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SEXUAL FUNCTIONING IN DEPRESSED OUTPATIENTS TAKING MIRTAZAPINE

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Objectives—One-third of patients with untreated depression have sexual difficulties manifested by decreased libido, erectile dysfunction or delayed ejaculation. This dysfunction may be exacerbated by stimulation of post-synaptic serotonin 5HT2 receptors, a side-effect of most widely-used antidepressant medications, especially the selective serotonin reuptake inhibitors (SSRIs). Mirtazapine is an atypical antidepressant with α2 adrenergic antagonist and serotonin 5-HT2 and 5-HT3 receptor-blocking activity. In theory, it should not worsen and perhaps may improve sexual function. This pilot study investigated sexual functioning and antidepressant activity in depressed patients taking mirtazapine. Experimental design—Twenty-five (F = 18, M = 7) sexually active adult outpatients with a DSM-IV-diagnosis of major depressive episode entered a 12-week, flexible-dosing, open-label pilot study. The Arizona Sexual Experiences Scale (ASEX) assessed sexual functioning and the Hamilton Depression Rating Scale (HAM-D) assessed depressive symptoms on a bimonthly basis. Principal Observations—Desire, arousal/lubrication, and ease/satisfaction of orgasm improved (by 41%, 52%, and 48%, respectively) in the depressed women. In men, desire, arousal/erection, and ease/satisfaction of orgasm also improved (by 10%, 23% and 14%, respectively) but much more modestly. HAM-D, Clinical Global Impression (CGI) Sheehan Disability Scale (SDS), and Symptom Checklist-90 (SCL-90) scores improved in both groups. There was a 50% dropout rate among women before six weeks of treatment. However, the ASEX and HAM-D scores of the groups terminating before and after six weeks of treatment showed similar rates of improvement. Conclusions—Mirtazapine has a beneficial effect on sexual functioning in both depressed women and men. Longer-term double-blind research assessing sexual function during the administration of mirtazapine as well as other antidepressants is recommended. Depression and Anxiety 9:175–179, 1999.

Key words: *5-HT2 serotonin antagonists; depression; sexual dysfunction; antidepressants; alpha adrenergic antagonists*

INTRODUCTION

One-half of patients with untreated depression have sexual difficulties manifested by decreased interest and/or libido, erectile dysfunction or delayed ejaculation [Nofzinger et al., 1993]. Unfortunately, most antidepressants create or increase sexual dysfunction. The selective serotonin reuptake inhibitors (SSRIs) [Waldinger et al., 1998; Seagraves, 1989; Patterson, 1993; Feiger et al., 1996], venlafaxine [Physician's Desk Reference, 1998], the tricyclics, and monoamine oxidase inhibitors (MAOIs) are all associated with decreased sexual desire, impotence, delayed ejaculation, and anorgasmia. Bupropion and nefazodone are the only antidepressants that appear to generally cause little or no sexual dysfunction [Crenshaw and Goldberg, 1996; Feiger et al., 1996; Reynolds, 1997].

Serotonergic 5-HT2 receptor antagonism facilitates increased copulatory behavior in male rats [Foreman et al., 1992; Watson and Gorzalka, 1994] and appears

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to improve libido and sexual function in humans as well. Alpha-2 adrenoceptor antagonists have been shown to enhance erectile function in the adult male [Munoz et al., 1994] by decreasing or preventing problems with erection and ejaculation.

Mirtazapine is an atypical antidepressant with α2 adrenergic and serotonergic 5-HT2 and 5-HT3 receptor-blocking activity [Stahl et al., 1998]. It does not decrease and theoretically may increase sexual desire, arousal, and/or function. During the initial field trial registration studies, deBoer (1995) reported similar rates of impotence in both the mirtazapine-treated group and the placebo group. The baseline occurrence of impotence or other sexual dysfunction was not reported in these studies.

