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Antidepressant-induced sexual dysfunction during treatment with fluoxetine, sertraline and trazodone; a randomized controlled trial☆

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ABSTRACT

Background: Selective serotonin reuptake inhibitors (SSRIs) are common treatments for patients with major depressive disorder (MDD). However, adverse effects of SSRIs on sexual function are common in the treatment of patients with MDD. There is a discrepancy in the reported frequency of SSRI-induced sexual dysfunction. On the other hand, there is also less evidence about sexual dysfunction with serotonin receptor antagonists and reuptake inhibitors (SARIs). Therefore, we aimed to assess sexual dysfunction in MDD patients who received fluoxetine, sertraline and trazodone.

Method: In a single-blind, randomized, controlled trial in Kermanshah, Iran, during 2009–2010, 195 patients who met the DSMIV-IR criteria for MDD were enrolled. The patients completed the Hamilton Depression Rating Scale (HAM-D) and the sexual function questionnaire (SFQ). Eligible patients were allocated in three treatment groups (receiving fluoxetine, sertraline or trazodone) for 14 weeks randomly. Measurement of HAMD was repeated in 4-week interval. Analysis for comparing sexual dysfunction among three groups and men and women was performed.

Results: There were 102 men and 93 women in the three groups receiving fluoxetine ($n=64$), sertraline ($n=67$) and trazodone ($n=64$). There was no significant difference in the sexual dysfunction of the patients in the three groups at baseline ($P>.05$). After treatment, both men and women who had received fluoxetine had the most impairment in desire/drive items (43%–51% and 44%–50%, respectively), while patients receiving trazodone had the least impairment in these items (12%–18% and 23%–24%, respectively). Trazodone was also induced with a lower rate of impairment in arousal/orgasm items in men (9%–15%) compared with the other two drugs. Compared with fluoxetine and trazodone, sertraline was associated with intermediate impairment in sexual function (39%–42% in desire/drive items and 32%–39% in arousal/orgasm items) that was lower than that with fluoxetine and more than that with trazodone.

Conclusion: There were different rates of sexual dysfunction with different antidepressants drugs in under treated patients. Compared with fluoxetine, and sertraline, trazodone was associated with the fewest sexual dysfunction. Fluoxetine was also associated with more sexual dysfunction than sertraline. Further research to better identify the differences among antidepressant drugs is recommended.

1. Background

Depression is a health problem worldwide. Major depressive disorder (MDD) is among the disabling psychiatric disorders that can affect one out of every five individuals and 16% of adults in different points in life [1,2]. Because of the costs of adverse effect of depression on patients, their families, work places and communities, it is also considered as the fourth most important cause of loss of disability-adjusted life years worldwide [3]. Therefore, several treatment strategies including pharmacotherapy, psychotherapy and their combination have been recommended for the management of patients with MDDs [4].

Among antidepressant drugs, selective serotonin reuptake inhibitors (SSRIs) are very commonly prescribed medications for these patients. Due to comparable efficacy, simpler titration, better tolerability and greater safety in event of overdose, they have replaced the older generation of antidepressant agents [5,6].

However, there are several reports of induced sexual dysfunction as an important adverse side effect of SSRIs that leads to the discontinuation of treatment. Accordingly, SSRIs can negatively affect the sexual response cycle causing decrease in libido, impaired arousal, erectile dysfunction and absent or delayed orgasm. These dysfunctions result in marked interpersonal difficulties [6–11]. Prevalence rates of up to 80% of SSRI-induced dysfunction have been reported, but the frequency and differences between different SSRIs are unknown [11]. Therefore,

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discontinuation of treatment is common in patients who experienced sexual dysfunction induced by SSRIs [6].

On the other hand, trazodone, a triazolopyridine derivative, is an FDA-approved drug marketed worldwide. It belongs to the class of serotonin receptor antagonists and reuptake inhibitors (SARIs) and has comparative efficacy with other classes of antidepressant for treatment of MDDs [12]. Lower rate of induced sexual dysfunction in comparison with other antidepressants including SSRIs is another advantage of trazodone [12]. There are also some case reports on enhanced sexual desire induced by trazodone [13]. It can be said that trazodone can be considered as an effective antidepressant with a lower rate of induced sexual dysfunction.

It should be remembered that although bupropion, an atypical antidepressant, may be associated with a lower rate of sexual dysfunction, due to some reasons, we did not include it in our trial. Bupropion has been considered as a weak norepinephrine–dopamine reuptake inhibitor, while trazodone is a weak serotonin reuptake inhibitor. Therefore, trazodone is the appropriate one to compare SSRI drugs that directly act on serotonin reuptake. On the other hand, it is often added to SSRIs to complete their effect in nonresponse cases and reduce their sexual side effect in nondepressed patients [13]. Therefore, we designed our trial to compare induced sexual dysfunction of two SSRI drugs with trazodone.

