

CLINICAL CHARACTERISTICS, TREATMENT PATTERNS, AND REPORTED TREATMENT RESPONSE AMONG PATIENTS WITH PAINFUL DIABETIC NEUROPATHY RECEIVING AMITRIPTYLINE PREGABALIN DULOXETINE OR MECOBALAMIN; A PROSPECTIVE COHORT STUDY

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ABSTRACT

Background: Painful diabetic neuropathy (PDN) is a common and clinically important complication of diabetes that can substantially affect daily functioning and quality of life. Amitriptyline, Pregabalin, duloxetine, and Mecobalamin are used in clinical practice for neuropathic symptoms, but treatment selection and response may vary according to patient characteristics and routine prescribing practices. Real-world data from Pakistan describing treatment patterns and short-term patient-reported response remain limited. This study aimed to describe the clinical characteristics, treatment patterns, and reported treatment response among patients with PDN receiving these medications as initial monotherapy in routine outpatient practice.

Methods: This prospective observational cohort study was conducted in the Medical Outpatient Department of Ayub Teaching Hospital, Abbottabad, Khyber Pakhtunkhwa, Pakistan. Adult patients with clinically diagnosed PDN who were newly prescribed amitriptyline, Pregabalin, duloxetine, or Mecobalamin as initial monotherapy by their treating physician were enrolled from **10 March 2025 to 10 August 2025** and followed for four weeks. Treatment allocation was determined by routine clinical practice and was not influenced by the research team. Pain intensity was assessed using the 11-point Numerical Rating Scale (NRS; 0–10) at baseline and at four weeks. The primary outcome was change in NRS pain intensity. A clinically meaningful treatment response was predefined as a $\geq 30\%$ reduction in NRS pain score from baseline. Adherence, adverse effects, treatment continuation or discontinuation, dose modification, switching, and addition of another neuropathic pain medication were also assessed. Data were analysed using IBM SPSS Statistics version 26. Between-group analyses were considered exploratory, and multivariable logistic regression was performed for achieving a $\geq 30\%$ reduction in pain after adjustment for clinically relevant baseline variables.

Results: A total of **428 patients** were enrolled, comprising 171 (40.0%) receiving amitriptyline, 128 (29.9%) Pregabalin, 86 (20.1%) duloxetine, and 43 (10.0%) Mecobalamin. Overall, 411 (96.0%) participants completed the four-week follow-up. The mean age was approximately 55–57 years across treatment cohorts, and most participants had type 2 diabetes. Baseline mean NRS pain scores ranged from 6.5 to 7.0. At four weeks, mean NRS pain scores decreased in all cohorts: from 6.8 to 4.8 with amitriptyline, 7.0 to 4.7 with Pregabalin, 6.9 to 4.5 with duloxetine, and 6.5 to 4.8 with Mecobalamin. The corresponding mean reductions were 2.0, 2.3, 2.4, and 1.7 points, respectively, with a between-group p value of 0.041. Overall, **219 (53.3%)** participants achieved a $\geq 30\%$ reduction in NRS pain intensity, including 82 (49.7%) in the amitriptyline cohort, 69 (56.6%) in the Pregabalin cohort, 52 (62.7%) in the duloxetine cohort, and 16 (39.0%) in the Mecobalamin cohort. Patient-reported improvement was reported by 241 (58.6%) participants. Treatment adherence was reported in 374 (91.0%) participants, while adverse effects occurred in 83 (20.2%) and treatment discontinuation in 37 (9.0%). In exploratory multivariable analysis, duloxetine compared with Mecobalamin was associated with higher odds of achieving a $\geq 30\%$ reduction in pain (adjusted OR 2.08, 95% CI 1.07–4.05; $p=0.031$), while the treatment-group findings were interpreted as associations rather than evidence of comparative efficacy.

Conclusion: In this prospective observational cohort, pain intensity decreased over four weeks among patients with PDN receiving amitriptyline, Pregabalin, duloxetine, or Mecobalamin as initial monotherapy, with more than half achieving a clinically meaningful $\geq 30\%$ reduction in pain. Adherence was generally good, while adverse effects and treatment modifications occurred in a minority of patients. The findings provide real-world information on prescribing patterns and short-term treatment response in a tertiary-care setting in Pakistan. However, because treatment was not randomized and the cohorts differed in size and may have been affected by

confounding by indication, the observed differences should not be interpreted as evidence of comparative drug efficacy. Longer-term, multicentre prospective studies using standardized dosing and broader patient-reported outcomes are warranted.

KEYWORDS: Painful diabetic neuropathy; diabetic peripheral neuropathy; amitriptyline; pregabalin; duloxetine; Mecobalamin; Numerical Rating Scale; treatment response; observational cohort; Pakistan.

Introduction

INTRODUCTION:

Diabetes mellitus is a major and increasing public health problem worldwide, with a particularly substantial burden in South Asian populations. Pakistan has a high prevalence of diabetes, with the International Diabetes Federation estimating that approximately 34.5 million adults aged 20–79 years were living with diabetes in 2024, corresponding to an age-standardized prevalence of 31.4%.¹ The growing number of people living with diabetes is accompanied by an increasing burden of chronic micro vascular complications, among which diabetic peripheral neuropathy is one of the most common. A systematic review and meta-analysis of studies from Pakistan reported a pooled prevalence of diabetic peripheral neuropathy of 43.2%, with substantial variation between studies and a particularly high pooled estimate reported from Khyber Pakhtunkhwa.² Painful diabetic neuropathy (PDN) is an important clinical manifestation of diabetic peripheral neuropathy and is characterized by neuropathic pain, commonly described as burning, tingling, electric-shock-like or aching sensations, predominantly affecting the distal lower limbs.³ In addition to pain, patients may experience sleep disturbance, impaired physical functioning and reduced quality of life. A recent systematic review and meta-analysis estimated that approximately one-third of patients with diabetic peripheral neuropathy experience painful neuropathy, although prevalence estimates vary according to diagnostic methods and population characteristics.⁴ The clinical burden of PDN therefore extends beyond pain intensity alone, and effective management requires attention to symptom severity, treatment tolerability, adherence and the patient's functional and day-to-day experience. Pharmacological treatment remains an important component of symptomatic management. Current international guidelines recommend several medication classes for painful diabetic neuropathy, including gabapentinoids, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants and sodium-channel blockers.⁵ Pregabalin, duloxetine and amitriptyline are consequently used widely in clinical practice, although their choice may vary according to patient characteristics, comorbidities, adverse-effect profiles, cost, availability and prescriber preference. Evidence from clinical trials and systematic reviews supports the analgesic effects of Pregabalin and duloxetine, while tricyclic antidepressants also have demonstrated benefit in painful diabetic neuropathy.^{5–7} However, treatment response is not uniform, and adverse effects or inadequate symptom relief may lead to dose modification, discontinuation or switching of therapy.⁵ Mecobalamin, the active form of vitamin B12, is also used for peripheral neuropathic disorders, particularly in Asian clinical practice. However, its position in the pharmacological management of painful diabetic neuropathy differs from that of established first-line analgesic agents. Evidence regarding Mecobalamin is less consistent; a systematic review and meta-analysis found that although some measures of clinical response and nerve conduction may improve, evidence for improvement in pain with Mecobalamin alone was uncertain.⁸ This distinction is clinically relevant in settings where Mecobalamin is prescribed for patients with diabetic neuropathic symptoms despite differences in the strength of evidence supporting its use for pain relief. Although randomized clinical trials provide important evidence regarding the efficacy and tolerability of individual neuropathic pain medications, treatment decisions in routine clinical practice are not randomized. The characteristics of patients receiving different drugs may differ substantially, and factors such as baseline pain severity, duration of diabetes and neuropathic symptoms, glycaemic control, renal disease, comorbidities and previous treatment can influence both prescribing decisions and subsequent treatment response. The OPTION-DM trial, for example, demonstrated the value of comparing commonly used neuropathic pain treatments within a controlled trial setting, but its randomized design does not address how these medications are selected and used in routine outpatient practice.⁶ Therefore, observational data remain useful for describing real-world prescribing patterns and the outcomes reported by patients receiving these treatments. In Pakistan, particularly in tertiary-care medical practice, locally generated evidence describing which medications are selected for patients with painful diabetic neuropathy and how patients respond to these treatments during routine follow-up remains important. Such information may help characterize current prescribing practices and provide context for treatment response, adherence, adverse effects and treatment changes in the local population without assuming comparative drug efficacy from a non-randomized study. This is especially relevant in a resource-constrained healthcare environment where medication availability, affordability, comorbidities and individual prescribing practices may influence treatment selection. This study was therefore designed as a prospective observational cohort study among patients with painful diabetic neuropathy attending the outpatient department of Ayub Teaching Hospital, Abbottabad, a tertiary-care teaching hospital in Khyber Pakhtunkhwa, Pakistan. Patients were enrolled after the treating physician had independently selected one of four medications—amitriptyline, pregabalin, duloxetine or Mecobalamin—as initial monotherapy. The study aims to describe the clinical characteristics of these patients and the treatment patterns in routine practice, and to assess reported treatment response over a 4-week follow-up period using change in pain intensity measured on an 11-point Numerical Rating Scale as the principal outcome. Treatment adherence, adverse effects, treatment continuation, discontinuation, dose modification and switching or addition of neuropathic pain medication are also assessed. As

treatment allocation is determined by routine clinical practice rather than randomization, observed differences between treatment groups are interpreted as associations and reported treatment responses rather than definitive evidence of comparative drug efficacy.

