Gabapentin and Fluoxetine for treatment of psychological symptoms: a cross over study

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ABSTRACT

The somatic and metabolic changes due to menopause can result in numerous symptoms including psychological symptoms. This study compares the effectiveness of Gabapentin vs. Fluoxetine in treatment of psychological symptoms of menopause. Methods:Eighty menopausal women with history of hot flashes and predefined psychological symptoms participated in a cross-over study conducted at the Amir-Al-Momenin hospital, Semnan, Iran. Participants were randomly divided into two groups: A and B. The study included two rounds of treatment, each 4 weeks long, separated by a two-week washout period. In the first round of treatment, group A was treated with Fluoxetine 20mg/d and group B with Gabapentin 300 mg/d. In the second round of treatment, group A received Gabapentin while group B received Fluoxetine (cross-over).All participants were asked to fill out the "Green Climacteric Scale" questionnaire at the beginning of the study and also following each round of treatment. They were also asked to monitor and keep track of the side effects of the medications by filling out another form. There was no significant difference between the two groups in age, body mass index, and age at menopause ($p>0.05$). The severity of irritability, fatigue, difficulty in concentrating, difficulty in sleeping, nervousness, and palpitation reduced to a significantly greater extent when the participants were treated with Gabapentin than when they were treated with Fluoxetine. Side effects (tremor) developed in only 2 Fluoxetine users and 2 Gabapentin users during the first 4 weeks of treatment. Our findings suggest that Gabapentin is more effective in alleviating the psychological symptoms of menopause than Fluoxetine. Thus, we recommend Gabapentin 300 mg/d for menopausal women who primarily complain about psychological symptoms, or those with contraindication to hormonal therapy.

Keywords: Gabapentin, menopause, Fluoxetine, women

INTRODUCTION

The World Health Organization defines menopause as the permanent cessation of a woman's menstrual cycle due to the termination of ovarian follicular activity. If a woman has missed her menstrual cycle for at least 12 consecutive months, and this has not been due to pregnancy, breastfeeding, or hormonal disorders, then she is considered to be in her menopause [1]. Not only a woman's reproductive ability ceases with menopause, the quality of her life is also affected by the associated physical and metabolicchanges. For example, osteoporosis and heart conditions are among common consequences of menopause [2]. The average age of menopause is 51 years old, and despite the increase in life expectancy, the menopausal age has remained the same [3]. Considering that the average life expectancy of American women is 81 years [4], they spend more than a third of their lives in postmenopause [3].

The main consequence of menopause is reduced estrogen level [3] which in turn causes a wide range of symptoms in postmenopausal women. Psychological symptoms are very common during perimenopause and menopause[5,6] and can be divided into two main groups: those that indicate anxiety and those that are considered as signs of depression [7,8]. The risk of depression in women is greatest between the ages of menarche and menopause [9,10] indicating that hormonal changes during this period most likely contribute to mood disorders in women [11].

Sleep disorders are also very common in menopausal women. In a study involving a large group of French women between the ages of 50

and 64 years, 25% reported sleep disorders [12]. From one hundred women who attended a menopause clinic, 80% complained from insomnia and over 90% complained from fatigue[13]. In another study by Kravitz and colleagues , 40 to 48% of perimenopausal and menopausal women complained from sleeping difficulty[14].

For over 60 years estrogen has been used as a hormonal supplement for treatment of menopausal symptoms. However, recent studies have shown that long term use of estrogen can cause numerous side effects including cardiovascular events, breast cancer and endometrial cancer [15-18]. Furthermore, many women are reluctant to use estrogen therapy. In addition, hormonal therapy has contraindication in women with estrogen-sensitive tumors, chronic liver dysfunction, acute thrombosis (with or without embolism) and vascular diseases of visual nervous system [19]. The aforementioned signifies the importance of other approaches, e.g. using other hormones and non-hormonal and non-medical treatments, for treatment of menopausal symptoms.

Fluoxetine is an antidepressant and belongs to a class of medications called Selective Serotonin Reuptake Inhibitors (SSRIs). Fluoxetine is used for treatment of obsessive-compulsive disorders, anxiety and sleep disorders [20,21]. Gabapentin is an anti-seizure medication that reduces the vasomotor symptoms of menopause [22,23]. Gabapentin has also been shown to alleviate a sleep disorder unique to women with low serum estradiol [24].

