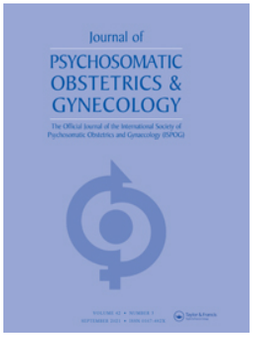

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RESEARCH ARTICLE

Escitalopram and progressive muscle relaxation training are both effective for the treatment of hot flashes in patients with breast cancer: a randomized controlled trial

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ABSTRACT

Introduction: Available treatments for hot flashes in patients with breast cancer are not always tolerable or effective for all patients.

Methods: Patients diagnosed to have primary breast cancer were randomly allocated to receive 10 mg of escitalopram, placebo, or progressive muscle relaxation therapy. Patients were asked to report the frequency and duration of hot flashes during day and night, at baseline and after ten weeks of treatment, and completed the menopause rating scale.

Results: Eighty-two patients were randomly assigned to receive escitalopram ($n = 26$), PMRT ($n = 28$), and placebo ($n = 28$). PMRT and escitalopram could effectively decrease number and duration of diurnal and nocturnal HFs in patients with breast cancer, with a better effect observed from escitalopram. They could both decrease the total score of MRS.

Conclusion: Both escitalopram ad PMRT can reveal nocturnal and diurnal HFs in terms of frequency and duration in patients with breast cancer.

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Breast cancer; hot flashes; escitalopram; progressive muscle relaxation

Introduction

Breast cancer is the major cause of malignant tumors among females [1] and one of the most important causes of death [2]. The number of breast cancer survivors (BCS) has increased in recent decades due to early detection and advances in treatment modalities [3–5]. Adjuvant chemotherapy and/or ovarian suppression result in premature menopause, and vasomotor symptoms (VMS) are occasionally more severe in young patients [6]. Hot flashes (HFs) are the main and widely reported VMS affecting approximately 65% of patients [7,8]. This results in the termination of endocrine therapy by nearly 20% of patients, despite its proven efficacy [9].

HFs are triggered by a decline in estrogen level [10] and characterized by an abrupt feeling of warmth that usually begins at the upper chest and face, accompanied by spreading to the rest of the body. The feeling lasts for several minutes and might contribute to sweating, palpitation, and anxiety. In many patients, HFs can trigger awakening at night [11], anxiety, and a pronounced decline in sleep quality [12]. The frequency and intensity of HFs influence the quality of life and disturb daily life of breast cancer patients.

Anti-VMS therapies include a broad spectrum of interventions. The most effective anti-VMS treatment is hormone replacement therapy (HRT) in healthy women [13]. However, it is not a perfect choice for women with breast cancer, especially for those with hormone receptor-positive tumors. There are studies linking estrogen and progesterone supplementation with increased breast cancer incidence among healthy women [14,15] and increased risk of recurrence in patients [16,17]. Selective serotonin reuptake inhibitors (SSRIs) and selective serotonin-norepinephrine reuptake inhibitors (SNRIs), in open and controlled trials, demonstrated to be effective non-hormonal alternatives for the treatment of VMS [18,19]. Numerous SSRIs (e.g. paroxetine, sertraline, fluoxetine, venlafaxine, citalopram, escitalopram) have been studied in

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various studies [20–24], demonstrating benefits in reducing the frequency and severity of menopausal HFs. Escitalopram has been demonstrated to be superior to other SSRIs in terms of efficacy for HFs among healthy women [25], with beneficial outcomes for patients with breast cancer in reducing the intensity and frequency of HFs and depressive symptoms [26].

Given that non-hormonal medications might be successful in minimizing VMS [27], they also have various adverse side effects [28,29]. According to the literature, the dropout rates from treatment with antidepressants are near 50% in three months and over 70% after six months [30].

The other promising methods of non-hormonal treatments are the non-pharmacological interventions, like cognitive behavioral therapy [31,32]. Non-pharmacological treatments, which incorporate relaxation training, might provide the most excellent advantages in relieving debilitating symptoms of patients with breast cancer [33–35]. There is growing evidence that VMS can be positively influenced by behavioral therapies such as progressive muscle relaxation training (PMRT) [36–39] most likely resulting from decreased sympathetic nervous system activity [40]. PMRT is the technique consisting of continuous and systematic stretching and relaxing of the muscles until the whole body becomes "relaxed" [41]. The present study aimed to assess and compare the efficacy of escitalopram and PMRT to alleviate HFs in patients with breast cancer.

