

Comparison of efficacy and safety of gabapentin vs nortryptiline in menopausal symptoms, an open label study

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Abstract

Menopause is an important physiological process in a female's life. It is not free from different variety of symptoms affecting day to day life. With increasing life expectancy, female spends many years with menopausal symptoms. Having knowledge about these symptoms provides us a guide about treatment for various symptoms to be introduced into postmenopausal health guidelines.

Materials and Methods: The present study was undertaken in Medicine OPD of Govt. Medical College Jammu. Total 60 patients were divided into two groups and were given tab gabapentin and nortryptiline. The readings were taken at 0 week, 4 weeks and 8 weeks after noting the demographic profile.

Results: Most of the females in both the groups were from rural areas, housewives and with natural menopause. Both the study drug were effective in decreasing the postmenopausal symptoms were none was better than the other.

Conclusion: both nortryptiline and gabapentin have potential to be used as drugs in postmenopausal symptoms besides other treatment options.

Keywords: Nortryptiline, Menopausal.

Introduction

Menopause is a well universal reproductive physiological phenomenon experienced by all women in all cultures. It is defined as cessation of menstruation for one year. Age at which natural menopause occurs is 45-55 years worldwide.¹ With increasing life expectancy, women spend about one third of their life span in postmenopausal state. Therefore, there is a need of high level of health care and priority. Menopause is associated with variety of symptoms. These symptoms may be affected by many factors like age at menopause, type of menopause-natural/ surgical menopause, other associated co-morbidities.^{2,3}

Postmenopausal women experience a wide and a varied spectrum of vasomotor, psychosomatic, psychological and genitourinary symptoms. These symptoms may be well tolerated by many women but sometimes these symptoms can be distressing which requires treatment to combat these issues.

Although hormone replacement remained the main line of treatment but the findings of various studies changed the perspective of hormone therapy for menopausal symptoms.⁴

⁶ It was established by in HERS study that hormone replacement therapy have no benefit to reduce risk of cardiovascular diseases (CVS) and all cause mortality benefit related to HRT in women.^{4,5} In another study it was established that estrogen progesterone combined therapy causes increased annual risk of breast cancer (26%), thromboembolism (42%), CHD (29%), stroke (41%).⁷ Even vide India, guidelines issued by Indian Menopausal Society to treat menopausal symptoms has recommended that hormones should be used only for premature menopause, surgical menopause and menopause with aggressive symptoms that too with low dose or ultra low dose of hormones for short term that too with vigorous follow up

and monitoring.⁸ In view of these studies, the world is looking towards other possibilities of non-hormonal therapy for treatment of menopausal symptoms. Various drugs like phytoestrogens, selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, clonidine, antiepileptics (gabapentin, pregabalin), anxiolytics, sedative and hypnotics like benzodiazepines are being explored. Other treatment options being explored are exercise, yoga, herbal therapies, acupuncture.⁸ We failed to cite any study comparing the effect of Gabapentin Vs Nortryptiline on Menopausal Symptoms, hence the current study was undertaken.

Materials and Methods

A comparative study was conducted in Department of Medicine after permission from Institutional Ethical Committee, Govt. Medical College, Jammu vide No. IEC/Pharma/Res/17B/2018/593. 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

1. Associated uncomplicated co-morbid condition

Exclusion Criteria

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

1. Associated complicated co-morbid condition
2. Intolerance to study drugs

Greene Climacteric Scale

1. 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
2. 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
3. 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.
4. 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 0.08¹¹⁻¹⁴. Construct validity has been demonstrated in relation to life stress, bereavement, psychological treatment and hormone replacement therapy
5. 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 (9:21- urban: rural ratio), where as in nortryptiline group the ratio was 11:19. In both the groups more females were housewives. Associated comorbid condition was present in 6 patients in gabapentin group and in 9 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 26:4 in gabapentin group and 28:2 in Nortryptiline group. Mean years since menopause in gabapentin group was 49.32±4.06yrs and in nortryptiline group was 51.32±2.08yrs. mean age at menopause in gabapentin group was 2.18±3.59yrs and in nortryptiline group was 2.05±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 11.26± 4.84, at 4 weeks was 9.18± 3.09 and 8 weeks 8.92± 3.36. In nortryptine group baseline Mean Menopausal symptom score was 12± 3.51, at 4 weeks 10.34± 3.40 and at 8 weeks 7.66± 2.80. 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 0.5005, 0.172, 0.120 respectively and all the values were statistically non significant. (Table 2) Where as 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 reactions 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=30)	Group B Nortryptiline (n=30)
Residence Urban: Rural	9:21	11:19
Housewife: Working	16:14	20:10
Associated co-morbid conditions	6	9
Natural Vs Surgical menopause	26:4	28:2
Mean years since menopause	49.32±4.06yrs	51.32±2.08yrs
Mean age at menopause	2.18±3.59yrs	2.05±1.09yrs