To the best of our knowledge, the effectiveness of Fluoxetine and Gabapentin in treatment of psychological symptoms of menopause and their potential side effects have not been examined yet. Therefore, in this study we examined and compared the effectiveness of Fluoxetine (20 mg/d) and Gabapentin (300 mg/d) in reducing the psychological symptoms of menopause. Specifically, we measured the participants' scores on irritability and feeling tired or lacking in energy as indications of depression, and their scores on feeling tense or nervous, heart beating quickly or strongly, difficulty in sleeping and difficulty in concentrating as indications of anxiety. We also monitored and compared the side effects of Fluoxetine and Gabapentin.

MATERIALS AND METHODS

Participants

Menopausal women who visited Amir-al-Momenin University Hospital in Semnan, Iran, complaining from hot flashes were invited to participate in this study. Volunteers were screened for the following inclusion and exclusion criteria: 1. It had been at least a year since they had their last monthly menstrual cycle; 2. They had at least 2 episodes of hot flashes per day and primary complaints of the psychological symptoms examined in this study; 3. They have not been taking any medications for treatment of menopausal symptoms during the last month prior to the study; 4. They have not been using multivitamins or blood thinners such as Warfarin; 5. They were not undergoing chemotherapy; 6. They were not receiving hormone therapy for menopause. Those with thyroid disorders, hemophilia, autoimmune disorders, diabetes, hypertension, or heart disease were also excluded from the study. Eighty volunteers who met the aforementioned inclusion/exclusion criteria were selected to participate in this study.

Procedure

Participants were briefed about menopause and its symptoms, prevention and treatment of these symptoms, effects of proper nutrition and exercise, the purpose of the study, experimental procedures and the potential side effects of the medications used in the study before signing a consent form. All procedures were approved by the Research Morality Committee of the Semnan Medical Science University.

Participants were randomly divided into two equal groups: A and B. The study included two four-week rounds of treatment separated by a two-week washout period. In the first round of treatment, group A received Fluoxetine 20mg/d while group B received Gabapentin 300 mg/d. In the second round of treatment, group A received Gabapentin and group B received Fluoxetine (cross-over). Neither of the groups received any medications during the two-week washout period.

At the beginning of the study and also after each round of treatment participants were asked to answer the questions related to the psychological symptoms of menopause in the "Green Climacteric Scale" questionnaire[7].

They were also asked to fill out a separate form created to track the side effects of the two medications used in the study, i.e., Gabapentin and Fluoxetine.

Data Analysis

Statistical analyses were performed using Kolmogorov–Smirnov test, t-test, Mann-Whitney, paired t-test, and Wilcoxon test. SPSS 18.0 was used for statistical analyses. For all tests, a significance value (p) of less than .05 was used to test statistical significance.

RESULTS

One participant did not comply with the instructions regarding the medication use and therefore her data were excluded from the analysis.

There was no significant difference between the two groups in age, body mass index and age at menopause (P>0.05) (Table 1).

Table 2 shows the scores of the two groups of participants on psychological symptoms based on the Greene Climacteric Scale, at the baseline (before any medical intervention) and at the end of the first and second rounds of treatment. The effect of medications on each psychological symptom was as follows:

Irritability

In comparison with baseline measures, Fluoxetine reduced the severity of irritability in group A by 20% (P=0.001) and in group B by 25% (P=0.002). Gabapentin reduced the severity of irritability in group A by 56% (P<0.001) and in group B by 76% (P<0.001).

Changes in the severity of irritability at the end of the first round of treatment were significantly greater in group B (Gabapentin users) than in group A (Fluoxetine users) (P=0.001).

Changes in the severity of irritability at the end of the second round of treatment were significantly greater in group A (Gabapentin users) than in group B (Fluoxetine users) (P<0.001).

Fatigue

In comparison with baseline measures, Fluoxetine reduced the severity of fatigue in group A by 30% (P<0.001) and in group B by 30% (P=0.001). Gabapentin reduced the severity of fatigue in group A by 57% (P<0.001) and in group B by 77% (P<0.001).

Changes in the severity of fatigue at the end of the first round of treatment were significantly greater in group B (Gabapentin users) than in group A (Fluoxetine users) (p=0.003).

Changes in the severity of fatigue at the end of the second round of treatment were significantly greater in group A (Gabapentin users) than in group B (Fluoxetine users) (p=0.029).

