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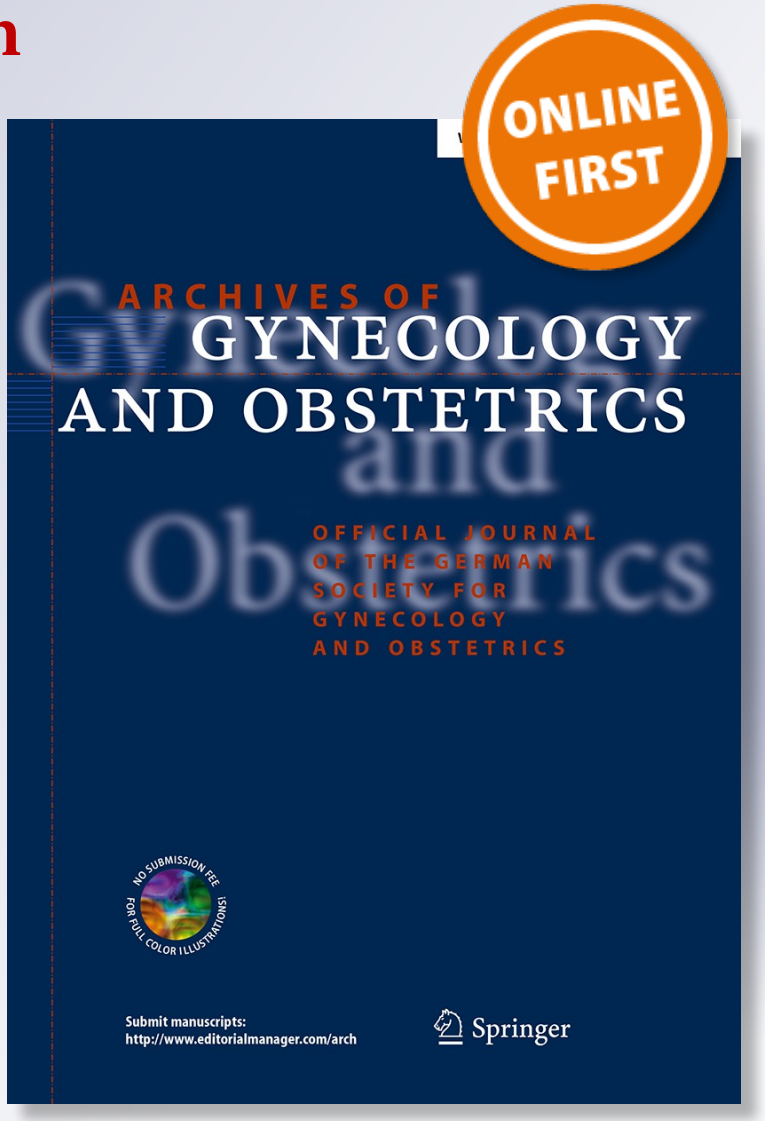

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GENERAL GYNECOLOGY

Comparison of citalopram and venlafaxine's role in treating sleep disturbances in menopausal women, a randomized, double-blind, placebo-controlled trial

Fatemeh Davari-Tanha[1] · Mohammad Soleymani-Farsani[1] · Mojgan Asadi[2] · Mamak Shariat[3] · Mahboobeh Shirazi[1] · Hasti Hadizadeh[1]

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Abstract

Introduction Sleep disturbance is a common complaint in postmenopausal women. Few studies compared symptom improvement taking antidepressants versus placebo. This study aims to evaluate the efficacy of venlafaxine and Citalopram compared to placebo in treatment of sleep disturbance in healthy postmenopausal women.

Method This randomized, double-blind, placebo-controlled clinical trial was conducted in three groups of 20 postmenopausal women. The patients took venlafaxine 75 mg/daily (group I) or citalopram 20 mg/d (group II) or placebo (group III). Each patient filled Pittsburgh sleep quality index (PSQI) and Pittsburgh and Beck depression questionnaires. The frequency of hot flashes in a day and its severity were measured through diaries. Somatic symptoms and adverse side effects were evaluated. Follow-up visit was conducted after 3 months. The prior and the later results were compared.

