ORIGINAL ARTICLE

Safety and efficacy of gabapentin in management of psychosomatic and sexual symptoms in postmenopausal women: A pilot study

Nutan Agarwal, Smita Singh, Alka Kriplani, Neerja Bhatla, Nilanchali Singh

Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, New Delhi, India

ABSTRACT

Objective: To evaluate safety and efficacy of gabapentin in management of psychosexual symptoms in postmenopausal women.

Materials and Methods: Fifty symptomatic postmenopausal females were randomly allocated into two groups; Group I received gabapentin 900 mg/day along with calcium 500 mg and Group II was given only calcium for 6 months and followed-up at 1,3, and 6 months. Data was analyzed in terms of percentage reduction of psychosomatic and sexual symptoms. Change in lipid profile and other blood parameters by the end of study were measured.

Results: Maximum improvement was seen in insomnia (90-98%) in gabapentin group. Improvement in anxiety was noted by 40.5, 49.5, and 53.8% at 1, 3, and 6 months, respectively, in Group I. While in Group II, maximum improvement noted was 18.6, 19.7, and 20% at 1, 3, and 6 months, respectively. Similarly for depression, improvement was 40.4,47, and 49.5%at 1, 3, and 6 months, respectively, in Group I; while it was 15.4, 16.6, and 17% at 1, 3, and 6 months, respectively, in Group II. No significant improvement in vaginal dryness and dyspareunia noted at all follow-ups in either group. Somatic symptoms reduced by 33, 36.8, and 40% at 1, 3, and 6 months, respectively, in Group I compared to 18% improvement at all follow-up in Group II. Low density lipoprotein (LDL) was raised in Group I significantly more than Group II. Other blood parameters were comparable in both groups.

Conclusion: Gabapentin can lead to improvement in postmenopausal psychosomatic symptoms, while sexual symptoms show no improvement. Gabapentin can lead to increase in serum LDL, hence, precaution should be taken in patients with deranged lipid profile before starting therapy and it should be monitored during course of therapy. This drug can cause minor side effects like somnolence and dizziness.

Key Words: Gabapentin, postmenopausal, psychosomatic, sexual symptoms, side effects

INTRODUCTION

Menopause is a universal and irreversible part of the overall aging process involving a woman's reproductive system and affects her physical and mental health in the form of various vasomotor and psychosexual symptoms. Hormone replacement therapy with agents such as estradiol is effective in reducing these symptoms, but interest in nonhormonal therapies has increased recently. Till date hormone replacement therapy is the only Food and Drug Administration (FDA) approved treatment for postmenopausal symptoms, but recent primary and secondary prevention trials show associated increased risk of coronary disease, thromboembolism, and stroke.[1] Women Health Initiative (WHI) also points towards increased risk of breast cancer and slight increased risk of Alzheimer disease with HRT.[2] Recent evidence-based reviews of complementary and alternative therapies and non-hormonal agents conclude that there are insufficient data regarding their effectiveness.[3,4] There is little

Address for Correspondence: Dr. Nutan Agarwal, Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, New Delhi - 110 039, India.
E-mail: nutan.agarwal1@gmail.com

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emerging evidence in literature regarding gabapentin, an F-aminobutyric acid, for treatment of hot flushes, but therapy is still evolving.[5-8] Gabapentin is FDA approved for many neurological conditions like neuralgia and epilepsy. However, the role of gabapentin in menopausal psychosexual and somatic symptoms has not been studied much. Hence, this study was undertaken to assess the efficacy of gabapentin in these postmenopausal symptoms.

MATERIALS AND METHODS

This was a pilot study conducted in Department of Obstetrics and Gynecology at a tertiary care hospital from October 2009 to March 2011. Ethical clearance was obtained from institutional ethical committee. Fifty women with natural or surgical menopause presenting to menopause clinic of tertiary care center were recruited in the study after taking informed consent. Complete menstrual, obstetric, and medical history was taken. Presence and severity of menopausal symptoms were noted. Each patient underwent a thorough general and gynecological examination and a battery of investigations: Blood sugar, lipid profile, Pap smear, mammography as screening investigations; ultrasonography to evaluate endometrial thickness and any associated genital pathology.