Clinical efficacy studies and prescribing physicians may miss diagnosing sexual dysfunction because it is not asked about directly. Careful investigation of the rate of sexual dysfunction shows that it is substantially higher than the patients are asked specifically about sexual functioning. Montejo-González et al. (1997) discovered a 44% increase in the incidence of sexual dysfunction in patients whose physicians asked their patients direct questions, as opposed to those patients who spontaneously reported sexual dysfunction.

Because the receptor profile of mirtazapine has a theoretically positive effect on sexual function and because of positive anecdotal reports, we embarked on an open-label pilot study of the effects of mirtazapine on sexual desire, arousal, and function in a sample of sexually active men and women with DSM-IV-diagnosed major depressive episode.

MATERIALS AND METHODS

PATIENTS

Patients were recruited through newspaper ads and psychiatrist referrals at the Department of Psychiatry and Behavioral Sciences of the University of Texas Medical Branch at Galveston (UTMB). All patients meeting DSM-IV criteria for major depressive disorder (single episode or recurrent) [American Psychiatric Association, 1994] and who scored ≥ 17 on the Hamilton Depression Rating Scale (HAM-D) [Hamilton, 1960] were invited to enter the study.

Patients invited to participate in this study were medically healthy, sexually active, on a suitable birth control method, with no evidence of thought disorder or bipolar disorder, not on antipsychotic medications, and antidepressant-free for at least one week. There were no patients taking fluoxetine at baseline, and so an extended washout period was not required for any subject. Patients were not taking any concomitant medications that had psychoactive properties or were known to affect sexual function. Patients did not meet criteria for alcohol or other substance abuse disorder within three months prior to study entry. All patients gave written informed consent to participate in the study after the nature of the study and its procedure was explained. The Structured Clinical Interview for the DSM-IV (SCID) [First et al., 1995], a physical exam, an electrocardiogram, and screening laboratory studies including serum pregnancy test (if applicable) were then administered. The study protocol and consent forms were approved by the institutional review board at UTMB.

Mirtazapine was started at initial doses of 15 mg per day at baseline (week 0) and increased as tolerated or needed to resolve depression, to a maximum dose of 45 mg per day. Medication was increased or decreased at bimonthly visits, depending upon response to depressive symptoms and side effects.

RESULTS

Twenty-five sexually active male (N = 7) and female (N = 18) outpatients were recruited for inclusion in the study and were given mirtazapine. Ages ranged from 21 and 64 years. At baseline, women were more depressed than men, as reflected by their HAM-D ratings (Table 1). Baseline Arizona Sexual Experiences Scale (ASEX) total, scores were similar between men and women, both groups exhibiting mild-to-moderate sexual function difficulties.

Of the 25 subjects starting on mirtazapine at baseline (week 0), seven did not return for a second visit at week two (one dropped out because of drowsiness, the other six were lost to follow-up). An additional nine subjects dropped out after week two because of (a) withdrawal of consent (one woman had feelings she wanted to hurt herself, one woman developed extreme anger in dealing with her spouse), (b) adverse event (one man and one woman with intolerable drowsiness, one woman with water retention), (c) serious unrelated adverse event (one woman with pre-existing heart disease who had another myocardial infarction), (d) marked improvement (one woman), and (e) two women who were lost to follow-up.

Therapeutic doses of mirtazapine ranged from 15 mg–45 mg with a mean dose of mg ± 22.5. HAM-D scores dropped dramatically in both sexes, registering a 61% improvement rate compared to baseline in men and 79% improvement in women (Fig. 1). The ASEX total (Fig. 2) and all three subscales (Fig. 4) showed substantial improvement in women in the areas of desire, arousal, and orgasm, from an impaired to an unimpaired status. Men showed more modest gains in both global and subscale sexual functioning (Fig. 1 and 3), returning closer to, but not within, the range of unimpaired functioning. Both men and women showed notable improvement in Sheehan Disability Scale (SDS), Symptom Checklist-90 (SCL-90), and Clinical Global Impression (CGI) scores (Table 1).

