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Pharmacological and Non-pharmacological Therapeutic Strategies for Improvement of State-Trait Anxiety: A Randomized Controlled Trial Among Iranian Infertile Women With Sexual Dysfunctions

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Abstract

Objective: To compare the effects of pharmacological and non-pharmacological therapeutic strategies for improvement of state-trait anxiety among Iranian infertile women with sexual dysfunctions (SDs).

Material and Methods: In a randomized controlled clinical trial, 105 women with infertility suffering from SDs were randomly assigned to participate in a 2-hour group weekly session of psychosexual therapy (PST) (n=35), took a tablet of bupropion ER 150 mg/d (BUP ER) (n=35), or control (n=35) for 8 weeks during 2014–2015. The Female Sexual Function Index (FSFI) and Spielberger State-Trait Anxiety Inventory (STAI) were completed before and after of the study.

Results: State and trait anxiety levels had mean values of 47.80 ± 10.93 and 48.78 ± 11.34, respectively. Mean values of state and trait anxiety levels observed at baseline significantly decreased toward the end of the study in each of the treatment groups (PST, $P<0.0001$ and $P<0.0001$; BUP, $P<0.005$ and $P<0.001$, respectively), and the decrease was more significant in the PST group than in the BUP ER group ($P<0.001$ and $P<0.007$, respectively) and the control group ($P<0.0001$) and $P<0.0001$, respectively). Significantly high improvement in state and trait anxiety levels was observed in the PST group than the BUP and control groups. However, the decrease in the BUP group was not significant than the control group ($P<0.076$ and $P<0.186$, respecttively).

Conclusion: PST compared to bupropion ER treatment was found to be a more favorable strategy for improvement of state and trait anxiety symptoms.

Keywords: Anxiety, STAI, Psychotherapy, Bupropion, Infertility, Sexual dysfunctions

Introduction

Infertility is a life crisis and associated with several psychological changes such as feeling of loss, sense of isolation and loneliness, low self-esteem, low self-efficacy, depression, stress, and anxiety (1-3), which may have a negative effect on quality of life, marital intimacy, and sexual function and causes fear of the end of the marital relationship (4). Anxiety is defined as feeling of uneasiness, stress, perturbation, apprehension, worry, and concern associated with physiological arousal. In other words, this emotional state is adaption with motivating behavior that helps individuals in order to manage threatening circumstances (5). The 2 poles of the normal affect curve of anxiety are state anxiety (A-state) and trait anxiety (A-trait) (6). State anxiety is described as a displeasing emotional arousal facing threatening request or risks, while trait anxiety express stable individual discrepancies in response to the state anxiety where threatening situations are found (7).

Anxiety has the significant role in development of problem related to sexual dysfunctions (SDs) (1). Some researchers believe that anxiety symptoms are the cause of SDs, but others consider psychological anxiety as the result of sexual problems. A review of literature showed that sexual disorders create levels of distress, which may decrease therapeutic success rate in women who experience infertility (8,9). Another study showed that anxiety has an increased risk for sexual problems (10). However, the specific role of anxiety is still unclear (1).

Both psychosexual therapy (PST) and pharmacotherapy are selective treatments for the anxiety and SDs associated with infertility. A review of literature showed that psychopharmacological and cognitive behavioral interventions were effective in treatment of anxiety (11). Another study suggested that cognitive behavioral therapy significantly

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decreased anxiety more than other groups in women with infertility (12). Bakhtiari et al reported that group PST improved sexual desire and sexual satisfaction (13). Psychological intervention can decrease anxiety and increase sexual satisfaction and fertility success rate (14-16). Several studies have also evaluated the effects of bupropion on anxiety and sexual function; however, the findings were controversial. Some of them reported that bupropion aggravated anxiety and cannot be used in patients with anxiety and depression (17-19), while other studies reported that bupropion had comparable anxiolytic activity and a favorable effect on sexual function (20-23). Treatment with the sustained or extended -release formulation of bupropion decreased anxiety (21, 24), and studies have also revealed a rapid onset of clinically significant anxiolytic efficacy (20).