Inclusion criteria were age between 45 and 55 years, no menses for ≥1 year, serum follicle stimulating hormone level of ≥40 mIU/ml, clinically normal pelvic examination, and normal Pap smear with any of the following psychosomatic and sexual symptoms like insomnia, fatigue, depression, irritability, nervousness, vaginitis, or dyspareunia. Exclusion criteria were asymptomatic women, abnormal screening investigations, prior hormonal or antidepressant treatment in last 6 months, and renal or liver disorders.

Randomization

Total 58 women were recruited out of which eight were excluded due to elevated thyroid-stimulating hormone (TSH; $n = 4$), not willing for follow-up ($n = 2$), currently on hormone therapy ($n = 2$). Rest 50 women were randomized into two groups using computerized randomization table. Opaque envelope method was used to assign the randomization group.

Intervention

Detailed history was taken regarding presence of psychosexual (anxiety, depression, vaginal dryness, and dyspareunia) and somatic symptoms (insomnia, fatigue, lethargy, body aches, and heaviness) and their baseline severity. Psychological, sexual, and somatic symptoms were recorded and graded on Likert scale by putting self-administered questionnaire to the patient as 0-4 for absent, mild, moderate, and severe symptoms, respectively [Table 1]. Pretrial investigations included all baseline blood chemistry along with fasting lipid profile. Group I patients received gabapentin 900 mg/day (300 mg thrice daily) along with tablet calcium 500 mg once daily. Group II patients received only tablet calcium (500 mg once daily). Gabapentin was gradually increased from once daily at bedtime to thrice daily 1st week to avoid the side effects. Similar tapering was also required during discontinuation of therapy. Patients were asked to keep record of symptoms.

Follow up

Follow-ups were made after 1, 3, and 6 months of therapy. At each follow-up, symptoms were questioned and scored and any adverse effects were assessed. At 6 months follow-up, serum chemistry and fasting lipid profile were repeated.

Outcome measures

At the end of study, data was analyzed in terms of percentage reduction of psychosomatic and sexual symptoms. Change in lipid profile or any alteration

Table 1: Grading of various psychosexual and somatic symptoms

Symptom	Score 1	Score 2	Score 3
Anxiety	Mild	Moderate	Severe
Depression	Feeling only on questioning	Spontaneously reported	Through facial expression, posture and tendency to weep
Insomnia	Occasional	Difficulty during night	Severe
Other somatic symptoms (heaviness in limbs, back, head)	Mild symptoms not requiring drugs	Severe symptoms requiring drug treatment	Symptoms not relieved by drugs
Work and activity problems	Feeling fatigue and weakness	Loss of interest in activities	Stopped working
Vaginal dryness	Mild	Moderate	Severe
Dyspareunia	Mild discomfort	Moderate discomfort	Does not allow intercourse

in hemoglobin, total protein, and urea/creatinine was measured between baseline and at the end of study. The study protocol is depicted in Figure 1.

Statistical analysis

Data was analyzed using Statistical Package for Social Sciences (SPSS)15. Changes in continuous parameters were analyzed by repeated measure analysis of variance (ANOVA)/Friedman test within groups and by independent *t*-test/Wilcoxon rank-sum test between the two groups. Multiple comparisons were done by Wilcoxon signed-rank test with Bonferroni correction. Categorical variables between two groups were compared by chi-square test/Fischer's exact test. *P*-value <0.05 was taken as statistically significant.

