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Comparing the Efficacy of Bupropion and Amantadine on Sexual Dysfunction Induced by a Selective Serotonin Reuptake Inhibitor

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Abstract

Background: Antidepressant-induced sexual dysfunction (SD) is a common problem, associated with a significant risk of non-adherence. Selective Serotonin Reuptake Inhibitors (SSRIs) are associated with a substantial risk of SD. Only 10 % of patients show spontaneous improvement during follow up period.

Objectives: This study aimed to compare two proposed medication (bupropion vs. amantadine) in alleviating SD in patients treated with SSRIs.

Patients and Methods: In a randomized, single-blinded, clinical trial in Iran, 46 patients were recruited based on DSM-IV-TR criteria and semi-structured interview. Then, they were randomized into two treatment groups using table of random numbers. Eight patients were excluded and finally 38 patients completed the study which lasted for 4 weeks. Twenty patients were given bupropion, 18 patients were randomly assigned to another group, and given amantadine. Patients were assessed with the Arizona sexual experience scale (ASEX) at baseline and 4 weeks after the treatment.

Results: A total of 38 patients completed the study (18 patients in amantadine vs. 20 patients in bupropion).The mean ASEX scores gradually declined in both study groups during the trial. The reduction of ASEX score in bupropion group was more than that of amantadine group that was statistically significant. So, the addition of bupropion at higher doses appears to be more effective approach in comparison with amantadine.

Conclusions: These results provide empirical support for conducting a further study on comparing different add-on strategies for treating drug-induced SD.

Keywords: SSRIs, Sexual Dysfunction, Bupropion, Amantadine

1. Background

Selective serotonin reuptake inhibitors (SSRIs) are among the most commonly prescribed drugs for the treatment of major depressive disorder (1, 2). These drugs affect anxiety disorders such as panic disorder, post-traumatic stress disorder (PTSD), social phobia, and generalized anxiety disorder (3). Sexual dysfunction (SD) is one of the side effects of such drugs that can decrease drug compliance or even cause drug withdrawal (4, 5). Post-SSRI sexual dysfunction is a disorder that appears 2 months after taking antidepressants and does not appear at the beginning of treatment (6). This disorder can affect various sexual aspects such as desire, orgasm, and arousal; however, lack of or delay in orgasm is more common than decreased sexual desire as well as arousal difficulties (7). The prevalence of this disorder is observed among 40% - 45% of women and 20% - 30% of men taking serotonergic antidepressants (8-10). Continuing their treatment, only 10% of patients reported spontaneous improvement in their sexual dysfunction (6).

One of the strategies recommended to deal with this issue is SSRI combination therapies with another drug. The recommended drugs include yohimbine (11), amantadine (12, 13), cyproheptadine (14), bupropion (9, 15), nefazodone (16), buspirone (17), granisetron (16), and sildenafil (18). Bupropion is an antidepressant with neurotransmitter properties different from SSRI; it inhibits norepinephrine and dopamine reuptake (3). This drug can be used in reinforcing the effect of SSRI drugs or reducing drug side effects such as sexual side effects (8, 9).

Some studies indicate that adding high-dose bupropion is effective in reducing SSRI-induced sexual side effects, with greater effect on women (19-21). A comparison on the effect of bupropion on sexual dysfunction showed that bupropion XL had the greatest effect on most stages

of sexual arousal (22). Amantadine is also a dopamine agonist and glutamate receptor antagonist. Dopaminergic stimulation probably reinforces sexual response so that its continuous use increases sexual response without development of tolerance even in mice (23). A study by Devaangam et al. on mice showed that amantadine was not effective in reducing sexual side effects of SSRI, especially clomipramine (24). Human studies in this field are limited. However, a study by Balogh et al. shows that amantadine is effective in improvement of fluoxetine-induced sexual side effects (12).

2. Objectives

Despite various drugs recommended for reducing this side effect, no studies have been conducted on comparing these two drugs so far. Given the lack of empirical evidence on comparing therapeutic strategies in this regard and different results reported on the effects of each of these drugs alone, this study aimed to compare the effects of bupropion and amantadine on SD.

3. Patients and Methods

3.1. Trial Design

This randomized, single-blinded, clinical trial was performed in Tehran, Iran, during the winter 2013. Two matched groups of outpatients, treated with SSRIs for depression (in remission stage) for at least 8 weeks were included in this study. Diagnosis was made according to diagnostic and statistical manual of mental disorders, fourth edition, text revision (DSM-IV-TR) criteria and screened using the 17-item Hamilton rating scale for depression (HAMD-17) (25). Patients with score of ≤ 10 on the HAMD-17 (26) and SD, emerged during treatment with the SSRI, were enrolled. The research was done in outpatient psychiatric clinic of a general hospital in Tehran (Capital of Iran) from October 2009 to August 2010.

