Research Article

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Analysis of Comorbid Conditions and Drug Utilization Patterns in Neuropathic Pain in India (The NEUTRON study).

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ABSTRACT

Background and Objective: Neuropathic pain caused by a lesion or disease of the somatosensory nervous system is a common chronic pain condition with major impact on quality of life. Objective of the present analysis is to investigate the comorbidities and pharmacological management practices employed in patients with neuropathic pain in India.

Methods: A retrospective, multi-centric, cross-sectional, observational study enrolled 9,481 patients. Using medical records of the patients, clinical parameters such as diagnosis, symptom type and severity, patient demographics, and comorbid conditions were collected. Chi-square tests, and independent and paired samples t-tests were used for statistical analysis.

Results: A significant proportion (41%) of the patients had diabetic peripheral neuropathy. The burning sensation was the most commonly reported symptom (68.5%), followed by shooting pain (45.7%) and paraesthesia (26.6%). Anxiety (28.3%) and depression (27.8%) were the most common psychological comorbidities. Combination therapy of drugs was prescribed in 61.8% of patients, while 38.5% received monotherapy. Reduction in pain score from 7.15 to 4.16 (55%) was observed post-treatment. Patients without comorbid conditions experienced a greater pain reduction compared to those with comorbidities (66% vs 53.5%, p = 0.001).

Conclusion: The study identified diabetic peripheral neuropathy as the leading cause of neuropathic pain in India, with a high prevalence of psychological disorders among affected patients. While existing pharmacological management approaches have demonstrated effectiveness by significantly reducing pain scores, there is a need for improved pharmacological and non-pharmacological therapies, or a combination of both, to enhance outcomes further.

Keywords : neuropathic pain, diabetic neuropathy, chronic pain, combination therapy, comorbidities**.**

INTRODUCTION

Neuropathic pain is a debilitating chronic condition stemming from abnormalities in the somatosensory system.[1] Currently, an estimated 7-8% of the general population is affected by neuropathic pain, with projections indicating a rise in its prevalence in the following years.[2] The prevalence of neuropathic pain data in India is highly heterogeneous, with results suggesting the frequency of the condition ranges between 5-2400 cases per 10,000 people.[3] Among the general population, older individuals bear a significant burden of neuropathic pain, with its effects on this demographic group being particularly pronounced.[4,5]

Despite its prevalence, neuropathic pain is frequently misdiagnosed or underdiagnosed, leading to a series of ineffective treatments, translating to negative clinical symptoms in the patients.[2] The underlying causes of neuropathic pain are diverse, encompassing infectious viruses such as herpes zoster and human immunodeficiency virus (HIV), abnormal metabolic conditions like diabetes, inflammatory conditions including radiculopathy, oncological factors, post-surgery or trauma-related complications, and central nervous system pathologies, such as stroke and spinal cord injuries.[2] Frequently encountered clinical symptoms of neuropathic pain are neuralgia presenting as allodynia, intermittent stabbing or piercing pains, and constant burning pain.[6,7]

Various therapeutic approaches exist for managing neuropathic pain, spanning from pharmacological to non-pharmacological therapies.[8,9,10] First-line therapy for neuropathic pain typically involves the use of tricyclic antidepressants and anticonvulsants like pregabalin and gabapentin, which have proven effective in pain resolution.[8,10] When initial therapies

fail to provide adequate relief, second and third-line therapies may be considered, including agents such as lidocaine, alternative antidepressants, additional anticonvulsants, and opioids like tramadol and oxycodone. However, it is essential to exercise caution with pharmacological agents due to the risk of long-term dependency.[8,10–12]

A holistic understanding of the prevalence of neuropathic pain and its common comorbidities is essential for effective management, including treatment selection.[13] Frequently associated co-morbid conditions, such as depression, anxiety, diabetes, autoimmune disorders, and chronic musculoskeletal issues, not only exacerbate neuropathic pain but also complicate its management, highlighting the need for a comprehensive approach.[14] By advancing our understanding of neuropathic pain and developing better treatment strategies, healthcare providers can improve the quality of life of neuropathic pain patients, helping them lead a more comfortable life.[13]

Effectively managing neuropathic pain presents a significant challenge for medical practitioners. Achieving symptom reduction and enhancing the quality of life for patients requires tailored treatment strategies that address the condition's unique characteristics and underlying causes. General physicians serve as the frontline healthcare providers for patients with chronic pain, with pain representing a substantial proportion of approximately 40% of primary care consultations.[15] Therefore, they receive first-hand experience with neuropathic pain patients, making them crucial for understanding the epidemiology, prevalence, and treatment patterns in neuropathy pain patients.