In Iran, there is little evidence of sexual dysfunction in depressed patients who are treated with SSRIs [12,14]. They have mainly focused on the efficacy of saffron (*Crocus sativus* L.) on SSRI-associated sexual dysfunction in both depressed men and women. Since MDD treatment and related problems are important issues in any community, studying antidepressant drugs in our country is necessary. Based on the above-mentioned evidence, we hypothesized that prevalence of induced sexual dysfunction by SSRIs is more than that of trazodone, which implies a difference among SSRI drugs (fluoxetine, sertraline) in this regard. We aimed to compare the effects of fluoxetine, sertraline and trazodone on sexual function in patients with MDDs in Kermanshah, Iran (2010).

2. Methods

2.1. Trial design

This was a randomized, single-blind, controlled trial conducted in the outpatient clinic of a psychiatry hospital in Kermanshah, Iran (registration number: IRCT138810281522N3, www.irct.ir/searchresult.php?id=1522&number=3).

2.2. Patients

We enrolled the patients who met the DSMIV-IR criteria for major depressive disorders and scored a minimum of 16 in the Hamilton Depression Rating Scale (HAM-D) in the study. They were MDD patients with no psychotic features that had no physical disorders such as diabetes, hypertension, dyslipidemia, ischemic heart disease, other psychiatric disorders, and suicidal and homicidal ideations. Both menopause and pregnant women were also excluded. They also did not take antidepressant drugs during the 5 weeks prior to the study. We considered the protocol for recurrent MDD patients and did not confront any problem in these patients.

2.3. Setting

The study was conducted in Kermanshah, the capital city of Kermanshah province in western Iran. There is a psychiatry hospital in Kermanshah called Farbi Hospital. It is an educational hospital affiliated to Kermanshah University of medical sciences (KUMS). The outpatient clinic of Farabi Hospital is the main center for visiting psychiatric patients. There is a regular schedule for visiting patients in this clinic.

2.4. Procedures

After the study design was established and approved by the Ethics Committee of KUMS, a psychiatrist interviewed eligible patients according to DSMIV-IR. HAM-D was completed for each patient by another member of the research team. The sexual function questionnaire (SFQ) was completed by each patient. The patients were then allocated to three groups randomly and started on one of the drugs (fluoxetine, sertraline and trazodone). Patients were blind to the group that they were allocated in. Each patient was visited in 4-week intervals by a psychiatrist, while repeat measure of HAM-D was performed in 4-week intervals by the same member. Finally, SFQ was collected after 14 weeks (time 2). In addition to providing patients with complete information about procedure of the study, a member of the research team was responsible for calling patients to remind them of the timetable of the study. It should be noted that all the patients provided informed consent before being enrolled in the study.

2.5. Intervention

The patients were randomly assigned to three treatment groups (fluoxetine, sertraline and trazodone). We used the suggested doses of these drugs for MDD [13]; i.e., fluoxetine was started at 20 mg per day and adjusted upward (up to 40 mg), initial doses for sertraline was 50 mg per day that escalated to 200 mg in 4–7 days after treatment, and trazodone was started at 100 mg per day at bed time, with an increase in dose of 50 mg per day at 4- to 7-day intervals, depending on the sensitivity to side effects (therapeutic range of 150 to 300 mg within 2 to 4 weeks).

2.6. Measures

We used two measures in this study. The SFQ was used to assess sexual function of the patients before and after the intervention. It is a self-report questionnaire that assesses three domains of sexual function (desire, arousal and orgasm). It has two subscales: one subscale for assessing drive and desire, and another for assessing arousal and orgasm. The first subscale with four questions is identical for men and women, but the second subscale has five questions for men and three questions for women [14]. In this study, we considered score 1 for problems created or worsened by drugs and score 0 for continuation of preexisting problems and absence of problems. The psychometric properties of SFQ have been assessed in a sample of Iranian individuals [15]. As reported in this study, internal consistency (Cronbach's alpha coefficient was 0.70) and test–retest reliability (*R* values for Pearson correlation coefficient for individual domains were reported: 0.9 for arousal–orgasm domain, 0.85 for enjoyment–desire domain, 0.81 for pain domain, 0.96 for partner domain and 0.91 for unusual sex domain) were reasonable in the Persian version of SFQ. Advantages of measuring sexual function in both males and females, and documented psychometric properties of the questioner in an Iranian sample [15] made SFQ an appropriate measure for this study.

The other measure was HAM-D for assessing depression before and after of treatment. The HAM-D is a standard 21-item clinical test that evaluates depression. It is one of the most reliable scales in depression assessment. Scoring is done using the Likert method. We used the HAM-D as a gold standard of depression diagnosis in this study because of its acceptability for this application [16,17]. The cutoff point of 16 was considered in this study.