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The comparison of paroxetine and gabapentin in the management of postmenopausal symptoms

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Abstract

Objective: To compare the clinical efficacy of gabapentin, an anticonvulsant agent, and paroxetine, a selective serotonin reuptake inhibitor in the management of post-menopausal symptoms.

Methods: In this clinical trial, two groups of patients with menopause who had hot flashes were included. One group received gabapentin (600 mg daily, 23 cases) for 8 weeks. The other group received paroxetine (one capsule daily at the morning or at bedtime, 23 cases) for 8 weeks. The MRS (Menopause Rating Scale) as well as the Beck's Depression Inventory were used to assess the efficacy of the studied medications.

Results: In paroxetine and gabapentin groups, hot flashes, sleep problems, muscle/joint pains, depression, irritability, anxiety, memory problems, and lack of concentration severity significantly decreased after 8 weeks of treatment. Only urinary problems in two treatment groups did not show any significant difference. There was no significant difference in dryness and burning sensation before and after gabapentin ($P > 0.05$). However, these changes were significant in paroxetine group ($P < 0.05$).

Conclusion: Both paroxetine and gabapentin were effective options in decreasing the severity of menopausal symptoms namely hot flashes, heart discomfort, sleep problems, and muscle/joint pains. In addition, the two medications had favorable results regarding psychological aspects of menopause.

Keywords: Gabapentin; Paroxetine; Menopause; Hot flashes

1. Introduction

Menopause is associated with several symptoms and complications. Following decreased secretion of ovarian estrogen, several menopausal symptoms begin to develop including After the extinction of the ovaries and the reduction of sex hormones, the effects of estrogen reduction appear as symptoms such as hot flashes, headaches, dizziness, frequent urination, depression, pruritus, and so on. Many of these complications can be prevented and treated [1]. Vasomotor symptoms (hot flashes and night sweating) are the most important and widely studied menopausal symptoms. Hot flash has been reported as a prevalent symptom in about half of the patients [2]. Vasomotor symptoms, not only bother the patients, but also affect the quality of life of the women adversely [3].

In addition to hormonal treatments suggested for short-term management of menopausal symptoms as the most effective and first-line treatment [4], other agents have been studied as well. This is mainly due to limitations for long term use of hormonal therapy and its potential side effects, especially breast and ovarian cancers as well as higher risk

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of developing thromboembolism which have been shown to become significantly more common following combined hormonal therapy [4-6].

Among the potential alternatives to hormonal therapy, antidepressants have gained widespread acceptability. Paroxetine, a selective serotonin reuptake inhibitor (SNRI), which is used for management of depression has been studied and showed acceptable efficacy in the management of vasomotor symptoms after menopause [7-9]. Although the exact mechanism that serotonin and norepinephrine in vasomotor symptoms is not understood completely, paroxetine decreases the skin blood flow and affects thermoregulation [10] and therefore ameliorates flushing associated with hot flashes [4]. Several studies have shown reduction of both frequency and severity of hot flashes after administration of paroxetine for 1 to 6 months [9].

Gabapentin is an anticonvulsant medication used in epilepsy, migraine prophylaxis, and neuropathic pain [11]. It is a GABA analogue which has been studied in menopausal women and shown to be effective in decreasing the severity of hot flashes [10,12,13]. Both paroxetine and gabapentin have been shown as effective and tolerable alternatives to manage vasomotor symptoms. However, it seems that further studies are required to demonstrate the effectiveness of these agents as well as the effect of these agents on a wider array of menopausal symptoms including psychological aspects. Therefore, the current study was designed to compare the effectiveness of gabapentin and paroxetine in menopausal women.

2. Material and methods

In this clinical trial, the study population consisted of women who presented to out academic gynecology clinic with the diagnosis of menopausal-related hot flashes. Considering the previous studies [14] and reduction rate of hot flashes of 71% for gabapentin and 33% for paroxetine and a power of 80% and confidence level of 95%, the required sample size was calculated as 23 patients in each group (a total of 46 patients).

Inclusion criteria were those women who experienced hot flash 7 times or more daily along with sweating and more than 12 months of menstruation cessation with FSH (follicle stimulating hormone) level of > 40 mIu/ml. Women with a history of chemotherapy, radiation therapy, depression, systemic diseases, liver disease, cancer, and diseases that cause hormonal disorders, or a history of panic or bipolar disorders (mood change with medication administration) were excluded. Patients were asked not to take any SSRI for any reason during the study period. After matching the two groups with at least 5 hot flashes per day, the first group received capsules of gabapentin (600 mg daily) for up to 8 weeks (56 days). Patients in the second group were administered paroxetine (one capsule daily at the morning or at bedtime) for 8 weeks (56 days).

