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Retrospective Analysis of the Effectiveness and Safety of Pregabalin and Duloxetine Fixed-Dose Combination Therapy in the Management of Neuropathic Pain (RESET Study)

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ABSTRACT

Background: Neuropathic pain is a complex, chronic pain condition arising from somatosensory nervous system lesions or disease. Pregabalin and duloxetine are individually established pharmacological agents for neuropathic pain management; however, their combined efficacy as a fixed-dose combination (FDC) remains underexplored in real-world clinical settings.
Objective: To retrospectively evaluate the effectiveness and safety of pregabalin–duloxetine FDC therapy in patients with neuropathic pain over a 3-month treatment period.
Methods: A retrospective chart review was conducted enrolling 11,559 patients with confirmed neuropathic pain diagnoses receiving pregabalin/duloxetine FDC. Pain intensity was assessed using the Numeric Rating Scale (NRS, 0–10) and sleep interference using the Daily Sleep Interfering Rating Scale (DSIRS, 0–10) at baseline and 3 months post-treatment. Safety was evaluated by adverse drug reaction (ADR) monitoring and physician global assessment (PGA).
Results: The mean NRS score decreased significantly from 6.79 ± 2.45 at baseline to 4.19 ± 2.32 post-3 months (mean reduction: 2.60 ± 3.24; $p < 0.001$). Similarly, DSIRS scores improved from 6.65 ± 2.38 to 4.15 ± 2.41 (mean reduction: 2.50 ± 3.31; $p < 0.001$). The treatment was well tolerated with 0.4% reported any ADR, predominantly mild in nature. PGA rated as Good or Excellent in 94.5% of patients.
Conclusion: Pregabalin–duloxetine FDC therapy demonstrates statistically significant and clinically meaningful improvements in pain intensity and sleep quality in patients with neuropathic pain, with a favourable tolerability profile with low reported ADRs. These findings support its use as an effective therapeutic strategy in real-world clinical practice
Keywords: *neuropathic pain, pregabalin, duloxetine, fixed-dose combination, NRS, DSIRS, retrospective analysis, RESET study*

INTRODUCTION

Neuropathic pain (NP) is defined as pain arising as a direct consequence of a lesion or disease affecting the somatosensory nervous system [1]. It is characterized by spontaneous pain, allodynia, hyperalgesia, and dysesthesia, significantly impairing quality of life and functional capacity [2,3]. The global prevalence of neuropathic pain is estimated at 6.9–10% of the general

population, with substantial burden on patients and healthcare systems alike [4].

Current pharmacological guidelines for neuropathic pain management recommend first-line therapies including gabapentinoids (pregabalin, gabapentin), serotonin-norepinephrine reuptake inhibitors (SNRIs) such as duloxetine and venlafaxine, and tricyclic antidepressants [5–7]. Pregabalin exerts its analgesic effect through binding to the α2δ subunit of voltage-gated calcium channels, thereby reducing the release of excitatory neurotransmitters [8]. Duloxetine, a potent SNRI, modulates descending pain inhibitory pathways by enhancing serotonergic and noradrenergic neurotransmission [9].

Fixed-dose combination (FDC) therapy offers potential pharmacodynamic advantages by targeting multiple pain pathways simultaneously, potentially achieving superior efficacy at lower individual doses, thereby reducing dose-related adverse effects [10,11]. Despite growing clinical interest, large-scale real-world evidence on the combination of pregabalin and duloxetine in a fixed-dose formulation remains limited [10].

