International Journal of Gynecology and Obstetrics xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Gynecology and Obstetrics

journal homepage: www.elsevier.com/locate/ijgo

CLINICAL ARTICLE

A crossover study comparing gabapentin and fluoxetine for the treatment of vasomotor symptoms among postmenopausal women

Mojgan Rahmanian [a], Arash Mohseni [a], Raheb Ghorbani [b,*]

[a] Research Center of Abnormal Uterine Bleeding, Semnan University of Medical Sciences, Semnan, Iran
[b] Research Center for Social Determinants of Health, Department of Community Medicine, Faculty of Medicine, Semnan University of Medical Sciences, Semnan, Iran

ARTICLE INFO

Article history:
Received 29 November 2014
Received in revised form 31 March 2015
Accepted 18 June 2015

Keywords:
Fluoxetine
Gabapentin
Hot flash
Night sweats
Vasomotor symptoms

ABSTRACT

Objective: To compare the effectiveness of fluoxetine and gabapentin for treatment of vasomotor symptoms (VMS) after the menopause. *Methods:* Between March 2011 and March 2012, a randomized crossover study was performed at a center in Semnan, Iran, among postmenopausal women aged 45–57 years with hot flashes (≥2 per day for previous 4 months) for which they had received no previous treatment. Participants were divided into two groups with consecutive numbers assigned in order of recruitment. In the first treatment round (4 weeks), group A received 20 mg/day fluoxetine and group B received 300 mg/day gabapentin. After a 2-week washout period, group A received gabapentin and group B received fluoxetine in a second round (4 weeks). Information about VMS was obtained with the Greene Climacteric Scale questionnaire. Participants and all investigators except one were masked to group assignment. *Results:* Data for 79 participants (39 in group A, 40 in group B) were analyzed. In both treatment rounds, gabapentin caused greater reductions in the severity of hot flashes than did fluoxetine ($P < 0.001$ for both). After the first round of treatment, those who had received gabapentin reported greater reductions in the severity of night sweats ($P < 0.001$). *Conclusion:* Gabapentin at a dose of 300 mg/day is more effective for treatment of VMS among postmenopausal women than is 20 mg/day fluoxetine.

Iranian Registry of Clinical Trials: IRCT2014092711019N3.

1. Introduction

Menopause is the permanent cessation of a woman's menstrual cycle. Despite the increasing life expectancy worldwide, the average age at menopause has remained at approximately 51 years [1]. Considering that the average life expectancy of US women is 81 years [2], they are postmenopausal for more than one-third of their lives [1].

The main consequence of menopause is a reduced estrogen level [1], which in turn causes a wide range of symptoms. The most prevalent of these symptoms are vasomotor symptoms (VMS) [1,3,4], such as hot flashes and night sweats [4,5]. The underlying physiological mechanisms of hot flashes are not well understood. However, it is speculated that a central process initiates in the hypothalamus due to increased central body temperature, metabolism, and skin temperature, which leads to peripheral vasodilation and sweating in some women [1]. Over 65% of menopausal women report some type of VMS [3,4,6]. VMS usually diminish within the first year after the menopause; however, in some women these symptoms last for over 30 years [7]. VMS can interfere with a woman's work and activities of daily living [2], negatively affecting the quality of her life [6].

Estrogen-replacement therapy is the most effective treatment for VMS among postmenopausal women [1]. It is also the only common method of treatment approved by the US Food and Drug Administration [1,3,5]. Estrogen has been used as a hormonal supplement for treatment of menopausal symptoms for over 60 years [8]. However, recent studies have revealed multiple adverse effects of prolonged estrogen therapy, including cardiovascular events and cancers [5,9], and therefore many women are reluctant to use such treatment. Additionally, estrogen therapy is contraindicated for the treatment of VMS among women with estrogen-sensitive tumors, chronic liver dysfunction, acute thrombosis (with or without embolism), and vascular diseases of visual nervous system [6].

