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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.

2.7. Sample size

Considering a confidence interval (CI) of 95% and power of 90%, the sample size was determined to be at least 190 patients. In this study, 64, 67 and 64 patients were allocated to trazodone, fluoxetine and sertraline therapy, respectively.

2.8. Randomization, allocation concealment and blinding

Patients who met the inclusion criteria were randomly assigned to three groups using computer-generated randomization. The psychiatrist who performed the professional interviews to assess MDD according to DSMIV-IR and the psychologist who assessed the patients with HAM-D and SFQ were blinded to the allocations of patients to groups. Fig. 1 shows the procedures of the study.

2.9. Statistical analysis

We used *t* test and one-way analysis of variance to determine mean differences for continued scores on the SFQ among and between groups. χ^2 analysis was used for dichotomous variables. Regression analyses were used to determine the correlation between response to treatment and sexual dysfunction.

3. Results

3.1. Patients and characteristics

One hundred ninety-five patients (102 men and 93 women) were enrolled into the study during 2009–2010. There were 64 patients in the trazodone group, 67 patients in the fluoxetine group and 64 patients in the sertraline group. No significance differences were found among the three groups with respect to age, duration of illness, number of previous episodes of illness and sex distribution in any group using one-way analysis of variance. Table 1 shows the demographic characteristics of the patients in the three groups. As illustrated in Fig. 1, after starting the study, 21, 11 and 12 patients dropped out of the trazodone, fluoxetine and sertraline groups, respectively.Dropped out patients have been divided into two groups. The first group was composed of patients who unilaterally discontinued their treatment and did not respond to any contact from research team, and we referred to them as lost to follow-up. The second group was composed of patients who responded to the