3.2. Participants

The patients were recruited based on DSM-IV-TR criteria and a semi-structured interview, performed by an expert psychiatrist. If a patient met inclusion criteria, he or she would be interviewed face-to-face, during which, purpose of the study was explained. To determine

the sample size, preliminary data were obtained. As there were no studies in the same topic, we used other relevant studies as guidelines. The quantitative dependent variables were determined according to the study of Michelson et al. (27). Therefore, a sample size of 46 patients consented for the study.

Patients were randomized to 2 treatment groups using table of random numbers. A different psychiatrist, unaware of the treatment assignment, evaluated the participants. Evaluator was not involved in the recruitment procedure, and did not know the randomization list.

3.3. Inclusion and Exclusion Criteria

The population of the study included all adult patients, aged 18 to 60 years, who were referred to the private clinic or visited in the psychiatry clinic (Imam Hossein general hospital) with a diagnosis of major depressive disorder and they were in remission while taking a stable dose of SSRI for at least 8 weeks. Patients, who were experiencing constant SD for more than 4 weeks, provided they were in a stable sexual relationship with their spouse or partner for more than 6 months, were included in the study.

Patients with these exclusion criteria were excluded from the study: history of any previous SD; relapse of major depression; under any drugs or herbal medications for the treatment of SD, concurrent psychiatric or medical condition associated with SD such as diabetes mellitus, impairment of liver or renal function, cardiovascular disease, endocrinopathy, and neurological disease; engaged in alcohol or substance abuse; cigarette smoker of more than 5 cigarettes per day; behavioral and relational problems; a body mass index of ≥ 30 kg/m^2; and a sexual partner with a history of SD. Patients whose prescribed dose or SSRI type changed during the study, and judged of not adhering to the study protocol, were also excluded.

Of 57 patients eligible for screening, 46 met the inclusion and exclusion criteria and consented for the study. The trial was performed in accordance with the Declaration of Helsinki and subsequent revisions (world medical association, declaration of Helsinki, 2000) and approved by the ethics committee at Shahid Beheshti university of medical sciences. Written informed consents were obtained from the participants before entering the study (IRCT code: IRCT201409275280N17).

3.4. Intervention

The patients were randomly allocated into 2 groups using table of random numbers. Twenty patients were assigned to one study group and were given bupropion 200 mg/day. Eighteen patients were assigned to another group and were given amantadine 200 mg/day for the period of 4 weeks; patients were assessed with Arizona sexual experience scale (ASEX) at baseline and 4 weeks after the start of the treatment. Assessment of the patients during the treatment period was performed by a trained psychiatrist.

3.5. Arizona Sexual Experience Scale

Arizona Sexual Experience Scale (ASEX) is a standardized, validated, reliable, 5-item rating scale (rated by the patient) that quantifies sexual desire, arousal, penile erection, ability to reach orgasm, and satisfaction. Each question is scored with a 6-point Likert-type system. Possible total scores ranges from 5 to 30 with the higher scores representing greater SD. A total ASEX score of ≥ 19 denotes SD. It should be noted that reliability and validity of the test was determind by McGahuey et al. (28) (Cronbach $\alpha = 0.95$). It was also validated in Iran by Rahimi-Movaghar (29).

3.6. Statistical Analysis

Data were collected and analyzed using intention-to-treat (ITT) analysis. An ITT analysis is based on the initial treatment assignment and not on the treatment eventually received. ITT analysis is intended to avoid various misleading artifacts that can arise in intervention research such as nonrandom attrition of participants from the study or crossover. ITT is also simpler than other forms of study design and analysis because it does not require observation of compliance status for units assigned to different treatments or incorporation of compliance into the analysis.

According to normality of average in 2 groups, the independent t test was used to compare the averages between 2 groups and the paired t test to compare the averages of data before and after taking drugs. Moreover, regarding nonnormal data, we used nonparametric test (Mann-Whitney test) to compare the components of sexual dysfunction.

4. Results

4.1. Demographic Characteristics and Attrition

A total of 57 patients were initially entered the study, among them, 6 were not satisfied with participation in the study and 5 did not meet the inclusion criteria. Therefore, 46 patients enrolled in the study; 24 were assigned to the bupropion group and 22 patients to the amantadine group, of whom, 18 patients from amantadine and 20 patients from bupropion completed the study. In other words, 4 patients in each group refused to complete the study. Four patients from the bupropion group left the trial due to personal reasons unknown to the authors. Three patients in the amantadine group withdrew from the study due to insomnia, nausea, and vomiting and another patient discontinued the trial because of moving to another city (Figure 1).