OUTCOME MEASURES

Primary efficacy variables included the 17-item HAM-D, measuring depressive symptoms, and the

TABLE 1. Scales: Baseline and end of study

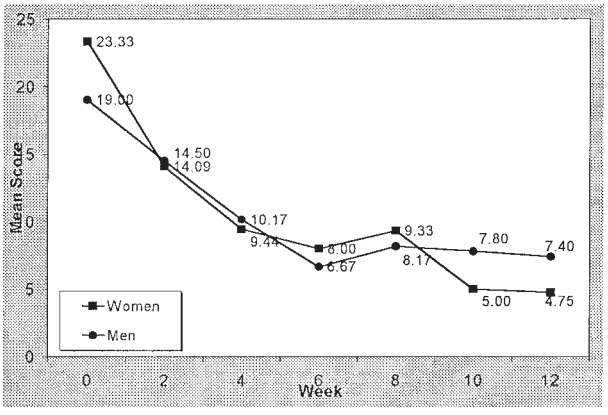
	Men (n = 6)			Women (n = 12)			Total group (n = 18)		
Scale	Baseline	End of study	% Change	Baseline	End of study	% Change	Baseline	End of study	% Change
ASEX, total	18.5	15.2	17.8	19.0	10.3	47.3	18.8	13.0	32.2
Desire	4.0	3.6	10.0	4.6	2.8	40.5	4.4	3.0	31.5
Arousal	4.0	3.1	22.5	3.5	1.8	51.7	3.7	2.5	33.2
Orgasm	3.3	2.8	13.8	3.7	2.0	47.5	3.6	2.4	32.8
HAM-D, total	19.0	7.4	61.1	23.3	4.8	79.4	21.9	6.2	71.7
SCL-90	93.8	8.7	90.8	182.5	23.3	87.2	157.1	17.0	89.2
SDS	27.0	7.4	72.6	25.3	4.3	83.0	25.8	4.4	82.9
CGI, global	4.5	3.3	26.7	4.9	1.6	67.3	4.8	2.4	50.0

ASEX [McGahuey et al., 1997], measuring sexual function. The ASEX is a gender-specific, five-item, self-report measure. It has demonstrated internal consistency, with test-retest reliability significant at the .01 level. Sensitivity and specificity of the ASEX in identifying subjects with sexual dysfunction is 82% and 90%, respectively. Subjects rate, on a 6-point Likert scale, their current level of sexual drive, psychological arousal, physiologic arousal (erections or vaginal lubrication), ease of orgasm, and orgasm satisfaction. Scores ranged from extremely strong (6) to none (1) for each of the five items for a total score ranging from 5 to 30. Average total score for adults without clinical sexual dysfunction is 14 in women and 10 in men. A total ASEX score of 19 or greater, any one item with an individual score of 5 or greater, or any three items with individual scores of 4 or greater are highly correlated with the presence of clinician-diagnosed sexual dysfunction [McGahuey et al., 1999]. ASEX item scores were divided into subscores of (1) desire, (2) arousal, including sex drive and arousal, and (3) orgasm, including ease of orgasm and orgasm satisfaction. Subscores of arousal and orgasm, each containing two items, were averaged for a single mean score.

Secondary efficacy variables included the SDS [Leon et al., 1997] and SCL-90 [Derogatis et al., 1973], completed at baseline and week 12 of the study or the last study visit. The CGI [Guy, 1976] was completed at each visit. Three physicians and a research associate completed study ratings, seeing patients on a bimonthly basis for 12 weeks for a total of seven visits.

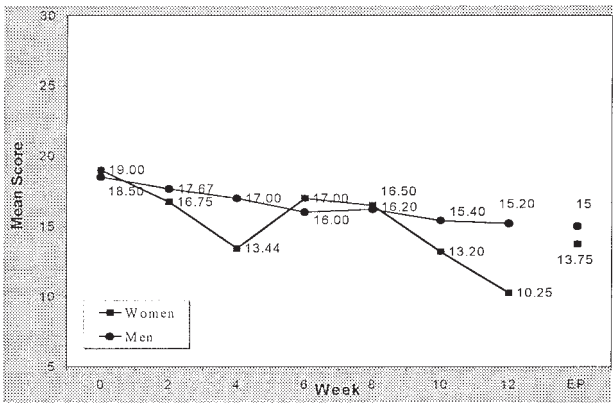
Because of the substantial number of women who dropped out before week six of the study, we split the female group into two post hoc groups (Fig. 5). Those leaving the study before six weeks, completing 2–3 visits (n = 6) were called the non-completer group, and those completing more than six weeks of the study (completing 4–7 visits, n = 6) were called the completer group. The non-completer group of six women, who dropped out at or before week six, had HAM-D and ASEX scores at endpoint that were comparable to the HAM-D and ASEX scores of the completer group (six women) at their endpoint. When the completer subgroup was plotted separately on a graph (Fig. 5), there was a gradual decline in ASEX, total, scores as well.

