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Mirtazapine augmentation in depressed patients with sexual dysfunction due to selective serotonin reuptake inhibitors

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Objective To evaluate the effect of mirtazapine augmentation in patients with sexual dysfunction induced by current selective serotonin reuptake inhibitor (SSRI) treatment.
Methods Forty-nine outpatients in remission from major depressive disorder with SSRI treatment and experiencing treatment-emergent sexual dysfunction were invited to participate and 33 (25 women and 8 men) were included in this 8-week open-label study. All patients continued her/his current SSRI treatment (dosages unchanged) and started on mirtazapine augmentation of 15 mg/day during the first week and 30 mg/day throughout the rest of the study. The Hamilton rating scale for depression (HAM-D), the psychotropic-related sexual dysfunction questionnaire (PRSexDQ), and the Golombok and Rust Inventory of Sexual Satisfaction (GRISS) were given to all patients at baseline and at each follow-up (end of the first, second, fourth, sixth, and eight weeks).
Results Mirtazapine augmentation led to significant reductions in HAM-D, PRSexDQ, and GRISS scores throughout the study especially after week 4 and 48.5% of patients ($n = 16$) reported that they had no overall sexual dysfunction at the end of the study.
Conclusions Mirtazapine augmentation is a good choice for the treatment of SSRI-induced sexual dysfunction, and the results are typically seen later after 4–8 weeks. Copyright © 2008 John Wiley & Sons, Ltd.

KEY WORDS — sexual dysfunction; mirtazapine; depression

INTRODUCTION

Sexual dysfunction associated with selective serotonin reuptake inhibitors (SSRIs) has gained more recognition with the extensive use of those agents for the treatment of major depressive disorder. Sexual dysfunction is a common side effect of SSRIs (Steffens *et al*., 1997) and may be present during the course of the treatment. According to DSM-IV-TR, the symptoms develop either within 1 month of medication use, or the use of the medication is etiologically related to the disturbance. In those patients suffering from both major depressive disorder and sexual dysfunction, it is difficult to determine the degree of contribution of the antidepressive agents to or the duration of sexual dysfunction, because of the bidirectional etiological relationship (Werneke *et al*., 2006) between those two disturbances.

Although the estimated prevalence of sexual dysfunction in the first 3 months of treatment with an SSRI or SNRI ranges between 26.6 and 39.2% by using an algorithm (Williams *et al*., 2006), the incidence of SSRI-associated sexual dysfunction in patients can be as high as 73% (Montejo *et al*., 2001) and varies by antidepressant (Montgomery *et al*., 2002). Those incidences are reported as 24–58% for fluoxetine (Clayton *et al*., 2002; Montejo *et al*., 2001), 18–62% for fluvoxamine (Montejo *et al*., 2001; Montgomery *et al*., 2002), 27–63% for sertraline (Clayton *et al*., 2002; Montejo *et al*., 2001), 30–73% for citalopram (Clayton *et al*., 2002; Montejo *et al*., 2001), 9–34% for escitalopram (Clayton *et al*., 2006; Hirschfeld and Vornik, 2004), and 27–71% for paroxetine (Clayton *et al*., 2002; Montejo *et al*., 2001).

It is suggested that sexual dysfunction may contribute to patient noncompliance and this is