Results The PSQI scores in three placebo, venlafaxine, and citalopram groups before treatment were 14.25 ± 3.85, 11.55 ± 3.96, and 13.50 ± 3.56, respectively ($p = 0.076$). These values after treatment reached 9.95 ± 5.07, 8 ± 3.06, and 6.95 ± 1.84, respectively. PSQI score in citalopram and venlafaxine group was not significantly different ($p = 0.19$) but the score in both groups was significantly lower compared with placebo group after treatment ($p = 0.01$). The frequency of hot flashes in a day was reduced significantly by both citalopram and venlafaxine ($p < 0.05$), although it was more reduced by citalopram than venlafaxine ($p = 0.03$). Severity of hot flashes in both venlafaxine and citalopram was significantly lower in comparison with placebo group ($p = 0.02$), and there was no significant difference between two drugs, though ($p = 0.84$). Beck score decreased more in venlafaxine group in comparison with other groups but it did not reach significant ($p = 0.06$).

Conclusion Citalopram and venlafaxine are equally more effective than placebo in reducing sleep disturbance and severity of hot flashes, while citalopram is more effective in reducing frequency of hot flashes than venlafaxine. Meanwhile, venlafaxine is more effective than citalopram in treatment of depression in postmenopausal women.

Trial registration Iranian Registry of Clinical Trials 201210152576N6.

Keywords Citalopram · Venlafaxine · Sleep disturbances · Menopause

Introduction

Sleep difficulty is one of the most common complaints in perimenopausal and postmenopausal women. In comparison with general population with prevalence of 15 % sleep difficulty, one forth to one half of menopausal women has sleep complaints. A menopausal woman is 3, 4 times more likely to experience sleep difficulties than a premenopausal woman [1–4]. Sleep trouble in menopausal women is

✉ Fatemeh Davari-Tanha
fatedavtanha@gmail.com

[1] Department of OBS & GYN, Women Hospital-Vali-e-Asr Health Research Center, Tehran University of Medical Sciences, Tehran, Iran

[2] Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

[3] Maternal Fetal Neonatal Research Center, Tehran University of Medical Sciences, Tehran, Iran

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associated with hot flashes [5, 6]. There is also an association between menopause and depression which may be multifactorial and insomnia can be one of the reasons [7–9].

Hormone replacement therapy (HRT), as a treatment for hot flashes, has been reported to have cardiovascular benefit and reducing osteoporotic fractures, while it increases the risk of breast cancer [10]. Clonidine has been one of the treatments (reducing 34–44 % of symptoms) but it is now less applicable because of its side effects including dry mouth, fatigue, and hypotension [11, 12]. Gabapantin with dose of 300–900 mg has also been effective and reduced 66 % of symptoms [13]. Antidepressants are the most popular treatment other than HRT in hot flashes. Fluoxetine reduces 50 % of symptoms [14]. Paroxetine also decreases hot flashes 50–60 % [15]. A 5-week Randomized pilot trial has shown 64 % reduction of symptoms by using citalopram as treatment [16]. In a 4-week trial, prescribing higher doses of venlafaxine (75 and 115 mg) has shown 60 % reduction in symptoms [17]. These treatments are helpful in depressed patients with vasomotor symptoms. Besides, one of the side effects of Antidepressants is insomnia. However, an 8-week trial concluded that selective serotonin reuptake inhibitors (SSRIs)/serotonin–norepinephrine reuptake inhibitors (SNRIs) may improve sleep quality along with reducing hot flashes [18]. Few studies have evaluated the effect of SSRIs/SNRIs on sleep difficulty and concluded that it reduces insomnia symptoms. Yet they have suggested further trial studies to evaluate the efficacy of SSRIs such as Citalopram/SNRIs such as Venlafaxine in improving insomnia symptoms [18].

Study participants

In this double-blind, placebo-controlled trial, we compared the effect of venlafaxine with citalopram and placebo in reducing sleep difficulty and improving sleep quality in menopausal women.

