

# Comparative Efficacy and Safety of Clonazepam versus Nortryptiline on Menopausal Symptom among Forty Plus Women: A Prospective, Open-Label Randomized Study

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ABSTRACT

**Aims and Objectives:** The aim of this study is to compare the effect of clonazepam and nortryptiline on menopausal symptoms in above 40 years women. **Materials and Methods:** A prospective, randomized, open-label comparative study was conducted in a tertiary care teaching hospital for 1 year. Patients were randomized into two groups. Both the groups had 60 patients, out of which Group A had 39 menopausal patients and Group B had 31 menopausal patients, respectively. Group 1 received tablet clonazepam 0.5 mg bed time orally daily. Group 2 received tablet nortryptiline 25 mg bed time orally daily. The primary efficacy end points were effect on menopausal symptoms evaluated by at 0, 4, and 8 weeks. **Results:** Mean age since menopause was  $45 \pm 4.06$  years, and the mean number of years since menopause was  $9.18 \pm 7.59$  years clonazepam and nortryptiline recorded statistically comparable effect with numerical superiority of nortryptiline both at 4 and 8 weeks on mean Menopausal Symptom Score, thereby indicating that both the drugs may have directly/indirectly improved the mean menopausal symptoms equally. Improvement in the clonazepam group was numerically and statistically more than nortryptiline group at 4 and 8 weeks on mean Vasomotor Symptom Score with  $P < 0.01$  in clonazepam group and  $P < 0.05$  in nortryptiline group both at 4 and 8 weeks. Both the drugs showed comparable results on psychosocial symptom score both at 4 and 8 weeks with numerical superiority in nortryptiline group. Clonazepam group showed more improvement on mean physical score than nortryptiline group numerically and statistically. Both the drugs showed comparable results on mean sexual symptom score at 4 weeks, but nortryptiline proved to be statistically better at 8 weeks  $P < 0.01$  versus  $P < 0.05$  in clonazepam group. **Conclusion:** Clonazepam and nortryptiline recorded statistically comparable effect at 4 and 8 weeks on mean menopausal symptom. Both the drugs were equally safe and did not recorded any serious Adverse Drug Reaction (ADRs).

**KEYWORDS:** Clonazepam, menopausal symptoms, nortryptiline, plus forty age, study drugs, women

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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

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by many factors such as age at menopause and natural/surgical menopause.<sup>[1]</sup> A holistic approach is required to combat menopausal symptoms such as physical, psychosocial, sexual, and vasomotor symptoms.<sup>[2]</sup>

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.<sup>[3-6]</sup>

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.<sup>[3,4]</sup>

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%).<sup>[6]</sup>

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.<sup>[7]</sup>

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.<sup>[8]</sup>

We failed to cite any study comparing the effect of clonazepam versus nortriptyline on menopausal symptom among forty plus women; hence, the current study was undertaken.

## MATERIALS AND METHODS

A prospective, randomized, open-label comparative study was conducted at a tertiary care teaching hospital for 1 year.

The study protocol was approved by the Institutional Ethics Committee (IEC) vide no. IEC/Thesis/Research/

T19B (a)/2015/232 dated November 4, 2015. A written informed consent was obtained from the patients fulfilling inclusion, exclusion criteria after explaining the nature and purpose of study. All principles of bioethics were followed.

### Inclusion criteria

- Age more than 40 years and <65 years
- Legitimate consent
- Any uncomplicated co-morbid condition.

### Exclusion criteria

- Pregnancy
- Lactation
- Complicated comorbid conditions
- Primary psychiatric disorders
- Allergy and intolerance to research drugs
- History of any substance dependence or abuse
- Patients who are on clonazepam or nortriptyline for the last 4 weeks or more.

### Greene climacteric scale

It is a pretested and validated menopausal symptom scale widely used in the 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.<sup>[9]</sup>

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 four main areas such as psychological (1–11), physical (12–18), vasomotor (19, 20), and sexual (21).<sup>[10]</sup>

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.<sup>[11-14]</sup> Construct validity has been demonstrated in relation to life stress,<sup>[15]</sup> bereavement,<sup>[10]</sup> psychological treatment, and hormone replacement therapy.<sup>[16]</sup>

Adverse drug events were also compared between the two groups.

Both the groups had 60 patients, out of which group A had 39 menopausal patients and B group had 31 menopausal patients, respectively.