Two of the eighteen patients in the study experienced decreases in sexual desire or functioning while taking mirtazapine. One woman had slight decreases



Males (n)	7	6	5	5	5	5	5
Females (n)	18	13	9	6	6	4	4

Figure 1. Men vs. women, with number of study participants at each rating period, weeks 0–12.



Males (n)	7	6	5	5	5	5	5
Females (n)	18	12	9	6	6	4	4

Figure 2. Arizona Sexual Experiences Scale, men vs. women, weeks 0–12, and at study endpoint.

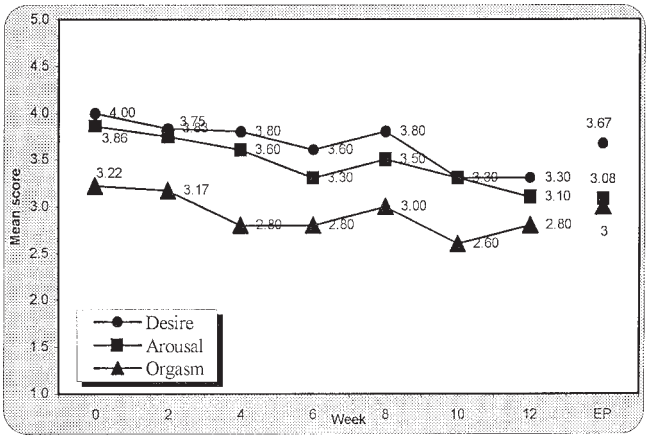


Figure 3. Arizona Sexual Experiences Subscales of desire, arousal (taking the mean of items 2 and 3) and orgasm (taking the mean of items 4 and 5) in the male sample.

in both drive and arousal (a two point total increase in her score from baseline through week 12). Shortly after week 12, she had discovered she was pregnant and discontinued the medication. The parameters were within the range of normal sexual functioning (below a total score of 14) at all times during the study. Another woman had an increase in all subscales in the range of sexual dysfunction, dropped out of the study after week 10 and was lost to follow-up. Her HAM-D scores dropped from 30 at baseline to 22 at week 8, but physical symptoms of drowsiness increased during the study and may have been an adverse effect affecting her sexual functioning.

Follow-up telephone calls were made to all subjects 4–8 weeks post study termination. Of the four women who completed the study, three were no longer taking mirtazapine but felt they were doing well without antidepressants regarding both depressive symptoms and sexual functioning. One of these three women had stopped mirtazapine due to pregnancy. The female subject who had continued taking mirtazapine felt she

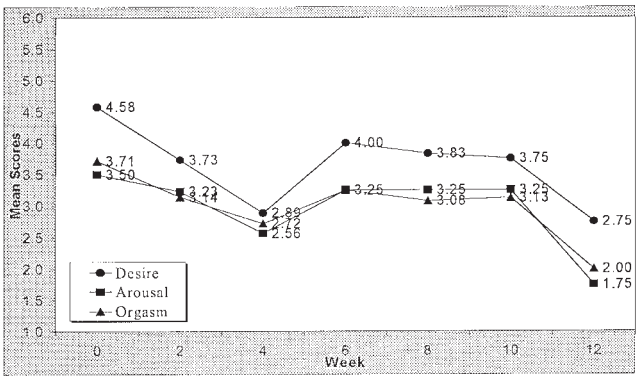


Figure 4. Arizona Sexual Experiences Subscales of desire, arousal (taking the mean of items 2 and 3) and orgasm (taking the mean of items 4 and 5) in the female sample.