The MRS (Menopause Rating Scale) was used. The validity of this scale and its content has been confirmed [15]. The MRS is a valuable international instrument for assessing menopausal symptoms that has been used in many clinical and epidemiological studies to determine the frequency and severity of menopausal symptoms in women [16]. This tool consists of 11 symptoms of menopause in three areas: somatic (4 questions), psychological (4 questions), and urogenital (3 questions). In the area of somatic problems, conditions including hot flashes, perspiration, heart discomfort, sleep disorders, and muscle and joint discomfort are assessed. In the psychological domain, depressive mood, irritability, anxiety, memory problems and lack of concentration are evaluated. In the urogenital domain, items include decreased sexual desire and satisfaction, urination problems, and vaginal dryness and burning. These items are scored on a 5-point Likert scale. In this study, score of 1 corresponded to the response “I do not have” and the score of 5 corresponded to the response “very severe”. The total score of the MRS falls in the range of 11 to 55. The lower the overall score of the MRS or the score for each domain, it reflects milder menopausal symptoms.

After determining the patients’ treatment groups (gabapentin r paroxetine), a code was determined for each patient. The patients were visited twice, once at the time of enrollment and for the second time 8 weeks after starting the study. At each visit, the MRS was filled out.

In order to assess depression in this study, the Beck’s Depression Inventory was used. The reliability and validity of this inventory in menopausal women has been studied previously with acceptable results [17]. According to the total score, the respondent is categorized as normal (score of 5 to 10), mild depression (score of 11 to 16), psychiatric consultation is suggested (score of 17 to 20), rather depressed (score of 21 to 30), and severe depression (score of 31 to 40).

2.1. Statistical analyses

Frequency, percentage, mean and standard deviation (SD) were used to express the data. The Kolmogorov-Smirnov (KS) test was used to determine normal distribution of continuous variables. Comparison of categorical variables between the study groups was done using the Chi-squared test or the Fischer's exact test. In order to compare the contiguous data, the student t test or Mann-Whitney U test was used. The Wilcoxon test was used to compare the change in the severity of the MRS domain items before and after the treatments. The paired t test was used to compare the Beck's Depression Inventory in each group after treatment. The analyses were done using SPSS software (ver. 16.0). The significance level was defined at 0.05.

3. Results

3.1. Demographic variables

Table 1 compares demographic variables between gabapentin and paroxetine groups. As observed, no significant difference was seen regarding the demographic variables between paroxetine and gabapentin groups.

Table 1 Comparison of demographic variables between gabapentin and paroxetine groups.

		Gabapentin	**Paroxetine**	**P value**
Age		50.78 (3.27)	50.70(3.48))	0.931
Marriage age		19.65 (4.19)	22.17 (4.23)	0.049
Menopause age		49.3 (3.02)	48.7 (3.03)	0.499
Number of Marriage	Once	19 (86.4%)	21 (91.3%)	0.668
	Twice	3 (16.3%)	2 (8.7%)	
Residence	Urban	9 939.1%)	14 (60.9%)	0.14
	Rural	14 (60.9%)	9 (39.1%)	
Occupation	Clerk	5 (21.7%)	9 (39.1%)	0.433
	Market	1 (4.3%)	1 (4.3%)	
	Unemployed	17 (73.9%)	13 (56.5%)	
Education	Illiterate	9 (39.1%)	3 (13%)	-
	Writing and reading	6 (26.1%)	5 (21.7%)	
	High school diploma/ secondary school	4 (17.4%)	8 (34.8%)	
	University	4 (17.4%)	7 (30.4%)	
Menstruation	Regular	15 965.2%)	18 (78.3%)	0.514
	Irregular	8 (34.8%)	5 (21.7%)	

3.2. MRS (Menstruation Rating Scale)/Somatic domain

Table 2 presents change in the severity of somatic items in paroxetine recipients. At baseline, 87% of the patients had very severe hot flashes. However, after 8 weeks of treatment, none of the patients had very severe hot flashes. As observed, except for heart discomfort, other items including hot flashes, sleep problems, and muscle/joint pain severity decreased significantly after eight weeks of treatment with paroxetine.

Table 2 Change in the severity of somatic items in paroxetine recipients.