Subjects and method

Sixty consecutive menopause patients with sleep trouble from menopause clinic of Women hospital in Tehran, Iran, were recruited during the year 2012.

Ethics

The ethics committee of Tehran University of Medical Sciences approved the study protocol. All of the collected data were stored and treated according to the ethical guidelines of medical research. All patients were given an informed consent about the aims and procedures and voluntarily. The data file was anonymous, and the identity of participants was protected.

Menopausal patients with sleep trouble complaint were recruited. Postmenopausal women were diagnosed based on Staging of Reproductive Aging Workshop (STRAW) staging system. Patients who were receiving Antidepressants or Benzodiazepines or hormone (replacement) therapy were not included. In the first visit, we performed history taking and physical examination of the patients, and then participants filled the Pittsburgh, and Beck questionnaire was filled for each participant.

Assessment

After history taking and physical examination and filling the Pittsburgh questionnaire, patients were randomly divided into three groups. Randomization was in blocks as follows: Each group received their medication in the following order: Group A: Venlafaxine, Group B: Citalopram, Group C: placebo. Blocks had three allele sizes in the following way: AACCBB, AABBCC, BBAACC, BCBCAA, CACABB, CBCBAA, etc., until the sample size was reached. The first group received Venlafaxine with the dose of 75 mg (began with 37, 5 mg during the first week then increased to 75 mg) for 8 weeks. The second group received Citalopram with the dose of 20 mg (began with 10 mg during the first week and then increased to 20 mg) for 8 weeks. The third group received placebo for 8 weeks. Medications were packed identically so that neither the patient nor the distributor knew about the contents of the pack. In the second and third month of the study, the Pittsburgh questionnaire was filled again. Measured variables were sleep quality, frequency of hot flashes per day, severity of hot flashes per day, somatic symptoms, and level of depression. Main outcome parameter was drug efficacy which was measured by a questionnaire asking about amount and severity of hot flashes based on 0–10 scales and the presence or the absence of somatic symptoms. PSQI questionnaire which measures quality of sleep and Beck questionnaire for depression were filled. Secondary outcome parameters were side effects including nausea, vomiting, headache, constipation, and drowsiness.

Statistical analysis

All of the data obtained from the checklists and questionnaires were entered into SPSS software version 20 (IBM; Chicago, IL, USA). Numerical variables are described using the mean and standard deviation (SD). The relative frequency percentage is also used to describe the nominal or categorical variables. Chi 2 test was used to compare qualitative outcomes between three groups, and ANOVA test was used to compare quantitative outcomes between

three groups. Independent *t* test was used to compare each two groups. The effect of Citalopram and Venlafaxine was compared with placebo in improving the sleep quality and decreasing sleep difficulty.

Results

Sixty women were evaluated in this study who were randomly divided into three groups. The first group received placebo, second group received venlafaxine, and third group received citalopram. Mean age of patients was 51.02 (±3.51), which was not significantly different between the groups (p value = 0.22).

We evaluated sleep quality with PSQI which is an index with maximum score of 21. Each group of our study completed this questionnaire before and after treatment. Mean of PSQI score before treatment was 14.25 (±3.85), 11.55 (±3.96), and 13.50 (±3.56), respectively, which was not significant difference between three groups (p value = 0.07). This score was 9.95 (±5.07), 8 (±3.06), and 6.95 (±1.84) after treatment. There was a significant difference between PSQI score in citalopram and placebo group (p value = 0.01), while there were no significant difference between other groups (p value >0.05). Figure 1 shows PSQI score in three groups before and after treatment.

The number of daily hot flashes was measured in the three groups. These attacks were 3.85 (±2.05), 3.85 (±2.34), and 3.70 (±2.08), respectively, before treatment, and 3.15 (±1.95), 2.80 (±2.06), and 1.60 (±1.18) after treatment. Hot flashes were not significantly different between three groups before treatment (p value = 0.96). Mean number of hot flashes was significantly different between placebo and citalopram group (p value = 0.04) and also venlafaxine and citalopram group (p value = 0.03). Figure 2 compares these attacks between the three groups.