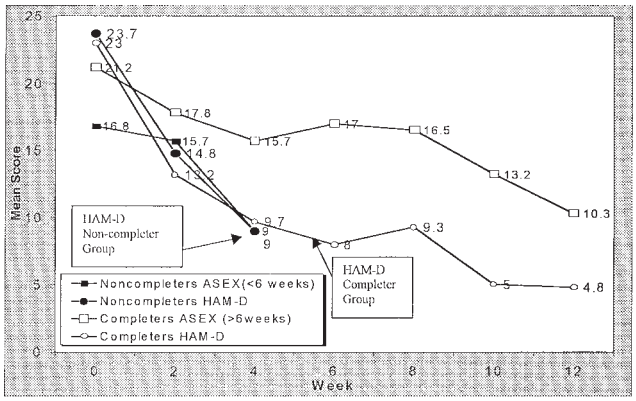


Figure 5. HAM-D and ASEX scores of women who ended the study before 6 weeks (n = 6) vs. women who ended the study after 6 weeks (n = 6).

was doing well, without depressive symptoms or sexual difficulty. Of the five men who completed the study, four continued on mirtazapine and one changed to paroxetine for unresolved depression.

DISCUSSION

Although this was an open-label pilot study, some conclusions can be drawn. Mirtazapine appeared to have a substantial beneficial effect on sexual functioning in depressed women and a modest beneficial effect in depressed men. ASEX scores showed general improvement in the non-completer and completer female subgroups as well as the male group. The sex difference in improvement from baseline scores was surprising. There was only a 10% change in the ASEX desire subscale in men, compared to a 40% change in women. There was twice the improvement from baseline in the ASEX orgasm subscale and three-fold improvement in the ASEX arousal subscale in women as compared to men.

Sexual desire, arousal, and functioning did not improve for two study females and appeared to be independent of remission of depression. If improvement had been secondary to remission of depression, one would expect that unresolved depression would be accompanied by unimproved sexual dysfunction. However, this did not appear to be the case. The two women who reported decreases in sexual functioning with resultant increases in ASEX scores had remission of depressive symptoms as well. Only one woman had an increase in HAM-D scores; her ASEX scores decreased during her visits, denoting improvement in sexual functioning.

We were intrigued by the substantial number of women who dropped out within six weeks of beginning the study. When we compared this subgroup (non-completers) to the subgroup that completed at least six weeks (completers), we were surprised to find few differences. Both subgroups had comparable re-

coveries from depression and sexual dysfunction as seen in decreases of HAM-D and ASEX ratings. We have no good explanation for this; little is known about post-depressive sexual response. Of the six women in the non-completer subgroup, telephone follow-up showed two left the study because they were markedly improved, two because of side effects (water retention and drowsiness), one because of decreased impulse control and one who was lost to follow-up. We speculated that the non-completer subgroup might have faster sexual response rates to either resolution of depression or mirtazapine and might have left the study when they had remission of both depression and sexual dysfunction, possibly secondary to drug side effects. A limitation of this study included the high dropout rate among the women.

CONCLUSIONS

Further research is needed to determine whether mirtazapine itself improves sexual functioning in depression and whether the gender difference is replicated, or whether it simply does no harm to sexual functioning during the resolution of depression. Testing the drug on a non-depressed population would help differentiate positive drug effect from resolution of depression and its accompanying symptoms of sexual dysfunction. If an increase in sexual functioning is found to be a property of the drug itself, it may be added to medications causing sexual dysfunction, i.e., SSRI's, mood stabilizers, antihypertensive agents, and anti-ulcer agents. The drug might prove useful as adjuvant therapy for illnesses resulting in erectile dysfunction and anorgasmia due to functional, diabetic, or cardiac causes. Long-term, double-blind, placebo-controlled research assessing sexual function in patients taking mirtazapine as well as comparisons with patients taking other antidepressants is recommended.

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