However, there is a lack of real-world evidence from India related to the underlying comorbid conditions and pharmacological treatments in neuropathic pain patients. While studies on the Western population exist, it is important to particularly assess the scenario of neuropathic pain prevalence and management in the diverse population of India. To fill this research gap, the present retrospective analysis aims to investigate the comorbidities and pharmacological management practices employed in Indian patients with neuropathic pain. Additionally, the study aims to assess the demographic characteristics, clinical presentations, and efficacy of the treatments in pain management.

METHODS

Study design and population

A retrospective, multi-centric, cross-sectional, observational study was conducted. Data was collected from different healthcare settings across India including clinics, hospitals, and healthcare institutes. Inclusion criteria are patients with a clinical diagnosis of neuropathic pain with data on existing comorbidity and management approaches, and patients receiving pharmacological agents for managing neuropathy pain. Patients with alternative diagnoses or missing data for any field were excluded.

Data collection

Physicians treating patients with neuropathy pain retrospectively extracted data from existing medical records and documented them under standard reporting systems. The study collected data on a range of clinical and demographic parameters from neuropathic pain patients. This included the diagnosis of neuropathic pain, along with patient-specific factors such as age, gender, obesity status, and history of smoking. Presenting symptoms were documented, such as the type and severity of symptoms reported by patients. Data on comorbid conditions were also gathered.

In addition, information on management strategies was recorded. Specifications of the prescribed medications for neuropathic pain management, whether monotherapy or combination therapy were documented. The treatment outcomes were analyzed using changes in the pain scores (0-10) at baseline and post-treatment.

Data analysis

Data were analyzed using descriptive and inferential statistics to evaluate demographic characteristics, comorbidities, treatment patterns, and outcomes among neuropathic pain patients. Continuous variables such as age and pain scores were summarized using means and standard deviations. For categorical variables like gender and therapy type, frequencies and percentages were computed. Chi-square tests were employed to examine the association between gender and various outcomes (e.g., comorbidity presence and drug utilization patterns). Independent samples t-tests were used to compare means between groups, such as age differences and treatment outcomes. Paired samples t-tests evaluated changes in pain scores pre- and post-treatment, with statistical significance set at $p<0.05$.

Ethical considerations

As per ICMR "Ethical Guidelines for Biomedical Research on Human Participants", the protocol presents less than minimal risk. Appropriate Ethics Committee (EC) approval was obtained to initiate the study. Since it was a retrospective study where the participants were de-identified, permission for waiver of consent was obtained from the EC. Data confidentiality was maintained throughout the study period.

RESULTS

Patient demographics and baseline characteristics

The total study population that met the inclusion criteria and was used for data analysis was 9,481 neuropathic pain

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patients. The demographic characteristic is outlined in **Table 1**. The mean age of the study cohort was 51.3 years (11.5), with a slight male predominance (58%). The average height and weight were 162.0 cm (8.7) and 67.2 kg (10.8), respectively. Most patients were non-smokers (87.8%), and 74.3% had a normal BMI, while 17.2% were overweight. Obesity was less common, affecting only 2.8% of the population. These data indicate a relatively middle-aged cohort, with a predominance of healthy BMI categories but a significant proportion of individuals at risk for weight-related health issues.

A substantial portion of the cohort had diabetic peripheral neuropathy (41.0%), reflecting the high prevalence of metabolic disorders. Anxiety (28.3%) and depression (27.8%) were common psychological comorbidities. Cardiovascular diseases, including hypertension (12.2%) and stroke (3.7%), were less frequent but notable due to their relevance to neuropathic pain. The distribution of comorbidities emphasizes the complex medical profile of neuropathic pain patients, particularly the high co-occurrence of metabolic and psychological conditions.

Table 1: Demographic characteristics of the study population.