Severity of hot flashes also was evaluated with a scale, ranged from 1 to 10. The mean score was 5.15 (±2.70), 4.50 (±2.83), and 5.15 (±2.36), respectively, in the three groups before treatment, which was not significantly different (p value = 0.06). This score reached 4.15 (±2.27), 2.65 (±1.78), and 2.75 (±1.33) after treatment. Severity of hot flashes was significantly different between venlafaxine and placebo group (p value = 0.026) and also citalopram and placebo group (p value = 0.023). Figure 3 shows these differences.

For evaluating severity of depression, Beck questionnaire was completed by patients. Beck score was 11.38 (±2.54), 11.75 (±2.62), and 12.19 (±2.72) before treatment which was not significantly different between three groups (p value = 0.69). The score reached 14.45 (±10.29), 7.75 (±6.62), and 12.40 (±9.47), respectively, after treatment. There were no significant differences in depression score between the three groups (p value = 0.06), although Beck score in venlafaxine group was lower than the other groups. Somatic symptoms and side effects are shown in Tables 1 and 2, which included vomiting, nausea, headache,

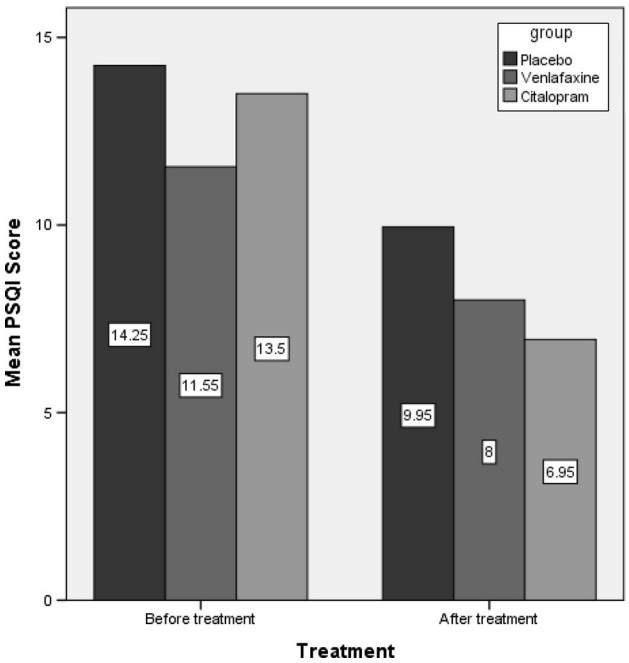

Fig. 1 Sixty patients in three groups of 20 are shown in the *bar*. Mean of PSQI score before and after treatment, which was not significantly different between three groups (p value = 0.07)

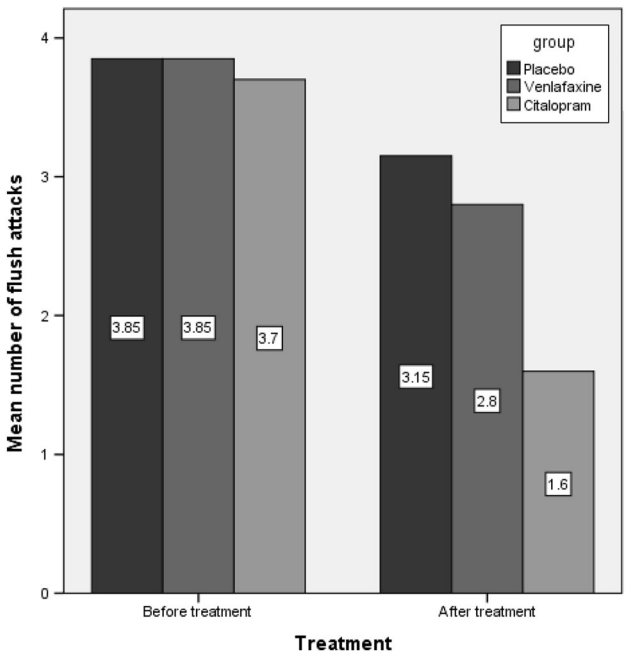

Fig. 2 Sixty patients in three groups of 20 are shown in the *bar*. Mean number of hot flashes was significantly different between placebo and citalopram group (p value = 0.04) and also venlafaxine and citalopram group (p value = 0.03)

