Trazodone for the Treatment of Sexual Dysfunction Induced by Serotonin Reuptake Inhibitors: A Preliminary Open-Label Study

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Introduction: Treatment with selective serotonin reuptake inhibitors (SSRIs) may lead to sexual dysfunction in up to 70% of patients. Because the SSRIs are widely used antidepressants, their propensity to cause sexual dysfunction may affect compliance with therapy and ultimately treatment success. To date, the pathophysiological mechanism of sexual dysfunction caused by SSRIs remains incompletely understood, and the management of SSRIs-induced sexual dysfunction remains unsatisfactory. We suggest that medications that antagonize serotonin receptors such as trazodone may improve sexual dysfunction reverting the stimulation of serotonin receptors by SSRIs.

Objective: The aim of this study was to investigate the efficacy of trazodone administration in the management of SSRI-induced sexual dysfunction.

Methods: Twenty patients (11 men/9 women) with SSRIs-induced sexual dysfunction were recruited for the study. Trazodone was added to the existing SSRI regimen in open-label fashion for 4 weeks (50 mg for the first week increased to 100 mg until the completion of the study). The improvement in the 4 dimensions of sexual function (desire, erection or lubrication problems in women, ejaculation or orgasm in women, and overall satisfaction by both sexes) was the primary outcome measure of the study.

Results: Fifteen subjects completed the study. Results indicated improvement in sexual function and overall clinical improvement (depression, anxiety) as well. Specific gender differences indicated improvement in erectile performance in men and lubrication in women. No correlations were noted between clinical improvement of depression or anxiety and improvement in sexual dysfunction.

Conclusions: The 5-HT2 antagonist, trazodone, may be beneficial in the management of SSRI-induced sexual dysfunction. Large-scale, placebo-controlled, double-blind studies with 5-HT2 antagonists are required to substantiate these preliminary observations.

Key Words: trazodone, SSRI, sexual dysfunction, 5-HT2, serotonin, antidepressants

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Selective serotonin reuptake inhibitor (SSRI) sexual dysfunction (SD) is common side effect occurring in as many as 70% of patients. Because trazodone (TRZ) produces priapism as a side effect, we report here a trial of the addition of TRZ to the SSRI on SD.[1–4] Because the SSRIs are widely used antidepressants, their propensity to cause SD may affect compliance with therapy and ultimately treatment success. To date, the pathophysiological mechanism of SD caused by SSRIs remains incompletely understood,[4] and the management of SSRI-induced SD remains unsatisfactory. This is despite considerable advances in the pharmacological treatment of erectile dysfunction including the use of medications such as sildenafil, an inhibitor of cyclic Guanosine monophosphate-specific phosphodiesterase type V, and apomorphine, a centrally acting dopaminergic agent.[5]

Trazodone is an effective triazolopyridine antidepressant with a low incidence ofserious adverse effects. It may be particularly useful in depressed patients who are intolerant of anticholinergic effects of other antidepressants and who have cardiac conduction disturbances.[6,7]

Trazodone has been used in the treatment of erectile dysfunction not caused by antidepressants with mixed results.[8–13] Large-scale studies exploring TRZ efficacy in ameliorating SSRI-induced SD have not be conducted yet. The aim of the present study was to examine the beneficial effect of TRZ in SD induced by SSRIs, albeit in a preliminary open-label treatment trial.

METHODS

Study Population and Admission Criteria

Subjects were recruited from the outpatient clinics of Beer Yaakov Mental Health Center. For study inclusion, patients were required to be in the age range of 18 to 60 years treated with SSRIs regardless of primary diagnosis for at least 4 weeks (at least 20 mg/d of paroxetine, fluoxetine, or citalopram or at least 50 mg of fluvoxamine or sertraline). All subjects were required to be demonstrating SD induced or worsened by SSRIs. A clinical interview for the recruitment of patients was performed to detect SD because most patients do not report this problem spontaneously.

Sexual dysfunction was considered in the primary interview when one or more of the following 4 dimensions of SD were reported by the patient: desire, erection or lubrication problems in women, ejaculation or orgasm in women, and overall satisfaction by both sexes.[14] Excluded were patients who had significant systemic disease such as hypertension, diabetes mellitus, or neurologic disorder (dementia, parkinsonism, or multiple sclerosis) that could affect compliance or cause SD per se. Patients who demonstrated any psychotic disorder or substance abuse were also excluded. The study was approved by the local hospital institutional review board. All subjects signed an informed consent to participate in the study after a full explanation of the nature of the study and the possible side effects of TRZ, including priapism (an uncommon,

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however, potentially serious side effect of TRZ), sedation, and hypotension.