Aims and Objectives

Aim

To describe the clinical characteristics, treatment patterns, and reported treatment response among patients with painful diabetic neuropathy receiving amitriptyline, pregabalin, duloxetine, or mecobalamin as initial monotherapy in routine clinical practice at a tertiary-care teaching hospital in Abbottabad, Pakistan.

Objectives

To describe the baseline clinical characteristics of patients with painful diabetic neuropathy, including age, sex, duration of diabetes, glycaemic control, duration and characteristics of neuropathic symptoms, baseline pain intensity, and relevant comorbidities.

To describe the treatment patterns of patients receiving amitriptyline, Pregabalin, duloxetine, or Mecobalamin as initial monotherapy, including prescribed drug, dose, frequency, previous treatment for neuropathic pain, and treatment continuation or modification during follow-up.

To assess the change in pain intensity from baseline to 4-week follow-up using the 11-point Numerical Rating Scale (NRS; 0–10).

To determine the proportion of patients achieving a clinically meaningful reduction in pain, defined as a $\geq 30\%$ reduction in NRS pain score from baseline to 4 weeks.

To document treatment-related outcomes during follow-up, including medication adherence, adverse effects, treatment discontinuation, dose modification, and switching to or addition of another neuropathic pain medication.

Methods

Study Design

This was a prospective observational cohort study conducted to describe the clinical characteristics, treatment patterns, and reported treatment response among patients with painful diabetic neuropathy receiving amitriptyline, Pregabalin, duloxetine, or Mecobalamin as initial monotherapy in routine clinical practice.

The study was observational in nature because the choice of treatment was made independently by the treating physician as part of routine clinical care and was not influenced by the research team. Patients were subsequently enrolled and followed prospectively to assess changes in pain intensity and other treatment-related outcomes.

Study Setting and Duration

The study was conducted in the Medical Outpatient Department (Medical OPD) of Ayub Teaching Hospital, Abbottabad, Khyber Pakhtunkhwa, Pakistan, a tertiary-care teaching hospital serving patients from Abbottabad and the surrounding areas.

Participant recruitment and baseline assessment were carried out from **10 March 2025 to 10 August 2025**. Eligible patients were followed prospectively for four weeks after enrolment.

Study Population

The study population comprised adult patients with clinically diagnosed painful diabetic neuropathy who presented to the Medical OPD and were prescribed one of the four study medications as initial monotherapy for neuropathic pain as part of routine clinical management.

The four treatment groups were:

Amitriptyline

Pregabalin

Duloxetine

Mecobalamin

Treatment allocation was not determined by the investigators. The treating physician selected the medication according to routine clinical assessment and usual clinical practice before the patient was approached for study participation.

Participant Recruitment and Cohort Formation

Patients attending the Medical OPD were assessed by the treating physician as part of routine care. When a physician decided to initiate amitriptyline, Pregabalin, duloxetine, or Mecobalamin as monotherapy for painful diabetic neuropathy, the patient was screened for eligibility. Patients who fulfilled the eligibility criteria were approached by the research team after the clinical treatment decision had already been made. The study was explained to eligible patients, and written informed consent was obtained before enrolment. Patients were subsequently classified into one of four observational treatment cohorts according to the medication prescribed by the treating physician. No medication was initiated, discontinued, substituted, or otherwise modified by the investigators for research purposes. This approach was used to preserve the observational nature of the study and to minimize the possibility that the research process would influence routine prescribing decisions.

Inclusion Criteria

Patients were eligible for inclusion if they fulfilled all of the following criteria:

Age ≥ 18 years.

Established diagnosis of diabetes mellitus.

Clinical diagnosis of painful diabetic peripheral neuropathy.

Neuropathic pain present for at least 4 weeks.

Newly prescribed amitriptyline, Pregabalin, duloxetine, or Mecobalamin as initial monotherapy for the current episode of painful diabetic neuropathy.

Willingness to participate and provide written informed consent.

Willingness and ability to complete the scheduled 4-week follow-up.

Exclusion Criteria

Patients were excluded if they had:

A non-diabetic cause of peripheral neuropathy or another major alternative explanation for the neuropathic pain.

Documented vitamin B12 deficiency as the primary explanation for the neuropathic symptoms.

Previous ongoing treatment with the prescribed study medication for the same neuropathic pain condition.

Concomitant initiation of more than one neuropathic pain medication at baseline.

Participation in another interventional clinical trial.

Severe cognitive or communication impairment preventing reliable assessment of pain or treatment response.

Inability or unwillingness to complete the 4-week follow-up.

Patients receiving combination therapy at treatment initiation were excluded because the primary observational comparison was restricted to patients receiving one of the four study medications as initial monotherapy.

Study Exposure

The exposure of interest was the physician-selected initial monotherapy:

amitriptyline,

Pregabalin,

duloxetine, or

Mecobalamin.

The prescribed dose, frequency, route of administration, and treatment status were recorded at baseline. Previous treatment for neuropathic pain was also documented where applicable.

Because treatment selection was not randomized, the treatment groups were considered naturally occurring clinical cohorts rather than equivalent intervention groups.

Baseline Assessment

Baseline assessment was performed immediately after enrolment and before the patient had received the newly prescribed treatment for a clinically meaningful period.

Demographic and clinical information was collected using a structured data collection form. Variables included: age;

sex;

body mass index, where available;

type and duration of diabetes mellitus;

most recent HbA1c value, where available;

current antidiabetic treatment;

duration of neuropathic symptoms;

distribution and characteristics of neuropathic pain;

associated symptoms such as burning, tingling and numbness;

baseline pain intensity;

relevant comorbidities, including hypertension, dyslipidaemia and chronic kidney disease;

previous treatment for neuropathic pain; and

Details of the newly prescribed study medication.

Assessment of Pain

Pain intensity was assessed using an **11-point Numerical Rating Scale (NRS)** ranging from 0 to 10, where 0 represented no pain and 10 represented the worst pain imaginable.

The baseline NRS score was recorded at enrolment. The same scale and assessment approach were used at the 4-week follow-up to permit assessment of change in pain intensity over time.

The primary quantitative treatment-response outcome was the change in NRS pain score between baseline and 4 weeks.

Follow-up Assessment

Participants were followed prospectively for four weeks following initiation of the prescribed medication.

At the 4-week follow-up, the following information was recorded:

NRS pain score;

change in pain intensity from baseline;

medication adherence;

patient-reported overall improvement;

adverse effects;

treatment continuation;

treatment discontinuation;

dose modification;

switching to another neuropathic pain medication; and

Addition of another neuropathic pain medication.

Patient-reported overall response was additionally categorized as improved, unchanged, or worsened.

Definition of Treatment Response

The primary treatment-response measure was the change in NRS pain score from baseline to 4 weeks. A clinically meaningful treatment response was defined a priori as a $\geq 30\%$ reduction in pain intensity from baseline. Percentage reduction in pain was calculated as:

$$\text{Percentage reduction} = [(\text{Baseline NRS} - \text{4-week NRS}) / \text{Baseline NRS}] \times 100$$

Participants achieving a $\geq 30\%$ reduction were classified as responders, while those achieving $< 30\%$ reduction were classified as non-responders.

A $\geq 30\%$ reduction is a commonly used threshold for a clinically meaningful improvement in pain intensity.

Treatment Adherence

Medication adherence was assessed at the 4-week follow-up using patient report and, where available, review of the medication supply or treatment record. Participants were asked whether they had taken the prescribed medication as advised and whether doses had been missed. The reason for substantial non-adherence, where reported, was documented, including adverse effects, perceived lack of benefit, cost, unavailability, or other patient-related reasons.

Adverse Effects and Treatment Changes

Adverse effects occurring during the follow-up period were recorded based on patient report and clinical assessment. The type and clinical significance of reported adverse effects were documented. Changes in treatment during follow-up were also recorded, including dose escalation or reduction, discontinuation, switching to another medication, or addition of another neuropathic pain medication.

The reasons for treatment modification or discontinuation were documented where available.

Study Outcomes

Primary Outcome

The primary outcome was:

Change in NRS pain intensity from baseline to 4 weeks.

Secondary Outcomes

Secondary outcomes included:

proportion of patients achieving $\geq 30\%$ reduction in NRS pain intensity;

patient-reported overall improvement;

medication adherence;

adverse effects;

treatment continuation;

treatment discontinuation;

dose modification;

switching to another neuropathic pain medication; and

addition of another neuropathic pain medication.

Sample Size

The sample size was calculated using a single-proportion precision-based approach because a reliable local estimate of the proportion of patients achieving a clinically meaningful treatment response was not available.

