysis) were used to test the significance of the association between variables of interest.

RESULTS

SOCIODEMOGRAPHIC AND CLINICAL CHARACTERISTICS

The mean age of the total sample was 46.08 (sd 11.3) and 65% of the participants were female. No significant differences were found with respect to age or sex in the treatment groups, although the nefazodone group had the highest average age (48.6 years) and the moclobemide group the highest percentage of women (80%). Ninety-four percent were married, the mean length of time of living together was 20.9 years (sd 11), and 84% reported the relationship with their partner as being good.

Forty-nine percent had a diagnosis of a single episode, 22% of recurrent depressive disorder, and 29% of dysthymia. Eighty-five percent were considered as moderate, and 15% as severe, according to the CGI-SI. Significant differences were found with respect to the diagnostic subtype as well as the degree of the illness, depending on the treatment group (Table 1). Almost 38% of the dysthymic patients belonged to the moclobemide group, as opposed to 14.3% of those patients with a single episode, and 9.1% of those with recurrent disorder (P=0.03). None of the patients deemed to have a severe degree of illness belonged to the moclobemide group, as opposed to 15.8% of the moderately ill patients (P=0.002).

The MADS mean score was 29.34 (sd 5.2). The clomipramine and venlafaxine groups scored significantly higher than the paroxetine, moclobemide, and nefazodone groups (33.1, 31.1, 28.8, 27.5, and 26.1 respectively, P<0.000). The average duration of the current depressive episode was 26.98 (sd 57.01) months. The duration for the patients receiving moclobemide was significantly (P<0.01)
Table 1
Distribution of antidepressants among patients, based on diagnostic subtype and baseline severity (CGI-SI)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Single episode (% patients)</th>
<th>Recurrent disorder (%)</th>
<th>Dysthymia (%)</th>
<th>Moderate (%)</th>
<th>Severe (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clomipramine</td>
<td>18.4</td>
<td>31.8</td>
<td>13.8</td>
<td>19.3</td>
<td>35.7</td>
</tr>
<tr>
<td>Moclobemide</td>
<td>14.3</td>
<td>9.1</td>
<td>37.9</td>
<td>15.8</td>
<td>0</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>14.3</td>
<td>22.7</td>
<td>27.6</td>
<td>15.8</td>
<td>21.4</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>24.3</td>
<td>22.7</td>
<td>10.3</td>
<td>29.8</td>
<td>0</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>28.6</td>
<td>13.6</td>
<td>10.3</td>
<td>19.3</td>
<td>42.9</td>
</tr>
</tbody>
</table>

Sexual dysfunction

At the time of their baseline visit, 9% of patients had suspended sexual activity. Furthermore, 64% reported a decrease in sexual interest, 39% a loss of sexual pleasure, 30% inability to achieve adequate arousal, and 27% difficulties in achieving orgasm. Significant differences were found according to drug group as regards arousal (P=0.01), orgasm (P=0.000), and ejaculatory absence (P=0.04). At that time, 67% of the patients showed dysfunction in at least one of the SFQ items (except frequency), which is to say that they demonstrated global sexual dysfunction as defined in our study. The dysfunction was significantly associated with drug group (P=0.000); 95% of the paroxetine group had sexual dysfunction vs. 90% of the venlafaxine, 75% of the clomipramine, 55% of the nefazodone, and 20% of the moclobemide groups.

When results for new cases appearing at month 4 are recorded according to the drug (Figure 1), no new case of loss of interest is observed in the moclobemide and nefazodone groups, whereas 10% of the patients treated with clomipramine and venlafaxine, and 15% of those on paroxetine, developed dysfunction in this area. Under the heading of pleasure, 0% of the moclobemide group, 15% of the clomipramine, nefazodone, and paroxetine groups, and 20% of the venlafaxine group developed dysfunction. Arousal dysfunction appeared in 0% of the patients being treated with moclobemide, 10% of those on nefazodone, 15% of those on clomipramine, 20% of those on paroxetine, and 25% of those on venlafaxine. None of the moclobemide group, 10% of the nefazodone group, 40% of the clomipramine group, 45% of the venlafaxine group, and 80% of the paroxetine group developed orgasm dysfunction at month 4. Ten per cent of those patients treated with clomipramine and with venlafaxine ceased to have sexual relations.