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important especially for the maintenance treatment of major depressive disorder (Bolling and Kohlenberg, 2004; Hirschfeld, 1999; Werneke *et al*., 2006). Quality of life is an important issue and includes sexual functioning (Williams *et al*., 2006) and concern about antidepressant-induced sexual dysfunction has continued to grow; however, the mechanism of action of sexual dysfunction associated with SSRIs is not well understood (Saiz-Ruiz *et al*., 2005). Studies examining the pharmacologic treatment for SSRI-induced sexual dysfunction are limited, although there are more studies of switching to different agents than augmentation. Several drugs with different mechanisms have been used to restore such symptoms. Those agents have effects on dopaminergic (Masand *et al*., 2001), serotonergic (Landen *et al*., 1999), noradrenergic (Hollander and McCarley, 1992) or both noradrenergic and specific serotonergic (Koutouvidis *et al*., 1999) receptors, or local effects on blood flow in the genitals (Nurnberg *et al*., 1999). Mirtazapine blocks postsynaptic 5-HT2 and 5-HT3 receptors and has an antagonistic effect on presynaptic α-2 adrenergic autoreceptors and heteroreceptors (Saiz-Ruiz *et al*., 2005; Stimmel *et al*., 1997). The antagonist effects at 5HT and 5HT3 receptors may enhance libido (Mendelson, 1992) and antagonism of α2-adrenoceptors may enhance erectile function (Munoz *et al*., 1994). Since mirtazapine, with the above pharmacological profile, has minimal cardiovascular and anticholinergic effects, and essentially lacks serotonergic effects such as gastrointestinal symptoms, insomnia, and sexual dysfunction (Stimmel *et al*., 1997), it may be an effective antidepressant for patients suffering from SSRI-induced sexual dysfunction (Gelenberg *et al*., 2000). Consequently, in this study, it was aimed to analyze the effect of mirtazapine augmentation in patients who had a remission from an episode of major depressive disorder and suffered from sexual dysfunction induced by current SSRI treatment.

METHOD

Subjects

This open-label pilot study consisted of outpatients who had achieved a remission from an episode of DSM-IV major depressive disorder during treatment with different SSRIs and experienced treatment-emergent sexual dysfunction. All of the participants were from the follow-up program of Mood Disorders Unit in Department of Psychiatry of Gülhane School of Medicine, in Ankara, Turkey. The ethics committee of Gülhane School of Medicine approved the study protocol, and written consent from all study participants was obtained. The inclusion criteria were (a) being between 18 and 60 years of age, (b) having no medical/psychiatric conditions other than major depressive disorder with SSRI-associated sexual dysfunction, (c) using no medications or substance use other than SSRIs, (d) no sexual dysfunction prior to the SSRI treatment, (e) being in remission from an episode of major depressive disorder and also having a score of <14 on 17 item Hamilton rating scale for depression (HAM-D) which was the threshold for the depression severity of mild or normal (Hamilton, 2000) at initiation of study, and (f) being not pregnant (for women).

Measurements

Turkish version of HAM-D (Akdemir *et al*., 1996; Hamilton, 1960) was used to assess the degree of depression at intake and at other assessment points of the study. Sexual functioning was evaluated by the psychotropic-related sexual dysfunction questionnaire (PRSexDQ) (Montejo *et al*., 2001) and the Turkish version of Golombok and Rust Inventory of Sexual Satisfaction (GRISS) (Rust and Golombok, 1986; Tuğrul *et al*., 1993).

The PRSexDQ detects clinical changes in sexual dysfunction and has two sections. In the first section, it has two ''yes/no'' questions without any score. The first question of this step is ''Have you observed any type of change in your sexual activity (excitation, erection, ejaculation, or orgasm) since you began receiving the drug treatment?'' This is used to determine whether she/he has sexual dysfunction associated with the current psychotropic medication or not. A ''yes'' answer to this question was accepted as an inclusion criterion. The second question inquires about the willingness of the patient in expressing her/his sexual dysfunction. In the second section there are five questions focusing on the five dimensions of sexual dysfunction: loss of libido, delayed orgasm or ejaculation, absence of orgasm or ejaculation, erectile dysfunction in men and vaginal lubrication dysfunction in women, and patient's tolerance of the sexual dysfunction. The first four questions are rated between 0 and 3, whereas the last one is rated between 0 and 2. Thus, there is a maximum score of 14 from the five questions.

The GRISS is a questionnaire that assesses the existence and severity of sexual problems. There are separate forms for men and women, each consisting of 28 items. The responses are scaled in a Likert format,

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from "0 = always" to "5 = never", and yield a total score and seven subscale scores. The subscales of sexual frequency, communication, satisfaction, avoidance, and sensuality are common for women and men. There are additional two subscales specific for each gender which are anorgasmia and vaginismus for women, erectile dysfunction and premature ejaculation for men. Higher scores indicate sexual dysfunction. Both total scores and the subscale scores are converted to a score from one to nine, and can be used separately. The converted scores of 1–4 reflect normal sexual functioning and scores of 5–9 indicate increasing levels of sexual dysfunction.