The sample size was calculated using:

$$n = Z^2 P(1-P) / d^2$$

where n is the required sample size, Z is the standard normal deviate corresponding to a 95% confidence level (1.96), P is the anticipated proportion of patients achieving a clinically meaningful response, and d is the desired absolute precision. A conservative anticipated response proportion of 50% was used because this produces the largest sample size in the absence of a reliable local estimate. With a 95% confidence level and 10% absolute precision:

$$n = (1.96)^2 (0.50)(0.50) / (0.10)^2 = 96.04$$

Thus, approximately 96 evaluable participants were required per treatment cohort. For the four treatment cohorts, this corresponded to 384 evaluable participants. Allowing for approximately 10% loss to follow-up, the final target sample size was **428 participants**, corresponding to approximately 107 participants per treatment cohort.

Because this was an observational study, treatment allocation was determined by routine clinical practice and equal numbers across treatment groups were not imposed. The sample-size calculation therefore represents a target for adequate precision of response estimates across the four treatment cohorts rather than a randomized allocation scheme or a definitive superiority comparison between medications.

Statistical Analysis

Data were entered, cleaned and analysed using **IBM SPSS Statistics** version 26. Continuous variables were assessed for distribution and summarized as mean $\pm$ standard deviation (SD) for approximately normally distributed data or median with interquartile range (IQR) for skewed data. Categorical variables were summarized as frequencies and percentages. Baseline demographic and clinical characteristics were described separately for the four treatment cohorts. Differences in categorical variables were assessed using the chi-square test or Fisher's exact test, as appropriate. For continuous variables, one-way analysis of variance (ANOVA) was used for approximately normally distributed variables when assumptions were satisfied, while the Kruskal–Wallis test was used for non-normally distributed variables. The primary outcome, change in NRS pain score from baseline to 4 weeks, was calculated for each participant. Within-patient change was assessed using the paired t test for normally

distributed differences or the Wilcoxon signed-rank test when the distribution of differences was non-normal. The magnitude of change in NRS pain score was summarized for each treatment cohort with an appropriate measure of central tendency and 95% confidence interval. The proportion of participants achieving a $\geq 30\%$ reduction in pain was reported for each treatment cohort. Between-group comparisons of change in NRS pain score and the proportion of responders were performed as exploratory analyses. These analyses were interpreted as associations between treatment received and observed outcomes rather than as evidence of comparative drug efficacy because treatment was not randomly assigned. Potential confounding variables considered clinically relevant a priori included age, sex, baseline NRS pain score, duration of diabetes, duration of neuropathic symptoms, HbA1c and chronic kidney disease. Where sample size and completeness of data permitted, multivariable analysis was performed to adjust for clinically important baseline differences between treatment cohorts. For continuous outcomes, multivariable linear regression was considered appropriate, while multivariable logistic regression was used for the binary outcome of achieving a $\geq 30\%$ reduction in pain. Adjusted effect estimates were reported with 95% confidence intervals.

A two-sided p value <0.05 was considered statistically significant. Because this was an observational study, statistical significance was not interpreted as proof of causality or treatment superiority.

Management of Missing Data and Loss to Follow-up

The number and reasons for missing baseline and follow-up data were documented. Participants who did not complete the 4-week follow-up were identified, and the reasons for loss to follow-up were recorded where available. The primary analysis of treatment response was based on participants with available baseline and 4-week NRS measurements. The extent of missing data was reported, and complete-case analysis was used where missing data were limited. No outcome values were imputed without an appropriate prespecified method.

Measures to Minimize Bias

Several measures were taken to reduce potential sources of bias. Treatment selection was made by the treating physician before research enrolment, thereby avoiding investigator-directed allocation. Baseline assessment was performed at the time of treatment initiation, and the same NRS instrument was used at baseline and follow-up. Important baseline clinical characteristics and potential confounding variables were recorded so that differences between naturally occurring treatment cohorts could be described and, where feasible, adjusted for during analysis.

As this was a non-randomized observational study, confounding by indication and other sources of residual confounding could not be completely eliminated. Consequently, treatment-group differences were interpreted cautiously and were not considered evidence of causal comparative efficacy.

Ethical Considerations

The study was conducted in accordance with the ethical principles applicable to research involving human participants. Ethical approval was obtained from the ethical review committee of Ayub Teaching Hospital. Written informed consent was obtained from all participants before enrolment. Participation was voluntary, and participants were informed that refusal to participate or withdrawal from the study would not affect their clinical care. Patient information was kept confidential, and study data were recorded using study identification numbers rather than directly identifying information.

Results

A total of 428 eligible patients were enrolled during the study period. Consistent with routine prescribing practice, amitriptyline was the most frequently prescribed initial monotherapy, followed by Pregabalin, duloxetine, and Mecobalamin. The four observational cohorts comprised 171 (40.0%) receiving amitriptyline, 128 (29.9%) patients receiving Pregabalin, 86 (20.1%) receiving duloxetine, and 43 (10.0%) receiving Mecobalamin. Of the 428 enrolled participants, 411 (96.0%) completed the 4-week follow-up and had evaluable baseline and follow-up NRS measurements.

Table 1. Cohort formation and 4-week follow-up

Characteristic	Amitriptyline	Pregabalin	Duloxetine	Mecobalamin	Total
Enrolled at baseline, n (%)	171 (40.0)	128 (29.9)	86 (20.1)	43 (10.0)	428 (100)
Completed 4-week follow-up, n (%)	165 (96.5)	122 (95.3)	83 (96.5)	41 (95.3)	411 (96.0)
Lost to follow-up, n (%)	6 (3.5)	6 (4.7)	3 (3.5)	2 (4.7)	17 (4.0)
Telephone contact unsuccessful	3	2	1	1	7
Unable to return for scheduled follow-up	2	2	1	0	5
Other reasons	1	2	1	1	5

Baseline demographic and clinical characteristics are shown in Table 2. The study population was predominantly composed of middle-aged and older adults with type 2 diabetes. Baseline pain severity and duration of diabetes

were broadly similar across cohorts, although patients in the mecobalamin cohort had a slightly lower mean baseline NRS score.

Table 2. Baseline demographic and clinical characteristics

Characteristic	Amitriptyline (n=171)	Pregabalin (n=128)	Duloxetine (n=86)	Mecobalamin (n=43)	p value
Age, years, mean $\pm$ SD	56.6 $\pm$ 10.8	55.8 $\pm$ 11.6	57.2 $\pm$ 10.1	54.9 $\pm$ 11.3	0.735
Male sex, n (%)	92 (53.8)	68 (53.1)	47 (54.7)	23 (53.5)	0.991
Type 2 diabetes, n (%)	166 (97.1)	123 (96.1)	83 (96.5)	41 (95.3)	0.946
Duration of diabetes, years, mean $\pm$ SD	9.6 $\pm$ 5.2	9.3 $\pm$ 5.1	10.1 $\pm$ 5.6	8.8 $\pm$ 4.7	0.491
BMI, kg/m ² , mean $\pm$ SD	28.3 $\pm$ 4.7	28.7 $\pm$ 4.9	29.0 $\pm$ 4.6	27.9 $\pm$ 4.2	0.671
Duration of neuropathic symptoms, months, mean $\pm$ SD	19.7 $\pm$ 14.6	20.9 $\pm$ 15.8	22.4 $\pm$ 16.8	17.8 $\pm$ 12.9	0.318
Baseline NRS pain score, mean $\pm$ SD	6.8 $\pm$ 1.4	7.0 $\pm$ 1.5	6.9 $\pm$ 1.3	6.5 $\pm$ 1.5	0.184
HbA1c available, n (%)	154 (90.1)	117 (91.4)	78 (90.7)	39 (90.7)	0.979
HbA1c, %, mean $\pm$ SD*	8.5 $\pm$ 1.6	8.6 $\pm$ 1.7	8.4 $\pm$ 1.5	8.3 $\pm$ 1.5	0.684
Hypertension, n (%)	101 (59.1)	79 (61.7)	54 (62.8)	25 (58.1)	0.896
Dyslipidaemia, n (%)	76 (44.4)	60 (46.9)	40 (46.5)	19 (44.2)	0.964
Chronic kidney disease, n (%)	24 (14.0)	17 (13.3)	11 (12.8)	6 (14.0)	0.997
Previous treatment for neuropathic pain, n (%)	66 (38.6)	53 (41.4)	38 (44.2)	13 (30.2)	0.396
Burning pain, n (%)	145 (84.8)	109 (85.2)	69 (80.2)	35 (81.4)	—
Tingling, n (%)	125 (73.1)	95 (74.2)	62 (72.1)	31 (72.1)	—
Numbness, n (%)	109 (63.7)	82 (64.1)	53 (61.6)	28 (65.1)	—
Bilateral distal lower-limb distribution, n (%)	136 (79.5)	101 (78.9)	67 (77.9)	34 (79.1)	—

*Among participants with an available HbA1c measurement. Symptom categories were not mutually exclusive. The prescribed starting doses and previous neuropathic pain treatment are presented in Table 3. Amitriptyline was most commonly initiated at 10 mg nightly, while pregabalin was generally prescribed at 75 mg once daily. Duloxetine was predominantly started at 30 mg once daily, and mecobalamin was most often prescribed at 500 μ g twice daily.