As SDs can be a symptom of anxiety (1) and no comprehensive reports were available comparing the effects of PST and bupropion therapy on anxiety among infertile women suffering from SDs, this study aimed at comparing the effects of 2 types of pharmacological and nonpharmacological interventions on state and trait anxiety symptoms among infertile women with SDs.

Material and Methods

Patient Selection

This study was an 8-week parallel randomized controlled trial. The data were collected at the Fatemeh Zahra Infertility and Reproductive Health Center of Babol University of Medical Sciences from December 2014 to June 2015. Primary objective of this protocol was treatment SD with subsequent improvement of anxiety symptoms. Subjects who were aged less than 45 years, literate, suffering from more than 1 year of infertility, not undergoing fertility treatment up to 2 months, availability of partner, and having SDs (a score of ≤26.55) were included. Infertile women with any of the following criteria were excluded: history of seizure disorder, head/brain injury (traumatic), history of substance abuse, cerebral tumor, mental illness or other psychotic disorder, having suicidal ideas or have made a suicide attempt within the past 6 months or other serious medical conditions, taking medication with known effect on efficacy of evaluation, under psychological support (such as relaxation training, yoga, psychotherapy sessions, and psychological support), or experiencing a stressful event in 3 months ago. In this protocol both the researcher and the subjects were not blinded. The calculation of the sample size was 22 participant in each group, with 95% CI, power = 90% and approximate standard deviation = 10.5 based on previous studies (25) and accuracy = 10.6 for each group. After using the corrected sample size formula ($N = \sqrt{k}\ n$, $k = 2$) and consideration of sample dropping out of the study (10%) (26), a total of 105 eligible subjects were selected through computer-based randomization in equal 3 groups (35 subject in each group). Two midwives with no clinical involvement in the trial enrolled subjects, and assigned participants to interventions. Of the 485 infertile women, 124 met exclusion criteria, 127 were not willing to participate, and 129 had no SD. A total of 105 women with infertility accepted to take part in this protocol and 99 remained at the end of the study and consented to proceed with the study protocol (Figure 1). All eligible women were randomly assigned on a 1:1:1 basis to PST (group 1, n = 35), receiving 150 mg/d of bupropion extended-release (ER) (group 2, n = 35), or a matching control group (group 3, n = 35). The PST group

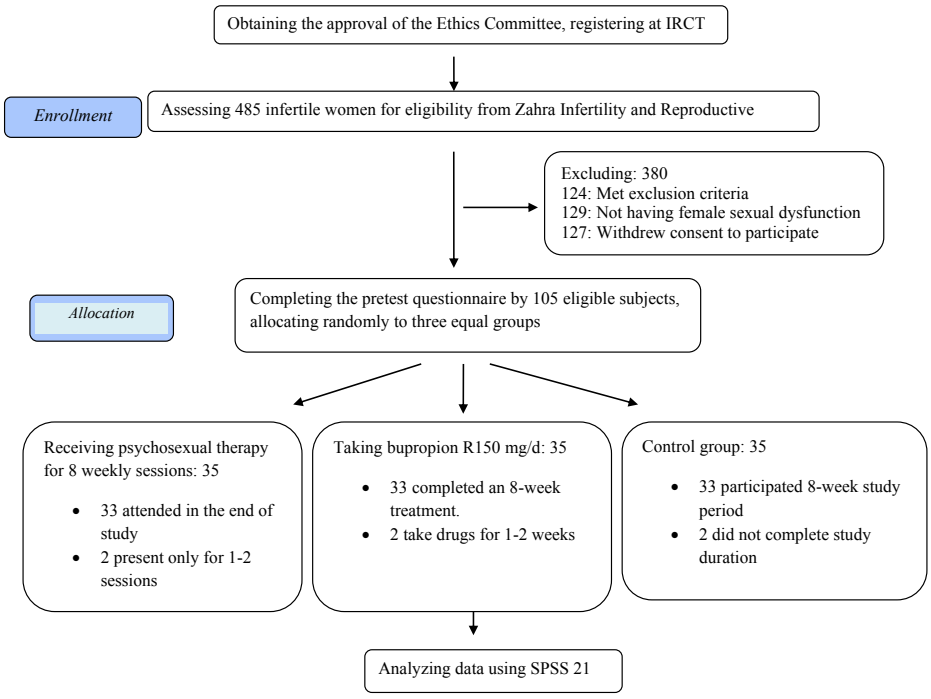

Figure 1. Flowchart of Recruited Infertile Women in the Study Groups.

