



## Comparative Study of Efficacy and Safety of Gabapentin versus Nortriptyline for Diabetic Neuropathy in a Tertiary Care Hospital of Eastern India

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### ABSTRACT

**Introduction:** Diabetic Peripheral Neuropathy (DPN) is among the most common diabetic consequence, and it is an important contributor of foot ulcers, disabilities, and amputation. Many studies have shown that nortriptyline is effective in treating neuropathic pain; however, due to its wider range of action and potential side effects, its usage may be restricted. Gabapentin has shown significant efficacy in therapy of neuropathic pain.

**Aims/ objective:** To compare efficacy and safety of gabapentin versus nortriptyline in patients of diabetic peripheral neuropathy.

**Materials and Method:** 100 patients with peripheral diabetic neuropathy were randomised into two groups. 50 patients in Group G were prescribed Gabapentin 10 mg once daily whereas 50 patients in Group N were prescribed Nortriptyline 10 mg once daily. Pain intensity was measured with help of visual analogue scale. Sleep disruption due to neuropathy was measured by insomnia severity index. Safety was compared with respect to incidence of adverse events.

**Results:** At baseline and 1 month, there was no significant difference between group G and group N with respect to VAS pain level ( $p > 0.05$ ). At 3 months and 6 months of follow-up, patients receiving gabapentin had significantly lesser pain level with respect to VAS ( $P < 0.05$ ). At 6 months of follow-up, patients receiving gabapentin had significantly lesser disruption in sleep due to neuropathy ( $P < 0.05$ ). There was more incidence of drug related constipations, fatigue, weight gain and blurred vision in patients receiving nortriptyline. There was more incidence of ataxia in patients receiving gabapentin.

**Conclusion:** gabapentin was found to be significantly more effective with respect to pain scores and disruption of sleep. Safety was gabapentin was also found to better in gabapentin group with respect to incidence of adverse effects.

**Keywords:** Gabapentin, Nortriptyline, Peripheral Diabetic Neuropathy, Pain Severity, VAS.

### INTRODUCTION

Chronic hyperglycaemia is the hallmark of diabetes mellitus (DM), a metabolic disease brought on by insufficient insulin synthesis or activity.<sup>1</sup> This disease is thought to be among the most serious health issues impacting about 400 million people worldwide.<sup>2</sup> By the end of 2030 and 2045, the prevalence of this condition is expected to reach 10.2% and 10.9%, respectively. Furthermore, the overall prevalence of diabetes is 7.2% in rural areas versus 10.8% in urban areas.<sup>3,4</sup>

Furthermore, 9.2 million individuals are expected to have diabetes by 2030, per national data on the disease's prevalence. 5 Most types of diabetes, particularly type 2, are on the rise as a result of sedentary lifestyles and poor diets.<sup>6,7</sup> Nephropathy, retinopathy, and neuropathy are the three primary effects of diabetes mellitus.<sup>8</sup>

Diabetic Peripheral Neuropathy (DPN) is among the most common diabetic consequence, and it is an important contributor of foot ulcers, disabilities, and amputation. Diabetic neuropathic pain (DN), affecting the nerves, affects around 50% of diabetic individuals.<sup>9</sup> Moreover, acute neuropathic pain, which is typically strong,

persistent, and challenging to manage or cure, affects 20–30% of people with DPN.<sup>10,11</sup>

Furthermore, tingling (pins and needles), greater susceptibility to heat and cold, numbness, as well as loss of sensation in the feet are symptoms that affect one-third of DPN patients.<sup>12</sup> Neuropathy-related discomfort can significantly raise treatment expenses and have a detrimental impact on a patient's quality of life. Peripheral neuropathy patients also have twice the annual therapy payments in addition to these expenses.<sup>13</sup>

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Many studies have shown that nortriptyline is effective in treating neuropathic pain; however, due to its wider range of action and potential side effects, its usage may be restricted.<sup>14-19</sup>



GABA and gabapentin share a structural relationship. Although the exact mode of action of gabapentin's analgesic properties is unknown,<sup>20</sup> research on animals indicates that its ability to modulate pain may be related to the discharge of GABA in spinal-cord circuits that alter pain perception.<sup>21</sup>

The FDA has approved gabapentin as a therapy of post-herpetic neuralgia in adults as well as for use as an adjuvant treatment in patients with epilepsy who are 3 years of age and older who are experiencing partial-onset episodes. For the pharmacotherapy of DPN patients, it is not approved. However, as a less costly option to pregabalin, recognized treatment guidelines have recommended the administration of gabapentin in this indication.<sup>22</sup>

Thus, this study was conducted to compare efficacy and safety of gabapentin versus nortriptyline in patients of diabetic peripheral neuropathy.