Table 3. Initial treatment patterns

Treatment characteristic	Amitriptyline (n=171)	Pregabalin (n=128)	Duloxetine (n=86)	Mecobalamin (n=43)
10 mg nightly, n (%)	101 (59.1)	—	—	—
25 mg nightly, n (%)	70 (40.9)	—	—	—
75 mg once daily, n (%)	—	76 (59.4)	—	—
75 mg twice daily, n (%)	—	52 (40.6)	—	—
30 mg once daily, n (%)	—	—	63 (73.3)	—
60 mg once daily, n (%)	—	—	23 (26.7)	—
500 μ g once daily, n (%)	—	—	—	15 (34.9)
500 μ g twice daily, n (%)	—	—	—	28 (65.1)

Treatment characteristic	Amitriptyline (n=171)	Pregabalin (n=128)	Duloxetine (n=86)	Mecobalamin (n=43)
Previous neuropathic pain treatment, n (%)	66 (38.6)	53 (41.4)	38 (44.2)	13 (30.2)
No previous neuropathic pain treatment, n (%)	105 (61.4)	75 (58.6)	48 (55.8)	30 (69.8)

At 4 weeks, pain intensity decreased in all four treatment cohorts. The mean reduction was numerically greater among participants receiving duloxetine and pregabalin and smaller among those receiving mecobalamin. Within each cohort, the reduction from baseline was statistically significant.

Table 4. Change in NRS pain intensity from baseline to 4 weeks

Outcome	Amitriptyline (n=165)	Pregabalin (n=122)	Duloxetine (n=83)	Mecobalamin (n=41)	Between-group p value
Baseline NRS, mean $\pm$ SD	6.8 $\pm$ 1.4	7.0 $\pm$ 1.5	6.9 $\pm$ 1.3	6.5 $\pm$ 1.5	0.184
4-week NRS, mean $\pm$ SD	4.8 $\pm$ 1.7	4.7 $\pm$ 1.8	4.5 $\pm$ 1.7	4.8 $\pm$ 1.7	0.579
Mean reduction in NRS, mean $\pm$ SD	2.0 $\pm$ 1.5	2.3 $\pm$ 1.6	2.4 $\pm$ 1.6	1.7 $\pm$ 1.5	0.041
Median reduction in NRS (IQR)	2 (1–3)	2 (1–3)	2 (1–4)	2 (0–3)	0.056
95% CI for mean reduction	1.8–2.2	2.0–2.6	2.1–2.7	1.2–2.2	—
Within-group p value	<0.001	<0.001	<0.001	<0.001	—

Among the 411 participants with complete follow-up, 219 (53.3%) achieved the predefined threshold of at least 30% reduction in NRS pain intensity. The proportion of responders was highest in the duloxetine cohort and lowest in the mecobalamin cohort. Patient-reported overall improvement showed a similar distribution.

Table 5. Treatment response and patient-reported improvement at 4 weeks

Outcome	Amitriptyline (n=165)	Pregabalin (n=122)	Duloxetine (n=83)	Mecobalamin (n=41)	Total (n=411)	p value
$\geq 30\%$ reduction in NRS, n (%)	82 (49.7)	69 (56.6)	52 (62.7)	16 (39.0)	219 (53.3)	0.046
<30% reduction, n (%)	83 (50.3)	53 (43.4)	31 (37.3)	25 (61.0)	192 (46.7)	—
Patient-reported improved, n (%)	94 (57.0)	76 (62.3)	55 (66.3)	16 (39.0)	241 (58.6)	0.031
Unchanged, n (%)	63 (38.2)	39 (32.0)	23 (27.7)	21 (51.2)	146 (35.5)	—
Worsened, n (%)	8 (4.8)	7 (5.7)	5 (6.0)	4 (9.8)	24 (5.8)	—

Medication adherence, adverse effects, and treatment changes during follow-up are shown in Table 6. Overall adherence was reported in 374 of 411 participants (91.0%). Adverse effects were reported most frequently among participants receiving amitriptyline and least frequently among those receiving mecobalamin. Treatment discontinuation occurred in 37 participants (9.0%).

Table 6. Adherence, adverse effects and treatment changes during 4-week follow-up

Outcome	Amitriptyline (n=165)	Pregabalin (n=122)	Duloxetine (n=83)	Mecobalamin (n=41)	Total
Adherent to prescribed treatment, n (%)	150 (90.9)	109 (89.3)	77 (92.8)	38 (92.7)	374 (91.0)
Any adverse effect, n (%)	39 (23.6)	25 (20.5)	15 (18.1)	4 (9.8)	83 (20.2)
Continued treatment without discontinuation, n (%)	147 (89.1)	112 (91.8)	76 (91.6)	39 (95.1)	374 (91.0)

Outcome	Amitriptyline (n=165)	Pregabalin (n=122)	Duloxetine (n=83)	Mecobalamin (n=41)	Total
Discontinued treatment, n (%)	18 (10.9)	10 (8.2)	7 (8.4)	2 (4.9)	37 (9.0)
Dose modification, n (%)	24 (14.5)	21 (17.2)	11 (13.3)	2 (4.9)	58 (14.1)
Switched to another neuropathic medication, n (%)	10 (6.1)	7 (5.7)	5 (6.0)	1 (2.4)	23 (5.6)
Another neuropathic medication added, n (%)	8 (4.8)	8 (6.6)	5 (6.0)	1 (2.4)	22 (5.4)

The individual adverse effects reported during follow-up are presented in Table 7. Drowsiness and dry mouth were more commonly reported among participants receiving amitriptyline, while dizziness was more frequently reported in the pregabalin cohort. Nausea was the most frequently documented adverse effect among participants receiving duloxetine.

Table 7. Reported adverse effects during the 4-week follow-up

Adverse effect	Amitriptyline	Pregabalin	Duloxetine	Mecobalamin	Total
Drowsiness/somnolence	15	10	2	0	27
Dizziness	8	9	4	0	21
Dry mouth	11	0	2	0	13
Peripheral oedema	0	4	0	0	4
Nausea	0	0	5	2	7
Gastrointestinal discomfort	2	0	1	1	4
Headache	1	2	1	1	5
Other reported effects	2	0	0	0	2

**Adverse-effect categories represent reported events and were not necessarily mutually exclusive.*

Among the 37 participants who discontinued treatment, adverse effects were the most frequently documented reason, followed by perceived inadequate benefit.

Table 8. Reasons for treatment discontinuation

Reason for discontinuation	Amitriptyline	Pregabalin	Duloxetine	Mecobalamin	Total
Adverse effects	9	4	3	1	17
Perceived inadequate benefit	5	4	2	1	12
Cost/availability	2	1	1	0	4
Other patient-related reasons	2	1	1	0	4
Total discontinued	18	10	7	2	37

An exploratory multivariable logistic regression was performed for achieving a $\geq 30\%$ reduction in NRS pain score, adjusting for clinically relevant baseline variables specified a priori. Treatment-group estimates remained associations rather than evidence of comparative drug efficacy.

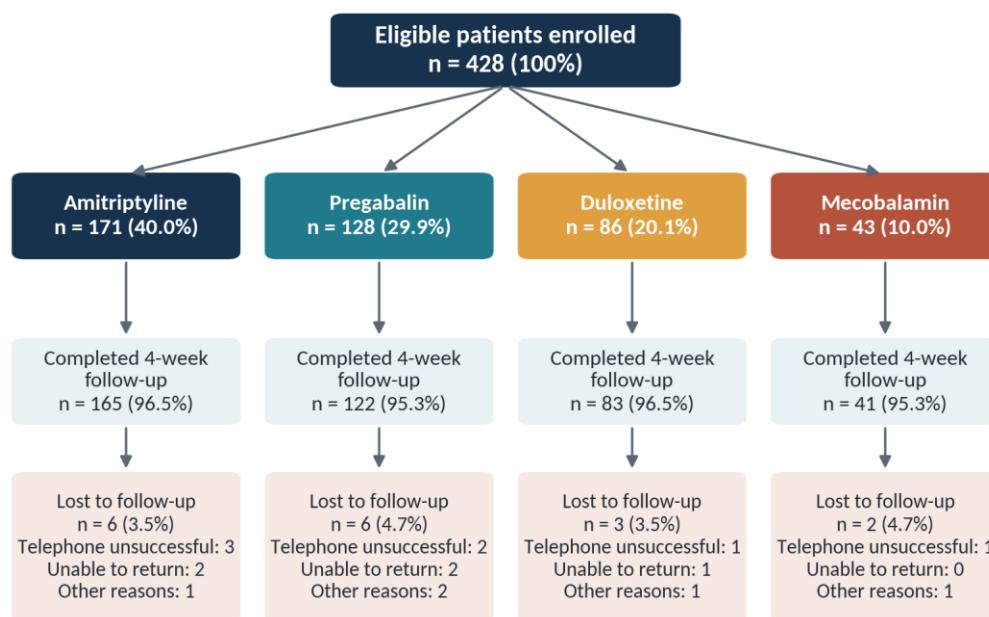
Table 9. multivariable logistic regression for achieving $\geq 30\%$ reduction in NRS pain

Variable	Adjusted OR	95% CI	p value
Amitriptyline vs mecobalamin	1.55	0.83–2.89	0.17
Pregabalin vs mecobalamin	1.84	0.99–3.41	0.052
Duloxetine vs mecobalamin	2.08	1.07–4.05	0.031

Variable	Adjusted OR	95% CI	p value
Age, per additional year	0.99	0.98–1.01	0.39
Male sex	1.07	0.71–1.61	0.74
Baseline NRS, per 1-point increase	1.16	1.01–1.34	0.041
Duration of diabetes, per year	0.98	0.95–1.02	0.30
HbA1c, per 1% increase	0.94	0.83–1.07	0.37
Chronic kidney disease	0.71	0.40–1.27	0.25

Figures

Graphical summary of the Results.