Study Design

This study was an open-label trial of 4-week duration in which TRZ was added to an existing SSRI regimen. Trazodone was added to the SSRI at a dose of 50 mg/d before bedtime for the first 7 days and increased to 100 mg/d for the following 3 weeks. In the event of poor tolerance to the TRZ dose of 100 mg/d, the dose was decreased to 50 mg/d until the completion of the study. Outcome measures were performed at baseline and at the completion of the study and included the Valevski-Weizman (V.W.) SD rating scale (severity rated on a scale of 1–4, with 1 indicating least function and 4 best function), which includes 4 dimensions of SD: desire, erection or lubrication problems in women, ejaculation or orgasm in women, and overall satisfaction by both sexes[14]; the Hamilton rating scale for depression (HAM-D)[15]; the Hamilton rating scale for anxiety (HAM-A)[16]; and the Yale Brown Obsession Compulsion Scale (Y-BOCS).[17] Assessments of side effects and pill counting were performed once a week to assess safety and study medication compliance, respectively.

Statistical Analysis

Statistical analysis of results used 2-tailed paired *t* test.

RESULTS

Sample Population

Twenty patients were recruited for the study (11 men/9 women), with 15 patients (9 men/6 women) completing the 4-week trial (mean age = 44.6 ± 8.98 years, range = 28–59 years). Five patients discontinued the study due to side effects (sedation and headache). Although primary diagnosis was not an entrance criterion, patients had either a diagnosis of major depression (n = 6) (at study inclusion, patients suffered from mild depression), anxiety disorder (n = 8), adjustment disorder (n = 4), or somatization disorder.

Clinical Outcome

A significant improvement was observed in the completers in all subscales of the V.W. SD rating scale, more specifically, desire: improvement from baseline (1.13 ± 0.51) to study completion 3.86 ± 0.74 ($P < 0.0001$, $df = 14.0$, $t = -12$); erection/lubrication: improvement from baseline 1.86 ± 0.83 to study completion 3.73 ± 1.03 ($P < 0.001$, $df = 14.0$, $t = -4.8$); ejaculation/orgasm: improvement from baseline 1.67 ± 0.72 to study completion 3.93 ± 0.88 ($P < 0.001$, $df = 14.0$, $t = -7.2$); and overall satisfaction: improvement from baseline 1.53 ± 0.74 compared to study completion 3.93 ± 1.22. ($P < 0.001$, $df = 14.0$, $t = -8.3$). No significant difference was obtained in the magnitude of improvement between women and men as assessed by the total V.W. SD rating scale ($P = 0.2323$, nonsignificant).

There was a significant reduction in HAM-D scores from baseline 9.53 ± 5.16 (mild depression) to study completion 4.2 ± 3.54 ($P < 0.001$, $df = 14$, $t = 4.30$). Similarly, a significant reduction was noted in HAM-A scores from baseline 14.13 ± 7.23 to study completion 7.0 ± 6.08 ($P < 0.001$, $df = 14$, $t = 4.31$). No statistical significant change in Y-BOCS scores was noted during the course of the study ($P = 0.126$).

Clinical Correlations

No significant correlations were noted between changes of HAM-D, HAM-A, or Y-BOCS scores and the change of overall V.W. SD rating scale at baseline or at study completion.

DISCUSSION

Our findings in this preliminary study suggest that TRZ may improve all domains of SD associated with SSRI treatment. The lack of correlation between sexual function improvement and any of the clinical rating scale scores (for depression, anxiety, or obsessions) suggests independent effect of TRZ on SD induced by the SSRIs, rather than nonspecific beneficial effect on clinical parameters. Sexual function improvement thus seemed to be achieved regardless of improvement in depressive or anxiety symptomatology.

Trazodone blocks the postsynaptic 5-HT2A/2C receptors and presynaptic alpha-2 autoreceptors and heteroreceptors enhancing the neurotransmission of both serotonin and noradrenaline. Trazodone also inhibits the alpha-1 postsynaptic receptor, and this effect probably accounts for some of its adverse effects including priapism, postural hypotension, and sedation. It has been suggested that the effect of TRZ on penile erection may be due to peripheral adrenoreceptor antagonism as well as due to a central mechanism of unknown nature.[6,7,18] In a fairly recent meta-analysis of 6 treatment trials with TRZ for erectile dysfunction, Fink et al[19] proposed that TRZ may be beneficial in men with erectile dysfunction, possibly more so at higher doses, and in men with psychogenic erectile dysfunction.

Interestingly, despite a lack of firm evidence indicating the efficacy of TRZ in the management of SSRI-induced SD, in a survey of more than 300 psychiatrists, 78% chose adding TRZ as an option in the management of this condition. This is despite a majority of the clinicians opting to switch antidepressants as the best option rather than adding a specific medication to the existing SSRI such as TRZ.[20] In this preliminary pilot study, we thus suggest that TRZ may be a useful and effective augmentation for the treatment of SSRI-induced SD.

Although conclusions from the study are most certainly limited by small sample size and the lack of a double-blind placebo-controlled design, observations from such a preliminary pilot study may serve as a springboard for larger placebo-controlled trials.

In conclusion, we provide evidence, to our knowledge for the first time in the context of a preliminary study, of the efficacy of TRZ in the management of SSRI-induced SD. Although conclusions that may be generalized from the observations are somewhat restricted due to the nature of the study design, results are most certainly encouraging. Thus, although TRZ at this stage cannot be definitively be recommended for the management of this distressing condition, it may become an option in treatment-resistant cases. Future investigation should be recommended in the context of a larger scale, double-blind, placebo-controlled trials.

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