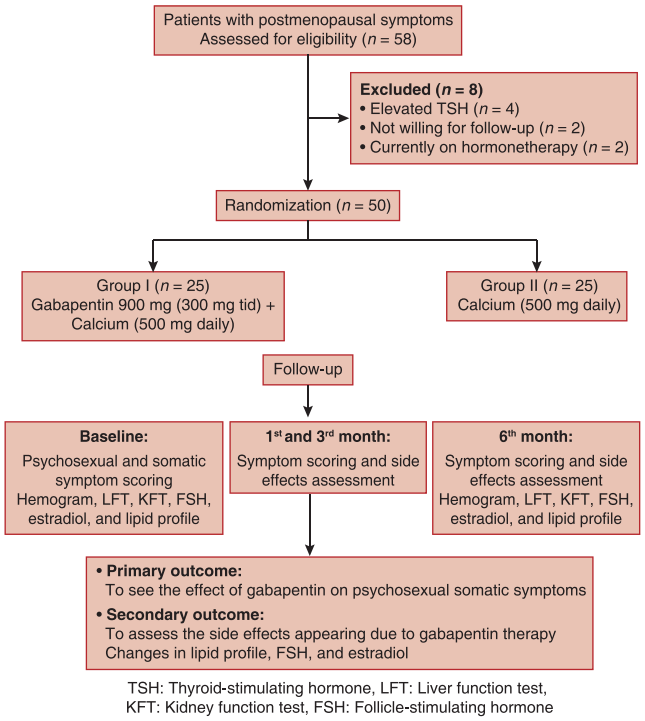

Figure 1: Consort flowchart

RESULT

All baseline characteristics were comparable in participants of both groups. No statistical difference was found between groups in terms of age or participant distribution in natural and surgical menopause ($P = 0.37$). Duration of menopause was comparable in both groups ($P = 0.11$). Baseline lipid profile and TSH values were comparable too [Table 2].

Maximum improvement was observed in insomnia (90-98% improvement in Group I compared to marginal improvement of around 4% in Group II). Improvement in anxiety was noted by 40% at 1 month to a maximum of 49% at 3 months with marginal improvement noted beyond, in Group I. While in Group II, maximum improvement noted was around 20% (18.6, 19.7, and 20% at 1, 3, and 6 months, respectively). Similarly for depression, improvement was seen by 40.4% at 1 month, 47% at 3 months, and 49.5% at 6 months in Group I; while it was <20% (15.4, 16.6, and 17% at 1, 3, and 6 months, respectively) in Group II. No significant improvement in vaginal dryness and dyspareunia noted at all follow-ups in either group. Somatic symptoms reduced by 33, 36.8, and 40% at 1, 3, and 6 months, respectively, in Group I compared to18% improvement at all follow-up in Group II [Table 3].

No significant change in serum cholesterol was found between baseline and at end of therapy in both groups, neither was there any significant difference in serum triglycerides in both the groups. Serum low density

Table 2: Baseline characteristics of cases in both groups

Baseline characteristics	Group 1	Group 2	*P*-value
Age (years), mean±SD (range)	46.2±6.6 (25-56)	45.84±6.8 (25-53)	0.83
No. of patients			
Natural menopause	15	18	0.37
Surgical menopause	10	7	0.26
Duration of menopause (months) median (range)	12 (12-180)	24 (3-96)	0.11
Height (cm), mean±SD (range)	156.3±5.3 (158-166)	157.28±4.7 (157-167)	0.51
Weight (kg), mean±SD (range)	62.3±6.0 (60-65)	62.08±8.6 (60-64)	0.91
BMI (kg/m^2), mean±SD (range)	25.6±3.0 (24.3-26.8)	25±2.7 (23.8-26.1)	0.50
TSH (mIU/ml), mean±SD (range)	2.54±1 (1.3-4.8)	2.2±0.74 (0.86-4.1)	0.23
Total cholesterol (mg%), mean±SD (range)	157.1±25.4 (124-228)	155.26±30.3 (122-242)	0.78
S. LDL (mg%), mean±SD (range)	107.2±21.4 (78-152)	99.1±25.75 (66-154)	0.22
S. HDL (mg%), mean±SD (range)	49.9±8.1 (38-70)	49±4.3 (40-56)	0.61
S. triglycerides (mg%), mean±SD (range)	117.9±44.5 (60-200)	111.5±23.12 (83-180)	0.52