Frequency of Sexual Relations

At the baseline, the frequency of relations was significantly associated with the number of years of education (those patients who had frequent sexual relations were those who had studied for significantly fewer years, P=0.04), employment status (the higher the status the lower the frequency of relations, P=0.02), alcohol consumption (g/d) (those having no sexual relations were those who consumed significantly less, P=0.04), number of prior episodes (those with no relations had had significantly more prior episodes, P=0.03), number of hospitalizations (those with no relations had had more hospitalizations, P=0.01), and the severity of the depression evaluated by the MADS (those
with no relations scored higher, $P=0.000$), and the CGI-SI (the greater the severity the lower the frequency, $P=0.001$).

At 4 months, years of education ($P=0.04$), employment status ($P=0.01$), the severity of the depression (MADS, $P=0.000$) and the improvement as measured by the CGIS (0% of those patients experiencing a complete improvement had no relations as opposed to 22.2% of those who had experienced no changes, $P=0.03$) showed statistical association with the frequency of sexual relations.

### Sexual Interest

At baseline, age (those who presented alterations in the area of interest were significantly older, $P=0.04$), years of living together (the subgroup with dysfunction had been living together for significantly more years, $P=0.008$), employment status (85.7% of those patients with a higher employment status presented with dysfunction with regard to sexual interest as opposed to 58.2% of those with a mid-level status, $P=0.01$), alcohol consumption (the dysfunctional subgroup consumed significantly less alcohol per day, $P=0.001$), the age of onset of the first symptoms (significantly older in the group with dysfunction, $P=0.001$), and the degree of severity of the illness, both as measured by the MADS score (the dysfunctional subgroup scored significantly higher, $P=0.000$) and the CGI-SI (86.7% of the serious cases presented dysfunction as opposed to 60% of those classified as moderate, $P=0.04$) were significantly associated with a decrease in sexual interest.

At the 4-month visit, the variables significantly associated with dysfunction in the area of interest were: alcohol consumption (in contrast to the finding that at baseline, the dysfunctional subgroup consumed significantly greater amounts of alcohol/day, $P=0.01$), the degree of extroversion-introversion at baseline in males (the dysfunctional male subgroup was significantly more introverted, $P=0.01$), and severity of illness as measured by both the MADS score ($P=0.000$) and the CGIS (14.6% of those patients experiencing a complete improvement presented dysfunction as opposed to 77.8% of those that had experienced no changes, $P=0.000$).

### Sexual Pleasure

At the baseline, the following variables were significantly associated with lack of pleasure: duration of living together (the subgroup with dysfunction had been living together for significantly more years, $P=0.04$), the degree of extroversion-introversion in men (the men in the dysfunctional subgroup were significantly more introverted, $P=0.01$), and the severity of the illness as determined both by the MADS score ($P=0.000$) and the CGIS (93.3% of the serious cases presented dysfunction as opposed to 29.4% of those classified as moderate, $P=0.000$).

At month 4, the variables significantly associated with lack of pleasure were: severity of disease at baseline as determined by the CGI-SI (53.3% of those considered serious at the baseline presented dysfunction at month 4 vs. 23.5% of the moderate cases), severity of illness at month 4 as determined by the MADS (the subgroup with dysfunction scored significantly higher, $P=0.001$), and improvement of symptoms as determined by the CGIS (18.8% of those patients experiencing a complete improvement presented dysfunction as opposed to 55.6% of those who had experienced no changes, $P=0.04$).