		Absent	**Mild**	**Moderate**	**Severe**	**Very severe**	**P value**
Hot flashes	Baseline	1 (4.3%)	0	1 (4.3%)	1 (4.3%)	20 (87%)	< 0.001
	Week 8	6 (26.1%)	10 (43.5%)	5 (21.7%)	2 (8.7%)	0	
Heart discomfort	Baseline	14 (60.9%)	8 (34.8%)	1 (4.3%)	0	0	0.317
	Week 8	15 (65.2%)	7 (30.4%)	1 (4.3%)	0	0	
Sleep disturbences	Baseline	3 (13%)	3 (13%)	8 (34.8%)	6 (26.1%)	3 (13%)	< 0.001
	Week 8	14 (60.86%)	6 (26.1%)	3 (13%)	0	0	
Muscle and joint pains	Baseline	0	1 (4.3%)	3 (13%)	6 (26.1%)	13 (56.5%)	< 0.001
	Week 8	4 (17.4%)	7 (30.4%)	10 (43.5%)	1 (4.3%)	1 (4.3%)	

Table 3 presents change in the severity of somatic items in gabapentin recipients. As observed, except for heart discomforts, other somatic items including hot flashes, sleep problems, and muscle/joint pains decreased significantly after 8 weeks of treatment with gabapentin.

Table 3 Comparison of somatic domain of the Menstrual Rating Scale (MRS) in gabapentin group.

		Absent	**Mild**	**Moderate**	**Severe**	**Very severe**	**P value**
Hot flashes	Baseline	2 (8.7%)	4 (17.4%)	2 (8.7%)	5 (21.7%)	10 (43.5%)	< 0.001
	Week 8	3 (13%)	7 (30.4%)	11 (47.8%)	1 (4.3%)	1 (4.3%)	
Heart discomfort	Baseline	9 (39.1%)	9 (39.1%)	2 (8.7%)	2 (8.7%)	1 (4.3%)	0.107
	Week 8	9 (39.1%)	10 (43.5%)	3 (13%)	1 (4.3%)	0	
Sleep problems	Baseline	6 (26.1%)	1 (4.3%)	7 (30.4%)	3 (13%)	6 (26.1%)	0.003
	Week 8	10 (43.74%)	5 (21.7%)	6 (26.1%)	2 (8.7%)	0	
Muscle and joint pains	Baseline	0	2 (8.7%)	9 (39.1%)	8 (34.8%)	4 (17.4%)	< 0.001
	Week 8	2 (8.7%)	9 (39.1%)	7 (30.4%)	5 (21.7%)	0	

At baseline, a significant difference was seen regarding hot flash severity between paroxetine and gabapentin groups (P= 0.003). However, after 8 weeks of treatment, no significant difference existed between gabapentin and paroxetine groups (P= 0.107). The severity of heart discomforts was comparable between gabapentin and paroxetine groups at baseline (P= 0.709) and after the treatments (P= 0.061). This was also seen regarding sleep disorders as their severity was not different between the groups at baseline (P= 0.964) and after the treatment (P= 0.088). Although muscle/joint pain severity was different at baseline (P= 0.006), this was comparable between the groups after treatment (P= 0.540).

3.3. MRS (Menstruation Rating Scale)/Psychological domain

Table 4 presents change in the severity of psychological items in paroxetine recipients. A significant decrease in the severity of all items of psychological domain including depression, irritability, anxiety, and memory/concentration problems was seen after 8 weeks of treatment with paroxetine.

Table 4 Change in the severity of psychological items in paroxetine recipients.

		Absent	**Mild**	**Moderate**	**Severe**	**Very severe**	**P value**
Depression	Baseline	0	2 (8.7%)	9 (39.1%)	9 (39.1%)	3 (13%)	< 0.001
	Week 8	13 (56.52%)	9 (39.1%)	1 (4.3%)	0	0	
Irritability	Baseline	0	5 (21.7%)	10 (43.5%)	6 (26.1%)	2 (8.7%)	< 0.001
	Week 8	15 (65.21%)	7 (30.4%)	1 (4.3%)	0	0	
Anxiety	Baseline	0	4 (17.4%)	10 (43.5%)	7 (30.4%)	2 (8.7%)	< 0.001
	Week 8	13 (56.52%)	9 (39.1%)	1 (4.3%)	0	0	
Memory problem and lack of concentration	Baseline	14 (60.86%)	5 (21.7%)	3 (13%)	1 (4.3%)	0	< 0.001
	Week 8	18 (78.26%)	3 (13%)	2 (8.7%)	0	0	

Table 5 presents change in the severity of psychological items in gabapentin recipients.