had attended eight sessions, each comprising 2-hour group training combined with mindfulness-based cognitive therapy, sexual skills, and relaxation (mixed method) (27,28). A free booklet with a free CD (a path to tranquility, mindfulness, and medication) was given to them for homework tasks (29). The groups of 9-13 members were formed, and a women psychotherapist guided psychological therapeutics. The BUP group took 150 mg bupropion ER (Wellban Extended-release, Abidy Company, Tehran, Iran) daily for 8 weeks. The 35 control subjects received no intervention. But they were referred to a sex therapy clinic, and educational package was given to them at the end of the 8 weeks. Study duration, and bupropion dosage were different in previous studies (6-24 weeks; and 100-450 mg/d) (12,30,31). Therefore, intervention duration, and bupropion dosage in this study was 150 mg orally once a day, and 8 weeks in subjects with anxiety symptoms treated for SD. AEs, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and body mass index (BMI) were serially measured for each of groups by researcher. For monitioring any complaint, or any change in health status of subjects were contacted with them by phone weekly. Demographic information was collected. Subjects were asked to fill out the Spielberger State-Trait Anxiety Inventory (STAI) at baseline and after treatment at the end of the study. STAI is a psychological inventory that includes 40 self-report items (20 items related to each of the A-trait and A-state scales) related to anxiety effect (32). Both state and trait anxiety levels are measured by this scale (6). The current form of STAI was revised in 1983 (32,33). They score on a 4-point Likert-type scale. Range of scores consist 20 to 80, in which higher scores show greater levels of anxiety symptoms (34,35). Cronbach α coefficients were 0.91 and 0.90 for the A-state and A-trait anxiety scales, respectively (36). The Female Sexual Function Index (FSFI), applied to measure sexual function. It includes 19 items and 6 different domains (desire, arousal, lubrication, orgasm, satisfaction, and sexual pain) (37). The overall FSFI score ranges from 2 to 36. A score ≤26.55 is considered as female SD (38). The Cronbach α was ≥ 0.8, and it also had excellent construct validity. The Iranian version of the FSFI was tested and validated in the Iranian population (4,37,39). A female psychologist conducted a clinical interview for the final diagnosis. Subjects with a suicide belief were referred to an appropriate psychiatry service.

Statistical Analyses

The results were analyzed by χ^2 test, paired *t* test, analysis of covariance (ANCOVA), and Tukey test in an intention-to-treat study. Scores for state-trait anxiety were compared before and after intervention using paired *t* tests in each study group, separately. ANCOVA was used to compare endpoint scores between groups taking into account the baseline score as covariates. If a significant difference was noted among the three groups, Tukey test was used to compare the mean differences. We considered the following 3 levels: "improved" (defined as a pre- to post-treatment decrease in anxiety levels), "worsening" (defined as increase in anxiety levels from baseline to the end of the study), and "unchanged" (defined as no change in anxiety levels from before to after of the study). SPSS version 21 was used for data analysis. A *P* value of below 0.05 was regarded as statistically significant level.

Results

Majority of infertile women and their husbands were aged <30 years. City dwellers comprised 54.3% of the total respondents. The male factors were described as the most common cause of infertility. The mean duration of marriage was 6.80 ± 4.11 years. The majorities of infertile women were childless. No significant difference was detected in the reproductive characteristics of groups (Table 1).

