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Comparative Effectiveness of Pharmacological Therapies on Neuropathic Pain Outcomes: A Prospective Observational Study

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ABSTRACT

Background: Neuropathic pain is a chronic and debilitating condition that significantly affects quality of life and often demonstrates suboptimal response to monotherapy. Combination pharmacotherapy has been increasingly utilized in clinical practice; however, real-world comparative evidence remains limited. **Objective:** To evaluate and compare the effectiveness of monotherapy and combination pharmacological therapies in patients with neuropathic pain using longitudinal S-LANSS score assessment. **Methods:** A prospective observational study was conducted among 430 adult patients diagnosed with neuropathic pain at a tertiary care center. Patients received gabapentin 100 mg, pregabalin 75 mg, pregabalin plus duloxetine (75/10 mg), or pregabalin plus nortriptyline (75/10 mg) as part of routine clinical care. Pain severity was assessed using the Self-report Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) questionnaire at baseline, 14 days, 28 days, 8 weeks, and 12 weeks. Comparative effectiveness was evaluated based on mean S-LANSS score reduction and responder rates (≥30% and ≥50%). Statistical analysis included chi-square test, one-way ANOVA, and repeated-measures ANOVA. **Results:** Combination therapy demonstrated significantly greater reduction in S-LANSS scores compared to monotherapy ($p < 0.001$). The greatest mean reduction was observed with pregabalin plus duloxetine (11.7), followed by pregabalin plus nortriptyline (10.5). At 12 weeks, ≥50% pain reduction was achieved in 72% of patients receiving pregabalin plus duloxetine, compared with 65.7% in the pregabalin plus nortriptyline group, 56% with pregabalin monotherapy, and 38.5% with gabapentin. Radiculopathy was the most common neuropathic pain etiology. **Conclusion:** Combination pharmacotherapy, particularly pregabalin combined with duloxetine, provides superior and sustained pain relief compared to monotherapy in patients with neuropathic pain. Early consideration of multimodal treatment strategies may optimize clinical outcomes in routine practice.

1. INTRODUCTION:

Neuropathic pain is a complex, chronic pain condition arising as a direct consequence of a lesion or disease affecting the somatosensory nervous system [1]. It is clinically characterized by symptoms such as burning sensations, electric shock–like pain, tingling, numbness, allodynia, and hyperalgesia, which significantly impair physical functioning, emotional well-being, and overall quality of life [2,3]. Globally, neuropathic pain is estimated to affect approximately 7–10% of the general population, with a higher prevalence

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observed among middle-aged and elderly individuals [4].

Common etiologies of neuropathic pain include radiculopathy, diabetic neuropathy, post-herpetic neuralgia, spinal disorders, traumatic nerve injury, and neuropathic components associated with osteoarthritis of the spine [5,6]. In clinical practice, radiculopathy and diabetic neuropathy remain among the most frequently encountered causes, particularly in patients with long-standing metabolic disorders and degenerative spinal conditions [7].

Management of neuropathic pain poses a significant therapeutic challenge due to its heterogeneous pathophysiology and variable response to treatment [8]. Current international guidelines recommend pharmacological therapy as the first-line approach, with anticonvulsants and antidepressants forming the cornerstone of treatment [9]. Among anticonvulsants, gabapentin and pregabalin are widely prescribed due to their efficacy in modulating calcium channel–mediated neurotransmitter release and reducing neuronal hyperexcitability [10,11].

Antidepressants, particularly serotonin–norepinephrine reuptake inhibitors (SNRIs) such as duloxetine and tricyclic antidepressants (TCAs) like nortriptyline, have also demonstrated effectiveness in neuropathic pain by enhancing descending inhibitory pain pathways [12,13]. Despite proven efficacy, monotherapy often provides incomplete pain relief, leading to persistent symptoms and reduced patient satisfaction [14].

As a result, combination pharmacotherapy has gained increasing attention in neuropathic pain management. Combining agents with complementary mechanisms of action may offer enhanced analgesic efficacy while allowing lower individual drug doses, potentially minimizing adverse effects [15,16]. Clinical trials and observational studies suggest that combinations such as pregabalin with duloxetine or tricyclic antidepressants provide superior pain control compared to monotherapy [17].