Patients were randomized into two groups. Group 1 received tablet clonazepam 0.5 mg bed time orally daily. Group 2 received tablet nortriptyline 25 mg bed time

orally daily and were followed at 0, 4, and 8 weeks for both efficacy and safety endpoints.

## RESULTS

The baseline characteristics of the patients are shown in Table 1. Urban versus rural population in clonazepam group was in the ratio of 1:1, whereas in nortriptyline group, it was 0.93:1.

In clonazepam group, 39 patients (65%) were postmenopausal, out of which 28 patients (71.7%) had natural menopause. Mean age since menopause was  $45 \pm 4.06$  years, and mean number of years since menopause was  $9.18 \pm 7.59$  years in nortriptyline group, 31 patients (51.6%) were postmenopausal out of which 23 patients (74.19%) had natural menopause. Mean age at menopause was  $46.81 \pm 4.98$  years, and mean no. of years since menopause was  $8.42 \pm 7.08$  years [Table 1].

Mean menopausal symptom score in the clonazepam group was  $11.26 \pm 4.84$  at 0 week,  $10.18 \pm 3.99$  at 4 weeks, and  $8.92 \pm 3.36$  at 8 weeks, and the difference was statistically significant in comparison to baseline with ( $P < 0.0001$ ) at 4 and 8 weeks. In nortriptyline group, the score at 0 week was  $12 \pm 3.51$ ,  $10.34 \pm 3.40$  at 4 weeks, and  $9.66 \pm 2.87$  at 8 weeks, and the difference was statistically significant in comparison to baseline with  $P < 0.001$  at 4 weeks and  $P < 0.0001$  at 8 weeks. Difference between respective baselines of both the groups was statistically insignificant at 4 and 8 weeks [Table 2].

Mean vasomotor symptom score in the clonazepam group was  $0.92 \pm 0.80$  at 0 week,  $0.69 \pm 0.73$  at 4 weeks, and  $0.64 \pm 0.66$  at 8 weeks, and the

difference was statistically significant in comparison to baseline ( $P < 0.01$ ) at 4 and 8 weeks. In nortriptyline group, the score was  $0.90 \pm 0.87$  at 0 week,  $0.77 \pm 0.71$  at 4 weeks, and  $0.65 \pm 0.60$  at 8 weeks, and the difference was statistically significant in comparison to baseline ( $P < 0.05$ ). Clonazepam proved to be statistically better in this regard. Difference between respective baselines of both the groups was statistically insignificant at 4 and 8 weeks [Table 3].

Mean psychosocial symptom score in the clonazepam group at 0 week was  $2.90 \pm 1.35$ ,  $2.62 \pm 1.04$  at 4 weeks, and  $2.26 \pm 0.91$  at 8 weeks, and the difference was statistically significant ( $P < 0.001$  at 4 weeks and  $P < 0.0001$  at 8 weeks). The score at 0 week in nortriptyline group was  $3.84 \pm 1.48$ ,  $3.32 \pm 1.37$  at 4 weeks, and  $2.97 \pm 1.35$  at 8 weeks, and the difference was statistically significant with  $P < 0.0001$  at 4 and 8 weeks. Nortriptyline proved to be better in decreasing the score, and the difference was statistically significant [Table 4].

Mean physical symptom score in the clonazepam group at 0 week was  $6.92 \pm 3.11$ ,  $6.49 \pm 2.79$  at 4 weeks, and  $5.87 \pm 2.38$  at 8 weeks, and the difference was statistically significant w. r. t baseline ( $P < 0.0001$ ) at 4 and 8 weeks. In nortriptyline group, the score at 0 week was  $6.26 \pm 3.17$ ,  $6.13 \pm 2.90$  at 4 weeks, and  $5.71 \pm 2.74$  at 8 weeks. The difference was statistically insignificant at 4 weeks and significant at 8 weeks ( $P < 0.0001$ ) in the nortriptyline group. The difference between respective baselines of two groups was statistically insignificant at 4 and 8 weeks [Table 5].