		Absent	**Mild**	**Moderate**	**Severe**	**Very severe**	**P value**
Depression	Baseline	1 (4.3%)	3 (13%)	13 (56.52%)	4 (17.4%)	2 (8.7%)	< 0.001
	Week 8	8 (34.78%)	12 (52.2%)	3 (13%)	0	0	
Irritability	Baseline	6 (26%)	3 (13%)	11 (47.8%)	2 (8.7%)	1 (4.3%)	0.006
	Week 8	12 (52.17%)	6 (26.1%)	5 (21.7%)	0	0	
Anxiety	Baseline	9 (39.1%)	5 (21.7%)	9 (39.1%)	0	2 (8.7%)	0.046
	Week 8	14 (60.86%)	6 (26.1%)	2 (8.7%)	1 (4.3%)	0	
Memory problem and lack of concentration	Baseline	13 (56.52%)	4 (17.4%)	5 (21.7%)	0	1 (4.3%)	0.014
	Week 8	18 (78.26%)	3 (13%)	2 (8.7%)	0	0	

At baseline, no significant difference was seen regarding depression severity between paroxetine and gabapentin groups (P= 0.089). After 8 weeks of treatment, no significant difference existed between gabapentin and paroxetine groups (P= 0.078). Although the severity of irritability showed a significant difference between gabapentin and paroxetine groups at baseline (P= 0.039), after treatment this item was comparable between the groups (P= 0.297). Likewise, anxiety showed difference at baseline (P< 0.001), but not after treatment (P= 0.078). Lack of memory and concentration problems were comparable at both baseline (P= 0.606) and after treatment (P= 0.606).

3.4. MRS (Menstruation Rating Scale)/Genitourinary domain

Table 6 presents change in the severity of genitourinary items in paroxetine recipients. As seen, all three items in the genitourinary domain showed decreased severity after 8 weeks treatment with paroxetine.

Table 6 Change in the severity of genitourinary items in paroxetine recipients.

		Absent	Mild	Moderate	Severe	Very severe	P value
Sexual desire and satisfaction	Baseline	1 (4.3%)	3 (13%)	13 (56.52%)	4 (17.4%)	2 (8.7%)	< 0.001
	Week 8	8 (34.78%)	12 (52.2%)	3 (13%)	0	0	
Urination problems	Baseline	6 (26%)	3 (13%)	11 (47.8%)	2 (8.7%)	1 (4.3%)	0.006
	Week 8	12 (52.17%)	6 (26.1%)	5 (21.7%)	0	0	
Vaginal dryness and burning	Baseline	9 (39.1%)	5 (21.7%)	9 (39.1%)	0	2 (8.7%)	0.046
	Week 8	14 (60.86%)	6 (26.1%)	2 (8.7%)	1 (4.3%)	0	

Table 7 presents change in the severity of genitourinary items in gabapentin recipients. As seen, only urination problems improved after treatment. But, vaginal dryness/burning and sexual desire/satisfaction did not improve.

Table 7 Change in the severity of genitourinary items in gabapentin recipients**.**

		Absent	Mild	Moderate	Severe	Very severe	P value
Sexual desire and satisfaction	Baseline	4 (17.4%)	6 (26%)	9 (39.1%)	4 (17.4%)	0	-
	Week 8	5 (21.7%)	6 (26%)	8 (34.8%)	4 (17.4%)	0	
Urination problems	Baseline	16 (69.56%)	1 (4.3%)	6 (26.1%)	0	0	0.026
	Week 8	19 (82.60%)	4 (17.4%)	0	0	0	
Vaginal dryness and burning	Baseline	7 (30.43%)	5 (21.7%)	5 (21.7%)	6 (26.1%)	0	0.956
	Week 8	7 (30.43%)	4 (17.4%)	7 (30.43%)	5 (21.7%)	0	

At baseline, no significant difference was seen regarding sexual desire/satisfaction at baseline (P= 0.353) or after treatment (P= 0.071). Likewise, this was seen regarding urination problems at baseline (P= 0.269) and after treatment (P= 0.896). Vaginal dryness/burning was also showed no difference between paroxetine and gabapentin groups at baseline (P= 0.433) or after treatment (P= 0.657).