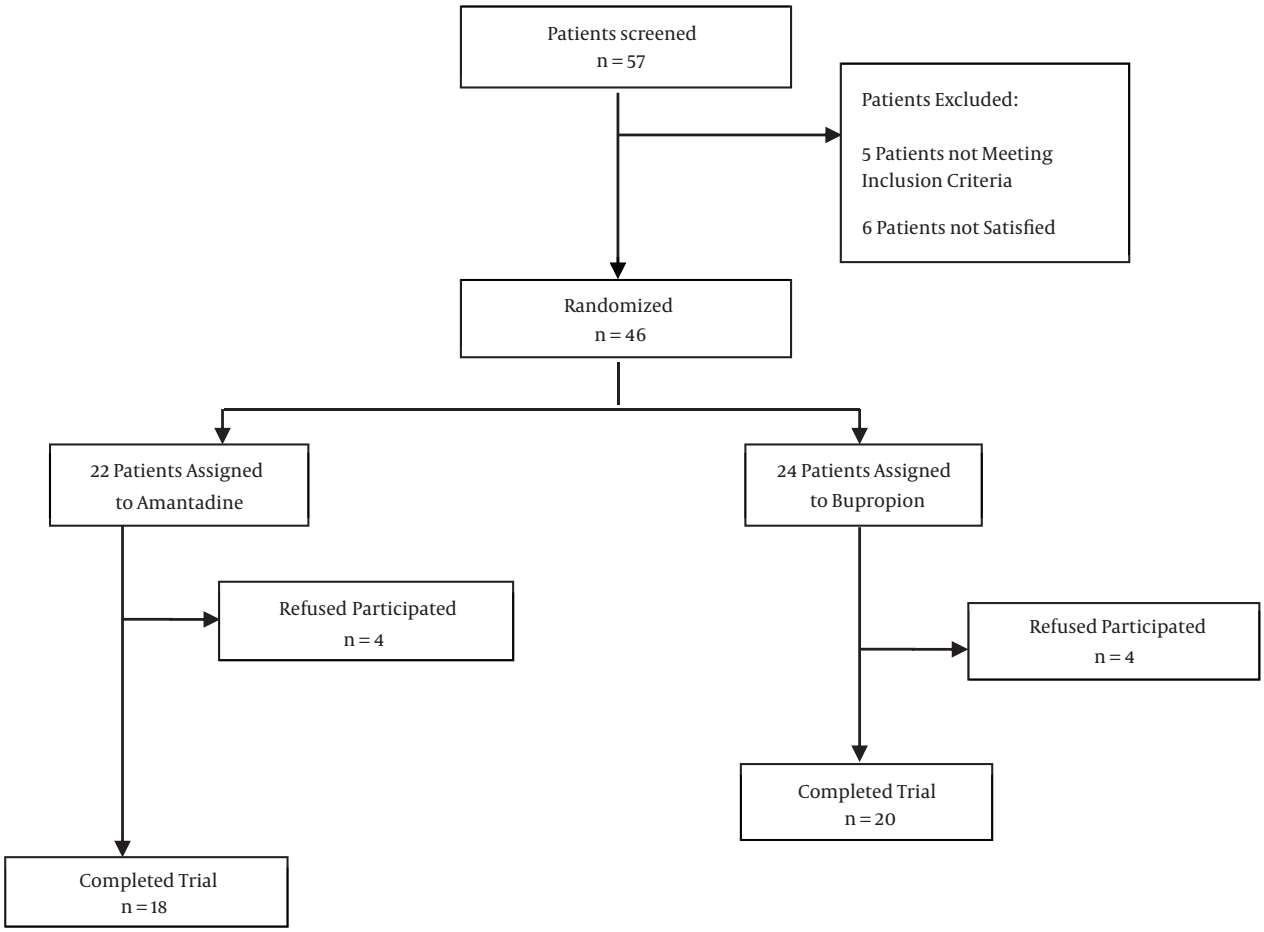

Figure 1. CONSORT Diagram Showing the Disposition of All Subjects Screened for the Study

Table 1. Comparison of Total and Component Scores of Sexual Dysfunction Before and After Drug Administration