Procedure

The structured clinical interview for DSM-IV (SCID-I) was performed on each study participant to confirm the diagnosis of major depressive disorder by the rotating psychiatry specialists of mood disorders unit (the last seven authors of this article). The first three authors (KNO, TK, and AB) determined whether the patients fulfilled the inclusion criterion of the study and followed up the included patients according to the study design. Those prospective participants with major depressive disorder but not on antidepressant treatment, with overt suicidality and/or psychotic features, with dementia and any other axis 1 psychiatric disorders such as psychotic spectrum disorders, obsessive compulsive disorder were excluded.

All of the above measurements were applied to each eligible patient to record her/his baseline data of remission (severity of major depressive disorder) and level of sexual dysfunction. The patients' current SSRI treatment, without dosage change, was augmented with a mirtazapine treatment of 15 mg/day for 1 week. At the end of the first week, the mirtazapine dosage was increased to 30 mg/day after the measurements of depression and sexual dysfunction were applied to each patient again. Subsequent evaluations were repeated at the end of the weeks 2, 4, 6, and 8, while the mirtazapine dosage was constant at 30 mg/day. The end of week 8 was the study endpoint. All adverse events whether reported by patients or evaluated by the physician were recorded. Treatment compliance was determined through counting of the mirtazapine pills remaining in the box and questioning the patient and/or the family members of the patient. Patients who did not want to continue the study or who did not come to appointments were excluded and patients suffering from intolerable adverse effects of mirtazapine were dropped out.

Statistics

Descriptive statistics were performed to determine the mean and standard deviation (SD) of HAM-D, total PRSexDQ score, and total GRISS score of each follow-up for each gender and the entire sample. The repeated-measures analysis of variance was used for analyzing the changes in the HAM-D, PRSexDQ, and GRISS with time as a within-subject factor. The multiple comparisons including paired sample *t*-test between the baseline scores and each follow-up were conducted when there were significant differences in any of the variables. The level for statistical significance for all was set at $p < 0.05$.

RESULTS

Thirty-three (25 women and 8 men) of the original 49 (38 women and 11 men) study participants completed the study. Sixteen patients were excluded before completing 8 weeks of mirtazapine treatment. The reasons for drop-out were unwillingness to continue the study (16.33%) ($n = 8$) (six women and two men) because the financial cost of every week transportation would be high due to living in a rural area far from the treatment center, missing any appointment (8.16%) (four women), and unacceptable adverse events due to mirtazapine (8.16%) ($n = 4$) (two women for enhanced appetite and weight gain and two men for excessive sedation). Data for the remaining 33 subjects who completed the study were analyzed.

The distribution of antidepressants used by the patients at baseline and during the mirtazapine augmentation was 36.4% paroxetine ($n = 12$, mean $\pm$ SD dose $= 20.0 \pm 0.0$), 27.3% sertraline ($n = 9$, mean $\pm$ SD dose $= 72.2 \pm 50.7$), 21.2% citalopram ($n = 7$, mean $\pm$ SD dose $= 28.6 \pm 10.7$), and 15.1% fluoxetine ($n = 5$, mean $\pm$ SD dose $= 32.0 \pm 10.9$). The age range of the study sample was 28–60 years with a mean of 39.67 ± 9.29 and the women (37.52 ± 8.45) were significantly younger than the men (46.38 ± 9.04) ($p = 0.016$). The results and differences of baseline and the study endpoint (week 8) for HAM-D, PRSexDQ, and GRISS as mean and SDs are listed in Table 1.