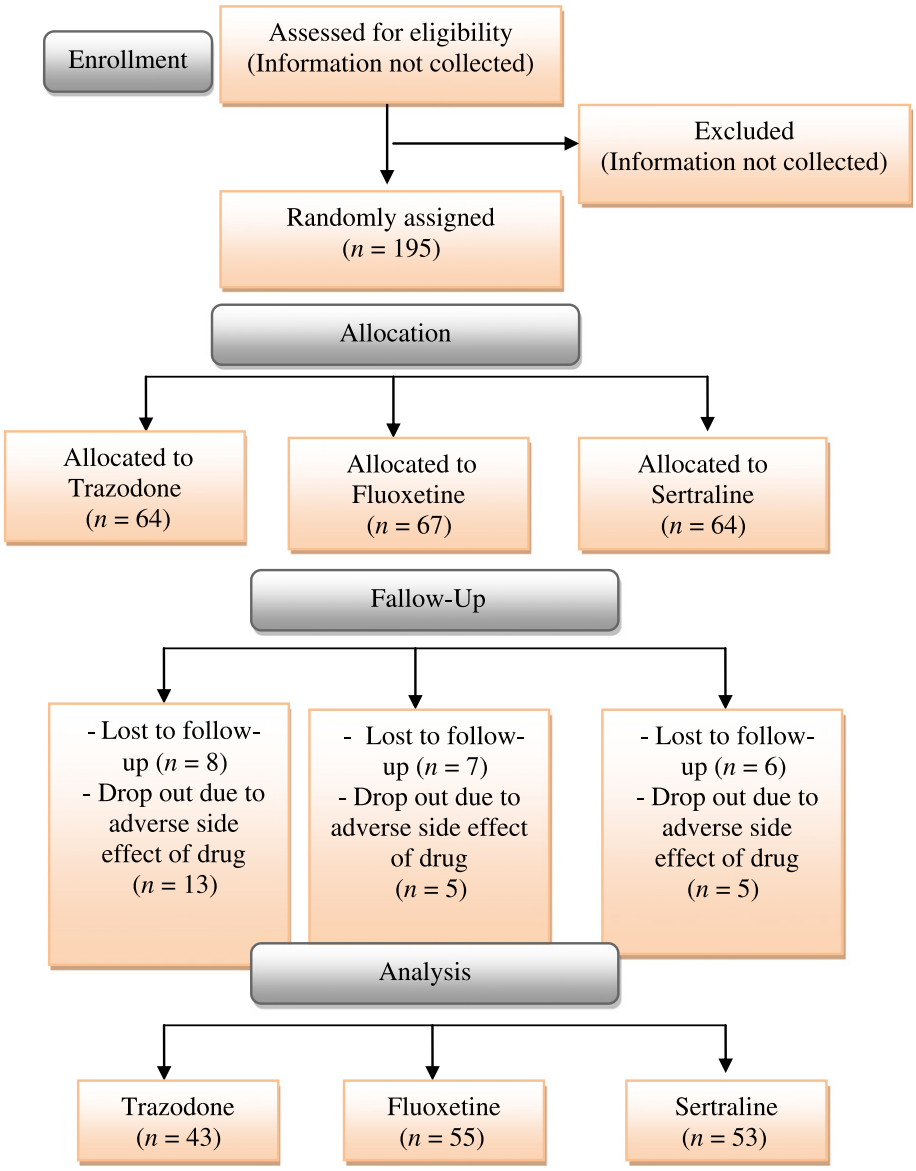

Fig. 1. Flow chart of trial.

Table 1
Demographic characteristics of patients in the trial

Variable	Trazodone	Fluoxetine	Sertraline	*P* value
Sex				.9
Men (%)	33%	34%	32%	
Women (%)	32%	34%	33%	
Age (mean±S.D.)	(38±12)	(37±11)	(38±11)	9
Duration of current episode (mean±S.D.)	2±3.6	2±3.6	2.1±38	.8
Previous episode (≥3)	11%	10%	9%	.99

research team member calling and stated that they want to discontinue their participation in the trial since they cannot tolerate the side effect of the prescribed drugs. We referred to this group as dropped out patients due to adverse side effect of drugs. Oversedation, headache, hypotension and agitation were among the common adverse side effects mentioned by these patients. Importantly, there were no complaints of sexual-dysfunction-related side effects in these patients; however, we could not assess them by SFQ,

Our results showed that there were no significant differences in items related to sexual dysfunction (desire/drive, arousal/orgasm) between the three groups before treatment ($P>.05$). However, after treatment, the rates seemed to be really high, although they were already significant before. Patients in the fluoxetine group had the highest impairment in desire/drive and arousal/orgasm items (43%–51% and 44%–50%, respectively; Table 2).

3.2. Gender differences

In the first set of our analysis, we addressed gender differences in sexual dysfunction. Accordingly, there was more dysfunction in desire-/drive-related items in women compared with men, while arousal dysfunction items were more prevalent in men than women. Fig. 2 shows antidepressant-associated sexual dysfunction percentage in women and men.

3.3. Antidepressant drug differences

Further analysis (second set) revealed that there were significant differences in sexual dysfunction items across different antidepressant drugs. Accordingly, significant differences were found in desire-/drive-related items in men ($P<.05$) so that trazodone was associated with minimum impairment (12%–18%) and fluoxetine was associated with maximum impairment (43%–51%). The related odds ratios compared to trazodone were 6.3 (95% CI: 2.5–15.5) and 4.5 (95% CI: 1.8–11.5) for fluoxetine and sertraline, respectively. In the sertraline group, impairment in desire-/drive-related items was more than that in the trazodone group and less than that in the fluoxetine group. On the other hand, in arousal-/orgasm-related items in men, minimum impairment (9%–15%) was found in the trazodone group ($P<.05$). However, premature ejaculation impairment was identical among three groups ($P>.05$, Table 3).

Impairment in desire-/drive-related items was more prevalent in women receiving fluoxetine (44%–50%) and less in those receiving trazodone (23%–24%).We found no significant differences in decrease of interest in the sexually explicit material item between the three groups ($P>.05$). Trazodone was associated with minimum impairment, and fluoxetine was associated with maximum impairment (Table 4). The related odds ratios compared to trazodone were 6.1 (95% CI: 3–14.5) and 5.3 (95% CI: 2.8–10.5) for fluoxetine and sertraline, respectively. Significant differences were also found in arousal-/orgasm-related items between the three groups. The frequency of impairment in these items was more in patients in the sertraline group than in the trazodone and fluoxetine groups (Table 4).