ASEX	Amantadine		P Value	Bupropion		P Value
	Baseline	After		Baseline	After	
Total score	23.76	22.58	.51	22.77	14.27	< .0001
Sexual desire	4.9	4.47	.461	5	3.36	< .0001
Sexual arousal	10.22	8.76	.593	7.8	5.2	< .0001
Sexual pleasure	9.7	9.35	.260	9.7	5.77	< .0001

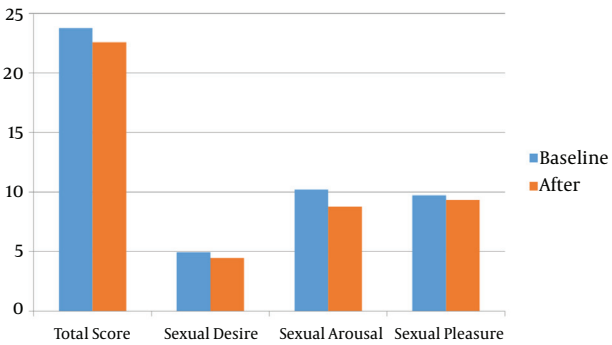

Figure 2. ASEX Score in Amantadine Group

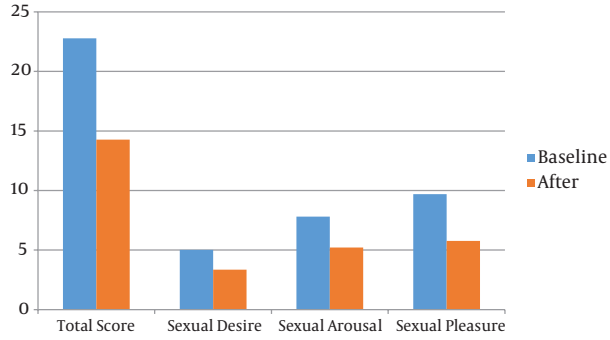

Figure 3. ASEX Score in Bupropion Group

The mean age of amantadine group was 37.37 ± 3.87 years and in bupropion group it was 35.75 ± 6.8 years. In both groups most of the participants were female (71% in amantadine group and 64% in bupropion group). The age range of amantadine group was 31 - 47 years and it was 24 - 54 years in bupropion group. There were no statistically significant differences between the groups regarding gender and age.

4.2. Effect on the Arizona Sexual Experience Scale Scores

Before the intervention, the total score of sexual problems in two groups were not significantly different. The mean ASEX scores gradually declined in both study groups during the trial.

The independent t-test and the paired t test were used to compare these averages between 2 groups and the average of data before and after taking drugs, respectively. Moreover, the Mann-Whitney test was used to compare the components of sexual dysfunction.

The independent samples t test showed that the decrease in the score of bupropion group was significantly greater than that of amantadine group. The score decreased in both groups, but it was greater in bupropion group to the extent that it caused a statistically significant difference (95% CI: 6.50 - 10.11, P < 0.0001).

Comparing amantadine and bupropion on reducing SSRI-induced sexual side effects showed that although the difference between scores before and after taking amantadine decreased, this difference was not statistically significant (P = 0.051).

Regarding bupropion, an 8-unit decrease was observed in the test scores before and after taking the drug, which was statistically significant.

With regard to the components of sexual dysfunction, there was a significant difference in the bupropion group between the 3 components (sexual desire, sexual pleasure, and sexual arousal) (P < 0.0001). However, in the amantadine group, only sexual pleasure after taking the drug showed a statistically significant decrease (P = 0.26) (Table 1, Figures 2 and 3).

4.3. Clinical Complications and Side Effects

In this study, bupropion and amantadine were well tolerated. Side effects included concentration difficulties, reduced duration of sleep, tremor, headache, dizziness, nausea, and vomiting. In this study, the disturbances were examined and there was no significant difference between the two groups in terms of these disturbances.

5. Discussion

Sexual dysfunction is one of the side effects of such drugs that can decrease drug compliance or even cause drug withdrawal. One of the strategies recommended to deal with this issue is SSRI combination therapies with another drug like amantadine or bupropion. Despite various drugs recommended for reducing this side effect, no studies have been conducted on comparing these two drugs so far. Given the lack of empirical evidence on comparing therapeutic strategies in this regard and different results reported by studies on the effects of each of these

drugs alone, this study aimed to compare the effects of bupropion and amantadine on SD.

According to our study results, patients' sexual function was improved after receiving both amantadine and bupropion. However, this difference was statistically significant only in the group receiving bupropion (95% CI: 6.50 - 10.11, P < 0.0001).

There were no studies quite similar to ours in which the two drugs were compared. Therefore, we just present some relevant studies in the following sections.