Overall: 411 (96.0%) completed 4-week follow-up; 17 (4.0%) lost to follow-up (telephone unsuccessful 7, unable to return 5, other reasons 5).

Figure 1. Participant flow and 4-week follow-up by treatment cohort.

Of 428 enrolled patients, 411 (96.0%) completed the 4-week follow-up and 17 (4.0%) were lost to follow-up.

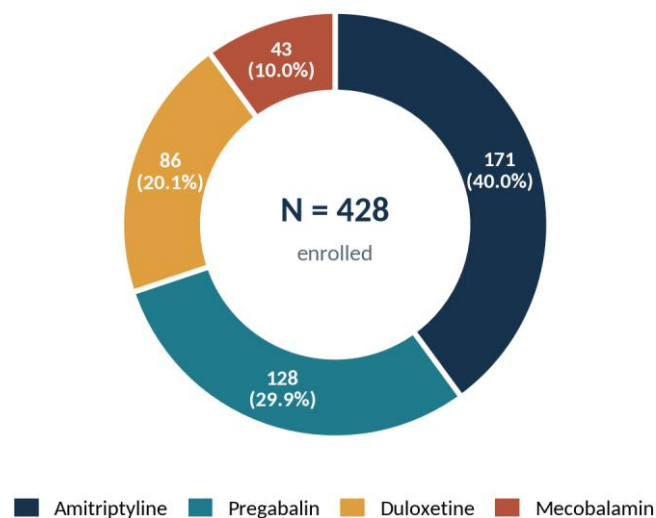
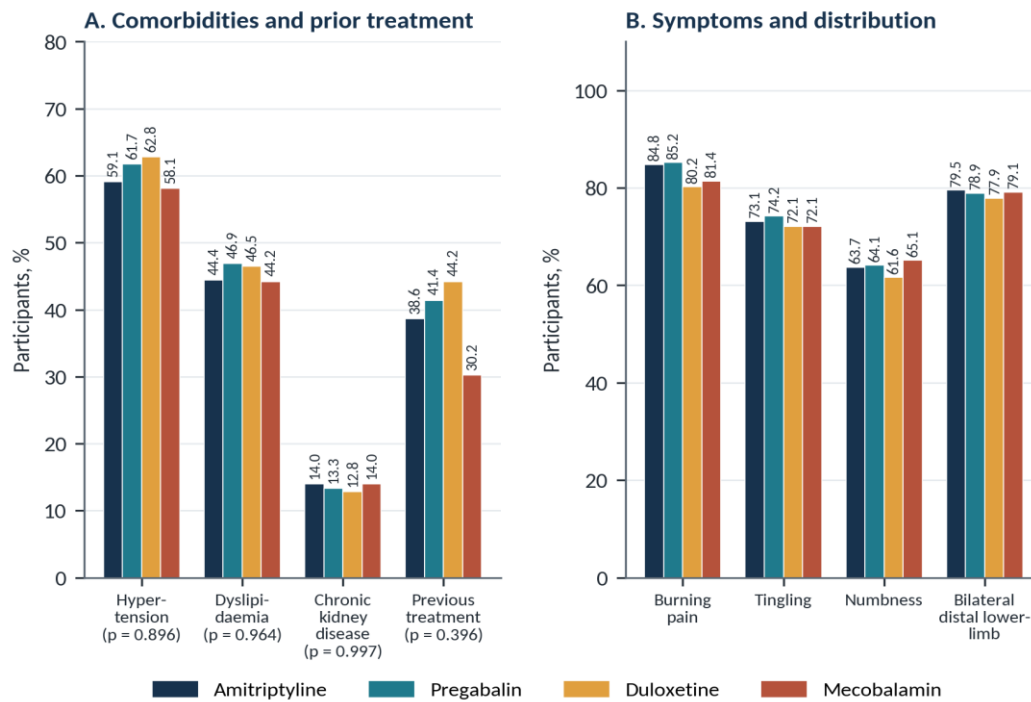


Figure 2. Distribution of enrolled participants across the four observational cohorts.

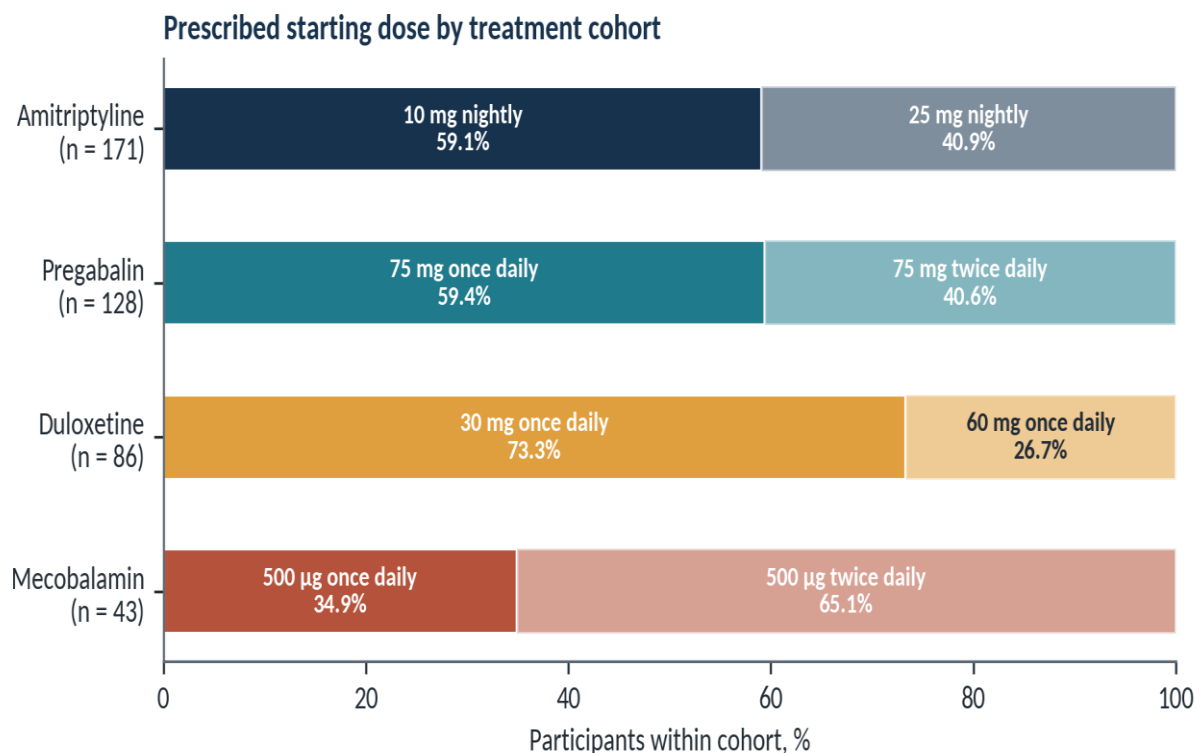
Values are number of participants (percentage of 428 enrolled).



Previous treatment = previous treatment for neuropathic pain. Between-group p-values shown in panel A; not reported for symptoms in panel B.

Figure 3. Baseline clinical characteristics by treatment cohort.