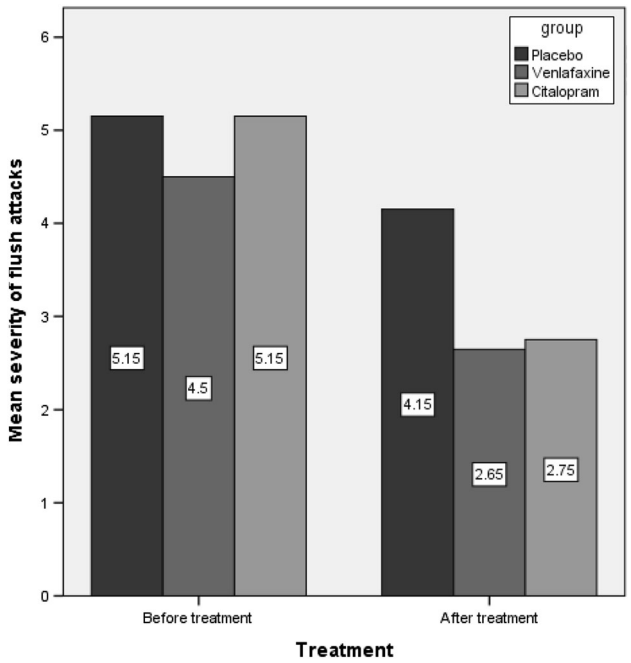

Fig. 3 Mean severity of hot flashes before and after treatment which was significantly different between venlafaxine and placebo group (p value = 0.026) and also citalopram and placebo group (p value = 0.023)

constipation, and lethargy. Although the only side effect which was significantly different among three groups was nausea which was 40 % in citalopram, 25 % in venlafaxine, and 0.05 % in placebo group (p value = 0.033). Among all participants, 35 % in citalopram, 42 % in venlafaxine, and 0.05 % in placebo group had vomiting. Headache was similar in citalopram and placebo group with the frequency of 15 %, while its frequency was 10 % in venlafaxine group (Fig. 4). Constipation was similar in citalopram and venlafaxine group with the frequency of 25 %, while its frequency was 15 % in placebo group. Lethargy was seen in 40 % of participants in citalopram group, 20 % in venlafaxine, and 15 % in placebo group.

Discussion

In this randomized placebo-controlled trial, there were no significant differences at baseline between groups for hot flashes times, PSQI, and Beck score.

There were no significant differences in terms of age between groups. There was also no significant correlation between age and indices. The role of age is described differently in various studies. Kravitz et al. deny any relationship of age and sleep disturbance [19]. Unlike them, Timur et al claimed that the risk of sleep disturbances increases 5 % with every year [20]. According to Wood et al., there is a significant relation between age and some parameters of sleep disturbances [21].

PSQI score decreased significantly in citalopram group, after treatment. Although there are not many studies on the effect of citalopram on sleep quality, lots of studies discussed SSRIs specially paroxetine. Stearns et al. and Weizner et al. claimed a significant improvement in sleep quality with six- and five-week therapy of paroxetine, respectively [22, 23].