The mean A-state and A-trait anxiety scores in before and after of the study were 47.80 ± 10.93 and 48.78 ± 11.34 and 40.83 ± 12.36 and 42.26 ± 11.85, respectively, in the infertile women. The mean A-state and A-trait anxiety scores for each of the three groups in before and after of the study are shown in Table 2. A significantly high proportion of women with infertility indicated "improved" in the PST group than the BUP and control groups in terms of state (71.4%, 37.1%, and 25.7%, respectively) and trait (65.7%, 42.9%, and 40%, respectively) anxiety symptoms levels ($P<0.001$) (Figure 2). Bupropion treatment was well tolerated. Paired *t* test revealed significant inter-individual changes for A-state ($P<0.0001$, $P<0.005$) and A-trait ($P<0.0001$, $P<0.001$) anxiety symptoms levels in both treatment groups, PST and BUP, respectively. Anxiety symptoms decreased significantly in both the PST and BUP groups at the end of the study. The inter-individual changes for A-state ($P=0.575$) and A-trait ($P=0.374$) anxiety symptoms were not significant in the control group (Table 2).

ANCOVA was used to control for the variability (the covariate variable). After adjusting for baseline values, the results remained significant for the mean state and trait anxiety symptoms scores in the three groups ($P<0.0001$ and $P<0.0001$, respectively). The results of ANCOVA are shown in Table 2. The treatment methods had significant effects on the A-state anxiety symptoms levels when compared between the treatments groups (PST and BUP) ($P<0.001$) and between the PST group and the control group ($P<0.0001$). However, a significant difference was not observed between the BUP group and the control group ($P<0.076$) (post hoc ANCOVA). Pairwise comparison of mean values of A-trait anxiety symptoms levels after the intervention revealed a significant differnce between the PST group and the BUP group ($P<007$) and between the PST group and the control group ($P<0.0001$). However, there was no significant difference between the BUP group and the control group ($P<0.186$). These results indicate that the PST method was superior to BUP ER intervention in improving of both A-state and A-trait anxiety symptoms in infertile women with SDs.

Table 1. Distribution of the Participarts According to the Sociodemographic Charecteristics

Variable	Treatment Groups		Control (n = 35)	*P* Value	All (N = 105)
	PST (n = 35)	BUP ER (n = 35)			
Marriage duration (y)[a]	7.43±4.38	6.60±3.67	6.37±4.29	0.531	6.80±4.11
No. (%)[b]					
Age				0.269	
<30	16 (45.7)	23 (65.7)	17 (48.6)		56 (53.3)
30-34	14 (40)	9 (25.7)	10 (28.6)		33 (31.4)
≥35	5 (14.3)	3 (8.6)	8 (22.8)		16 (15.2)
Husband age				0.389	
<30	10 (28.6)	16 (45.7)	12 (34.3)		38 (36.2)
30-34	12 (34.3)	13 (37.1)	12 (34.3)		37 (35.2)
≥35	13 (37.1)	6 (17.1)	11 (31.4)		30 (28.6)
Residency				0.891	
Urban	18 (51.4)	19 (54.3)	20 (57.1)		57 (54.3)
Rural	17 (48.6)	16 (45.7)	15 (42.9)		48 (45.7)
Infertility cause				0.816	
Female	3 (8.6)	2 (5.7)	6 (17.1)		11 (10.5)
Male	11 (31.4)	13 (37.1)	11 (31.4)		35 (33.3)
Female and male	10 (28.6)	10 (28.6)	8 (22.9)		28 (26.7)
Unknown	11 (31.4)	10 (28.6)	10 (28.6)		31 (29.5)
Having child				0.343	
Yes	7 (20.0)	3 (8.6)	4 (11.4)		14 (13.3)
No	28 (80.0)	32 (91.4)	31 (88.6)		91 (86.7)

Abbreviations: PST, psychosexual therapy; BUP-ER, Bupropion extended-release.
[a] Values are means ± standared deviation,
[b] Values are number (percent).
ANOVA was performed to compare the means of groups, χ^2 test was performed to shows difference between between groups ($P<0.05$).