Assessment of neuropathic pain severity and treatment response requires reliable and validated tools. The Self-report Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) questionnaire is a widely used instrument for identifying neuropathic pain and monitoring changes in symptom severity over time [18]. It has been validated in various clinical settings and is particularly useful in longitudinal observational studies [19].

Despite the availability of multiple therapeutic options, there remains a paucity of real-world comparative data evaluating the effectiveness of monotherapy versus combination therapy in routine clinical practice, especially in diverse neuropathic pain conditions [20]. Therefore, the present study was designed to evaluate and compare the effectiveness of commonly prescribed pharmacological therapies for neuropathic pain using S-LANSS scores over a 12-week follow-up period in a real-world clinical setting.

MATERIALS AND METHODS:

Study Design and Setting:

This study was conducted as a prospective observational study in a tertiary care teaching hospital. The objective was to evaluate and compare the real-world effectiveness of commonly prescribed pharmacological therapies for neuropathic pain. The study design allowed observation of routine clinical practice without intervention or alteration of prescribed treatment regimens.

Study Duration:

The study was carried out over a defined period, during which patients were enrolled consecutively and followed for 12 weeks from initiation of therapy. Follow-up assessments were performed at baseline (Day 0), 14 days, 28 days, 8 weeks, and 12 weeks.

Study Population:

A total of 430 patients diagnosed with neuropathic pain were included in the study.
Inclusion Criteria

- Patients aged 18 years and above
- Clinically diagnosed cases of neuropathic pain based on history and examination
- Patients willing to participate and provide informed consent
- Patients initiated on gabapentin, pregabalin, or combination therapy as part of routine care

Exclusion Criteria:

- Patients with acute nociceptive pain without neuropathic features
- Patients with severe psychiatric illness or cognitive impairment interfering with pain assessment
- Pregnant or lactating women
- Patients receiving opioids or interventional pain procedures during the study period

Data Collection:

Demographic details including age, gender, body mass index (BMI), and duration of symptoms were recorded at baseline. Social and lifestyle factors such as smoking status, alcohol consumption,

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physical activity, and occupation were documented. Clinical data including comorbidities (diabetes mellitus, hypertension, dyslipidaemia, and thyroid disorders) were also collected.

The etiology of neuropathic pain was classified into radiculopathy, diabetic neuropathy, osteoarthritis-related neuropathic pain, injury-related neuropathy, and post-herpetic neuralgia based on clinical diagnosis.

Treatment Groups:
Patients received pharmacological therapy as per the treating physician's discretion. Based on prescribed treatment, patients were categorized into four groups:

1. Gabapentin 100 mg (monotherapy)
2. Pregabalin 75 mg (monotherapy)
3. Pregabalin 75 mg + Duloxetine 10 mg (combination therapy)
4. Pregabalin 75 mg + Nortriptyline 10 mg (combination therapy)

No modification of drug dosage or regimen was performed for study purposes.

Outcome Measures:
Primary Outcome
The primary outcome was change in neuropathic pain severity, assessed using the Self-report Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) questionnaire.

Secondary Outcomes

- Proportion of patients achieving ≥30% reduction in S-LANSS score
- Proportion of patients achieving ≥50% reduction in S-LANSS score
- Comparative effectiveness of monotherapy versus combination therapy

Pain Assessment Tool
The S-LANSS questionnaire is a validated instrument used to identify and quantify neuropathic pain. It consists of symptom-based questions, with higher scores indicating greater pain severity. The questionnaire was administered at each follow-up visit to assess changes in pain intensity over time.

Statistical Analysis
Data were entered into a spreadsheet and analyzed using standard statistical software.

- Descriptive statistics were used to summarize demographic and clinical characteristics.
- Categorical variables were expressed as frequencies and percentages and compared using the Chi-square test.
- Continuous variables were expressed as mean ± standard deviation (SD).
- Changes in S-LANSS scores over time were analyzed using repeated-measures analysis of variance (ANOVA).
- Comparative effectiveness among treatment groups was assessed using one-way ANOVA.