3.5. Beck's Depression Inventory

There was no significant improvement in Beck's Depression Inventory after treatment (14.35) compared to baseline score (13.7) in paroxetine group (P= 0.610). At baseline, two patients were normal, 9 patients (56.25%) had mild depression, 3 (18.75%) required consultation, and two were rather depressed (12.5%). After treatment, normal score was found in 7 patients (43.75%), 8 had mild depression (50%) and only one patient required consultation.

In gabapentin group, similar to paroxetine group, no significant change was seen in the Beck's Depression Inventory from baseline (20.38) and after treatment (19.71); P= 0.552.

4. Discussion

Based on the current results, both paroxetine and gabapentin were effective in reducing the severity of menopausal symptoms. Hot flashes, muscle/joint pains, sleep problems, and heart discomfort decreased significantly after 8 weeks. These agents have gained attention in treatment of menopausal symptoms owing to the fact that hormonal therapy is associated with several morbidities. Several previous studies have confirmed the efficacy of gabapentin in the management of hot flashes [18, 19]. In a previous report [20], gabapentin was found to be superior to fluoxetine in the treatment of vasomotor symptoms of menopause. Gabapentin dose used in the latter study was 300 mg daily. Here, we used 600 mg of gabapentin daily. There is no consensus about the optimal dose of gabapentin for vasomotor symptoms, however, a dose range of 600 to 2,400 mg daily has been proposed as recommended gabapentin dosage [19]. We

observed a very good effect of gabapentin in both somatic and psychological domains of menopause. In a previous study, the effect of gabapentin in this regard has been reported as mild to moderate [21]. Also, in a study by Albertazzi et al . [22], gabapentin was considered to be a therapeutic option for women who have contraindication to receive hormonal contraceptives to reduce hot flushes, which is consistent with our findings.

Rahmanian et al. [20] studied women aged 45 to 57 years who had had at least 2 hot flashes in the past 4 months and who had received no previous treatment. Postmenopausal women received fluoxetine 20 mg in the first group, and patients in the second group received 300 mg of gabapentin. After two weeks, the first group received gabapentin and the second group received fluoxetine (for 4 weeks). Gabapentin treatment was associated with a higher reduction in the intensity of hot flashes than fluoxetine ($P < 0.001$). After the first round of treatment, those who received gabapentin had a greater reduction in the rate of night sweats ($P < 0.001$). In a study by Reddy et al . [23], a study aimed to compare the effects of gabapentin, estrogen and placebo in the treatment of hot flashes, 60 postmenopausal women were included in the study. The results showed that 12-week post-mortem scores of gabapentin (71%) and the estrogen group decreased by 72% compared with the placebo group. The combined score in both estrogen and gabapentin groups did not show a significant difference after treatment ($P = 0.63$). Our findings showed that gabapentin was effective for sleep disorders. Likewise, another study showed effective properties of gabapentin in patients with sleep disorders [24]. Although gabapentin was effective in most studied variables, it did not have effect on vaginal dryness/burning sensations which is in agreement with the results of a previous report [25].

Similar to gabapentin, paroxetine has been introduced as an effective, safe, and tolerable agent for vasomotor symptoms in menopause [4]. Our findings showed that paroxetine significantly decreased severity of hot flashes, sleep disturbances, muscle/joint pain and also psychological symptoms. These are comparable to several previously reported studies. It has been suggested that there are various indications for supporting serotonin reuptake inhibitor drugs, such as paroxetine, in menopausal management and the Food and Drug Administration [FDA] has introduced paroxetine in the treatment of moderate to severe menopause [9]. Several studies have investigated the therapeutic effect of serotonin reuptake inhibitors such as paroxetine. For example, a previous study [4] introduced paroxetine as an effective treatment for menopause. In this study, it was suggested that to minimize adverse effects of paroxetine, low doses of paroxetine, and also specific patient characteristics need to be considered. Similar to gabapentin, paroxetine did not show favorable effects regarding items of the Beck's Depression Inventory. This can be due to complexities regarding interactions between menopause itself on one side and related psychological problems on the other side.

4.1. Limitations

Here we were not able to examine different doses of gabapentin and paroxetine. Also, the studied variables covered mainly symptoms of menopause another aspect of quality of life such as general wellbeing and job productivity were not assessed. It is recommended to study these variables in the future studies.

5. Conclusion

Both paroxetine and gabapentin were effective options in decreasing the severity of menopausal symptoms namely hot flashes, heart discomfort, sleep problems, and muscle/joint pains. In addition, the two medications had favorable results regarding psychological aspects of menopause.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflict of interest.

Statement of ethical approval

Statement of informed consent

Informed consent was obtained from all participants included in the study.

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