

## Comparison of Efficacy and Safety of Gabapentin vs Nortryptiline in Menopausal Symptoms

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### Abstract

**Aim:** The aim of the present study was to compare the efficacy and safety of gabapentin vs nortryptiline in menopausal symptoms.

**Methods:** A comparative study was conducted in Department of Pharmacology, Darbhanga Medical College, Laheriasarai, Darbhanga, Bihar, India for 15 months (1 June 2020- 31 Aug 2021). 100 patients with menopause were included in the study and were randomized into two groups. One group was given Tab. Gabapentin 600mg once a day and the other group was given Tab. Nortryptiline 25mg once a day. Both the groups were followed up for 2 months and various parameters were seen and compared. Suitable statistics was applied after tabulating the data collected. The readings were taken at 0 week, 4 weeks and 8 weeks.

**Results:** Mean years since menopause in gabapentin group was  $48.32 \pm 3.06$  yrs and in nortryptiline group was  $50.32 \pm 2.08$  yrs. mean age at menopause in gabapentin group was  $2.28 \pm 3.59$  yrs and in nortryptiline group was  $2.15 \pm 1.09$  yrs. Mean menopausal symptom score was calculated in both the groups at baseline i.e., 0 weeks, 4 weeks and 8 weeks. Mean Menopausal symptom score at baseline in gabapentin group was  $10.26 \pm 3.84$ , at 4 weeks was  $8.18 \pm 2.09$  and 8 weeks  $7.92 \pm 2.36$ . In nortryptine group baseline Mean Menopausal symptom score was  $11 \pm 2.51$ , at 4 weeks  $9.34 \pm 2.40$  and at 8 weeks  $6.66 \pm 1.80$ . unpaired student t- test was applied in between both the groups and the p value at 0, 4 and 8 weeks came out to be 0.5025, 0.182, 0.130 respectively and all the values were statistically non-significant. Whereas on application of paired t test between 0,4 and 8 weeks in both the groups respectively, the values were statistically significant.

**Conclusion:** Currently many treatment options are available for treatment of menopausal symptoms, gabapentin and nortryptiline has a potential to be used as new drugs in this field.

**Keywords:** menopausal, symptoms, gabapentin, nortryptiline

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## Introduction

Menopause is a well-recognized universal reproductive physiological phenomenon experienced by all women in all cultures as cessation of menstruation for 1 year. With increasing life expectancy, women spend a significant part (one-third of their life) in postmenopausal state demanding a high level of health care and priority. It affects around a million of women. Age at which natural menopause occurs is 45–55 years worldwide. Symptoms experienced by woman during menopause is affected by many factors such as age at menopause and natural/ surgical menopause[1] A holistic approach is required to combat menopausal symptoms such as physical, psychosocial, sexual, and vasomotor symptoms[2]

Postmenopausal women experience a wide and a varied spectrum of vasomotor, psychosomatic, psychological, and genitourinary symptoms. Although well tolerated by some of the women, but many a times, these symptoms can be distressing affecting the quality of life of the suffering woman and thus require treatment.

Although hormone replacement remained the main line of treatment since time immemorial, but after the findings of various studies changed the perspective of hormone therapy for menopausal symptoms[3,6] It was established in HERS study that hormone replacement therapy has no benefit to reduce risk of cardiovascular diseases and all-cause mortality benefit related to HRT in women[3,6]

In another study, it was established that estrogen progesterone combined therapy causes increased annual risk of breast cancer (26%), thromboembolism (42%), Congestive heart diseases (CHD) (29%), and stroke (41%)[6]

Even in India, guidelines issued by Indian Menopausal Society to treat menopausal symptoms has recommended that hormones

should also be used for premature menopause, surgical menopause, and menopause with aggressive symptoms that too with low dose or ultra-low dose of hormones for short term with vigorous follow-up and monitoring[7]

In view of these studies, the world is looking toward other possibilities of nonhormonal therapy for the treatment of menopausal symptoms. Various drugs such as phytoestrogens, selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, clonidine, antiepileptics (gabapentin and pregabalin), anxiolytics, sedative, and hypnotics such as benzodiazepines are being explored. Other treatment options being explored are exercise, yoga, herbal therapies, and acupuncture[8]

## Materials and Methods

A comparative study was conducted in Department of Pharmacology, Darbhanga Medical College, Laheriasarai, Darbhanga, Bihar, India for 15 months (1 June 2020- 31 Aug 2021).