Patients and methods

The protocol was reviewed and approved by the Ethics Committee of Kermanshah University of Medical Sciences (ethics code: KUMS.REC.1396.2). The protocol is also registered with the Iranian Registry of Clinical Trials (IRCT2017072834482N2). Participants were recruited from Imam Reza Hospital, Kermanshah, Iran. All gave written informed consent.

The inclusion criteria were being diagnosed to have primary breast cancer (stages, T1-4, N0-1, and M0), premenopausal at the time of diagnosis, less than 50 years of age, having received and finished adjuvant chemotherapy (not less than six months ago or not more than five years ago) and/or hormonal therapy, reports of HFs in their profile. Patients with major cognitive or psychiatric conditions, using steroids or other medications for treating menopausal symptoms within the last two months, or using substances were excluded. Patients were then randomly assigned to receive either Escitalopram tablets, PMRT, or placebo using a computerized block randomization method.

The participants completed the menopause rating scale (MRS) at baseline and in the follow-up phase (ten weeks after being included in the study). To measure the primary outcome, patients were asked to record the frequency and duration of HFs during day and night at baseline before starting the treatment. They recorded these numbers every day on a diary for one week after inclusion, then a mean value was calculated for the number and duration of HFs for each patient. The same process was repeated after ten weeks of treatment.

Interventions

Progressive muscle relaxation (PMRT)

A trained psychologist trained patients to contract and relax muscle in 16 groups. A PMRT booklet manual was also provided to the patients. The 16 muscle groups consisted of right hand and forearm, right biceps, left hand and forearm, left biceps, forearm, the upper section of cheeks and nose, the lower area of cheeks and nose, neck and throat, chest, shoulders, and the upper part of the back, abdominal region, and stomach, right thigh, right calf, right foot, left thigh, left calf, and left foot. Patients were supposed to perform PMR twice a day, once in the morning (8 a.m. to 10 a.m.) and once in the evening (8 p.m. to 10 p.m.), 30 min each. A daily report was obtained from patients by the trainer. Non-adherence was defined as missing sessions more than one day per week.

Escitalopram

Escitalopram (Cipralex, Lundbeck, Denmark) was started at 5 mg per day, titrated up to a fixed dose of 10 mg for ten weeks. Non-adherence was defined as missing pills more than one day per week for any reason.

Placebo

The placebo was an escitalopram-like pill taken once every morning for ten weeks. The pill was developed in the School of Pharmacy, Kermanshah University of Medical Sciences.

The menopause rating scale (MRS)

The menopause rating scale (MRS) [42] was developed and validated as a self-administered scale to evaluate the aging women's symptoms/complaints in varying circumstances, determine the severity of symptoms

over time, and quantify changes in pre-menopause and post-menopause replacement therapy. Reliability measures (consistency and test-retest stability) were good across different countries [42]. In Iran, Cronbach's alpha was reported to be 0.93, and the intra-class correlation coefficient was reported to be 0.97 [43].

MRS measures three groups of somatic (including hot flashes), psychologic and urogenital signs and symptoms. Patients answered the presence of these symptoms on a 5-point Likert scale ranging from none (0) to extremely severe (4).

Statistical analysis

All the statistical analyses were performed with SPSS 22. Descriptive and demographic results were presented as means ± standard deviations (SD) for quantitative variables and percentages for categorical variables.

The primary outcome was the change in duration and severity of HFs. To probe the effectiveness of different treatments, the analysis of covariance (ANCOVA) was utilized with groups as independent variables and outcome variables (number and duration of hot flashes) as fixed factors, and the pretreatment measures were used as covariates. It was used to assess the differences between the mean number of daytime hot flashes and nocturnal hot flashes in the experimental (psychotherapy and pharmacotherapy) compared to the placebo group. Likewise, ANCOVA was used to compare the mean duration of diurnal hot flashes and nocturnal hot flashes between the experimental and placebo groups. ANCOVA is a combination of an analysis of variance and regression analysis that adjusts the mean scores for each treatment group by that of the mean deviation for the covariate (i.e. the pretest scores for each variable). Statistical significance was defined at $p \leq 0.05$.