### Table 2

Sexual dysfunction at baseline and at 4 months, based on drug group

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Clomipramine (%)</th>
<th>Moclobemide (%)</th>
<th>Nefazodone (%)</th>
<th>Paroxetine (%)</th>
<th>Venlafaxine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency (none)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interest</td>
<td>64</td>
<td>85</td>
<td>65</td>
<td>45</td>
<td>60</td>
<td>65</td>
</tr>
<tr>
<td>Pleasure</td>
<td>39</td>
<td>60</td>
<td>35</td>
<td>30</td>
<td>25</td>
<td>45</td>
</tr>
<tr>
<td>Arousal</td>
<td>30</td>
<td>45</td>
<td>20</td>
<td>25</td>
<td>15</td>
<td>40</td>
</tr>
<tr>
<td>Orgasm</td>
<td>27</td>
<td>35</td>
<td>25</td>
<td>30</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>Erection</td>
<td>14.3</td>
<td>20</td>
<td>0</td>
<td>18.2</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Spontaneous nocturnal erections</td>
<td>34.3</td>
<td>60</td>
<td>0</td>
<td>36.4</td>
<td>60</td>
<td>20</td>
</tr>
<tr>
<td>Ejaculation: none</td>
<td>2.8</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ejaculation: delay</td>
<td>5.7</td>
<td>20</td>
<td>0</td>
<td>9.1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

continued opposite
**SEXUAL EXCITEMENT**

The variables significantly associated with excitement dysfunction at the baseline were: age (the subgroup with dysfunction were significantly older, \( P=0.01 \)), number of years living together (the subgroup with dysfunction had been living together for significantly longer, \( P=0.03 \)), daily alcohol consumption (the subgroup with dysfunction consumed significantly less alcohol, \( P=0.01 \)), smoking (the subgroup with dysfunction smoked significantly fewer cigarettes, \( P=0.01 \)), age at onset of the illness (the subgroup with dysfunction experienced symptoms at a significantly older age, \( P=0.01 \)), the degree of extroversion – introversion in males (the subgroup with dysfunction was significantly more introverted, \( P=0.04 \)), and the severity of symptoms, both as determined by the MADS (the subgroup with dysfunction were significantly older, \( P=0.000 \)) and by the CGI-SI (60% of the serious cases presented dysfunction versus 24.7% of those classified as moderate, \( P=0.005 \)).

At month 4, only the drug (Table 2) and the MADS score (\( P=0.005 \)) were significantly associated with dysfunction.

**ORGASM**

At baseline, the variables significantly associated with orgasm dysfunction were: age (those with dysfunction were significantly older, \( P=0.02 \)), years living together (the subgroup with dysfunction had been living together for significantly longer, \( P=0.02 \)), number of months worked in the previous year (those with dysfunction had worked significantly fewer months, \( P=0.02 \)), and severity of illness as evaluated by the CGI-SI (46.7% of the serious patients presented dysfunction vs. 22.4% of the moderate cases, \( P=0.04 \)).

At month 4, only the drug type (Table 2) and the baseline severity of the depression (MADS, \( P<0.01 \)) were significantly associated with orgasmic dysfunction.

**ERECTILE CAPACITY**

No significant association was found between erectile capacity and clinical or sociodemographic variables at baseline. At month 4, the severity of depression (MADS) was significantly associated with erectile capacity (\( P=0.04 \)).
Insofar as nocturnal penile tumescence is concerned, at the baseline it was associated with the quality of social relationships, in that a higher percentage of patients with deteriorated social relationships presented with nocturnal penile tumescence ($p=0.03$). At the 4-month visit, an association was found with the degree of extroversion–introversion (dysfunctional patients were significantly more introverted, $p=0.03$) and with physical comorbidity (present in 76% of the patients without dysfunction as compared to 40% of those with dysfunction, $p=0.04$).

**Ejaculatory Disorders**

At baseline, no sociodemographic or clinical variable was significantly associated with ejaculatory disorders. At month 4, the type of drug (Table 2) and the severity of the depression (those patients who could not ejaculate scored significantly higher on the MADS, $p=0.04$) were significantly associated with an absence of ejaculation.