Mean sexual symptom score in the clonazepam group at 0 week was  $0.69 \pm 0.83$ ,  $0.51 \pm 0.60$  at 4 weeks, and

**Table 1: Demographic profile of patients in clonazepam and Nortriptyline group**

Parameter	Clonazepam (n=39)	Nortriptyline (n=31)
Mean age at menopause (mean±SD)	45±4.06 years	46.81±4.98 years
Mean number of years since menopause (mean±SD)	9.18±7.59 years	8.42±7.08 years
Residence	1:1	0.93:1
Urban: Rural		
Menstrual status, n (%) postmenopausal versus perimenstrual	39 (65%) versus 21 (35%)	31 (51.6%) versus 29 (48.3%)
Menopause, n (%) natural versus surgical	28 (71.7%) versus 11 (28.2%)	23 (74.19%) versus 8 (25.8%)

SD: Standard deviation

**Table 2: Comparative effect of clonazepam versus Nortriptyline on mean menopausal symptom score**

Duration	Mean±SD		T	P	Statistical significance
	Clonazepam (n=39)	Nortriptyline (n=31)			
Baseline	11.26±4.84	12±3.51	0.71	0.477	NS
4 weeks	10.18±3.99	10.34±3.40 <sup>##</sup>	0.17	0.859	NS
8 weeks	8.92±3.36	9.66±2.87	0.97	0.332	NS

The data is shown as mean±SD. Paired t-test in comparison to respective baselines <sup>##</sup> $P < 0.01$ , NS: Comparison between the groups at baseline, 4 weeks and 8 weeks with student unpaired t-test \* $P < 0.05$ ,  $P < 0.01$ ,  $P < 0.001$ , NS: Not significant, SD: Standard deviation

**Table 3: Comparative effect of clonazepam versus nortriptyline on mean vasomotor symptom score**

Duration	Mean±SD		T	P	Statistical significance
	Clonazepam (n=39)	Nortriptyline (n=31)			
Baseline	0.92±0.80	0.90±0.87	0.09	0.92	NS
4 weeks	0.69±0.73 <sup>##</sup>	0.77±0.71 <sup>#</sup>	0.46	0.64	NS
8 weeks	0.64±0.66 <sup>##</sup>	0.65±0.60 <sup>#</sup>	0.06	0.94	NS

The data is shown as mean±SD. Paired *t*-test in comparison to respective baselines <sup>#</sup>*P*<0.05, <sup>##</sup>*P*<0.01, NS: Comparison between the groups at baseline, 4 weeks and 8 weeks with student unpaired *t*-test \**P*<0.05, *P*<0.01, *P*<0.001, NS Not significant, SD: Standard deviation

**Table 4: Comparative effect of clonazepam versus nortriptyline on mean psychosocial symptom score**

Duration	Mean±SD		T	P	Statistical significance
	Clonazepam (n=39)	Nortriptyline (n=31)			
Baseline	2.90±1.35	3.84±1.48	2.77	0.007**	SS
4 weeks	2.62±1.04 <sup>##</sup>	3.32±1.37 <sup>####</sup>	2.43	0.017**	SS
8 weeks	2.26±0.91 <sup>####</sup>	2.97±1.35 <sup>####</sup>	2.62	0.010**	SS

The data is shown as mean±SD. Paired *t*-test in comparison to respective baselines <sup>##</sup>*P*<0.01, <sup>####</sup>*P*<0.001, NS: Comparison between the groups at baseline, 4 weeks and 8 weeks with student unpaired *t*-test \**P*<0.05, \*\**P*<0.01, *P*<0.001, NS Not significant, SS: Statistical significance, SD: Standard deviation

**Table 5: Comparative effect of clonazepam versus nortriptyline on mean physical symptom score**

Duration	Mean±SD		T	P	Statistical significance
	Clonazepam (n=39)	Nortriptyline (n=31)			
Baseline	6.92±3.11	6.26±3.17	0.87	0.384	NS
4 weeks	6.49±2.79 <sup>####</sup>	6.13±2.90	0.52	0.599	NS
8 weeks	5.87±2.38 <sup>####</sup>	5.71±2.74 <sup>####</sup>	0.26	0.794	NS

The data is shown as mean±SD. Paired *t*-test in comparison to respective baselines <sup>##</sup>*P*<0.01, <sup>####</sup>*P*<0.001, NS: Comparison between the groups at baseline, 4 weeks and 8 weeks with student unpaired *t*-test \**P*<0.05, *P*<0.01, *P*<0.001, NS Not significant, SD: Standard deviation

0.38 ± 0.54 at 8 weeks, and the difference was statistically significant in comparison to baseline (*P* < 0.01) at 4 weeks and (*P* < 0.05) at 8 weeks. In nortriptyline group, the score was 0.58 ± 0.67 at 0 week, 0.39 ± 0.49 at 4 weeks, and 0.26 ± 0.44 at 8 weeks, and the difference was statistically significant in comparison to baseline (*P* < 0.01) at 4 and 8 weeks. The difference between the respective baselines of two groups was statistically insignificant at 4 and 8 weeks [Table 6].