A p-value < 0.05 was considered statistically significant**.**

Ethical Considerations:
The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Prior approval was obtained from the Institutional Ethics Committee, and written informed consent was obtained from all participants before enrollment. Patient confidentiality was maintained throughout the study.

RESULTS:

Demographic and Clinical Characteristics of the Study Population
A total of 430 patients with neuropathic pain were included in the study, comprising 245 males (56.9%) and 185 females (43.1%). The demographic and clinical characteristics are summarized in Table 1. Age-wise distribution showed that the majority of patients belonged to the 46–60 years age group (n = 170, 39.5%), followed by 31–45 years (n = 155, 36.0%). Patients aged above 60 years accounted for 60 participants (14.0%). A statistically significant association was observed between age group and gender distribution ($p < 0.05$).

BMI analysis revealed that 46.5% of patients had normal BMI, while 30.2% were overweight and 19.3% were obese. Obesity was more prevalent among female participants, and the association between BMI category and gender was statistically significant ($p = 0.031$). Regarding duration of symptoms, 215 patients (50%) reported neuropathic pain lasting more than 6 months, indicating a predominantly chronic disease pattern. The association between symptom duration and gender was also statistically significant ($p < 0.05$).

Table 1 Demographic and Clinical Characteristics of Study Participants (n = 430)

Parameter	Category	Male (n=245) n (%)	Female (n=185) n (%)	Total (n=430) n (%)	p-value
Age (years)	18–30	25 (10.2%)	20 (10.8%)	45 (10.5%)	<0.05
	31–45	95 (38.8%)	60 (32.4%)	155 (36.0%)	
	46–60	75 (30.6%)	95 (51.4%)	170 (39.5%)	

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	>60	50 (20.4%)	10 (5.4%)	60 (14.0%)	
BMI (kg/m²)	<18.5	12 (4.9%)	5 (2.7%)	17 (4.0%)	0.031
	18.5–24.9	130 (53.1%)	70 (37.8%)	200 (46.5%)	
	25–29.9	65 (26.5%)	65 (35.1%)	130 (30.2%)	
	≥30	38 (15.5%)	45 (24.3%)	83 (19.3%)	
Duration of symptoms	<3 months	50 (20.4%)	25 (13.5%)	75 (17.4%)	<0.05
	3–6 months	85 (34.7%)	55 (29.7%)	140 (32.6%)	
	>6 months	110 (44.9%)	105 (56.8%)	215 (50.0%)	

Social, Lifestyle, and Comorbidity Profile:
The social, lifestyle, and clinical characteristics of the study population are presented in Table 2. Smoking was significantly more common among males (55.1%) compared to females (8.1%), and this difference was statistically significant ($p < 0.001$).Similarly, alcohol consumption was predominantly observed among male participants (49.0%) compared to females (5.4%), showing a strong gender association ($p < 0.001$). Physical activity assessment revealed that 47.7% of patients had a sedentary lifestyle, with no statistically significant gender difference ($p = 0.089$). Occupational distribution showed a significant association between occupation type and gender ($p < 0.05$).Among comorbidities, hypertension (30.2%) and diabetes mellitus (23.3%) were most common. Thyroid disorders were significantly more prevalent among females ($p = 0.041$).