In our study, number of daily hot flashes decreased significantly with citalopram. Both venlafaxine and citalopram led to less severe hot flashes, though. In a study by Loprinzi et al., a 4-week-use of placebo caused only

Table 1 Somatic symptoms of patients, before and after treatment. Tested significance between any treatment vs. placebo was non-significant

Somatic symptoms	Before treatment			After treatment		
	Placebo	Venlafaxine	Citalopram	Placebo	Venlafaxine	Citalopram
Vaginal dryness						
Yes	15	17	18	16	18	18
No	5	3	2	4	2	2
Sexual dysfunction						
Yes	13	14	11	15	17	14
No	7	6	9	5	3	6
Vaginal itching						
Yes	18	17	19	18	19	19
No	2	3	1	2	1	1
Skin changes						
Yes	17	15	17	17	18	18
No	3	5	3	3	2	2
Breast pain						
Yes	18	19	18	18	19	20
No	2	1	2	2	1	0

Table 2 Complication of treatments

Side effects	Placebo	Venlafaxine	Citalopram	*p* value*
Vomiting				
No	17	14	13	0.330
Yes	3	6	7	
Nausea				
No	19	15	12	0.032
Yes	1	5	8	
Headache				
No	17	18	17	0.866
Yes	3	2	3	
Constipation				
No	17	15	15	0.675
Yes	3	5	5	
Lethargy				
No	17	16	12	0.210
Yes	3	4	8	

* Tested significance is between any treatment vs placebo

27 % decrease in the frequency of hot flashes [24]. Barton et al. reported a 58 % reduction in the mean frequency of hot flashes in patients who received citalopram for 5 weeks [25].

Biglia et al. in an 8-week-study evaluated venlafaxine effect on frequency of hot flashes and found a 39 %-decrease in the frequency [26]. Suvanto-luukkonen et al. performed a 9-month-study on menopause symptom index in non-hormonal therapies and found no significant difference in number of hot flashes between citalopram, fluoxetine, and placebo groups [27].

Although there were no significant differences in Beck score between groups, this score was lower in venlafaxine group. Barton et al. suggested that a 5-week-treatment of citalopram decreased beck score and improved mood in patients [25]. Timur et al. suggested that depression will increase the risk of having sleep disorder 3.9 times in menopausal women. They also suggest that women with flushing attacks and depression are more likely to experience sleep disorders [20]. Hsu et al. showed a significant