	Mean	**SD**
Age	51.3	11.5
Gender	n	%
Male	5496	58.0%
Female	3985	42.0%
	Mean	SD
Height	162.0	8.7
Weight	67.2	10.8
Active Smoker	n	%
No	8319	87.8%
Yes	1162	12.3%
BMI	n	%
Normal BMI (18.5–22.9 kg/m2)	7034	74.3%
Over weight (23.0 –24.9 kg/m2)	1633	17.2%
Underweight (<18.5 kg/m2)	546	5.8%
Obese (≥25 kg/m2)	268	2.8%
Co-morbidities	n	%
Diabetic peripheral neuropathy	3880	41.0%
Diabetes	3007	31.8%
Anxiety disorder	2677	28.3%
Depression	2630	27.8%
Hypertension	1151	12.2%
Postherpetic neuralgia	571	6.0%
Spinal cord injury	469	5.0%
Autoimmune disorder	432	4.6%
Stroke	350	3.7%
Cardiovascular diseases	306	3.2%

Table 2: Correlation between demographic factors and drug utilization patterns.

		Drug utilization patterns		**Total**
		Combination therapy	**Monotherapy**	
Gender	**Female**	2607	1378	3985
	Male	3231	2265	5496
Total		5838	3643	9481

p-value = 0.001 through the Chi-square test

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	Drug utilization	N	Mean	Std. Deviation	Std. Error Mean
Age	1	3621	50.0682	11.89817	.19773
	2	5808	52.0010	11.14334	.14622

p-value = 0.001 through Independent samples t-test

Presenting Symptoms

Burning sensation was the most commonly reported symptom (68.5%), followed by shooting pain (45.7%) and paresthesia (26.6%) (**Table 3**). Less frequent symptoms included allodynia (15.6%) and intolerance to temperature (10.1%). The data suggest a wide range of sensory disturbances among patients, with substantial heterogeneity in symptomatology. However, no significant gender differences were observed in the distribution of symptoms (p = 0.759) (**Table 4**).

Table 3: Proportion of presenting symptoms reported at the time of diagnosis of neuropathic pain.

Symptoms	n	%
Burning sensation	6469	68.5%
Shooting pain/Electric shock like	4314	45.7%
Paraesthesia	2511	26.6%
Allodynia	1474	15.6%
Intolerance to temperature	957	10.1%

Table 4: Correlation between demographic factors and presenting symptoms

		Symptoms presence		Total
		Combination	Single	
Gender	Female	2040	1945	3985
	Male	2796	2700	5496
Total		4836	4645	9481

p-value = 0.759 through Chi-square test.

	Symptoms presence	N	Mean	Std. Deviation	Std. Error Mean
Age	1	4617	50.4087	11.42197	.16810
	2	4812	52.0744	11.47176	.16537

p-value = 0.001 through Independent samples t test.

Drug Utilization Patterns

Regarding treatment, 61.8% of patients were initiated on combination therapy, while 38.5% received monotherapy. The preference for combination therapy suggests a tailored approach to managing neuropathic pain, likely due to the refractory nature of the condition. Gender differences were observed, with males more likely to receive combination therapy (p = 0.001). Additionally, older patients were more frequently prescribed combination therapy (mean age: 52 years) compared to those on monotherapy (mean age: 50 years), a statistically significant difference (p = 0.001).

Treatment Outcomes

Pain scores significantly decreased following treatment, from a baseline mean of 7.15 to 4.06 at the endpoint, reflecting a 55.1% reduction (p = 0.001) (Table 5). The response was more pronounced in patients with successful treatment outcomes, where pain scores dropped by 71.2%, compared to 45.8% among those with less successful outcomes (p = 0.001). These findings highlight the efficacy of the treatment regimen but also indicate variability in individual responses.

The presence of comorbidities significantly influenced treatment response (Table 6). Patients without comorbid conditions

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experienced a 66.6% reduction in pain, while those with comorbidities saw a 53.5% reduction (p = 0.001). Despite this disparity, the between-group comparison did not yield a statistically significant difference (p = 0.786).

Table 5: Determination of the percentage differences in treatment response among neuropathic pain patients.