Difficulty in Concentrating

In comparison with baseline measures, Fluoxetine reduced the difficulty in concentrating in group A by 37% (P=0.001) and in group B by 25% (P=0.001). Gabapentin reduced the difficulty in concentrating in group A by 42% (P<0.001) and in group B by 19.5% (P=0.003). Changes in difficulty in concentrating were not different between the two groups, i.e., Fluoxetine and Gabapentin users, at the end of the first (P=0.328) and second (P=0.155) round of treatment.

Difficulty in Sleeping

Fluoxetine reduced sleeping difficulty in group A by 22% (P=0.002) and in group B by 17% (P=0.172). Gabapentin reduced sleeping disorders in group A by 34% (P<0.001) and in group B by 77% (P<0.001).

Changes in the severity of sleeping difficulties at the end of the first round of treatment were significantly greater in group B (Gabapentin users) than in group A(Fluoxetine users) (P=0.005). Changes in the severity of sleeping difficulties at the end of the second round of treatment were significantly greater in group A (Gabapentin users) than in group B (Fluoxetine users) (P=0.003).

Table 1. The Mean and Standard Deviation (SD) of Age, Body Mass Index (BMI) and age at menopause for the two groups

Characteristics	Group*	Number	Mean	SD	p-value
Age	Group A	39	52.4	4.4	0.128
	Group B	40	51.1	2.4	
BMI	Group A	39	27.5	3.6	0.358
	Group B	40	26.8	3.0	
Age at menopause	Group A	39	49.3	3.1	0.781
	Group B	40	49.5	2.2	

* During the first round of treatment (the first 4 weeks), group A received Fluoxetine and group B received Gabapentin. During the second round of treatment (the second 4 weeks), group A received Gabapentin and group B received Fluoxetine.

Table 2. Mean and Standard Deviation (SD) scores of participants on psychological symptoms based on the Greene Climacteric Scale, before any medical intervention and at the end of the first and second rounds of treatment in two groups

Symptom	Group*	Number	Severity before intervention		Severity at the end of the first round of treatment		Severity at the end of the second round of treatment	
			Mean	SD	Mean	SD	Mean	SD
Irritability	Group A	39	1.53	0.75	1.23	0.89	0.68	0.76
	Group B	40	1.10	0.74	0.28	0.64	0.88	0.75
	p-value		0.013		< 0.001		0.305	
Feeling tired or lacking in energy	Group A	39	1.15	0.95	0.80	0.85	0.50	0.88
	Group B	40	1.00	0.82	0.23	0.66	0.70	0.88
	p-value		0.476		< 0.001		0.170	
Difficulty in concentrating	Group A	39	1.08	0.73	0.68	0.69	0.63	0.63
	Group B	40	1.18	0.78	0.95	0.88	0.88	0.72
	p-value		0.676		0.178		0.120	
Difficulty in sleeping	Group A	39	1.48	1.06	1.15	1.03	0.68	0.83
	Group B	40	1.00	0.78	0.23	0.53	0.83	0.87
	p-value		0.034		< 0.001		0.406	
Feeling tense or nervous	Group A	39	1.48	0.91	1.15	1.08	0.40	0.90
	Group B	40	1.27	0.82	0.48	0.68	1.08	0.88
	p-value		0.373		0.003		< 0.001	
Heart beating quickly or strongly	Group A	39	0.80	0.61	0.63	0.67	0.23	0.53
	Group B	40	0.85	0.66	0.35	0.58	0.28	0.45
	p-value		0.760		0.043		0.360	

* During the first round of treatment (the first 4 weeks), group A received Fluoxetine and group B received Gabapentin. During the second round of treatment (the second 4 weeks) group A received Gabapentin and group B received Fluoxetine.

Nervousness

On average, Fluoxetine reduced the severity of nervousness in group A by 22% (P=0.002) and in group B by 17% (P=0.013). Gabapentin reduced the severity of nervousness in group A by 73% (P<0.001) and in group B by 79% (P<0.001). Changes in the severity of nervousness at the end of the first round of treatment were significantly greater in group B (Gabapentin users) than in group A (Fluoxetine users) (P=0.004).

Changes in the severity of nervousness at the end of the second round of treatment were significantly greater in group A (Gabapentin users) than in group B (Fluoxetine users) (P<0.001).

Palpitation

On average, Fluoxetine reduced palpitation in group A by 21% (P=0.008) and in group B by 67% (P<0.001). Gabapentin reduced the severity of nervousness in group A by 71% (P<0.001) and in group B by 59% (P<0.001).