## Methodology

The patients with menopause were included in the study and were randomized into two groups. Informed consent was taken after explaining them the nature of study. One group was given Tab. Gabapentin 600mg once a day and the other group was given Tab. Nortryptiline 25mg once a day. Both the groups were followed up for 2 months and various parameters were seen and compared. Suitable statistics was applied after tabulating the data collected. The readings were taken at 0 week, 4 weeks and 8 weeks.

## Inclusion Criteria

Menopausal patients of any age having symptoms who were not taking the study drugs

- Associated uncomplicated co-morbid condition

### Exclusion Criteria

Menopausal patients with symptoms who were on study drugs or some other drugs

- Associated complicated co-morbid condition
- Intolerance to study drugs

### Greene Climacteric Scale

- It is a pretested and validated menopausal symptom scale widely used in clinical practice and as a research tool. It was developed by J.G. Greene in 1998 to do symptom analysis of menopausal women visiting clinics.[9]
- It scores 21 symptoms which are rated depending on their severity on a four-point Likert scale from 0 to 3 (0= not at all and 3=extremely). These symptoms are divided into 4 main areas such as psychological (1-11), physical (12-18), vasomotor (19, 20) and sexual (21)[10]
- The psychological domain is further subdivided to measure anxiety (1-6) and depression (7-11). A higher score implies a greater number of symptoms and/ or more symptom severity.
- As far as construct validity is concerned, only symptoms having factor loading of > 0.35 in more than three studies were included in the scale. Its internal consistency as measured by Cronbach's alpha was found to be more than 0.08[11,14] Construct validity has been demonstrated in relation to life stress, bereavement, psychological treatment and hormone replacement therapy.
- Adverse drug events were also compared between two groups.

### Results

The data is shown as mean±S.D. Paired t test in comparison to respective baselines  $p<0.05$ ,  $p<0.01$ ,  $p<0.001$ ,  $p<0.0001$ , NS Not significant Patients in gabapentin group were predominantly from rural areas (15:35- urban: rural ratio), where as in nortryptiline group the ratio was 17:33. In both the groups more females were housewives. Associated comorbid condition was present in 10 patients in gabapentin group and in 13 patients in Nortryptiline group. Patients with uncomplicated co-morbid conditions were included, complicated co-morbid conditions were excluded. Ratio of natural Vs surgical menopause was 42:8 in gabapentin group and 45:5 in Nortryptiline group. Mean years since menopause in gabapentin group was  $48.32\pm 3.06$  yrs and in nortryptiline group was  $50.32\pm 2.08$  yrs. mean age at menopause in gabapentin group was  $2.28\pm 3.59$  yrs and in nortryptiline group was  $2.15\pm 1.09$  yrs. Mean menopausal symptom score was calculated in both the groups at baseline i.e. 0 weeks, 4 weeks and 8 weeks. (Table 1).

Mean Menopausal symptom score at baseline in gabapentin group was  $10.26\pm 3.84$ , at 4 weeks was  $8.18\pm 2.09$  and 8 weeks  $7.92\pm 2.36$ . In nortryptiline group baseline Mean Menopausal symptom score was  $11\pm 2.51$ , at 4 weeks  $9.34\pm 2.40$  and at 8 weeks  $6.66\pm 1.80$ . unpaired student t- test was applied in between both the groups and the p value at 0, 4 and 8 weeks came out to be 0.5025, 0.182, 0.130 respectively and all the values were statistically non-significant. (Table 2) Whereas on application of paired t test between 0,4 and 8 weeks in both the groups respectively, the values were statistically significant. (Table 3) Adverse drug rections were seen in both the groups but none of them was serious in nature and did not need dechallenge of drug. Both the drugs were well tolerated. (Table 4)