Table 2: Social, Lifestyle, and Clinical Profile of Study Participants

Parameter	Category	Male (n=245) n (%)	Female (n=185) n (%)	Total (n=430) n (%)	p-value
Smoking status	Smoker	135 (55.1%)	15 (8.1%)	150 (34.9%)	<0.001
	Non-smoker	110 (44.9%)	170 (91.9%)	280 (65.1%)	
Alcohol consumption	Alcoholic	120 (49.0%)	10 (5.4%)	130 (30.2%)	<0.001
	Non-alcoholic	125 (51.0%)	175 (94.6%)	300 (69.8%)	
Physical activity	Sedentary	110 (44.9%)	95 (51.4%)	205 (47.7%)	0.089
	Moderate	95 (38.8%)	65 (35.1%)	160 (37.2%)	
	Active	40 (16.3%)	25 (13.5%)	65 (15.1%)	
Occupation	Manual labour	115 (46.9%)	30 (16.2%)	145 (33.7%)	<0.05
	Non-manual	85 (34.7%)	100 (54.1%)	185 (43.0%)	
	Homemaker/Retired	45 (18.4%)	55 (29.7%)	100 (23.3%)	
Comorbidities	Diabetes mellitus	55 (22.4%)	45 (24.3%)	100 (23.3%)	0.214
	Hypertension	80 (32.7%)	50 (27.0%)	130 (30.2%)	0.067
	Dyslipidaemia	55 (22.4%)	35 (18.9%)	90 (20.9%)	0.182
	Thyroid disorder	20 (8.2%)	30 (16.2%)	50 (11.6%)	0.041

Distribution of Pharmacological Treatment:
The pharmacological treatment pattern is shown in Table 3. Monotherapy was prescribed to 54.7% of patients, while 45.3% received combination therapy. The distribution of treatment regimens showed a statistically significant difference between males and females ($p = 0.028$).

Table 3: Medication Pattern Among Study Participants

Medication	Male	Female	Total	Percentage (%)	p-value
Gabapentin 100 mg	75	60	135	31.4	0.028
Pregabalin 75 mg	55	45	100	23.3	
Pregabalin + Duloxetine	70	55	125	29.1	
Pregabalin + Nortriptyline	45	25	70	16.3	

Distribution of Neuropathic Pain Conditions:
Radiculopathy was the most common neuropathic pain condition (**51.2%**), followed by diabetic neuropathy (**23.3%**). The association between neuropathic pain etiology and gender was not statistically significant ($p = 0.118$).

Table 4: Distribution of Neuropathic Pain Conditions Among Study Participants (n = 430)

Condition	Male	Female	Total	Percentage (%)	p-value
Radiculopathy	125	95	220	51.2	0.118
Diabetic Neuropathy	55	45	100	23.3	
OA Spine	45	35	80	18.6	
Injury-related	12	8	20	4.7	
Post-herpetic Neuralgia	8	2	10	2.3	

Neuropathic Pain Condition vs Medication Used
A significant association was observed between neuropathic pain condition and prescribed medication ($p < 0.01$), with combination therapy more frequently used in radiculopathy and diabetic neuropathy (**Table 5**).

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Table 5: Neuropathic Pain Condition vs Medication Used

Condition	Gabapentin	Pregabalin	Preg + Duloxetine	Preg + Nortriptyline	p-value
Radiculopathy	60	45	70	45	<0.01
Diabetic Neuropathy	30	20	35	15	
OA Spine	20	25	15	20	
Injury-related	15	5	0	0	
Post-herpetic Neuralgia	10	5	5	0	

Comparative Effectiveness of Neuropathic Pain Therapies Based on S-LANSS Scores:

A progressive reduction in S-LANSS scores was observed across all treatment groups during the 12-week follow-up period (Table 6). However, the magnitude of pain reduction differed significantly between monotherapy and combination therapy groups.

Combination therapy with pregabalin + duloxetine demonstrated the greatest and fastest reduction in S-LANSS scores, followed by pregabalin + nortriptyline. Repeated-measures analysis showed a statistically significant difference in mean S-LANSS scores over time among treatment groups ($p < 0.001$).

At 12 weeks, patients receiving combination therapy achieved significantly lower pain scores compared to those on monotherapy, indicating superior analgesic efficacy.

Table 6: Change in S-LANSS Scores Over Time Across Treatment Groups

Medication	Baseline (0 Day)	14 Days	28 Days	8 Weeks	12 Weeks	p-value*
Gabapentin 100 mg	18.6	16.5	14.2	11.8	10.0	<0.001
Pregabalin 75 mg	18.2	15.9	13.8	11.5	9.7	<0.001
Pregabalin + Duloxetine	19.8	15.2	12.2	9.9	8.1	<0.001
Pregabalin + Nortriptyline	19.3	15.5	12.9	10.6	8.8	<0.001

*p-value calculated using repeated-measures ANOVA comparing within-group changes over time.