SD: Standard deviation, BMI: Body mass index, TSH: Thyroid-stimulating hormone, S. LDL: Serum low density lipoprotein, HDL: High density lipoprotein

Table 3: Comparison of improvement in psychosomatic and sexual symptoms in Group I (gabapentin) and II (placebo) at 1, 3, and 6 month follow-up

Symptoms	Group I (n = 25)	Group II (n = 25)	P-value
Psychological symptoms			
% Improvement in anxiety score (mean±SD)			
At 1st month	40.47±15.9	18.63±8.33	0.001
At 3rd month	49.52±14.6	19.77±7.15	0.001
At 6th month	53.8±14.3	20.22±7.47	0.001
% Improvement in depressive symptoms (mean±SD)			
At 1st month	40.4±14.88	15.41±12.5	0.001
At 3rd month	47.08.±13.3	16.66±11.2	0.001
At 6th month	49.58±13.01	17.08±11.2	0.001
Somatic symptoms			
% Improvement in insomnia (mean±SD)			
At 1st month	90.47±10.23	3.63±6.57	0.001
At 3rd month	98.57.± 4.7	4.09±6.66	0.001
At 6th month	99±4.4	4.09±6.66	0.001
% Improvement in work and activity score (mean±SD)			
At 1st month	29.1±15.0	18.1±8.44	0.002
At 3rd month	32.1±15.0	18.75±8.8	0.001
At 6th month	31.3±13.9	18.75±8.8	0.001
% Improvement in somatic symptoms (mean±SD)			
At 1st month	33.6±12.5	18.12±13.1	0.001
At 3rd month	36.8±12.8	18.54±12.3	0.001
At 6th month	40.4±15.4	18.54±12.3	0.001
Sexual symptoms			
% Improvement in vaginal dryness (mean±SD)			
At 1st month	1.7±5.2	2±5.2	0.79
At 3rd month	2.3±5.6	2.1±5.3	0.88
At 6th month	1.3±3.5	1.9±5.1	0.89
% Improvement in dyspareunia; median (min-max)			
At 1st month	0 (0-10)	0 (0-20)	0.82
At 3rd month	0 (0-10)	0 (0-20)	0.78
At 6th month	0 (0-20)	0 (0-20)	0.79
	Group I (n = 25)	Group II (n = 25)	P-value
Psychological symptoms			
% Improvement in anxiety score (mean±SD)			
At 1st month	40.47±15.9	18.63±8.33	0.001
At 3rd month	49.52±14.6	19.77±7.15	0.001
At 6th month	53.8±14.3	20.22±7.47	0.001
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At 6th month	49.58±13.01	17.08±11.2	0.001
Somatic symptoms			
% Improvement in insomnia (mean±SD)			
At 1st month	90.47±10.23	3.63±6.57	0.001
At 3rd month	98.57.±4.7	4.09±6.66	0.001
At 6th month	99±4.4	4.09±6.66	0.001
% Improvement in work and activity score (mean±SD)			
At 1st month	29.1±15.0	18.1±8.44	0.002
At 3rd month	32.1±15.0	18.75±8.8	0.001
At 6th month	31.3±13.9	18.75±8.8	0.001
% Improvement in somatic symptoms (mean±SD)			
At 1st month	33.6±12.5	18.12±13.1	0.001
At 3rd month	36.8±12.8	18.54±12.3	0.001
At 6th month	40.4±15.4	18.54±12.3	0.001
Sexual symptoms			
% Improvement in vaginal dryness (mean±SD)			
At 1st month	1.7±5.2	2±5.2	0.79
At 3rd month	2.3±5.6	2.1±5.3	0.88
At 6th month	1.3±3.5	1.9±5.1	0.89
% Improvement in dyspareunia; median (min-max)			
At 1st month	0 (0-10)	0 (0-20)	0.82
At 3rd month	0 (0-10)	0 (0-20)	0.78
At 6th month	0 (0-20)	0 (0-20)	0.79

SD: Standard deviation

lipoprotein (LDL) increased significantly in Group I from baseline mean of 107.2 ± 21.4 to 113.7 ± 22.5 mg/dl at 6 months (P = 0.003). High density lipoprotein (HDL) increased significantly in Group II from 48.9 ± 4.3 at baseline to 53.2 ± 2.4 mg/dl at 6 months (P = 0.001). No statistical difference in hemoglobin, urea, creatinine, or total protein was noted within the groups between baseline and at 6 months ($P \geq 0.05$) [Table 4].