Other hormones, and non-hormonal and non-medical treatments have been considered for VMS among postmenopausal women. Gabapentin is an antiseizure medication that reduces VMS [10,11]. Fluoxetine has also been reported to reduce the symptoms of hot flashes when used for treatment of depression [12]. Although it is not clear how fluoxetine works, it is assumed to work centrally through changes in dopamine, serotonin, or norepinephrine pathways, rather than through changes in hormonal (e.g. estrogen, progesterone, or androgen) pathways [13].

* Corresponding author at: Research Center for Social Determinants of Health, Department of Community Medicine, Faculty of Medicine, Semnan University of Medical Sciences, Semnan 35198–9951, Iran. Tel.: +98 23 33654367; fax: +98 23 33654209.
E-mail addresses: r_ghorbani@semums.ac.ir, ghorbani.raheb93@gmail.com (R. Ghorbani).

http://dx.doi.org/10.1016/j.ijgo.2015.04.042
0020-7292/

However, previous studies conducted to examine the effectiveness of these drugs for treatment of VMS among postmenopausal women have used varying doses of fluoxetine (10–40 mg/day [14–17]) and gabapentin (100–2700 mg/day [18–20]). Furthermore, the effectiveness of gabapentin and fluoxetine and their adverse effects do not seem to have been directly compared. Therefore, the purpose of the present study was to compare the effectiveness of fluoxetine (20 mg/day) and gabapentin (300 mg/day) in reducing VMS among postmenopausal women. The adverse effects were also monitored and compared.

2. Methods

Women aged 45–57 years who visited the Amir-al-Momenin University Hospital in Semnan, Iran, between March 21, 2011, and March 19, 2012, complaining of hot flashes were enrolled in a randomized crossover study. Women were eligible when their last menstrual cycle was at least 1 year previously, they reported at least two hot flashes per day for the previous 4 months, and they had not previously received any treatment for hot flashes. Women taking multivitamins, blood thinners (e.g. warfarin), or other antidepressants were excluded, as were those undergoing chemotherapy. Women with thyroid disorders, hemophilia, autoimmune disorders, diabetes, hypertension, or rheumatic heart disease were also excluded. All participants were informed about the experimental procedure and the potential adverse effects of the medications used in the study before signing a consent form. All procedures were approved by the Office of Research Ethics of Semnan Medical Science University.

Each participant was assigned a number in order of recruitment. Participants with an odd number formed group A, and those with an even number formed group B. Both groups received two rounds of treatment (4 weeks each) with a 2-week washout period in between. In the first round of treatment, group A received 20 mg/day fluoxetine (Abidi Pharmaceutical Company, Tehran, Iran) while group B received 300 mg/day gabapentin (Razak Pharmaceutical Company, Tehran, Iran). In the second round of treatment, group A received 300 mg/day gabapentin while group B received 20 mg/day fluoxetine. Participants were masked to group assignment throughout the study; all drugs were provided in unlabeled containers. Among the investigators, only one (M.R.) was not masked to group assignment.

Participants were asked to complete items 19 and 20 of the Greene Climacteric Scale questionnaire (vasomotor symptoms) [21] before the first round of treatment, on completion of the first round, and on completion of the second round. Items 19 and 20 relate to hot flashes and sweating at night, which are the symptoms of interest in the present study. The severity of these symptoms was rated by participants using a four-point rating scale. The instructions were: "Please indicate the extent to which you are bothered at the moment by each of these symptoms by placing a tick in the appropriate box." They could answer "Not at all," "A little," "Quite a bit," and "Extremely." A trained research assistant (A.M.), masked to group assignment, helped the participants to fill out the questionnaire. The instructions were given in Farsi and an example was provided to ensure participants understood the instructions correctly.

Before each round of treatment, participants were provided with a list of potential adverse effects of gabapentin and fluoxetine (e.g. tremor, loss of appetite, sleepiness, dizziness, headache, fatigue, gastrointestinal disturbances, dry mouth and ataxia). Participants were given a diary and asked to record whether they experienced any of these adverse effects during the course of the study, when they occurred, and for how long. They were also instructed to contact the primary researcher (M.R.) if they experienced any severe adverse effect, and the plan was to discontinue the medication in such cases.