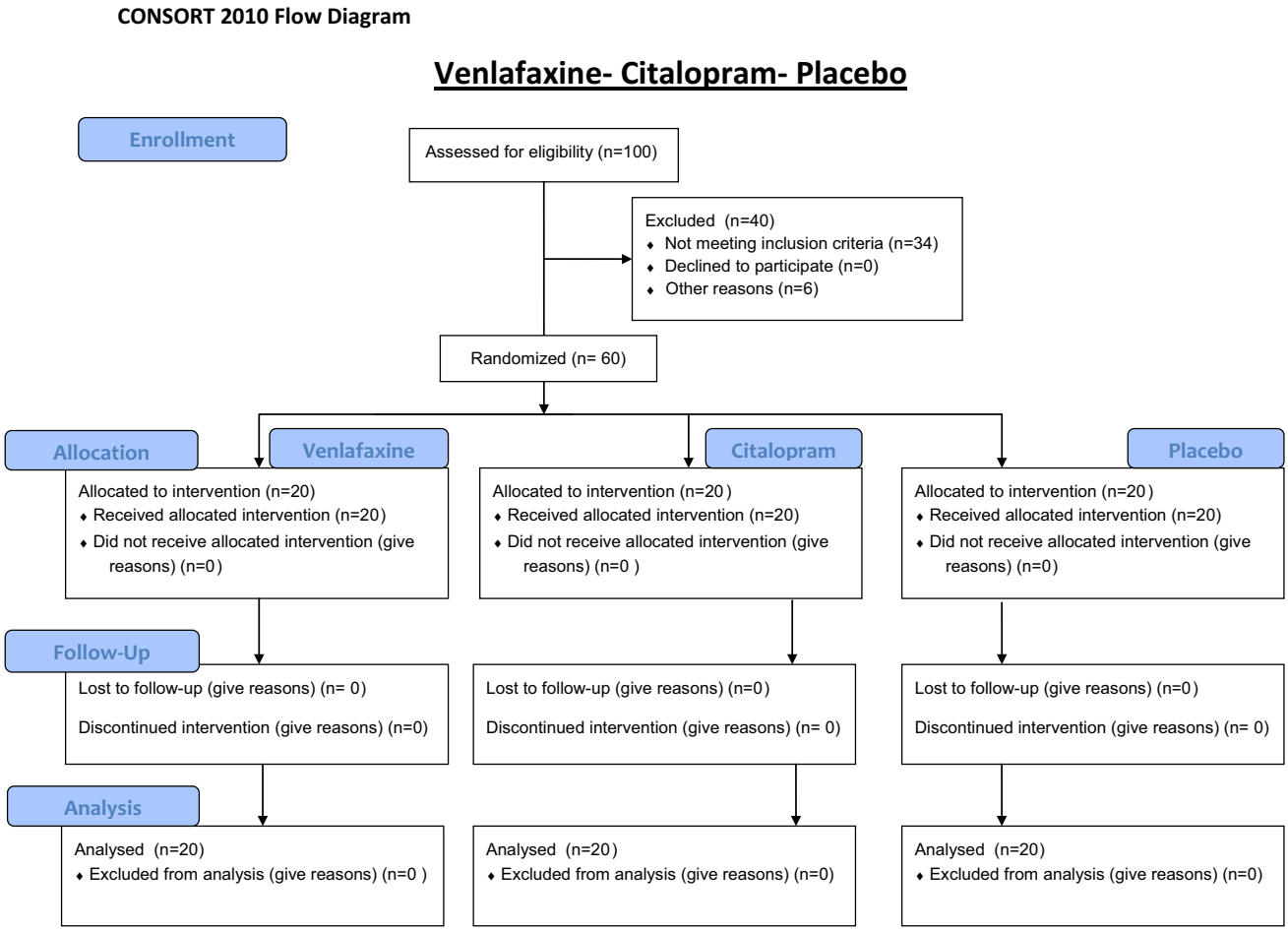

Fig. 4 Diagram of patients allocation in three groups

correlation between higher age and depression and sleep quality. We did not find the same result, though. Suvantolukkonen et al. conducted a longer term comparison study between citalopram, fluoxetine, and placebo and did not detect a significant difference in Beck score. The only index which improved in this study was insomnia in citalopram group. There was no significant correlation between sleep quality, Beck score, and number of hot flashes in their study [27].

One of the most important reasons for discontinuation of treatment with SSRIs and SNRIs is side effects of these drugs which are most gastrointestinal. In our study, the only significant complication was higher rate of nausea in citalopram group which was 40 % compared to 20 % in venlafaxine and 5 % in placebo group. Although the rate was high in venlafaxine group, it did not reach significant. Loprinzi et al. studied side effects of venlafaxine. Dry mouth, decreased appetite, constipation, and nausea were side effects of venlafaxine in their study [24]. Biglia et al. performed an 8-week-study on venlafaxine side effects. Complications were less common in this study and included dry mouth and nausea [26].

In a systematic review study, Warren et al. claimed that although there are many studies on the role of SSRIs and SNRIs on improvement in menopausal women and quality of sleep, fewer studies showed a significant difference between the effect of these drugs and placebo. There was only one SNRI (venlafaxine) which improved mood disturbances significantly among the studies reviewed, and two SSRIs (citalopram and paroxetine) improved quality of sleep significantly [28]. Our study almost yields similar results. The difference is that venlafaxine effect on mood disturbances improvement did not reach significance.

Limitations and suggestions

Studies with a longer period could evaluate drug effects and complications more precisely. Our study was performed in a single center. A multi-center study could strengthen the validity of results since it would facilitate a higher sample size including patients with different biological, ethnic-racial, and environmental characteristics. We did not study drug compliance in this study which is very important.

Conclusion

In this study, after treatment, PSQI score significantly decreased in citalopram group. Citalopram was also more effective on number of daily hot flashes. Hot flashes were significantly less severe in both venlafaxine and citalopram groups than placebo group. There were no significant differences in Beck score between groups, although this score was lower in venlafaxine group. Except for vomiting, complications and somatic symptoms did not differ significantly in three groups.

Compliance with ethical standards

Conflict of interest There is no conflict of interest.

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