Results

Eighty-two patients were randomly assigned to receive escitalopram ($n = 26$), PMRT ($n = 28$), and placebo ($n = 28$). The flow diagram of the study progress is in presented in Figure 1. Demographic characteristics of

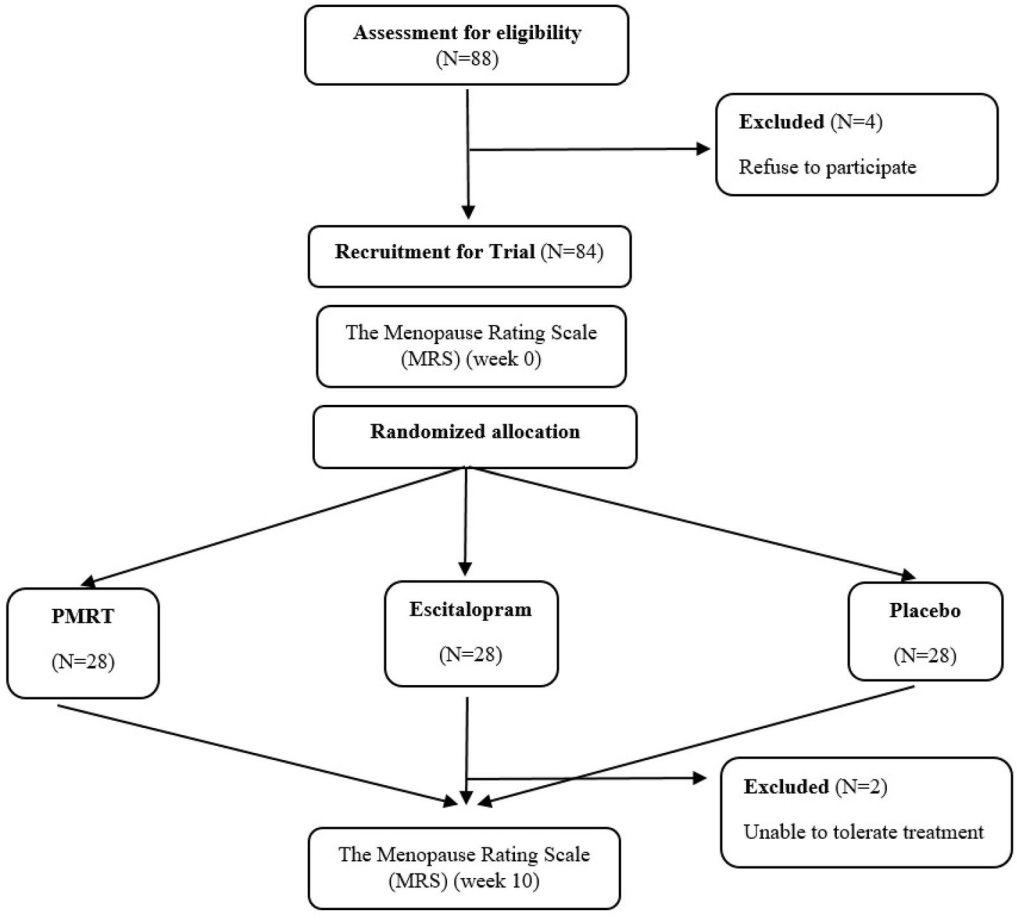

Figure 1. CONSORT flow diagram of the randomized trial.

the patients are described in Table 1. At the baseline, there was no significant difference in terms of duration and frequency of diurnal or nocturnal HF or the total score of MRS between groups.

One-way ANCOVA was used to compare the effect of three interventions on the number and duration of diurnal and nocturnal HFs. The results are presented in Table 2.

As shown in Table 2, there were significant differences in the mean number of diurnal HFs [$F_{(2,\ 78)}$=40.20, $p = 0.001$] between the groups. Therefore, *post hoc* tests were used, and their results showed significant differences between the PMRT and placebo groups ($p = 0.001$) and the escitalopram and placebo groups ($p = 0.001$), with no significant difference between the escitalopram and PMRT groups. A comparison of the estimated marginal means showed that the least diurnal HFs happened in the escitalopram and PMRT groups (mean = 2.11, 95% CI [1.46, 2.79] and 2.13, 95% CI [1.39, 2.82] respectively) compared to the placebo group (mean = 5.76, 95% CI [5.10, 6.41]). These findings reveal that both interventions decreased the number of diurnal HFs equally, whereas the placebo did not.