Both the groups were relatively safe and did not produce any change in biochemical parameters and were free from any serious or severe adverse events and overall, both the treatments were well tolerated. In clonazepam group, increased sleep (50%), followed by giddiness (30%), gastritis and constipation (10%) were the adverse events. In nortriptyline group, palpitations (33.33%) were maximum followed by giddiness, gastritis, and increased sleep (16.6%). Dry mouth and anxiety were also seen in nortriptyline group (8.3%).

## DISCUSSION

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.<sup>[17]</sup>

In a meta-analysis, it was established that antidepressant (paroxetine) is safe and effective therapy for the treatment of vasomotor symptoms and should be considered as first-line therapy.<sup>[18]</sup>

In a placebo-controlled randomized trial comparing the 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.<sup>[19]</sup>

In a placebo controlled trial on menopausal vasomotor symptoms established that antidepressant (paroxetine) is effective in treating these symptoms.<sup>[20]</sup>

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.<sup>[21]</sup>

In a randomized controlled trial by to evaluate the effect of eszopiclone (nonbenzodiazepine hypnotic) on insomnia and postmenopausal symptoms, mood and quality of life, it was concluded that eszopiclone

**Table 6: Comparative effect of clonazepam versus nortryptiline on mean sexual symptom score**

Duration	Mean±SD		T	P	Statistical significance
	Clonazepam (n=39)	Nortryptiline (n=31)			
Baseline	0.69±0.83	0.58±0.67	0.59	0.551	NS
4 weeks	0.51±0.60 <sup>##</sup>	0.39±0.49 <sup>##</sup>	0.89	0.371	NS
8 weeks	0.38±0.54 <sup>#</sup>	0.26±0.44 <sup>##</sup>	1.00	0.320	NS

The data is shown as mean±SD. Paired *t*-test in comparison to respective baselines <sup>#</sup>*P*<0.05, <sup>##</sup>*P*<0.01, NS: Comparison between the groups at baseline, 4 weeks and 8 weeks with student unpaired *t*-test \**P*<0.05, *P*<0.01, *P*<0.001, NS Not significant, SD: Standard deviation

provided significant improvement on all the said parameter.<sup>[22]</sup>

Low dose paroxetine is a selective serotonin reuptake inhibitor and is thought to help in decreasing vasomotor symptoms by regulating the body temperature through neurotransmitters.<sup>[23]</sup>

Our study drug nortryptiline also prevents reuptake of serotonin, which may be responsible for the 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 40 years women, recorded a significant improvement in menopausal symptom scores including all the parameters such as vasomotor, psychosocial, physical, sexual in a comparable fashion both by clonazepam 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 such as clonazepam as nonhormonal 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.<sup>[24]</sup>

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.<sup>[25]</sup> 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.

Further, the results of the current study are endorsed by a study of establishing gabapentin (GABA-modulating drug) to have modest effectiveness as nonhormonal therapy option for the treatment of moderate-to-severe hot flushes.<sup>[20]</sup>

Similarly, nortryptiline recorded improvement in the overall components of menopausal symptoms in the current study. The results are in accordance to various other studies by<sup>[17-23]</sup> wherein antiresearch to establish their role in menopausal symptoms.

Similar studies have also been conducted in our set up to see the efficacy and safety of clonazepam and nortryptiline on restless leg syndrome and quality of life in such patients and both the drugs proved to be effective.<sup>[26,27]</sup>

## CONCLUSION

Clonazepam and nortryptiline recorded statistically comparable effect at both at 4 and 8 weeks on mean menopausal symptom. Both the drugs were equally safe and did not recorded any serious ADRs. Anti-depressants other than nortryptiline have been well reported to improve directly or indirectly menopausal symptoms.

These two drugs are least studied drugs for the benefits of menopausal symptoms but *in lieu* of results of the current study, it appears that both nortryptiline and clonazepam have a great potential for future.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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