Adverse effects

None of the patients had major adverse effects. Thirty-two percent women had side effects with gabapentin. None of the patients withdrew from the study due to side effects. Sixteen percent patients in Group I had noted headache (one episode/week) after starting gabapentin therapy in 1st month, which responded to simple analgesics and no further episodes of headache were noted; 8% women complained of dizziness, however not so severe to discontinue the therapy; and 8% complained of somnolence during daily activities in 1st week, gradually settled over a week without any further complaints, however night time sleep duration were found to be prolonged by 1-2 h, no such complaints were noted in women of Group II.

Table 4: Various serum values in both the groups before any intervention and at the end of the study

Laboratory Values	Group I (n = 25)	Group II (n = 25)	*P*-value between two groups
Cholesterol (mg%), mean±SD			
Baseline	157.1±25.4	155.3±30.3	0.22
After 6 months	157.6±23.57	150.2±22.3	0.054
P-value (within group)*	0.82	0.38	
LDL (mg%), mean±SD			
Baseline	107.2±21.4	99.1±25.7	0.22
After 6 months	113.7±22.5	100.68±24.2	0.054
P-value (within group)*	0.003	0.57	
HDL (mg%), mean±SD			
Baseline	49.8±8.2	48.9±4.3	0.61
After 6 months	49.56±5.1	53.2±2.4	0.002
P-value (within group)*	0.83	0.001	
Triglycerides (mg%), mean±SD			
Baseline	117.9±44.5	111.5±23.1	0.52
After 6 months	122.8±45.1	116.5±19.9	0.52
P-value (within group)*	0.17	0.21	
Hemoglobin (g%), mean±SD			
Baseline	10.3±0.6	10.4±0.5	0.3
After 6 months	10.3±0.4	10.4±0.4	0.3
P-value (within group)*	0.71	0.93	
B. urea (mg%), mean±SD			
Baseline	22.7±4.7	21.2±3.7	0.2
After 6 months	22.7±4.8	21±3.8	0.1
P-value (within group)*	1.0	0.52	
S. creatinine (mg%), mean±SD			
Baseline	0.7±0.1	0.6±0.1	0.3
After 6 months	0.7±0.09	0.6±0.1	0.6
P-value (within group)*	0.62	0.71	
S. protein (g%), mean±SD			
Baseline	7.3±0.4	7.1±0.5	0.3
After 6 months	7.2±0.4	7.2±0.5	0.3
P-value (within group)*	0.5	0.67	

**P*-value between baseline and final values at the end of 6 months in each group. SD: Standard deviation, LDL: Low density lipoprotein, HDL: High density lipoprotein, S: Serum, B: Blood

DISCUSSION

Gabapentin has been found to be effective in reducing hot flush frequency and severity in postmenopausal women and was first reported by Guttuso in 2000, as an anecdotal experience.[7] Role of gabapentin for management of psychosomatic and sexual symptoms is in a naive stage. We evaluated the effect of gabapentin in management of psychosomatic and sexual symptoms and found that maximum improvement was noted in insomnia. It was observed that psychosomatic symptoms improved with gabapentin therapy, but no improvement was observed in sexual symptoms.