The checklists and the diaries were collected at the end of each round of treatment. Additionally, participants' age, years since menopause, weight, height, and body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) were recorded.

Statistical analyses were performed using the Kolmogorov–Smirnov test, *t* test, Mann–Whitney test, paired *t* test, and Wilcoxon test. SPSS version 18.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analyses. $P < 0.05$ was considered statistically significant.

3. Results

A total of 80 women were enrolled (Fig. 1). One participant assigned to group A failed to comply with the instructions regarding use of the medications; her data were excluded from the analysis. Therefore, data from 79 participants—39 in group A and 40 in group B—were used for the analysis. None of the participants had severe adverse effects that led to discontinuation of their treatment. There was no significant difference between the two groups in age, BMI, mean age at menopause, and time since menopause (Table 1). Before the first round of treatment, there was no significant difference between the two groups in the severity of hot flashes ($P = 0.210$) or night sweats ($P = 0.816$) (Table 2).

Both fluoxetine and gabapentin significantly reduced the severity of hot flashes for both groups: compared with baseline measures, fluoxetine reduced the severity of hot flashes in group A by 23% ($P = 0.011$) and in group B by 20% ($P < 0.001$), and gabapentin reduced the severity of hot flashes in group A by 55% ($P < 0.001$) and in group B by 68% ($P < 0.001$).

At the end of the first round of treatment, group B (who had received gabapentin) had a lower score for the severity of hot flashes than did group A (who had received fluoxetine; $P < 0.001$) (Table 2). At the end of the second round of treatment, group A (who had then received gabapentin) reported significantly less severe hot flashes than did group B (who had then received fluoxetine; $P < 0.001$) (Table 2).

Both drugs significantly reduced the severity of night sweats for both groups: compared with baseline measures, fluoxetine reduced the severity of night sweats in group A by 18% ($P = 0.001$) and in group B by 41% ($P < 0.001$); and gabapentin reduced the severity of night sweats in group A by 56% ($P < 0.001$) and in group B by 62% ($P < 0.001$).

At the end of the first round of treatment, group B (who had received gabapentin) had a significantly lower score for the severity of night sweats than did group A (who had received fluoxetine; $P < 0.001$) (Table 2). However, the scores for the severity of night sweats did not differ significantly at the end of the second round of treatment ($P = 0.071$) (Table 2).

Adverse effects were rare for both groups. Tremors were the only adverse effects reported while patients were taking gabapentin, and only 4 (5%) participants (two from each group) were affected. Lack of appetite was the only adverse effect reported for fluoxetine, and only 3 (4%) participants (one from group A and two from group B) were affected.

4. Discussion

In the present study, both fluoxetine and gabapentin reduced the severity of VMS among postmenopausal women. However, participants who received 300 mg/day gabapentin had a greater reduction in their VMS than did those who received 20 mg/day fluoxetine.

Gabapentin has been previously shown to effectively reduce hot flashes when compared with placebo. In a clinical experiment, Butt et al. [11] showed that 300 mg gabapentin three times per day (i.e. 900 mg/day) for 4 weeks significantly reduced the frequency of hot flashes. Similarly, Saati et al. [19] showed that 300 mg gabapentin three times per day for 3 months decreased the severity, frequency, and duration of hot flashes in menopausal women. In a systematic review of seven randomized controlled trials, Toulis et al. [22] showed that gabapentin (900–2400 mg/day) reduced the severity and frequency of hot flashes by 20%–30% among women with natural or tamoxifen-induced menopause.

Reddy et al. [10] showed that 2400 mg/day gabapentin for 12 weeks was as effective as 0.625 mg/day conjugated estrogen for treatment of hot flashes in postmenopausal women. Similarly, Allameh et al. [20]

Please cite this article as: Rahmanian M, et al, A crossover study comparing gabapentin and fluoxetine for the treatment of vasomotor symptoms among postmenopausal women, Int J Gynecol Obstet (2015), http://dx.doi.org/10.1016/j.ijgo.2015.04.042