According to the HAM-D scores, all 33 patients maintained their remission from depression during the study and there was no significant gender difference at either baseline or study endpoint. The HAM-D score of week 8 was significantly lower than that of the baseline score for the whole sample and for the women

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Table 1. The mean scores of HAM-D, PRSexDQ, and GRISS at baseline and study endpoint

	Whole sample ($n=33$)		Women ($n=25$)		Men ($n=8$)		
	Mean ± SD	*p	Mean ± SD	*p	Mean ± SD	*p	**p
HAM-D							
Baseline	5.73 ± 3.07	0.04	5.68 ± 2.98	0.03	5.88 ± 3.56	0.433	0.879
Week-8	4.52 ± 1.97		4.28 ± 1.62		5.25 ± 2.82		0.231
PRSexDQ							
Baseline	9.91 ± 2.27	0.000	9.72 ± 2.15	0.000	10.50 ± 2.67	0.000	0.406
Week-8	5.82 ± 3.18		5.92 ± 3.17		5.50 ± 3.38		0.470
GRISS							
Baseline	46.69 ± 12.11	0.000	48.76 ± 12.69	0.000	40.25 ± 7.49	0.000	0.084
Week-8	34.82 ± 15.87		34.36 ± 17.05		36.25 ± 12.29		0.775

*Paired *t*-test for baseline and week-8.
**Student's *t*-test between genders.

(but not for the men) with paired sample *t*-test (Table 1).

There was not a significant gender difference in total PRSexDQ and GRISS scores at either baseline or study endpoint. Mirtazapine augmentation led to a significant reduction in total PRSexDQ and GRISS scores of both women and men from baseline to study endpoint (Table 1). The reduction in both sexual dysfunction scores of the whole sample also continued throughout the study (Table 2). Although PRSexDQ detected an improvement of sexual dysfunction at the end of the first week but GRISS did not, both PRSexDQ and GRISS detected improvements at each of the following weeks (Table 2). As shown in Table 2, compared to the baseline values, PRSexDQ and GRISS scores decreased significantly at each follow-up and the number of patients having improvement in sexual functioning with mirtazapine augmentation increased throughout the study (Table 2). The transformed total score for GRISS less than 5 was accepted as satisfactory improvement in sexual functioning. In addition, the answers ''well'' or ''fair'' to the question number seven concerning the patient's tolerance of the sexual dysfunction were accepted as satisfactory improvement if the patient had total score less than 6 in PRSexDQ.

According to the above criteria, none of the patients had normal sexual functioning at the end of first week with mirtazapine augmentation. Only two patients reported normal sexual functioning at the end of the second week, and an additional one patient at the end of fourth week. Fourteen patients (42.4% of all) in

Table 2. The reduction in sexual dysfunction measured by PRSexDQ and GRISS and as the number of patients throughout the study

	PRSexDQ		GRISS		The number of patients having improvement in sexual functioning	
	Mean ± SD	**p	Mean ± SD	**p	No	Yes
Baseline	9.91 ± 2.27	—	46.69 ± 12.11	—	—	—
Week-1	9.61 ± 2.22	0.016	46.09 ± 11.67	0.375	33	0
Week-2	8.97 ± 2.59	0.001	42.82 ± 13.94	0.001	31	2
Week-4	8.09 ± 2.74	0.000	38.73 ± 16.09	0.000	30	3
Week-6	6.64 ± 3.57	0.000	36.03 ± 16.77	0.000	19	14
Week-8	5.82 ± 3.18	0.000	34.82 ± 15.89	0.000	17	16
*p	0.000		0.000			

No = no improvement.
Yes = improvement in sexual functioning.
*Repeated-measures analysis of variance.
**Paired sample *t*-test for baseline and each week.

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week 6, and 16 patients (48.5%) at the end of study reported that they had no overall sexual dysfunction (Table 2). Twelve (48.0%) of 25 women and 4 (50.0%) of 8 men reported normal sexual functioning at the end of the study with no gender differences ($\chi^2 = 0.088$ and $p = 0.767$).