The results showed significant differences between the groups [$F_{(2,\ 78)}$=29.83, $p = 0.001$]. in terms of their effect on the number of nocturnal HFs. *Post hoc* tests showed significant differences between the PMRT and placebo groups ($p = 0.001$) as well as the escitalopram and placebo groups ($p = 0.001$), with no significant difference between the escitalopram and PMRT groups. The least nocturnal HFs were experienced by the escitalopram group (mean = 0.71, 95% CI [.31, 1.10]), followed by the PMRT group patients (mean = 0.88, 95% CI [.47, 1.29]) compared to the placebo group patients (mean = 2.78, 95% CI [2.37, 3.19]). The results revealed that both escitalopram and PMRT effectively decreased the number of nocturnal HFs, but the placebo was not effective. The same result was calculated for the total score of MRS and both escitalopram and PMRT (but not placebo), decreased total score of MRS.

The results were different about the duration of diurnal HFs [$F_{(2,\ 78)}$=7.70, $p = 0.001$]. The *post hoc* tests showed significant differences between the PMRT and

Table 1. Demographic characteristics of patients.

	PMRT $n = 28$	Escitalopram $n = 26$	Placebo $n = 28$	p
Mean age (SD)	42.71 (6.9)	43.84 (7.1)	41.42 (5.2)	0.534
Educational level (*n*, %)				
Illiterate	0 (0 %)	4 (15.38 %)	4 (14.3 %)	0.107
Primary education	17 (60.7 %)	2 (7.7 %)	8 (28.5 %)	
High school graduate	6 (21.4 %)	16 (61.5 %)	15 (53.5 %)	
University degree	5 (17.8 %)	4 (15.38 %)	1 (3.5 %)	
Daytime activity (*n*, %)				
Student	1 (3.5 %)	2 (7.7 %)	0 (0 %)	0.929
Office worker	5 (17.8 %)	2 (7.7 %)	2 (7.1 %)	
Self-employed	1 (3.5 %)	2 (7.7 %)	4 (14.3 %)	
Unemployed	21 (75 %)	20 (77%)	22 (78.5%)	

Table 2. Results of the one-way ANCOVA for group differences in treating hot flashes.

Group	Pretest *M* (SD)	Post-test *M* (SD)	*F*	Partial Eta squared
PMRT ($n = 28$)	5.25 (1.95)	1.65 (1.58)	40.20**	0.51
Escitalopram ($n = 26$)	9.88 (8.16)	2.89 (2.99)		
Placebo ($n = 28$)	6.03 (1.75)	5.50 (1.70)		
Number of nocturnal hot flashes				
PMRT ($n = 28$)	1.74 (2.09)	0.46 (1.13)	29.83**	0.43
Escitalopram ($n = 26$)	2.71 (1.11)	0.73 (1.04)		
Placebo ($n = 28$)	3.64 (1.06)	3.18 (1.34)		
Duration of diurnal hot flashes				
PMRT ($n = 28$)	4.92 (3.25)	2.89 (2.74)	7.69**	0.16
Escitalopram ($n = 26$)	4.15 (2.63)	1.36 (0.91)		
Placebo ($n = 28$)	3.21 (1.72)	3.10 (1.79)		
Duration of nocturnal hot flashes				
PMRT ($n = 28$)	4.53 (2.58)	2.35 (2.42)	13.23**	0.25
Escitalopram ($n = 26$)	4.38 (2.45)	1.28 (1.05)		
Placebo ($n = 28$)	3.32 (1.27)	3.25 (1.48)		
Score of PMRS				
PMRT ($n = 28$)	7.53 (5.48)	5.53 (4.36)	14.32**	0.93
Escitalopram ($n = 26$)	7.38 (5.55)	5.38 (3.05)		
Placebo ($n = 28$)	7.52 (6.27)	6.65 (4.50)		
Number of diurnal hot flashes				

Note. **$p < 0.001$.

escitalopram groups ($p = 0.01$), as well as the escitalopram and placebo groups ($p = 0.001$), but no significant difference between the PMRT and placebo groups. A comparison of the estimated marginal means showed that the least duration of diurnal HFs was experienced by the escitalopram group patients (mean = 1.35), compared to the PMRT and placebo group patients (mean = 2.68, 95% CI [1.96, 3.98] and 3.33, 95% CI [2.61, 4.05] respectively). The findings imply that only escitalopram decreased the duration of diurnal HFs effectively.