3.4. Response to antidepressant drugs and sexual dysfunction

In the last set of our analysis, response to drugs and sexual dysfunction were assessed. Using regression analysis, the association between posttrial sexual dysfunction in response to treatment, age, sex and pretrial sexual dysfunction was calculated. We found an association between sexual dysfunction before and after treatment, depicting that, after treatment, sexual dysfunction was affected ($P<.5$). There was no association between posttreatment sexual dysfunction and age and sex ($P>.5$). There was a significant association between decrease in sexual drive and decrease in interest in sexually explicit material and response to treatment; there was more impairment in these items in patients who were not responders to treatment. However, there were no relationships among other items and response to treatment.

There was no significant difference among the three antidepressant drugs on reduction of depression based on HAM-D score (Table 5). Score of 7 or less or reduction of 50% was considered as a basis for responsiveness to the drug.

4. Discussion

Comparing two classes of antidepressants (SSRIs and SARIs), our results showed that SSRI medications were associated with more sexual side effects. Accordingly, two SSRIS drugs of fluoxetine and sertraline were associated with more impairment in sexual dysfunction items in under treated patients, while trazodone was associated with improvement in these items. SSRI-induced sexual dysfunction has been reported in previous studies [6–11]. Sexual dysfunction is usually considered as a depression sign; however, causality role of depression in sexual dysfunction has not been ascertained, and there is also a bidirectional

Table 2
Distribution of SFQ1 items among three groups before and after treatment

Drugs	Trazodone			Fluoxetine			Sertraline		
SFQ1 items	Before trial (%)	After trial (%)	*P* value	Before trial (%)	After trial (%)	*P* value	Before trial (%)	After trial (%)	*P* value
Decrease in sexual drive	36.51	20.31	.001	31.34	50.75	.005	29.69	42.19	.006
Reduction in fantasizing about sex	35.94	20.31	.001	31.34	49.25	.914	31.25	45.31	.001
Decrease in interest in sexually explicit material	35.9	17.19	.005	29.85	43.28	.001	28.13	39.1	.005
Reduction in masturbation	35.94	17.19	.005	29.85	43.28	.001	28.13	39.06	.005
Less vigorous erections	35.29	21.88	.00	31.43	49.25	.001	33.3	40.63	.003
Fewer sustained erections	17.65	14.71	.00	17.14	45.7	.003	18.8	39.39	.001
Fewer spontaneous erections	20.59	14.71	.00	17.14	51.43	.009	15.5	42.42	.005
More frequent premature ejaculation	14.71	14.71	.00	17.14	45.71	.003	18.8	39.39	.001
More frequent delayed ejaculation	8.82	8.82	.00	11.43	57.14	.066	12.12	33.33	.003
Less sexual arousal	36.67	16.67	.02	28.13	50.00	.049	22.58	35.48	.02
Difficulty obtaining vaginal lubrication	20.0	13.33	.003	18.75	37.5	.102	16.13	22.58	.001
Difficulty achieving orgasm	30.00	16.67	.008	25.00	50.00	.10	22.58	32.26	.001