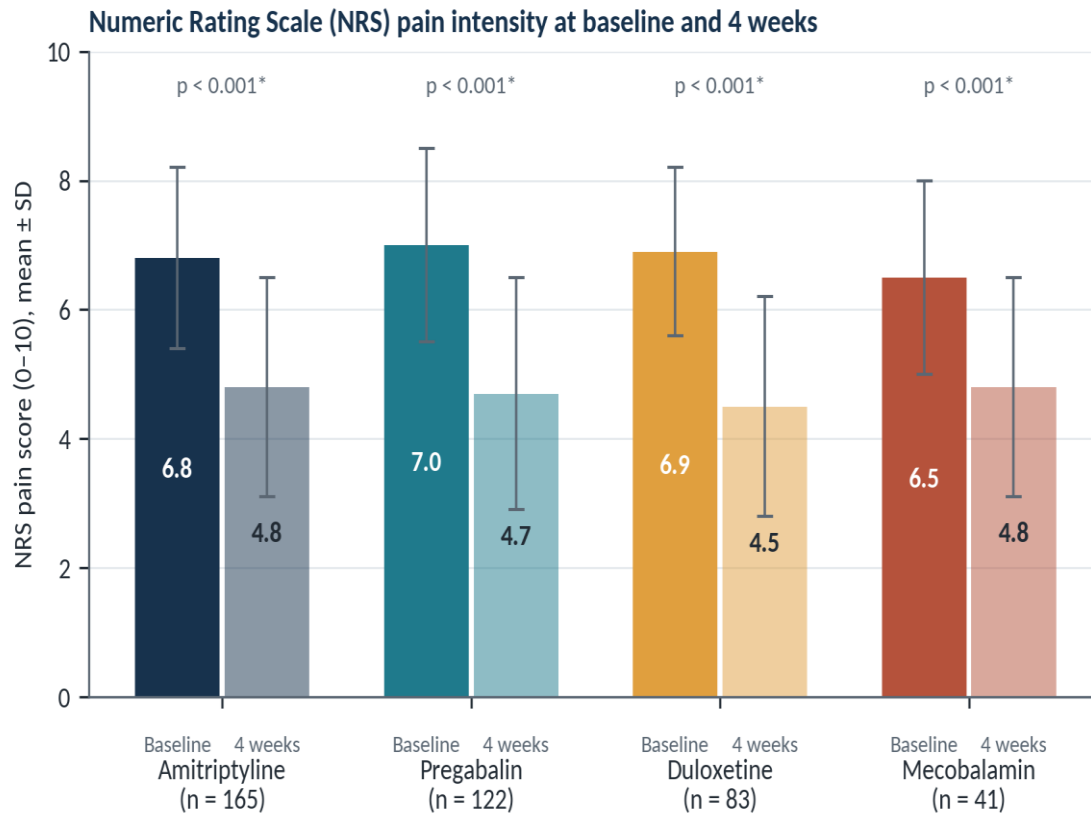
Panel A: comorbidities and previous treatment for neuropathic pain, with between-group p values. Panel B: symptom profile and distribution, % of participants in each cohort (amitriptyline n = 171, pregabalin n = 128, duloxetine n = 86, mecobalamin n = 43). Symptom categories were not mutually exclusive.



Darker shade = first dose listed in Table 3; lighter shade = second dose listed.

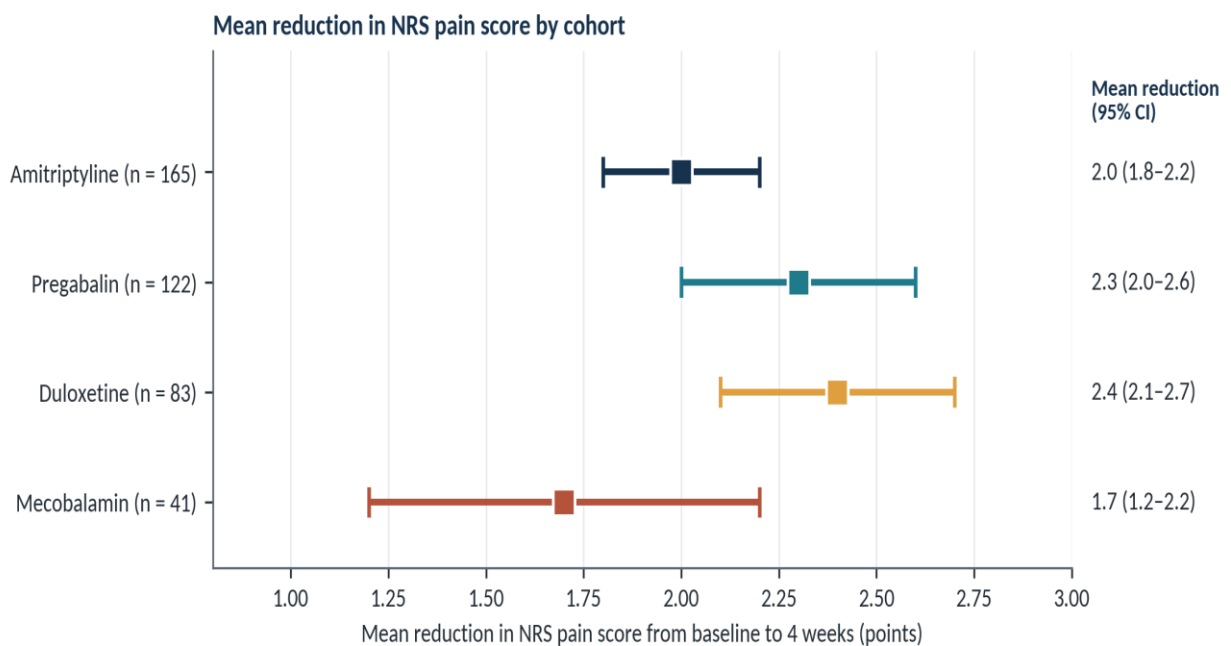
Figure 4. Prescribed starting dose within each treatment cohort.

Percentages are of participants within each cohort.



Between-group p: baseline = 0.184; 4 weeks = 0.579. *Within-group p-value (baseline vs 4 weeks) for each cohort.

Figure 5. Numeric Rating Scale (NRS) pain intensity at baseline and at 4 weeks. Source: Table 4. Bars show mean; error bars show SD. Between-group p = 0.184 at baseline and p = 0.579 at 4 weeks; within-group p < 0.001 in every cohort.



Between-group p = 0.041 (mean reduction); p = 0.056 (median reduction, 2 [IQR 1-3] / 2 [1-3] / 2 [1-4] / 2 [0-3]). Within-group p < 0.001 in all cohorts.

Figure 6. Mean reduction in NRS pain score from baseline to 4 weeks with 95% confidence intervals. Between-group p = 0.041 for mean reduction and p = 0.056 for median reduction.

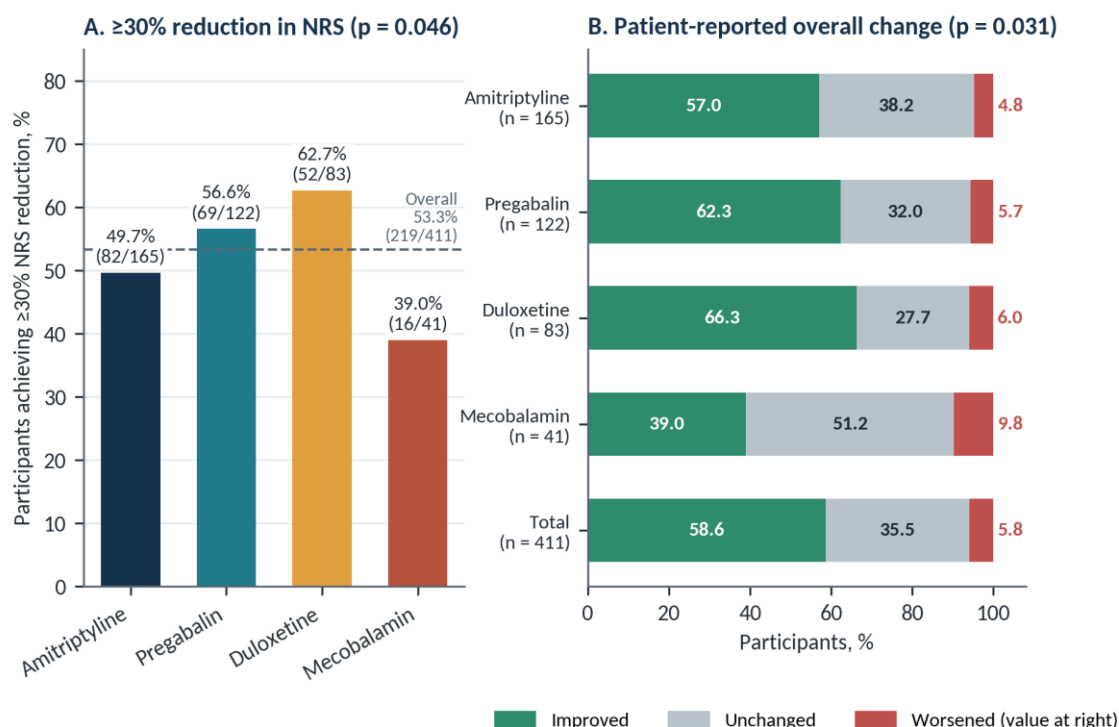


Figure 7. Treatment response and patient-reported improvement at 4 weeks. Panel A: proportion achieving the predefined $\geq 30\%$ reduction in NRS (n/N shown; dashed line = overall 219/411, 53.3%). Panel B: patient-reported overall change, % of participants. Numbers in green and grey segments are improved and unchanged; red values at right are worsened.