	Mean	N	Std. Deviation	% decrease	p-value
Pain baseline	7.1483	9481	2.38286	55.1%	0.001*
Pain endpoint	4.0648	9481	2.03379		

*p value through Paired samples t-test at 95% CI

Success of treatment			Mean	N	Std. Deviation	% decrease	p-value within group	p-value between group
No	Pair 1	Pain baseline	6.6728	6110	2.55376	45.8%	0.001*	0.001*
		Pain endpoint	4.1993	6110	2.15913			
Yes	Pair 2	Pain baseline	8.0101	3371	1.73134	71.2%	0.001*	
		Pain endpoint	3.8208	3371	1.75856			

*p value through Paired samples t-test and independent samples t-test at 95% CI

Table 6: Correlation of specific co-morbid conditions with treatment outcomes in neuropathic pain management.

Comorbidities presence			Mean	N	Std. Deviation	% decrease	p-value within group	p-value between group
No	Pair 1	Pain baseline	6.8341	1109	2.15204	66.6%	0.001*	0.786
		Pain endpoint	3.4139	1109	1.89456			
Yes	Pair 2	Pain baseline	7.1899	8372	2.40882	53.48	0.001*	
		Pain endpoint	4.1510	8372	2.03608			

*p value through Paired samples t-test and independent samples t-test at 95% CI

DISCUSSION

The comorbidity present in a majority of the patients was diabetes, and hypertension. Anxiety and depression were also prevalent psychological disorders present in neuropathic pain patients, indicating an impact on mental health due to the condition. Most of the patients received combination therapy for the management of pain, demonstrating synergistic use of multiple drugs for treatment. Burning sensation and shooting pain were the most commonly experienced clinical symptoms. The age of patients on combination therapy was significantly higher than those on monotherapy. The treatment approaches used by Indian physicians demonstrated a significant reduction in pain levels, with a more pronounced impact in those without the presence of comorbidities.

Diabetes and diabetic peripheral neuropathy collectively accounted for approximately 72.8% of the comorbidities present in neuropathic pain patients, highlighting a significant risk of neuropathic pain in patients with diabetes. This is higher than previous study findings. Mick et al. (2021) reported the prevalence of diabetes in a large multicentre study across 4 European countries as 20.87%.2 A single-center study in the United States observed 46.5% of neuropathic patients presenting with diabetes.16 Diabetic peripheral neuropathy is a common complication associated with prolonged diabetes, contributing significantly to morbidity and disability among diabetic patients.17 Previous studies have reported that approximately 60% of individuals with chronic diabetes mellitus experience neuropathic pain, while early-stage neuropathy affects 7–10% of newly diagnosed diabetic patients.18–20

Comparative epidemiological data suggest a higher prevalence of diabetic peripheral neuropathy in European populations relative to Asian groups.21 Additionally, approximately 25% of diabetic individuals report painful symptoms without concurrent

clinical manifestations of neuropathy.20 This condition can manifest in multiple patterns, with peripheral nerve damage to the sensory neurons. Such damage produces both positive symptoms (e.g., pain, burning, and tingling) and negative symptoms, including sensory deficits such as numbness.17 As neuropathic pain is a severe burden on diabetic patients, implementing strategies for early detection, risk assessment, and targeted treatment can help improve outcomes and reduce the burden of this debilitating condition.

Apart from the presence of diabetes in the majority of the patients, psychological distress was reported with a significant population experiencing depression and anxiety. Similar findings have been reported in existing literature. Callaghan et al. (2019) reported that 7.8% and 4.2% of the neuropathic patient population have anxiety and depression respectively.16 Cherif et al (2020) conducted a retrospective study on a small cohort of neuropathic pain patients, with 65.57% of the population presenting with depressive episodes.22 The average score on the hospital anxiety and depression scale of 0-21 points was 12.9, confirming depression and anxiety in patients with neuropathic pain. In a systematic literature review, researchers identified anxiety and depression to be frequently present in diabetic neuropathy patients with approximately one-fourth of the population having both.23 However, the association between neuropathic pain and psychological disorders is bidirectional. It is well established that depression can heighten the experience of pain by reducing the threshold for pain perception through neurological mechanisms.24,25 This is likely due to the overlap in brain regions responsible for mood regulation and pain modulation.22 Moreover, severe neuropathic pain may itself be a significant contributor to depressive symptoms and emotional distress. The nocturnal exacerbation of neuropathic pain, as reported in a previous study, could partially explain its adverse effects on sleep, which is a well-documented factor in the relationship between chronic pain and mood disturbances [main]. Additionally, intense neuropathic pain frequently leads to physical disability, which restricts daily activities, further contributing to the psychological burden.26