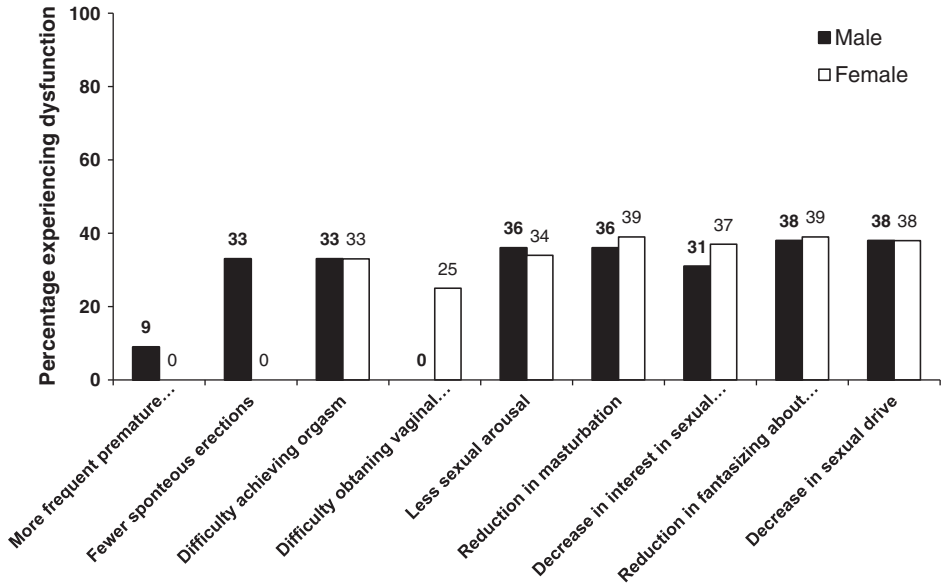

Fig. 2. Antidepressant-induced sexual dysfunction.

relationship between depression and sexual dysfunction. On the other hand, sexual dysfunction in depressed patient may be complicated by adverse sexual side effects of antidepressant drugs [18]. Role of antidepressant drugs in the genesis of sexual dysfunction has been explained by profile of their targeting receptors and so modulated neurotransmitters including serotonin, noradrenalin, dopamine, antihistamine and acetylcholine [19]. Accordingly, the physiology of SSRI-induced sexual dysfunction can be related to increased central serotonin. Serotonin may inhibit sexual desire, ejaculation and orgasm [13,20]. On the other hand, trazodone (a SARI drug) is a weak inhibitor of serotonin reuptake and potent antagonist of 5-HT2a and 5-HT2c receptors. By blocking 5-HT2a, trazodone may reduce likelihood of serotonin-induced sexual dysfunction [13,19]. The role of trazodone on improvement of SSRIs-induced sexual dysfunction [21], psychogenic erectile dysfunction [[22], and methadone induced erectile dysfunction [23] has been reported; however, there is evidence to support priapism genesis by trazodone [24]. In fact, it can be said that trazodone has a protective role against sexual dysfunction. However, the rate of dropouts due to the adverse side effects of trazodone, especially somnolence (10 of 13 dropped out patients), in our study is concerning and can restrict prescription of trazodone for MDD treatment. However, there is evidence to support the efficacy and tolerability of trazodone in MDD treatment [12].

On the other hand, the results suggest that two SSRI medications (fluoxetine and sertraline) had different profiles for producing sexual dysfunction. Patients in the fluoxetine group experienced more impairment in all items of SFQ than patients in the sertraline group. Although the finding is inconsistent with the report of Montego et al. [25], the different profiles should be explained in light of the mechanism of effects of these two drugs on different neurotransmitters. Blocking reuptake of dopamine in higher dose, sertraline may be associated with less sexual side effect [18]. In fact, less sexual side effect of sertraline is associated with its effect on increasing dopamine availability. In contrast with serotonin, dopamine enhances sexual function [13,19].

The differences in sexual dysfunction items between men and women are another finding of the study that should be noted. Our results showed that impairment in desire/drive items was more prevalent in women and impairment in orgasm/arousal items was more prevalent in men. The finding is consistent with the report of Farber and Smith [26], while Kennedy et al. reported that drive/desire impairment was more prevalent in men [27]. However, further research in this area is recommended.

Our results showed that there is an association between sexual dysfunction before and after treatment, i.e., worsening of sexual dysfunction items was more prevalent in patients with prior impairment in these items. The finding can be attributed to antidepressant effects on sexual dysfunction; however, decrease in sexual dysfunction during antidepressant therapy has been reported by Strohmaier et al. [28]. Finally, more impairment in sexual drive and decrease in interest in sexually explicit material were seen in patients who were not responders to treatment. Decrease in sexual drive and sexual interest has been considered as the common pattern of sexual dysfunction in depressed patients [18]; therefore, it can be said that, untreated depression and side effects of