Furthermore, for the duration of nocturnal HFs [$F_{(2, 78)}$=13.23, $p = 0.001$], *post hoc* tests revealed significant differences between the PMRT and escitalopram groups ($p = 0.05$), PMRT and placebo groups ($p = 0.001$), as well as escitalopram and placebo groups ($p = 0.001$). The least duration of nocturnal HFs was experienced by the escitalopram group (mean-= 1.18, 95% CI [.54, 1.81]), followed by the PMRT group (mean = 2.20, 95% CI [1.59, 2.82]) compared to patients receiving placebo (mean = 3.49, 95% CI [2.87, 4.12]). This finding indicated that both escitalopram and PMRT effectively decreased nocturnal HFs, but escitalopram was more effective than PMRT.

Finally, to test statistical power, we have run *post hoc* power analyses utilizing GPower [44], finding the power of ($1 - \beta = 0.9$) at $\alpha = 05$ level. As a result, it is unlikely that the results of this study can be attributable to the sample size.

Discussion

Relieving menopausal symptoms of patients with breast cancer remains challenging. Studies continue to find treatment for vasomotor symptoms, such as HFs and night sweats [45], because of some limitations for the availablemethds like hormone replacement which is contradicted in patients with BC [46]. Antidepressants are also good options because HFs are more common and severe in the presence of depressive symptoms [47], and both affect the quality of life of these patients [48,49], but not all patients tolerate medications. Consequently, the present study aimed to compare the medicinal (i.e. escitalopram) and psychological (i.e. PMRT) interventions [25,26,38,39] and placebo in a randomized trial and showed that PMRT and escitalopram could effectively decrease the number and duration of diurnal and nocturnal HFs in patients with breast cancer, with a better effect observed from escitalopram.

The effectiveness of escitalopram has been reported by previous studies, too, though Biglia et al.'s. (2018) used a higher dose of escitalopram. In this study, escitalopram was compared to duloxetine and showed equal effectiveness. Identical results have been reported for healthy postmenopausal women [21,50,51]. Our findings demonstrated the unique effectiveness of escitalopram compared to PMRT and placebo. There was no reduction in the duration of diurnal HFs in the PMRT and control groups. Though we find that escitalopram and PMRT both effectively reduced the duration of nocturnal HFs, with some superiority of escitalopram.

Previous reports have demonstrated the effectiveness of PMRT in patients with breast cancer. Though [52] showed this effect does not remain when the intervention is finished [53]. demonstrated the effectiveness of a similar protocol (i.e. relaxation response training) in reducing HFs intensity and duration. These results are in line with the present study. Moreover, the benefits might not be limited to the effect on HF, and [54] reported a significant effect on sleep disturbance and perceived fatigue in patients with breast cancer. In another study [55], found that relaxation and guided imagery effectively reduced fatigue and sleep difficulties and alleviating psychological distress. Another interesting finding in the present study was the high rate of adherence to PMRT. According to previous studies, several side effects hinder participants from long-term use of medications [28,29]. Some of these adverse effects (e.g. impaired sexual functioning, drowsiness, and weight gain) [56] were reported by patients in the escitalopram group and resulted in withdrawal, while PMRT was reported to be a "relaxing experience" by the group members.

This study could not be double-blind in nature, and there was no control group for PMRT. Designing a sham intervention for these types of studies is not feasible, as there is no inactive form of relaxation training. We could not establish a follow-up visit after the termination of the intervention, so promising results are limited to the time of intervention for both escitalopram and PMRT. Excluding patients with major psychiatric conditions, like depression, added to the value of results. A combination of escitalopram and PMRT might also be considered as an intervention that further studies can evaluate.

In conclusion, this study added to the evidence that both escitalopram ad PMRT can reveal HFs in patients with breast cancer. These approaches can be chosen based on patients' preferences.

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