5.1. The Effect of Amantadine on SSRI-Induced Sexual Dysfunction

In this study, taking amantadine was accompanied by a one-unit decrease in sexual dysfunction, which was not a statistically significant difference. These results were similar to the results of the studies by Devaangam et al. (24) and Ferraz et al. (23). In the first study in 2011 on 96 mice for 9 weeks, Devaangam et al. (24) showed that amantadine could not be effective in improving clomipramine-induced sexual dysfunction. In the second study in 2007 on 33 mice receiving amantadine for 23 weeks, Ferraz et al. (23) showed that amantadine could not be effective in SSRI-induced sexual side effects.

In another study by Michelson et al. (27), 57 women in remission phase who were taking SSRI for more than 6 months were divided into 3 groups. Among these women, 18, 19, and 20 participants received amantadine, bupropion, and placebo for 12 weeks, respectively. The results showed that amantadine and placebo had similar effects on improving sexual function (27).

In this study, improvement in sexual pleasure after taking amantadine was statistically significant in terms of improvement in components of sexual dysfunction. However, other studies reported no statistically significant difference in terms of improvement in components of sexual dysfunction (23, 27).

5.2. The Effect of Bupropion on SSRI-Induced Sexual Dysfunction

In this study, bupropion, as an antidote, was more effective in SSRI-induced sexual dysfunction than amantadine. It could also reduce sexual dysfunction by 8 units with a statistically significant difference. So far 7 clinical trials on comparing bupropion with another drug or placebo have been conducted, among them, 5 studies reported that bupropion was more effective than placebo in improving sexual dysfunction. The first study was conducted by Clayton et al. (30) in 2004 on 42 individuals who randomly received bupropion SR 150 mg BID or placebo for 4 weeks. The results of their study showed that bupropion, as an antidote, could be effective in SSRI-induced sexual dysfunction.

The second study was also conducted by Clayton et al. (30) on 11 individuals who randomly received bupropion SR 150 mg BID or placebo for 4 weeks. The results of this study were also similar to the first study (13).

Our study shows a significant reduction in 3 sexual components (desire, pleasure, and arousal) in terms of the components of sexual dysfunction whereas in the studies by Clayton et al. (30) and DeBattista et al. (31), there was a statistically significant difference only in improvement in sexual desire.

The third and fourth studies were conducted by Safarinejad et al. in 2010 on 228 men (20) and 218 women (21) for 12 weeks. The subjects then randomly received bupropion SR 150 mg BID or placebo. Both studies showed that bupropion was more effective than placebo (32).

In the fifth study, 42 subjects (37 women and 5 men) were randomly assigned to receive either bupropion SR 150 mg BID or placebo for 4 weeks. Endpoint changes in sexual functioning questionnaire, and desire–frequency scores favored bupropion (9).

Two other clinical trials showed that the effect of bupropion in improving SSRI-induced sexual dysfunction was similar to placebo. The first study was conducted by De Battista et al. in 2005 on 45 individuals who received bupropion SR or placebo for 6 weeks (31).

The second study was conducted by Masand et al. (8), in which 30 individuals were randomly given bupropion SR 150 mg per day or placebo. The results of both studies showed that the effect of bupropion in improving sexual function was similar to placebo. Unlike our study in which there was a statistically significant improvement in 3 components of sexual dysfunction, the study by Masand et al. showed that only sexual pleasure was significantly improved after receiving drug (8).

The clinical definition used for SD, type of trial (self-applicable questionnaire, mailed questionnaire, interview by phone, and personal interview) the characteristics of subjects studied, study methods, different outcome measures and sample size, were among the confounding factors in reported results of different studies.

Timely diagnosis and treatment of SSRI-emergent SD is critical for the patient's satisfaction, treatment compliance, and the quality of life.

This article is one of the studies that compared two drugs in treatment of sexual dysfunction. There are a few issues need to consider in this study. The sample size is one of limitations of this study. So the results of this review may not be extended to people, and the study was conducted almost on both women and men which limits its generalizability. The study was conducted on the patients referred to private clinics and results may vary in public sector.

Footnotes

Authors' Contribution: Farhad Faridhosseini: study concept and design, and writing the article; Najmeh Shahini: data collection, writing the article, and final approval of the article; Alireza Zahiroddin: writing the article, data collection, and literature review; Najmeh Shahini

and Azar Zamani: critical revision of the article, provision of the materials, patients, and resources; Alireza Zahiroddin: statistical analysis; and Farhad Faridhosseini: Administrative support.

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