Table 3
Antidepressant-induced sexual dysfunction in men

SFQ items	Trazodone	Fluoxetine	Sertraline	*P* value
	n (%)	*n* (%)	*n* (%)	
Decrease in sexual drive	6 (18)	18 (51)	12 (39)	.009
Reduction in fantasizing about sex	6 (18)	17 (49)	16 (48)	.01
Decrease in interest in sexual material	4 (12)	15 (43)	12 (36)	.013
Reduction in masturbation	6 (18)	17 (49)	14 (42)	.019
Less vigorous erections	5 (15)	18 (51)	14 (42)	.001
Fewer sustained erections	5 (15)	16 (46)	13 (39)	.016
Fewer spontaneous erections	5 (15)	16 (46)	13 (39)	.016
More frequent premature ejaculation	3 (9)	3 (9)	3 (9)	.99
More frequent delayed ejaculation	3 (9)	20 (54)	11 (33)	.0001

Table 4
Antidepressant-induced sexual dysfunction in women

SFQ items	Trazodone	Fluoxetine	Sertraline	*P* value
	n (%)	*n* (%)	*n* (%)	
Decrease in sexual drive	7 (23)	16 (50)	12 (39)	.095
Reduction in fantasizing about sex	7 (23)	16 (50)	13 (42)	.08
Decrease in interest in sexual material	7 (23)	14 (44)	13 (42)	.18
Reduction in masturbation	8 (24)	16 (50)	12 (39)	.16
Less sexual arousal	5 (27)	16 (50)	11 (35)	.02
Difficulty obtaining vaginal lubrication	4 (13)	12 (38)	7 (23)	.08
Difficulty achieving orgasm	5 (17)	16 (50)	10 (32)	.02

Table 5
Comparative efficacy of antidepressant drugs

Measure	Trazodone (n=6764)	Fluoxetine (n=67)	Sertraline (n=64)
HAM-D (before trial) Mean (±S.D.)	24.5 (3.9)	24.8 (3.9)	23.12 (4.1)
HAM-D (after trial) Mean (±S.D.)	7.3 (6.2)	7.17(5.7)	6.4 (5.4)
Responders[a] (%)	83	84	86

[a] Response was defined as a reduction of 50% and score of 7 or less on the HAM-D.

antidepressant drugs may have a cumulative effect on these sexual dysfunction items. However, further research in this area is recommended.

4.1. Strengths and limitations

As the first study addressing antidepressant-induced sexual dysfunction in Iran, the study should be seen in light of some strengths and limitations. The first strength was comparison of two classes of antidepressant medications (SSRIs with SARIs) and so two SSRI drugs (fluoxetine and sertraline) that could provide a profile of their efficacy in MDD treatment, adverse side effects and induced sexual dysfunction. Secondly, including both men and women in three trial groups could reveal sex-related differences of antidepressant-associated sexual dysfunction. Finally, the time frame of 14 weeks was relatively appropriate for the assessment of antidepressant-induced sexual dysfunction. However, our study had some limitations. Firstly, since SFQ is a self-report questionnaire, it may be prone to overestimation or underestimation that affects the results. Secondly, we could not assess the effects of sexual dysfunction on treatment discontinuation in the study period. Further research to overcome the limitations is recommended.

5. Conclusion and implications

In conclusion, antidepressant sexual dysfunction in MDD patients is an important issue that should not be overlooked. It can complicate preexisting sexual dysfunction and result in discontinuation of treatment. Therefore, clinicians should assess sexual dysfunction both before and after prescribing antidepressant drugs. It can be helpful to estimate drug-induced sexual dysfunction and to use appropriate strategies to manage it.

On the other hand, different classes of antidepressants may have different profiles of induced sexual dysfunction. Our study showed that while trazodone may have protective role against sexual dysfunction in MDD patients, SSRI drugs including fluoxetine and sertraline are associated with inducing significant sexual side effects. The results may be important from two aspects. Firstly, trazodone may be an appropriate treatment option for MDD patients if other side effects such as somnolence do not reduce its tolerability. In our study, dropout was more prevalent in the trazodone group. Secondly, since SSRIs are more commonly prescribed medications for MDD patients, careful assessment of the patients for adverse sexual side effect is necessary. Overall, all adverse side effects of drugs including sexual dysfunction and its management should be considered in therapeutic decision of prescribing of antidepressant drugs.

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