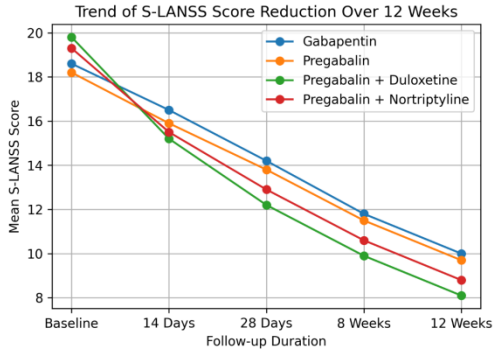

Figure 1: Trend of S-LANSS score reduction over 12 weeks across different treatment groups

Responder analysis revealed that combination therapy produced a significantly higher proportion of responders compared to monotherapy (Table 7). The highest ≥50% pain reduction rate was observed in patients receiving pregabalin + duloxetine (72%), followed by pregabalin + nortriptyline (65.7%).

Statistical comparison demonstrated a significant difference in responder rates among treatment groups ($p < 0.001$), supporting the superiority of combination regimens in neuropathic pain management.

Responder Analysis and Comparative Effectiveness

Table 7: Comparative Effectiveness of Neuropathic Pain Therapies Based on S-LANSS Scores

Therapy Type	Medication Regimen	n	Baseline S-LANSS (Mean ± SD)	12-Week S-LANSS (Mean ± SD)	Mean Reduction	≥30% Responders (%)	≥50% Responders (%)	p-value†
Monotherapy	Gabapentin 100 mg	135	18.6 ± 1.5	10.0 ± 1.1	8.6	64.4	38.5	<0.001
Monotherapy	Pregabalin 75 mg	100	18.2 ± 1.6	9.7 ± 1.0	8.5	71.0	56.0	
Combination	Pregabalin + Duloxetine	125	19.8 ± 1.4	8.1 ± 0.9	11.7	86.4	72.0	
Combination	Pregabalin + Nortriptyline	70	19.3 ± 1.5	8.8 ± 1.0	10.5	80.0	65.7	

DISCUSSION:

The present prospective observational study provides real-world evidence on the comparative effectiveness of commonly prescribed pharmacological therapies for neuropathic pain, with a particular focus on monotherapy versus combination therapy. By systematically evaluating demographic variables, clinical characteristics,

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treatment patterns, and longitudinal S-LANSS outcomes, this study offers clinically relevant insights into optimal pharmacological strategies for neuropathic pain management.

Demographic and Clinical Characteristics:
The demographic profile of the study population (Table 1) revealed a predominance of middle-aged and elderly patients, particularly in the 46–60-year age group. This observation is consistent with epidemiological studies reporting increased neuropathic pain prevalence with advancing age due to cumulative nerve injury, metabolic disturbances, and degenerative spinal changes [21,22]. The significant association between age and symptom duration further supports the chronic and progressive nature of neuropathic pain syndromes.

Body mass index analysis demonstrated a substantial proportion of overweight and obese patients, especially among females. Obesity has been recognized as an independent risk factor for neuropathic pain through mechanisms involving systemic inflammation, insulin resistance, and mechanical stress on peripheral nerves [23]. The high proportion of patients with symptoms persisting for more than six months indicates delayed diagnosis or suboptimal early pain control, a finding that aligns with previous reports highlighting underrecognition and undertreatment of neuropathic pain in routine clinical practice [24].

Lifestyle Factors and Comorbidities:
The lifestyle and clinical profile presented in Table 2 demonstrated significant gender-based differences. Smoking and alcohol consumption were markedly more prevalent among male patients, consistent with earlier studies suggesting that chronic exposure to tobacco and alcohol exacerbates neuropathic pain through microvascular compromise and neurotoxic effects [25,26].