## MATERIALS AND METHODS

This was an open label randomised controlled trial conducted on patients of diabetic peripheral neuropathy in a tertiary care hospital of eastern India from August 2023 to January 2024. Informed consent was taken by patients of diabetic peripheral neuropathy after providing and explaining participant information sheet under the recommendations of Good Clinical Practice and declaration of Helsinki.

### Inclusion Criteria:

- Patients of either sex of age between 18 to 70 years.
- Patients of type 2 diabetes mellitus
- Patients with diagnosis with peripheral diabetic neuropathy

Peripheral diabetic neuropathy is mostly diagnosed clinically, with previous episodes of neuropathic pain as well as confirmatory test results demonstrating neuropathy-related impairments serving as the basis for the diagnosis. Included were patients who had previously experienced "gloves and stocking"-like discomfort as well as numbness in their hands and feet.<sup>23</sup>

### Exclusion Criteria:

- Patients having ulcers, severe wounds or lesions, or foot injuries connected to diabetes were not included in the study due to the potential for bias in pain levels.
- Individuals suffering from any further diabetes-related complications, including cardiopathy, retinopathy, or nephropathy.

### Intervention:

Patients who satisfied the inclusion criteria during the screening visit day were enrolled in the study and were randomized 1:1 ratio into two groups:

**Group G:** Patients were prescribed Gabapentin 10 mg once daily.

**Group N:** Patients were prescribed Nortriptyline 10 mg once daily.

**Sample Size:** 100 Study Participants; 50 patients in each group

### Efficacy assessment

**VAS score:** Based on self-reported pain intensity measurements, which ranged from 0 (no pain) to 10 (worst pain), scores were calculated. A higher score indicates greater pain intensity.<sup>24</sup>

**Mean Insomnia Severity Index Score (ISI):** A seven-item self-report questionnaire called the ISI is used to evaluate the type, severity, and effects of insomnia. The dimensions assessed are: the extent of sleep onset, maintenance, and initial morning awakening problems; sleep discontentment; disruption of sleep; problems with daytime functioning; noticeability of the sleep issues by others; and distress triggered by the sleep difficulties. Typically, the recall period is the "last month." Each item is rated on a 5-point Likert scale, resulting in a total score that can range from 0 to 28. The interpretation of the total score is as follows: 0–7 indicates no insomnia; 8–14 indicates sub-threshold insomnia; 15–21 indicates moderate insomnia; and 22–28 indicates severe insomnia.<sup>25</sup>

**Safety assessments:** Patients who reported at least single adverse event throughout the course of treatment were counted and their percentage was evaluated. Adverse occurrences that were connected to, or potentially connected to, the study therapy was classified as drug-related adverse events. The events that were reported often were documented.

Follow-up was done at baseline, 1 month, 3 months, and 6 months of therapy.

### Statistical Analysis

The data collected from patients with peripheral diabetic neuropathy were compiled and coded on a Microsoft Excel spreadsheet (version- 365). Data analysis was performed using Statistical Package for social sciences (SPSS) for Windows version 24.0 (SPSS Inc., Chicago, IL). Mean clinical scores were expressed as mean  $\pm$  SD and were compared between group G and N using unpaired t test. Chi-square or fisher's exact test were used for comparison of categorical data such as gender, frequency of patients with ADR etc. between group G and group N. A p-value of less than 0.05 was taken as measure of statistical significance.

## RESULTS

50 patients receiving gabapentin and 50 patients receiving nortriptyline completed 6 months of follow-up. Their baseline demographic and clinical characteristics is given in table 1.