Changes in the severity of palpitation at the end of the first round of treatment was significantly greater in group B (Gabapentin users) than group A (Fluoxetine users) (P=0.002). Changes in the severity of palpitation at the end of the second round of treatment were not significantly different between the two groups (P=0.897).

Side Effects

In general, most participants did not experience any side effects. Two participants from each group reported tremor. One participant from group A and 2 participants from group B reported anorexia.

DISCUSSION

The first step in managing depression and anxiety in menopausal women is to rule out the possibility of other factors unrelated to menopause such as thyroid malfunction [25,26], preexisting mental illness, significant loss, and family history [27]. Different approaches have been considered for treatment of depression and anxiety due to menopause, including exercise, cognitive behavioral therapy and medical treatments. Group cognitive behavioral therapy has proven effective in treating anxiety in menopausal women [28]. Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs) have been used to treat moderate to severe depression or anxiety that doesn't respond to non-medical treatments. Previous studies have shown that estrogen, alone or in combination with progestin, is not effective in treatment of severe depression in menopausal women [29,30].

There was no difference in the severity of depression between menopausal women who were treated with estrogen and the control group. Furthermore, estrogen did not improve the mood of postmenopausal women with mild to moderate depression. However, it was beneficial when used in combination with an SSRI [31]. We found that both Gabapentin and Fluoxetine significantly reduce the severity of symptoms of depression (i.e., irritability and fatigue), and anxiety (i.e., difficulty in concentrating, difficulty in sleeping, feeling tense or nervous, and heart beating quickly or strongly). The effects of Gabapentin and Fluoxetine on difficulty in concentrating were not different from each other; however, Gabapentin was more effective than Fluoxetine in alleviating every other symptom.

Few studies have examined the effect of Gabapentin and Fluoxetine on the psychological symptoms of menopause. Depression and sleep disorders are among the most common symptoms of menopause and are likely due to changes in CNS transmitters, including serotonin, norepinephrine, dopamine, and endorphins [32]. Serotonin plays a vital role in sleep regulation [33]; therefore, changes in serotonin level in menopausal women may contribute to their sleep disorders. This proposition is supported by the fact that treatment with an SSRI alleviates sleep disorders in menopausal women [34]. While some suggest that sleep disorders in menopausal women are due to hot flashes [35], results of Freedman's study show that such speculation is not always true [36].

SSRIs have been widely studied as potential treatments for menopausal mood symptoms. SSRIs are considered an appropriate treatment for vasomotor symptoms of menopause, given the well-documented role of serotonin in thermoregulation. Results of short-term clinical trials have shown that administration of SSRIs may reduce the frequency and severity of hot flashes. SSRIs have also been shown to improve mood, sleep, anxiety, and quality of life of menopausal women and those undergoing estrogen-deprivation therapy for breast cancer [34, 37, 38].

Combining SSRIs with low-dose hormone therapy has also proven to be an effective treatment. Results of a small-scale trial have shown that a combination of fluvoxamine (50 mg/d) with low-dose estrogen (0.3125 mg/d) was significantly more effective than estrogen alone in alleviating depression symptoms following oophorectomy [39]. Although it is not clear how Fluoxetine works, it does not seem that it works through hormonal (e.g. estrogen, progesterone, or androgen) pathways. Rather, it is speculated that Fluoxetine works by changing dopamine, serotonin, or norepinephrine pathways [40]. Biglia and colleagues [41] have shown that Gabapentin 900 mg/d improves sleep quality of menopausal women. Guttuso [24] also showed that Gabapentin reduces a type of sleep disorder unique to women with low serum estradiol. It has been shown that both unopposed estrogen therapy (ET) [42,43] and combined estrogen–progesterone therapy (EPT) [44,45] are effective in treatment of sleep disorders in menopausal women [46]. Hormone therapy allows examining whether sleep disorders during menopause are due to hormonal changes or not. In a study by Polo-Kantola et al., menopausal women who had no vasomotor symptoms reported improved sleep quality and reduced morning tiredness following hormone therapy [43].

CONCLUSION

We conclude that Gabapentin is more effective than Fluoxetine for treatment of psychological symptoms of menopause. Therefore, we recommend Gabapentin 300 mg/d for treatment of psychological symptoms in postmenopausal women who do not respond well to non-medical treatments such as exercise and cognitive behavioral therapy or those with contraindications to hormonal therapy. Future studies should investigate the lowest effective dose of Gabapentin in order to minimize its side effects.

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