In our study, two to 2.5-folds improvement in anxiety and depression was noted in women in gabapentin group as compared to placebo group. Guttuso *et al*., in 2003 had evaluated the effect of gabapentin 900 mg and reported that it does not affect the tension or anxiety subscale or total mood disturbance score, compared to placebo ($P \geq 0.05$). Although the tension score and profile of mood state tension/anxiety subscale (POMS scale) were lesser in gabapentin group as compared to placebo group, statistical significance was not achieved.[7] Reddy *et al*., also measured the effect of gabapentin, estrogen, and placebo on depression by Zung depression scale and measured no significant difference between the groups.[8]

We also studied improvement insomatic symptoms in postmenopausal symptoms with gabapentin therapy. Patients in gabapentin group had 33, 36.8, and 40% improvement at 1, 3, and 6 months, respectively, comparedto18% improvement at all follow-up in placebo group accounting to a significant improvement. Guttuso *et al*., compared the effect of gabapentin vs placebo for somatic complaints on Greene Climacteric Scale and reported an increase in somatic complaints.[7] Agarwal *et al*., recorded the reduction in somatic symptoms by 14.9, 56.6, and 80.8% at 1, 3, and 6 months, respectively, with transdermal estrogen patch.[9]

When evaluation of improvement in sexual symptoms with gabapentin therapy was done in our study, improvement in vaginal dryness and dyspareunia ranged from 0 to 20% at all follow-up in both the groups, but no overall improvement was noted. Another study that recorded the improvement in sexual symptoms was by Butt *et al*., in which gabapentin 900 mg was compared with placebo.[10] They reported a decreasing trend in the sexual score in the gabapentin group as compared to placebo group. Agarwal *et al*., recorded the reduction in sexual symptoms by use of transdermal estrogen patch.[9] Hence, hormone therapy has greater efficacy compared to gabapentin in all the symptoms but on benefit-risk ratio ground nonhormonal agents had been evaluated.

Our study is the only one in which the effect of gabapentin on lipid profile is evaluated. No significant change in serum cholesterol and triglycerides was noted at end of therapy in both groups. Statistically significant increase was noted in serum LDL level in gabapentin group; however, no significant difference was noted in placebo group. Increase in HDL was also noted in gabapentin group; whereas, no significant difference was noted in placebo group. No significant difference was noted in hemoglobin, urea, and creatinine or total protein. Only one study that had compared these parameters was by Guttuso *et al*.[7] They found significant decrease in total protein between baseline

and 6 months in gabapentin group. They also found urea levels to be decreased in gabapentin group as compared to placebo at the end of 6 months of therapy. However, no significant difference in creatinine was found between both groups.

In our study, 32% women noted side effects in gabapentin group in the form of headache, dizziness, and somnolence. Guttuso *et al*., also reported somnolence and dizziness during initial weeks of therapy with gabapentin. Also, they reported decrease in total serum protein in gabapentin group unlike in our study, in which no such effect was seen. Peripheraledema was reported in 3% patients in their study.[7] Overall, 13% women withdrew from their study mainly due to dizziness, while in our study no women withdrew due to side effects. Pandya *et al*., compared the treatment side effects with various doses of gabapentin and reported higher incidence of somnolence with 900 mg, 300 mg, and placebo in that order.[5] Butt *et al*., reported greater incidence of dizziness, unsteadiness, and drowsiness at 1stweek of therapy with gabapentin as compared with placebo. However, these symptoms improved by 2ndweek and were comparable at 4thweek with baseline levels.[10] Our study reported a rise in LDL level with gabapentin therapy; hence, it needs to be monitored during therapy, especially in patients with deranged lipid profile.

Considering the beneficial effects of gabapentin on psychosomatic symptoms with minimal side effects as compared to hormonal agents, this can be used in selected women. Usefulness in improvement of sexual symptoms in postmenopausal women was not reported in our study.

CONCLUSION

Gabapentin can lead to improvement in menopausal psychosomatic symptoms. Sexual symptoms show no relief. As gabapentin can lead to increase in LDL cholesterol, precaution should be taken in patients with deranged lipid profile before starting therapy and it should be checked during course of therapy. This drug can cause minor side effects, though major side effects were reported in our study. Hence, gabapentin can be a better treatment option among the nonhormonal agents as an alternative to hormone therapy for management of some postmenopausal symptoms. Further studies and well-planned trials are required to validate this observation.

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