**Table 1:** Comparison of Baseline Demographic and Clinical Characteristics between Group G and Group N

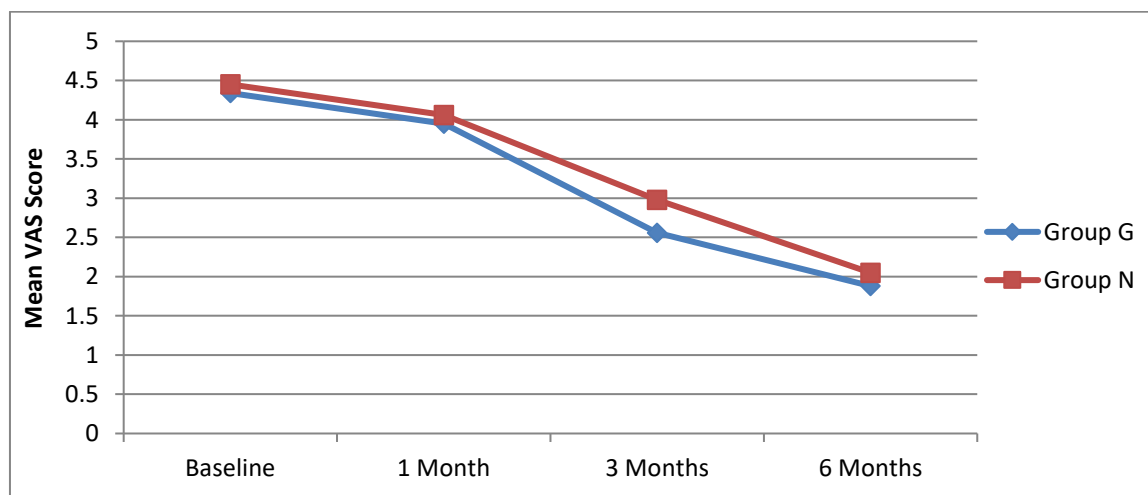
Parameters	Category	Number of Patients in Group G (n=50)	Number of Patients in Group N (n=50)	P-Value (Chi-Square Test)
Age	31-40	5	3	0.73
	41-50	12	14	
	51-60	24	21	
	61-70	9	12	
Gender	Male	27	29	0.84
	Female	23	21	
Duration of Diabetes in Years	0-5	14	11	0.78
	6-10	21	23	
	>10	15	16	

Most of the patients with PDN belonged to age group of 51-60 years. There was slight female preponderance in patients with PDN in either group G and N. Most of the patients with PDN had diabetes duration between 6-10 years. There was no significant difference between group G and N with respect to age, gender, and duration of diabetes ( $p>0.05$ ).

**Table 2:** Comparison of Mean Visual Analogue Score (VAS Score) between Group G and Group N

Time	VAS Score in Mean $\pm$ SD		P-Value (Unpaired t-test)
	Group G (n=50)	Group N (n=50)	
Baseline	4.34 $\pm$ 1.47	4.45 $\pm$ 1.92	0.75
1 Month	3.95 $\pm$ 1.02	4.06 $\pm$ 1.11	0.61
3 Months	2.56 $\pm$ 0.82	2.98 $\pm$ 0.93	<b>0.02</b>
6 Months	1.88 $\pm$ 0.29	2.05 $\pm$ 0.35	<b>0.01</b>

At baseline and 1 month, there was no significant difference between group G and group N with respect to VAS pain level ( $p>0.05$ ). At 3 months and 6 months of follow-up, patients receiving gabapentin had significantly lesser pain level with respect to VAS ( $P<0.05$ ).



**Figure 1:** Comparison of Mean Visual Analogue Score (VAS Score)

**Table 3:** Comparison of Mean Insomnia Severity Index Score (ISI) between Group G and Group N

Time	ISI Score in Mean $\pm$ SD		P-Value (Unpaired t-test)
	Group G (n=50)	Group N (n=50)	
Baseline	7.95 $\pm$ 1.77	8.00 $\pm$ 1.92	0.89
1 Month	6.98 $\pm$ 1.59	7.16 $\pm$ 1.68	0.58
3 Months	5.42 $\pm$ 1.23	5.85 $\pm$ 1.32	0.09
6 Months	3.85 $\pm$ 0.77	4.22 $\pm$ 0.93	<b>0.03</b>

At baseline, 1 month and 3 months, there was no significant difference between group G and group N with respect to severity of insomnia. At 6 months of follow-up, patients receiving gabapentin had significantly lesser disruption in sleep due to neuropathy ( $P < 0.05$ ).

**Table 4:** Comparison of Adverse Drug Reactions between Group G and Group N

Adverse Drug Reactions	Number of Patients in Group G (n=50)	Number of Patients in Group N (n=50)	P-Value (Fisher's Exact Test)
Constipation	5	11	0.17
Fatigue	3	7	0.31
Headache	1	4	0.36
Weight gain	1	3	0.62
Blurred vision	0	1	>0.99
Ataxia	2	0	0.49

There was more incidence of drug related constipations, fatigue, weight gain and blurred vision in patients receiving nortriptyline. There was more incidence of ataxia in patients receiving gabapentin. However, there was no significant difference between group G and N with respect to incidence of adverse drug reactions ( $p > 0.05$ ).