**Table 1: Showing demographic profile of patients**

Parameter	Group A Gabapentin (n=50)	Group B Nortryptiline (n=50)
Residence Urban: Rural	15:35	17:33
Housewife: Working	26:24	30:20
Associated co-morbid conditions	10	13
Natural Vs Surgical menopause	42:8	45:5
Mean years since menopause	48.32±3.06yrs	50.32±2.18yrs
Mean age at menopause	2.28±3.69yrs	2.15±1.19yrs

**Table 2: Comparative effect of Gabapentin vs Nortryptiline on Mean Menopausal Symptom Score**

Duration	Gabapentin n=50(mean±SD)	Nortryptiline n=50(mean±SD)	t	P	Statistical significance
Baseline	10.26± 3.84	11± 2.51	0.57	0.5025	Not significant
4 weeks	8.18± 2.09	9.34± 2.40	1.28	0.182	Not significant
8 weeks	7.92± 2.36	6.66± 1.80	1.47	0.130	Not significant

**Table 3: Comparative effect of Gabapentin vs Nortryptiline on Mean Menopausal Symptom Score (paired student t test)**

Duration	Gabapentin n=50 (mean±SD)	Nortryptiline n=50(mean±SD)
Baseline	10.26± 3.84	11± 2.51
4 weeks	8.18± 2.09	9.34± 2.40
8 weeks	7.92± 2.36	6.66± 1.80

**Table 4: Showing adverse drug reactions in both the groups**

Adverse Drug event	Gabapentin (14)	Nortryptiline (7)
Gastritis	2	0
Excessive sleep	3	3
Giddiness	5	2
Headache	3	2
Vertigo	1	0

## Discussion

Our study showed that both the drugs have positive effect on decreasing postmenopausal symptoms but no drug has superiority over each other. In a cross-over study comparing gabapentin and antidepressant (fluoxetine) for treating vasomotor symptoms among postmenopausal women by it was concluded that both the drugs were effective but gabapentin caused more improvement[15] In a placebo controlled randomized trial comparing efficacy of low

dose estradiol and antidepressant (venlafaxine) on menopausal related quality of life and other associated symptoms it was concluded that both the drugs are equally efficacious[16] In a placebo controlled trial on menopausal vasomotor symptoms established that antidepressant (paroxetine) is effective in treating these symptoms[17] In a systematic review of randomized controlled trial, it was established that paroxetine, citalopram, escitalopram, venlafaxine and desvenlafaxine are effective in reducing the frequency and severity of hot flashes.[18]

Low dose paroxetine is a selective serotonin reuptake inhibitor and is thought to help in decreasing vasomotor symptoms by regulating body temperature via neurotransmitters[19]. Our study drug nortryptiline also prevents reuptake of serotonin, which may be responsible for improvement of menopausal symptoms as recorded in the current study. In an interesting and additional finding of the current study, which was actually carried out to compare the efficacy and safety of nortryptiline and clonazepam in RLS in plus forty-year women, recorded a significant improvement in menopausal symptom scores including all the parameters like vasomotor, psychosocial, physical, sexual in a comparable fashion both by gabapentin and nortryptiline.

The findings are interesting because it shall provide an additional reason for the treating physician to prescribe any of these two drugs effectively for the management of components of menopause besides effectively treating RLS which is prevalent in this particular vulnerable population.

Although very less studied but recently some of the authors propose use of selected anti-depressants and GABA agonist like clonazepam as non-hormonal agents to treat vasomotor symptoms for those who should avoid or do not wish to take estrogens for managing menopausal symptoms in which they suggested that GABA agonists may have direct effect on anxiety, mood, sleep, depression and various other psychosomatic symptoms and may be improving indirectly vasomotor, sexual and physical symptoms by improving overall quality of life[20].

It was also pointed in a study that GABA inhibitory activity may be modulated directly or indirectly by estrogen, progesterone and their metabolic receptors and these GABA deficits may influence reproductive life cycle events including menstruation, pregnancy and menopause[21]. Thus, suggesting like our study the great potential of GABA

mediated intervention and particularly GABA agonist in prevention, treatment of menopausal symptoms directly or indirectly. Although these drugs may have some effects on co-morbid conditions too, but uncomplicated co-morbid conditions were only included and the effect of drugs was not studied.

### Conclusion

Currently many treatment options are available for treatment of menopausal symptoms, gabapentin and nortryptiline has a potential to be used as new drugs in this field.

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