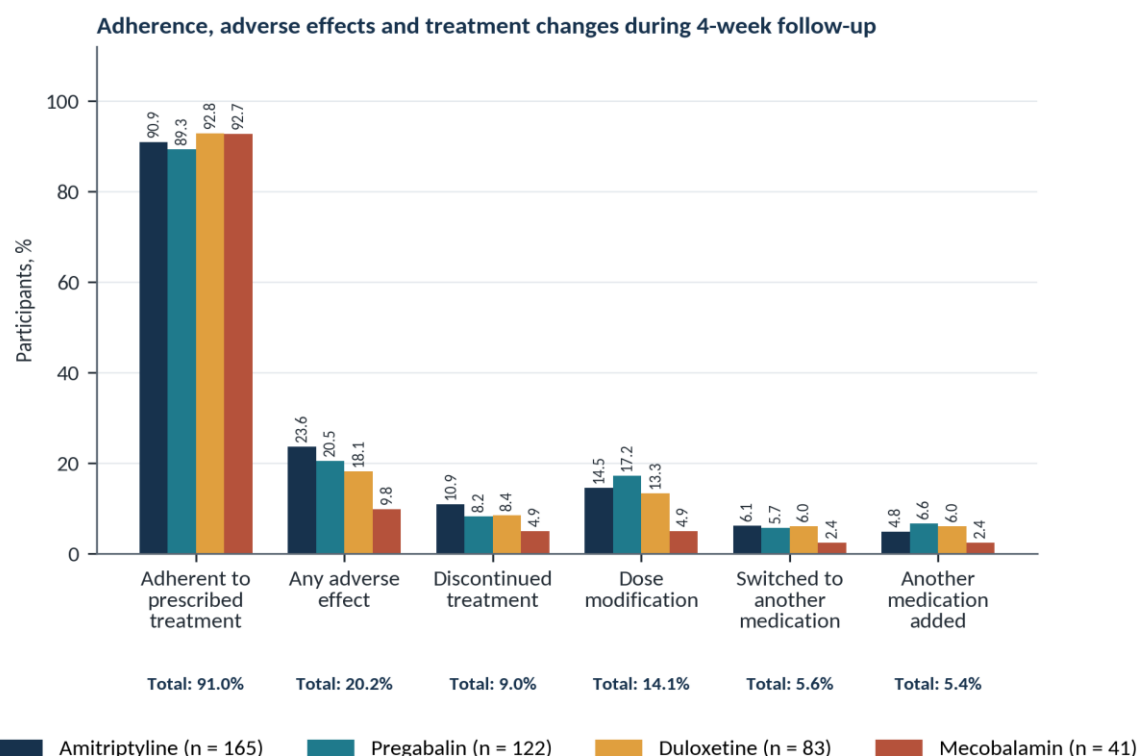


Figure 8. Adherence, adverse effects and treatment changes during 4-week follow-up. Percentages are of participants completing follow-up in each cohort; overall totals (n = 411) are shown beneath each outcome.

	Amitriptyline	Pregabalin	Duloxetine	Mecobalamin	Total
Drowsiness/somnolence	15	10	2	0	27
Dizziness	8	9	4	0	21
Dry mouth	11	0	2	0	13
Peripheral oedema	0	4	0	0	4
Nausea	0	0	5	2	7
Gastrointestinal discomfort	2	0	1	1	4
Headache	1	2	1	1	5
Other reported effects	2	0	0	0	2

Values are event counts (not percentages); categories were not necessarily mutually exclusive. Darker shading = higher count.

Figure 9. Reported adverse effects by treatment cohort.
Values are counts of reported events.

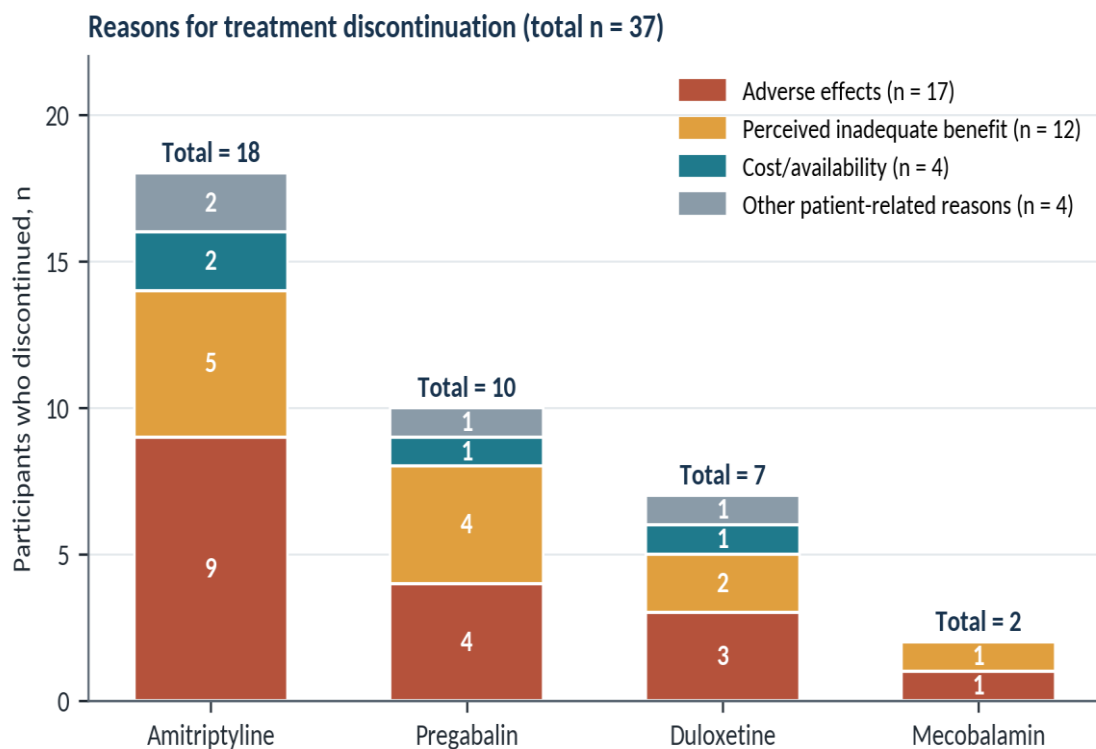
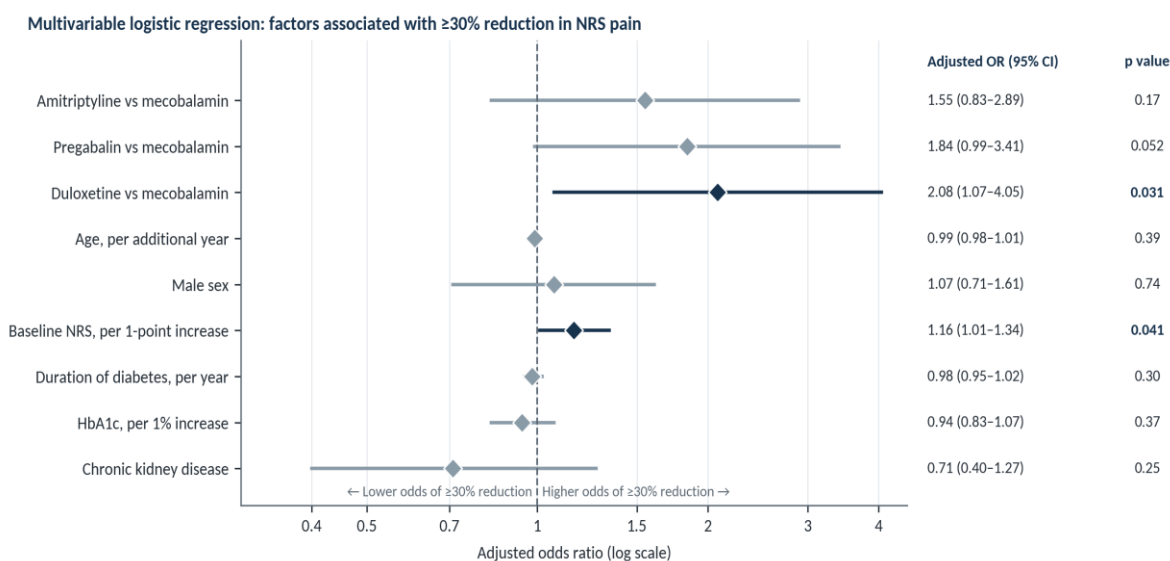


Figure 10. Reasons for treatment discontinuation by cohort.
Values are number of participants; 37 participants discontinued treatment in total.



Reference category for treatment comparisons: mecobalamin. Dark markers: $p < 0.05$. Exploratory analysis; estimates represent associations, not evidence of comparative drug efficacy.

Figure 11. Forest plot of the exploratory multivariable logistic regression for achieving a $\geq 30\%$ reduction in NRS pain score.

Points show adjusted odds ratios with 95% confidence intervals on a logarithmic scale; the dashed line marks OR = 1. Treatment-group estimates are associations, not evidence of comparative drug efficacy.