DISCUSSION

This open-label pilot study suggests that for outpatients who have a remission from an episode of DSM-IV major depressive disorder during treatment with different SSRIs but experiencing treatment-emergent sexual dysfunction, mirtazapine augmentation may be helpful in alleviating sexual dysfunction while continuing remission of depression and prescribed antidepressant treatment.

Mirtazapine augmentation caused a relatively late response in sexual functioning and none of the patients reported improvement in their sexual dysfunction until the end of first week. Only two patients (6.1%) reported at the end of second week that their sexual functioning was better than that before adding mirtazapine. This number was seven-fold ($n = 14$, 42.4%) and eight-fold ($n = 16$, 48.5%) at the end of weeks 6 and 8, respectively. The improvement of sexual functioning was detected by the scales of PRSexDQ and GRISS from week 4 to weeks 6 and 8.

The beginning of the response in sexual functioning mainly after week 4 was similar to the therapeutic lag time seen by antidepressant effect. Although it might be related to up and downregulation processes as in antidepressant response, the reason why the onset occurred so late was not obvious. This was in accordance with the hypothesis suggesting that the downregulation of hypersensitive 5-HT2 heteroreceptors on dopaminergic neurons intersects with the onset of antidepressant effect (Landen and Thase, 2006). On the other hand, why two patients did respond at the end of the second week remained another question and this issue might be evaluated in future studies in which receptor binding and occupation would be included.

The present study supports the affirmative effect of mirtazapine augmentation on patients suffering from both major depressive disorder and SSRI-induced sexual dysfunction. The response period for patients with SSRI-induced sexual dysfunction to mirtazapine treatment differs in various studies although it is generally described as useful. A male patient suffering from SSRI-induced sexual dysfunction was reported as having restoration in sexual functioning after switching to and receiving 8 days of mirtazapine treatment (Barkin *et al*., 1999). In a mirtazapine switching study, Gelenberg *et al.* (2000) showed that 11 (58%) out of 19 patients experienced a return of normal sexual functioning after 6 weeks of mirtazapine treatment. Another switching study suggested that mirtazapine led to a reduction in the mean total PRSexDQ score from day 30, achieving statistical significance on days 90 and 180 (Saiz-Ruiz *et al*., 2005). However, it was noted that augmentation with mirtazapine was not different from placebo in ameliorating the SSRI-induced sexual dysfunction of premenopausal women (Michelson *et al*., 2002). Those differences may arise from either study design or study population and make it difficult to find a consensus (Werneke *et al*., 2006). Discontinuing current treatment and switching it with mirtazapine after a washout period of 1–2 weeks, and using mirtazapine as an augmentation agent without stopping current treatment are different designs. Discontinuing current treatment may cause recurrence of depressive symptoms, and washout period may prolong the response time. The patients without remission from depression or with a medical condition such as premenopausal state that causes sexual dysfunction may have prolonged or no response to treatment agents. Since the likelihood of development and perpetuation of sexual dysfunction is determined by the balance of serotonergic, noradrenergic, and dopaminergic properties of individual antidepressant agents (Werneke *et al*., 2006) and pharmacological reversal of antidepressant-induced sexual dysfunction includes antidote use, augmenting with mirtazapine that has dual mechanism of action is said to be preferred to achieve greater efficacy and avoidance of adverse effects (de la Gandara *et al*., 2005).

The selection/inclusion criterion of patients may be a limitation of our study. The patients of the study who were in remission from major depressive disorder might already have had less adverse treatment effects and easily responded to the mirtazapine augmentation. But, it is unlikely to accept it as selection bias because of the reduction in HAM-D scores after mirtazapine augmentation. Our data are limited also by the drop-out rate (16 out of 49 patients) and the absence of a placebo or comparator control, and cannot be generalized. On the other hand, we concluded from our results and those of others that the presence of sexual dysfunction should not be the reason for the patient to discontinue his/her treatment and mirtazapine augmentation might be considered a good choice of relief from SSRI-induced sexual dysfunction. Since the positive effect of mirtazapine generally arose after week 4, patients and their physicians should wait 4–8 weeks for response.

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