Table 2. Analysis of Covariance of A-State and A-Trait and Pair Wise Comparisons in the Groups

Variable	Pre-test Mean (SD)	Post-test Mean (SD)	Sum of Squares	Mean Square	*df*	F statistics	Observed Power	*P* Value
A-State anxiety								
PST*	49.51 (11.72)	34.31 (10.34)						
BUP*	45.89 (10.88)	41.40 (11.73)	3069.238	1534.619	2	13.932	0.998	0.0001
Control*	48.00 (10.15)	46.77 (11.94)						
Pair wise comparisons								
Groups	PST vs. control *P* value		PST vs. BUP ER *P* value		BUP ER vs. control *P* value			
	0.0001		0.001		0.076			
A-Trait anxiety								
PST**	52.23 (11.31)	39.03(11.09)						
BUP**	46.71 (12.18)	42.14(12.67)	1577.569	788.784	2	8.642	0.965	0.0001
Control*	47.40 (9.94)	45.60(11.13)						
Pair wise comparisons								
Groups	PST vs. control *P* value		PST vs. BUP ER *P* value		BUP ER vs. control *P* value			
	0.0001		0.007		0.186			

Abbreviations: A-State, state anxiety; A-Trait, trait anxiety; PST, psychosexual therapy; BUP ER, bupropion extended-release.
Note: n=105 (each group of 35 participants)
*Paired *t* tests were significant in PST, $P < 0.0001$; BUP, $P < 0.005$; ** Paired *t* tests were significant in PST, $P < 0.0001$; BUP, $P < 0.001$; but no in Control group ($P < 0.575$, $P < 0.374$, respectively.

Discussion

This study showed that the infertile women with SDs suffered from moderate average of state-trait anxiety symptoms at the beginning of the study. This result was consistent with the majority of studies carried out among infertile women that have assessed the psychological problems and observed significant levels of anxiety (1,9,12,40). Another similar study reported high mean values of state and

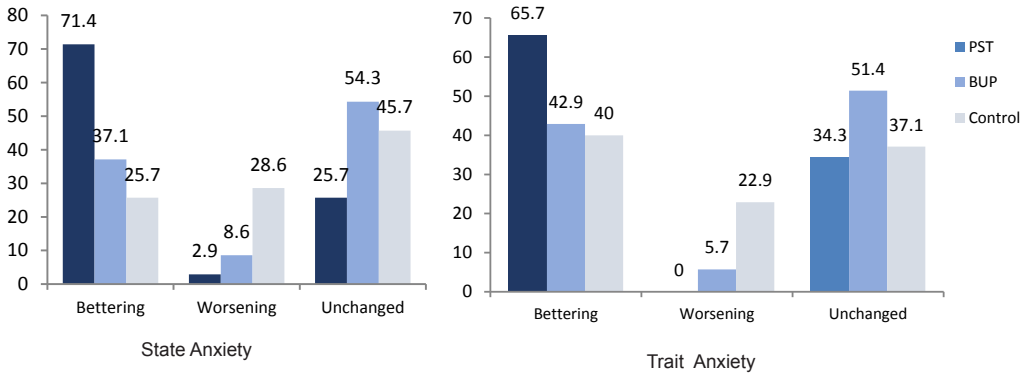

Figure 2. The Changes of Final Levels of Baseline State-Trait Anxiety Symptoms in 3 Groups.
Abbreviations: PST, psychosexual therapy; BUP ER, bupropion extended-release.
Note: n = 105 (each group of 35 participants). *P* value was < 0.001 (χ^2 test).

trait anxiety in a group of infertile women (9). Nelson et al and Shafaie et al believed that infertility caused stress, especially in women with infertility. It can lead to psychological difficulties such as depression and anxiety (3,40). In addition, various studies have underlined that sexual dissatisfaction resulted in anxiety, and psychological elements were generally associated with SDs. A high rate of anxiety symptoms has been showed in subjects affected by SDs (1,41-44).

Our finding showed that state and trait anxiety symptoms observed at baseline significantly decreased toward the end of the study in each of the treatment groups. The PST was a reliable treatment option in improving of state and trait anxiety symptoms among infertile women with SDs. In this context, Boivin indicated that marital distress significantly decreased in infertile women who received sex therapy program and psychosocial intervention (e.g., relaxation training, group support) (45). Infertile women who received support therapy showed lower anxiety levels and higher life satisfaction compared with the nonintervention group (14). Several studies have proposed that psychological and cognitive behavioral therapies were effective in improving anxiety and SD, and increasing the chance of pregnancy (8,15,16,46).