## DISCUSSION

In this randomised controlled study conducted on patients of diabetic neuropathy, we have compared efficacy and safety of gabapentin versus nortriptyline. At 3 months and 6 months of follow-up, patients receiving gabapentin had significantly lesser pain level with respect to VAS ( $P < 0.05$ ). At 6 months of follow-up, patients receiving gabapentin had significantly lesser disruption in sleep due to neuropathy ( $P < 0.05$ ).

Over the course of nine weeks, gabapentin at doses up to 2700 mg daily and nortriptyline at doses up to 150 mg daily were compared in active controlled research comprising 76 patients. Using a VAS pain scale, 13/38 (34%) of the gabapentin group and 14/38 (37%) of the nortriptyline group reported at least 50% reductions in pain over baseline; these results are somewhat consistent with rates of events in placebo-controlled studies.<sup>26</sup> In prior low dose therapy failures, Harden (2013) evaluated two gabapentin encarbil dosing regimens and found that approximately 13% showed improvement at the fifty percent pain reduction threshold.<sup>27</sup>

For patients with PDN, dose-limiting side effects continue to be an issue. TCA therapy's efficacy is sometimes restricted by unpleasant side effects such as drowsiness, retention of urine, orthostatic hypotension, ventricular arrhythmias, or a slow onset of action.<sup>28</sup>

In the medical management of PDN, gabapentin has been demonstrated in earlier studies to be well tolerated, better than a placebo, and on par with tricyclic antidepressants.<sup>29-31</sup> Nevertheless, a lot of these studies looked at a specific dose, a limited range of dosages, or a small sample size. Regardless of the effectiveness at lower levels, forced

titration schedules (as much as to 3,600 mg/day) or dose adjustments based on tolerance were employed in titration studies.

Reducing the degree of neuropathy can be achieved with the use of insulin and oral anti-diabetic medicine as established ways for improving blood sugar control. In this context, anticonvulsants, tricyclic antidepressants, SNRIs (serotonin norepinephrine reuptake inhibitors), and opioids are commonly used to treat pain.<sup>32</sup>

Initially developed as an anti-spasmodic and muscle relaxant, gabapentin is an anticonvulsant.<sup>33, 34</sup> Furthermore, gabapentin is used as a medication to treat a variety of conditions, including neuropathy.<sup>35, 36</sup> Both the positive and negative symptoms of PDN can be impacted by gabapentin.<sup>37</sup> Previous studies have shown the therapeutic mechanisms of gabapentin upon alpha-2 adrenergic receptors<sup>38</sup>, which can lessen central sensitivity and promote analgesic effects by reducing the release of activated neurotransmitters like glutamate.<sup>39</sup> In addition, gabapentin is linked to NMDA currents, calcium and sodium channels, and the modulation of monoamine neurotransmitters.<sup>40</sup> Consequently, it would make sense to highlight the calcium channel inhabitation, anticonvulsant action, and analgesic benefits of gabapentin for peripheral neuropathy.

But according to Chang CY et al. (2014), gabapentin cannot be metabolized by the human body. They also stated that, regardless of dosage, tiredness and dizziness are the most frequent side effects of gabapentin.<sup>41</sup> Further adverse effects of gabapentin comprise anxiety, tremors, blurred vision, and memory issues.<sup>42</sup>

The current study has certain limitations, such as the absence of a group that received combination therapy prescriptions. In this context, it is recommended that future study take a group approach to combination therapy alone. The small sample size of the study was another drawback that limited how broadly the findings could be applied.



## CONCLUSION

In this randomised controlled study conducted on patients of diabetic neuropathy, gabapentin was found to be significantly more effective with respect to pain scores and disruption of sleep. Safety was gabapentin was also found to better in gabapentin group with respect to incidence of adverse effects such as constipations, fatigue, weight gain and blurred vision. However, gabapentin was associated with 4% incidence of ataxia which was not reported in nortriptyline group. Clinical trials comparing combination therapy of gabapentin and nortriptyline could generate further evidences of achieving better effectiveness and safety with dose reduction.

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