Hypertension and diabetes mellitus were the most frequently observed comorbidities, reinforcing the established association between metabolic disorders and neuropathic pain, particularly diabetic neuropathy [27]. The higher prevalence of thyroid disorders among female patients is noteworthy, as thyroid dysfunction has been associated with peripheral neuropathy and altered nociceptive processing [28]. The presence of multiple comorbidities likely contributed to increased pain severity and reduced responsiveness to monotherapy, thereby influencing treatment escalation.

Treatment Patterns in Clinical Practice:
Analysis of pharmacological treatment patterns (Table 3) revealed that while monotherapy remained the initial approach in a majority of patients, nearly half of the cohort required combination therapy. This reflects real-world prescribing behavior, where inadequate pain relief with a single agent necessitates treatment intensification. Similar trends have been reported in observational studies from tertiary care settings, where combination therapy is frequently employed to achieve satisfactory analgesia [29,30].

Gabapentin and pregabalin were the most commonly prescribed monotherapies, consistent with guideline recommendations identifying these agents as first-line treatments for neuropathic pain [31]. However, the substantial use of combination therapy highlights the limitations of monotherapy in managing chronic and severe neuropathic pain.

Neuropathic Pain Etiology and Medication Use:
Radiculopathy emerged as the most prevalent neuropathic pain condition in the present study, followed by diabetic neuropathy (Table 4). This distribution is consistent with earlier reports identifying spinal disorders and diabetes as leading causes of neuropathic pain in clinical practice [32]. The absence of a significant gender difference in neuropathic pain etiology suggests that disease-related mechanisms, rather than sex-specific factors, predominantly determine pain origin.

The association between neuropathic pain conditions and prescribed medications (Table 5) demonstrated preferential use of combination therapy in radiculopathy and diabetic neuropathy. These conditions are characterized by both peripheral nerve injury and central sensitization, making them less responsive to single-mechanism therapies [33]. Current guidelines recommend multimodal pharmacological approaches in such cases, supporting the prescribing patterns observed in this study [34].

Comparative Effectiveness of Therapies:
Longitudinal evaluation of pain severity using S-LANSS scores (Table 6 and Figure 1) showed a progressive reduction in pain across all treatment groups over the 12-week follow-up period. However, the magnitude and rate of pain reduction were significantly greater in patients receiving combination therapy, particularly pregabalin combined with duloxetine.

The superior efficacy of the pregabalin–duloxetine combination can be attributed to complementary mechanisms of action: pregabalin reduces neuronal excitability by modulating voltage-gated calcium channels, while duloxetine enhances descending inhibitory pain pathways through serotonin and

norepinephrine reuptake inhibition [35,36]. These findings are consistent with randomized controlled trials and comparative studies demonstrating enhanced analgesic outcomes with this combination compared to monotherapy [37,38].

Similarly, the combination of pregabalin with nortriptyline demonstrated greater pain reduction than monotherapy, supporting earlier evidence that tricyclic antidepressants potentiate the analgesic effects of anticonvulsants in neuropathic pain syndromes [39]. The responder analysis (Table 7) further reinforces these findings, with combination therapy achieving substantially higher ≥30% and ≥50% responder rates.

Clinical Implications:

The results of this study have important clinical implications. The high responder rates observed with combination therapy suggest that early consideration of multimodal pharmacotherapy may improve pain control, particularly in patients with chronic symptoms and multiple comorbidities. Use of validated tools such as the S-LANSS questionnaire enables objective monitoring of treatment response and facilitates evidence-based treatment adjustments.

Strengths and Limitations:

The strengths of this study include its prospective design, large sample size, real-world clinical setting, and longitudinal assessment using a validated neuropathic pain scale. However, certain limitations must be acknowledged. The observational nature of the study precludes causal inference, and lack of randomization may introduce treatment selection bias. Additionally, adverse effects and quality-of-life outcomes were not formally assessed.

CONCLUSION:

Overall, the findings of this study provide robust real-world evidence supporting the superiority of combination pharmacotherapy over monotherapy in the management of neuropathic pain. These results align with existing literature and reinforce current guideline recommendations advocating individualized, mechanism-based treatment strategies.

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