**DISCUSSION**

A prospective, naturalistic, observational study was carried out in which eight parameters of sexual functioning—interest, pleasure, arousal, orgasm, frequency, erection, nocturnal penile tumescence, and ejaculation—were studied over a 4-month period in depressed outpatients who were receiving antidepressant drug therapy. Being a naturalistic study, the findings can be considered preliminary and subject to some limitations. First of all, no control group was used, which makes it difficult to eliminate the influence of the depressive syndrome itself on sexual dysfunction. Second, the sample is not very large, especially in numbers of men, which reduces its statistical value.

The present study confirms that antidepressants, especially paroxetine, clomipramine and venlafaxine, significantly affect sexual response, as demonstrated earlier by some authors. Furthermore, the aspects most affected by antidepressant drug therapy were orgasm and, in males, ejaculation, in agreement with the findings of other authors. Orgasmic dysfunction means substantial difficulties in achieving orgasm or total anorgasmia; when orgasm is reached, it is less intense and pleasurable. The antidepressants that affected orgasm to a greater degree were paroxetine, clomipramine, and venlafaxine. In the case of ejaculation, the most frequent effect associated with venlafaxine was the absence of ejaculation, and with paroxetine, ejaculatory delay. In fact, some authors propose its use as an effective treatment for premature ejaculation.

Arousal was shown to be affected by antidepressant drug therapy as well as by the severity of the depression. The drugs that caused a greater number of difficulties in the area of arousal were venlafaxine, clomipramine, and paroxetine. No significant differences were found between antidepressants with respect to erection. The most severe erectile difficulties were caused by clomipramine. This drug, possibly due to its anticholinergic effect in addition to its strong central and peripheral serotoninergic effect, also caused nocturnal penile tumescence. Paroxetine and nefazodone (in the first and second months) were shown to be linked to a considerable percentage of erectile dysfunctions (agreeing with the findings of some authors), which decreased considerably in the fourth month.

With respect to sexual satisfaction or pleasure, both the severity of the depression and the type of drug used had a similar influence, in that those patients who experienced less pleasure were those who received venlafaxine and clomipramine.

Sexual interest or desire, as well as the frequency of sexual relations, were affected primarily by the severity of the depression, although some sociodemographic variables were also shown to have an influence.

In summary, the drugs that interfered most with the sexual behaviour of depressed patients were paroxetine, clomipramine and venlafaxine. Some specific features emerged. Paroxetine was associated with considerable orgasmic dysfunction: delay in reaching orgasm, and less intense and pleasurable orgasm, as well as ejaculatory delay. Clomipramine is associated with orgasmic dysfunction in the same way as paroxetine, and with substantial difficulties in the area of arousal, an effect which has already been demonstrated several years ago. Failure to ejaculate has not turned out to be as frequent as with venlafaxine, which has been responsible for a large number of cases.

In this study, many different sociodemographic and clinical aspects, including personality, have also been considered. We have found that some of them have a particular influence on sexual behavior prior to antidepressant treatment. It is therefore significant that we found sexual interest to be related to age, years of living together, and employment status, such that when the patient is older, has lived more years with his/her partner, and has a higher employment status, the worse is sexual desire affected during untreated depression. Older age and a longer period of living together also had a negative effect on satisfaction, arousal, and orgasm. In addition, extroversion was associated with greater pleasure.

**CONCLUSIONS**

A great many depressed patients who receive clomipramine, paroxetine, or venlafaxine suffer from sexual

**KEY POINTS**

- Moclobemide and nefazodone cause practically no interference with sexual functioning
- Clomipramine, paroxetine, and venlafaxine induce arousal and orgasm dysfunctions at 4 months
dysfunction secondary to treatment. The sexual dysfunction produced by nefazodone or moclobemide is much less, although the efficacy of these drugs, especially in the case of moclobemide, in treating severe depression has yet to be proven. Further studies are needed to evaluate sexual dysfunction in larger samples, and in which the effects of depression and some sociodemographic variables on sexual behavior can be controlled.

REFERENCES