A trend observed in the drug utilization patterns is a slight predominance of combination therapy with more than one drug compared to monotherapy. This can be attributed to the high prevalence of comorbidities in the present patient population that require multiple drugs for optimal management. However, the higher rate of combination therapy is in contrast with the published guidelines that advocate for monotherapy at the initiation of the treatment.19,27,28 Furthermore, in cases where initial therapy fails to mitigate pain, it is advised to transition to an alternative first-line treatment. However, there is limited evidence regarding combination therapy in managing neuropathic pain.29 Despite the availability of various therapeutic options, a significant proportion of neuropathic pain patients fail to achieve adequate pain relief. Furthermore, many experience adverse effects that cause termination of the treatment.30 Consequently, clinicians frequently opt for the concurrent use of multiple pharmacological agents.31,32 A systematic literature review by Afonso et al. (2021) identified beneficial combinations of drugs that demonstrate synergistic activity.29 Combining an antidepressant, such as imipramine, with pregabalin may offer a viable alternative to monotherapy at higher doses. Similarly, the addition of duloxetine to an existing opioid–pregabalin therapy potentially provides enhanced benefits. Topical application of capsaicin along with medication also reduces neuropathic pain.29

The present study reports lower pain relief in patients with existing comorbidities compared to those with underlying comorbidities. However, the result was not statistically significant, suggesting that while comorbidities may hinder treatment efficacy, the overall improvement in pain scores remains substantial. This finding contradicts previous studies that report a significant impact of comorbidities on neuropathic pain score and symptom management. Patients with comorbid conditions exhibit lower adherence to self-monitoring practices, attend fewer primary care visits, engage in less physical activity, and maintain poorer dietary habits compared to those without comorbidities.33 Furthermore, a significant correlation between increased pain severity and elevated anxiety and depression scores has been observed.34 The co-occurrence of diabetes and anxiety reduces glycemic control, potentially contributing to the higher incidence of complications observed in these individuals.35 These observations underscore the importance of not only managing neuropathic pain but also its associated comorbidities to achieve maximal pain mitigation.

The present real-world evidence is gathered from a large population of 9,481 patients across various institutes in India. It provides novel insights into the comorbid and prevalence patterns of this specific population. It contributes to the limited data available on Indian patients with neuropathic pain, supporting a more evidence-based approach to managing the condition. However, several limitations must be acknowledged. First, the study categorizes drug therapy into mono- and combination therapies without examining specific drug classes or active compounds, such as antidepressants, analgesics, or opioids. Second, the identification of patients by physicians introduces the potential for selection bias. Third, the study lacks data on non-pharmacological interventions, such as behavioral or dietary modifications, which may have influenced the outcomes.

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CONCLUSION

The study identified diabetic peripheral neuropathy and diabetes as the leading cause of neuropathic pain in India, with a high prevalence of psychological disorders among affected patients. While existing pharmacological management approaches have demonstrated effectiveness by significantly reducing pain scores, there is a need for improved pharmacological and non-pharmacological therapies, or a combination of both, to enhance outcomes further. Identification of the most frequent comorbidities provides the rationale for further Indian studies on these patients to identify management approaches that are the most effective. While the current therapies alleviated symptoms for several patients, the majority of them did not achieve pain management, indicating lack of therapeutic efficacy of the existing drugs. Therefore, future studies must focus on developing better pharmacotherapies or improving efficacy by combining drugs to provide symptom control in a greater proportion of patients.

Authors contribution

All authors have contributed in study conception and design, interpretation of results and manuscript preparation. All authors have full access to all the data in the study.

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Disclosure

The authors declare no competing interests.

Data availability

The data generated and/or analysed during the trial are available from the corresponding author upon the request.

Institutional ethical clearance (IEC)/Institutional Review Board (IRB) Approval

This study is approved by independent ethics committee.

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