This study showed state and trait anxiety scores decreased significantly from baseline at the end of the study in bupropion users. A statistically significant negative relationship observed between the mean of state and trait anxiety with FSFI scores. Higher scores of FSFI are correlated with low anxiety scores. Studies showed that bupropion provided clinical signs of efficacy in anxiety and had a favorable effect on female sexual function (20,22,47). Therefore, it is important to know that the improvement of anxiety symptoms can associate with relieving sexual problem in infertile women**.** A review of current diagnosis and treatment of anxiety disorders by Bystritsky et al reported well response to pro-dopaminergic medicines (such as bupropion) in some persons with anxiety disorder (11). Basically, bupropion is a norepinephrine dopamine reuptake inhibitor. The studies showed dopamine functions in such a complex way in normal and pathological anxiety states. It is worth mentioning that the principal dopaminergic pathways might affect the anxiety state in various manners (48). Dopamine D_2 blockade is anxiolytic. Also, dopamine can be increases dopaminergic signaling through up-regulated with norepinephrine in anxiety. Therefore, it may impact on anxiety by mediating feelings of confidence and self-efficacy (24,49).

The results of this study demonstrated that PST was superior to bupropion ER 150 mg for the improvement of state and trait anxiety symptoms of infertile women with SD. The frequency of bettering in state and trait anxiety symptoms levels was more in the PST group compared with the BUP and control groups. Faramarzi et al showed that psychological intervention was superior to pharmacological treatment for the reduction of anxiety in infertile women (12). Fruhauf et al reported that group psychological interventions may be selective treatment and more effective, with better cost-effectiveness than other interventions (16). Another study showed that a brief psychoeducation (PED) consisting of sensate focus exercise, techniques to augment sexual arousal, and educational films was effective in reducing anxiety, sexual distress, depression, and SDs (50).

Our study also revealed no significant difference in state and trait anxiety symptoms between the BUP and control groups. Basically, prescribing bupropion for anxiety has contradictory results. Tomarken et al in evaluating of the effects of bupropion and placebo on mood and anxiety symptoms during a 6-week treatment phase showed that there was more decrease in all measures except anxiety in user bupropion than placebo group (30). A clinical trial study reported that bupropion significantly improved personal distress in women with hypoactive sexual desire disorder during a 12-week period (31). Another studies revealed that bupropion not increase anxiety and may be useful for treating generalized anxiety disorder (17,24), while other studies supported that bupropion users had some degree of increased anxiety (17-19), especially in high dose (450 mg) which need to more evaluation in future studies.

Limitations and Strengths

Several strengths and potential limitations of this study should be noted. First, this study was conducted based on a group of Iranian infertile women suffering from SD. Thus, the corresponding findings might not be generalized to all the infertile women populations. Secondly, only infertile women with SD were investigated where such research can also be implemented for men with SD. Moreover, a short duration of intervention of 8 weeks and a small sample size were chosen. However; future studies can be performed during a longer time with larger sample sizes. In addition, the state and trait anxiety symptoms was evaluated by STAI, although recent tool is useful to identify patients in need of medical care but it might not result in a good measure of clinical relevant anxiety; instead, using an efficient and powerful tool is required for the future studies. Finally, thanks to the in valuable valid Iranian version of questionnaires and counseling interviews which were employed in this investigation.

Conclusion

It was shown that PST can influence the anxiety symptoms of infertile women suffering from SD. Furthermore, the psychosexual program was shown as a promising substitute to pharmacotherapy in order to reduce the state and trait anxiety symptoms. As a result, psychological counseling is recommended to develop better coping with anxiety symptoms and emotional well-being. Moreover, further research to explore the effectiveness of bupropion on anxiety disorder is suggested.

Ethical Issues

The study was approved by the Ethics Committee of Babol University of Medical Sciences and then registered in the Iranian Registry of Clinical Trials (http://www.irct.ir/, identifier: IRCT2015042721955N2).

Conflict of Interests

The authors have no conflict of interest in this study.

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