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

Duration	Gabapentin n=30 (mean±SD)	Nortryptiline n=30 (mean±SD)	t	p	Statistical significance
Baseline	11.26± 4.84	12± 3.51	0.67	0.5005	Not significant
4 weeks	9.18± 3.09	10.34± 3.40	1.38	0.172	Not significant
8 weeks	8.92± 3.36	7.66± 2.80	1.57	0.120	Not significant

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

Duration	Clonazepam n=30 (mean±SD)	Nortryptiline n=30(mean±SD)
Baseline	11.26± 4.84	12± 3.51
4 weeks	9.18± 3.09###	10.34± 3.40##
8 weeks	8.92± 3.36####	7.66± 2.80####

Table 4: Showing adverse drug reactions in both the groups

Adverse Drug event	Gabapentin (10)	Nortriptyline(4)
Gastritis	1	0
Excessive sleep	2	2
Giddiness	4	1
Headache	2	1
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 nortriptyline 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 nortriptyline 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 nortriptyline.

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 life²⁰

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 nortriptyline has a potential to be used as new drugs in this field.

Limitations

Number of subjects is less. Study duration is less. Other parameters could have been studied.

Conflict of interest: None.

References

- McKinlay, S. M., Bigano, N. L., & McKilay, J. B. Smoking and age at menopause. *Ann Intern Med* 1985;103:350
- Kalra B, Agarwal S, Magon S. Holistic care of menopause: Understanding the framework. *J Mid-life health* 2012;3(2):66-9
- Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA* 1998;280(7):605-13
- Grady D, Herrington D, Bittner V, Blumenthal R, Davidson M, Hlatky M, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *JAMA* 2002;288(1):49-57
- Shumaker SA, Legault C, Rapp SR, Thal L, Wallace RB, Ockene JK, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA* 2003;289(20):2651-62
- Manson JE, Hsia J, Johnson KC, Rossouw JE, Assaf AR, Lasser NL, et al. Estrogen plus Progestin and the Risk of Coronary Heart Disease. *N Engl J Med* 2003;349:523-53
- Unni J. Third consensus meeting of Indian Menopause Society: A Summary. *J Midlife Health* 2010;1:43-7
- Krause MS, Nakajima ST. Hormonal and nonhormonal treatment of vasomotor symptoms. *Obstet Gynecol Clin North Am* 2015;42(1):163-79
- Greene JG. Constructing a standard climacteric scale. *Maturitas* 1998;29(1):25-31

10. Greene JG. Bereavement and social support at the climacteric. *Maturitas* 1983;5(2):115-24
11. Zollner YF, Acquardo C, Schaefer M. Literature review of instruments to assess health related quality of life during and after menopause. *Qual Life Res* 2005;14(2):309-27
12. Chen RQ, Davis SR, Wong CM, Lam TH. Validity and cultural equivalence of the standard Greene Climacteric Scale in Hong Kong. *Menopause* 2010;17(3):630-35
13. Chattha R, KulkarniR, Nagarathna R, Nagendra HR. Factor analysis of Greene's Climacteric Scale for Indian women. *Maturitas* 2008;59(1):22-27
14. Vasconcelos-Raposo J, Coelho E, Fernandes HM, RodriguesC, Moreira H, Teixeira C. Factor structure and normative data of the Greene Climacteric Scale among postmenopausal Portuguese women. *Maturitas* 2012;72(3):256-62
15. Rahmanian M, Mohseni A, Ghorbani R. A crossover study comparing gabapentin and fluoxetine for the treatment of vasomotor symptoms among postmenopausal women. *Int J Gynaecol Obstet* 2015;131(1):87-90
16. Caan B, LaCroix AZ, Joffe H, Guthrie KA, Larson JC, Carpenter JS, et al. Effects of estrogen and venlafaxine on menopause-related quality of life in healthy postmenopausal women with hot flashes: a placebo-controlled randomized trial. *Menopause* 2015;22(6):607-15
17. Pinkerton JV, Joffe H, Kazempour K, Mekonnen H, Bhaskar S, Lippman J. Low-dose paroxetine (7.5 mg) improves sleep in women with vasomotor symptoms associated with menopause. *Menopause* 2015;22(1):50-8
18. Handley AP, Williams M. The efficacy and tolerability of SSRI/SNRIs in the treatment of vasomotor symptoms in menopausal women: a systematic review. *J Am Assoc Nurse Pract* 2015;27(1):54-61
19. Weber L, Thacker HL. Paroxetine: a first for selective serotonin reuptake inhibitors - a new use: approved for vasomotor symptoms in postmenopausal women. *Womens Health (Lond)* 2014;10(2):147-54
20. Roberts H, Hicky M. Managing the menopause: An update. *Maturitas* 2016;86:53-8
21. Vigud SN, Strasbus H, Raskalakis ZJ, Blumberger DM. Systemic review of gamma amino butyric and inhibitory deficits across the reproductive life cycle. *Arch Women Ment Health* 2014;17(2):87-95

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