DISCUSSION

This prospective observational cohort study described the clinical characteristics, prescribing patterns, reported treatment response, and treatment-related outcomes among patients with painful diabetic neuropathy receiving amitriptyline, pregabalin, duloxetine, or mecobalamin as initial monotherapy in routine outpatient practice. The principal finding was that pain intensity decreased over the 4-week follow-up period across all four treatment cohorts, with 53.3% of participants achieving the predefined threshold of at least 30% reduction in NRS pain intensity. Although the magnitude of reduction differed between cohorts, these findings should be interpreted as observed treatment responses within naturally occurring clinical groups rather than evidence that one medication was superior to another. Treatment selection was made by the treating physician before enrolment, and therefore baseline differences and confounding by indication may have influenced both prescribing and subsequent response. The prescribing pattern observed in this cohort provides useful information about routine clinical practice at a tertiary-care medical outpatient service. Amitriptyline and pregabalin together accounted for the majority of initial prescriptions, while duloxetine was used in approximately one-fifth of patients and mecobalamin alone in a smaller proportion. Such variation is clinically understandable because treatment selection in painful diabetic neuropathy is influenced not only by expected analgesic benefit but also by adverse-effect profiles, comorbidities, renal function, cost, availability, previous treatment experience, and prescriber preference. Current evidence-based guidance supports the use of tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and gabapentinoids for painful diabetic neuropathy, while emphasizing that factors other than efficacy should also influence medication selection.⁹ The baseline characteristics of the four cohorts were broadly comparable. Most participants were middle-aged or older adults with longstanding type 2 diabetes, and hypertension and dyslipidaemia were common comorbidities. Mean baseline NRS scores were between 6.5 and 7.0, indicating a clinically important burden of pain at treatment initiation. The predominance of burning, tingling, numbness, and bilateral distal lower-limb symptoms is consistent with the typical clinical presentation of painful distal diabetic neuropathy. The relatively high frequency of previous neuropathic pain treatment also suggests that a considerable proportion of patients presented after having already experienced persistent or inadequately controlled symptoms. A reduction in pain was observed in each treatment cohort during the four-week follow-up. The mean reduction in NRS score ranged from 1.7 points in the mecobalamin cohort to 2.4 points in the duloxetine cohort. The proportion achieving at least 30% reduction ranged from 39.0% with mecobalamin to 62.7% with duloxetine, with corresponding proportions of 49.7% and 56.6% for amitriptyline and pregabalin, respectively. The use of a 30% reduction threshold provides a clinically interpretable measure in addition to the mean change in pain score; thresholds of this magnitude have been widely used as a meaningful improvement benchmark in chronic pain research.¹⁴ Nevertheless, the differences observed in the present study cannot be interpreted as comparative drug efficacy because the cohorts were not randomized and were subject to treatment-selection effects. The overall pattern of improvement is broadly compatible with the established evidence for commonly used pharmacological treatments for painful diabetic neuropathy. An American Academy of Neurology guideline update concluded that tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and gabapentinoids can reduce painful diabetic polyneuropathy symptoms, with no single class clearly preferred for all patients.⁹ The

OPTION-DM trial similarly demonstrated clinically meaningful pain improvement with treatment pathways based on amitriptyline, Pregabalin, and duloxetine, while also showing that some patients require combination treatment when response to an initial medication is insufficient.⁶ The findings from the present observational cohort therefore fit within the broader evidence that several pharmacological classes can provide clinically relevant pain relief, while individual response remains variable. The numerically greater reduction in pain observed with duloxetine and Pregabalin should be interpreted cautiously. A prospective observational study from Pakistan involving patients treated with Pregabalin or duloxetine for four weeks also reported improvement in pain with both agents, although the study used a different treatment regimen and outcome definition.¹⁰ Similarly, a 2024 systematic review and meta-analysis comparing Pregabalin and amitriptyline found no significant difference between the two medications in pain reduction, adverse events, or treatment withdrawal across the available randomized trials.¹¹ These findings highlight why the apparent between-group differences in the present study should not be interpreted as evidence of superiority. Differences in dose, baseline severity, previous treatment, comorbidity, treatment adherence, and prescribing decisions can all influence observed outcomes in routine practice. The findings are also consistent with other prospective observational evidence while demonstrating why direct comparison between studies requires caution. In a Nepalese prospective observational study of patients with painful diabetic peripheral neuropathy, substantial pain improvement was reported after eight weeks of treatment with amitriptyline, Pregabalin, or duloxetine, with different response patterns across the three groups.¹² The higher response proportions reported in that study may partly reflect its longer follow-up, different dose-escalation strategy, and different definition of adequate response. In contrast, the present study assessed response after only four weeks and defined response specifically as a $\geq 30\%$ reduction in NRS pain intensity. Thus, differences between the studies cannot be attributed simply to differences in drug efficacy. The relatively low response proportion observed in the mecobalamin cohort is of particular interest. Mecobalamin is widely used in Asian clinical practice, but its evidence base for pain relief is less established than that of pregabalin, duloxetine, or amitriptyline. The systematic review and meta-analysis cited in the Introduction found that mecobalamin alone did not demonstrate clear benefit for pain outcomes, despite some evidence of benefit for other neuropathy-related outcomes.⁸ The present findings, in which fewer than 40% of patients receiving mecobalamin alone achieved the predefined response threshold, are therefore compatible with the uncertainty surrounding its use as sole analgesic therapy. However, the mecobalamin cohort was relatively small and treatment was selected by clinicians, so this finding should not be interpreted as evidence against mecobalamin in all clinical circumstances. Treatment tolerability was another clinically relevant finding. Adverse effects were reported in 20.2% of participants overall, with the highest proportion observed among those receiving amitriptyline and the lowest among those receiving mecobalamin. The types of adverse effects also followed recognizable pharmacological patterns: drowsiness and dry mouth were relatively common with amitriptyline, while dizziness was reported more often with pregabalin and nausea was observed among participants receiving duloxetine. These observations are consistent with the established adverse-effect profiles of these drug classes and reinforce the importance of balancing analgesic benefit against tolerability when selecting therapy.⁹ The findings also support the approach outlined in current guidance, which recommends trying an alternative effective drug class when clinically meaningful improvement is not achieved or adverse effects limit treatment.⁹ Most participants reported adherence to their prescribed treatment during the 4-week period, although a proportion required treatment modification, discontinuation, switching, or addition of another neuropathic pain medication. This is clinically relevant because the response to neuropathic pain treatment is influenced not only by pharmacological activity but also by whether treatment can be continued at a tolerable and effective dose. Recent real-world evidence has demonstrated substantial treatment discontinuation and suboptimal adherence among patients receiving commonly prescribed therapies for painful diabetic peripheral neuropathy, illustrating the gap that can exist between prescribing and sustained treatment in routine care.¹³ The shorter follow-up in the present study does not permit direct comparison with longer-term discontinuation patterns, but the need for dose modification or treatment changes in a subset of patients nevertheless emphasizes the importance of early follow-up.

Strengths

The present study has several strengths. It was conducted prospectively in a real-world tertiary-care outpatient setting, and treatment selection was made independently by the treating physician before research enrolment. This allowed the study to capture naturally occurring prescribing patterns rather than an investigator-imposed treatment allocation. Baseline clinical characteristics, previous neuropathic pain treatment, medication exposure, pain intensity, adherence, adverse effects, and treatment changes were recorded systematically. Use of the same 0–10 NRS at baseline and follow-up also provided a simple and clinically interpretable measure of change in pain intensity. These features make the findings particularly relevant to routine clinical practice in a setting where resource availability and prescribing considerations may differ from those of randomized clinical trials.

LIMITATIONS

Several limitations should nevertheless be considered. First, this was a single-centre observational study, and treatment was not randomized. Consequently, confounding by indication and residual confounding cannot be excluded, even after adjustment for selected baseline factors. Second, the four treatment cohorts were unequal in size, with the mecobalamin group considerably smaller than the other groups, reducing the precision of estimates

for that cohort. Third, follow-up was limited to four weeks and therefore does not establish the durability of treatment response or longer-term adherence and discontinuation. Fourth, adherence and some treatment-related outcomes were based partly on patient report and may therefore be subject to reporting bias. Fifth, pain intensity was assessed using a single NRS measure, without a broader validated assessment of functional interference or health-related quality of life. Finally, because patients receiving more than one neuropathic medication at treatment initiation were excluded, the findings apply specifically to initial monotherapy and should not be generalized to combination-treatment strategies. The results should therefore be viewed primarily as a description of how commonly used neuropathic pain medications perform in routine clinical practice within this tertiary-care population rather than as a head-to-head efficacy comparison. The study demonstrates that clinically meaningful improvement was observed with each of the four treatment strategies, but response was variable and treatment modification was sometimes required. This supports an individualized approach to painful diabetic neuropathy in which medication choice considers the patient's clinical characteristics, comorbidities, tolerability, affordability, treatment history, and early response rather than relying on a single preferred medication.⁹

CONCLUSION

In this prospective observational cohort, patients with painful diabetic neuropathy showed improvement in pain intensity over four weeks following initiation of amitriptyline, pregabalin, duloxetine, or mecobalamin monotherapy. More than half achieved a $\geq 30\%$ reduction in NRS pain intensity, although response varied between observational treatment cohorts. Treatment adherence was generally good during the short follow-up period, while adverse effects and treatment modification occurred in a minority of patients. The findings provide real-world information on prescribing and short-term treatment response in a tertiary-care setting in Pakistan, but the non-randomized design and potential for confounding preclude conclusions regarding comparative drug efficacy. Longer-term, multicentre prospective studies using standardized dosing and broader patient-reported outcomes would help further define treatment effectiveness and tolerability in this population.

Additional Information

Conflicts of Interest: None

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Critical Review & Final Approval; Hasnat Ahmed¹, Tauqir Ahmad²

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