The RESET (Retrospective Analysis of Effectiveness and Safety of pregabalin-duloxetine combination) study was designed to evaluate the real-world effectiveness and safety of pregabalin–duloxetine FDC therapy in patients with neuropathic pain, using standardized patient-reported outcome measures over a 3-month treatment period. Neuropathic pain is a growing concern in India, largely driven by the country's high diabetes burden. In routine practice, pregabalin and duloxetine are often co-prescribed, but such regimens contribute to polypharmacy, complex dosing schedules, and poor adherence. Fixed-dose combinations (FDCs) offer a simplified alternative by reducing pill burden, standardizing dosing ratios, and potentially improving treatment persistence [10]. Despite guideline recognition of combination therapy, there remains limited real-world evidence from India specifically evaluating the effectiveness and safety of pregabalin–duloxetine FDCs compared to conventional co-prescription [5–7,10]. This retrospective analysis aims to address that gap, providing insights into adherence and clinical outcomes in Indian practice settings.

MATERIALS & METHODS

Study Design and Setting

This was a retrospective, observational, multicentre chart review study conducted across outpatient neurology and pain management clinics. Medical records of patients prescribed pregabalin–duloxetine FDC therapy for neuropathic pain were reviewed. The study received institutional approval and was conducted in compliance with the Declaration of Helsinki and applicable local regulations.

Study Population

Patients were included if they (i) had a confirmed diagnosis of neuropathic pain based on clinical assessment; (ii) had received pregabalin–duloxetine FDC therapy; (iii) had documented baseline (pre-treatment) and 3-month follow-up NRS and DSIRS scores. After application of data quality filters (excluding implausible anthropometric entries), the final analysis included 11,559 patients.

Intervention

Patients received pregabalin–duloxetine FDC in one of three dose configurations: pregabalin 50 mg/duloxetine 20 mg, pregabalin 75 mg/duloxetine 20 mg, or pregabalin 75 mg/duloxetine 30 mg, administered either once or twice daily at the treating physician's discretion.

Outcome Measures

The primary efficacy outcome was the change in pain intensity measured by the Numeric Rating Scale (NRS; 0 = no pain, 10 = worst imaginable pain) from baseline to 3 months. The secondary outcome was the change in sleep interference assessed by the Daily Sleep Interfering Rating Scale (DSIRS; 0 = no sleep interference, 10 =

complete sleep interference). Safety outcomes included adverse drug reactions (ADRs) and Physician Global Assessment (PGA) rated as Excellent, Good, Average, or Poor.

Statistical Analysis

Descriptive statistics were computed for all variables. Continuous variables were reported as mean ± standard deviation (SD). The paired Student's t-test was used to compare NRS and DSIRS scores before and after treatment. A two-sided p-value < 0.05 was considered statistically significant.

RESULT

Patient Demographics

A total of 11,559 patients met the inclusion criteria. The mean age was 52.9 ± 11.2 years (range: 18–99 years). The majority of patients were male (n = 7,662; 66.2%), and 3,897 (33.8%) were female. Mean body weight was 69.4 ± 19.3 kg, and mean BMI was 26.6 ± 8.2 kg/m². The age distribution was predominantly in the 40–59-year range, with 3,546 patients (31.8%) in the 40–49-year group and 3,604 (32.3%) in the 50–59-year group.

Table 1. Baseline Patient Characteristics

Characteristic	Value (N = 11,559)
Age (years), mean ± SD	52.9 ± 11.2
Age range (years)	12–99
Gender: Male, n (%)	7,662 (66.2%)
Gender: Female, n (%)	3,897 (33.8%)
Weight (kg), mean ± SD	69.4 ± 19.3
BMI (kg/m²), mean ± SD	26.6 ± 8.2
Dose: Pregabalin 75/Duloxetine 20 mg	7,434 (66.7%)
Dose: Pregabalin 50/Duloxetine 20 mg	2,894 (25.9%)
Dose: Pregabalin 75/Duloxetine 30 mg	824 (7.4%)
Dosing frequency: Once daily	7,569 (67.9%)
Dosing frequency: Twice daily	3,583 (32.1%)

Presenting Symptoms

The most prevalent presenting symptom was burning sensation, reported by 8,018 patients (71.9%), followed by shooting pain/electric shock-like sensation (4,949; 44.4%), paresthesia (3,648; 32.7%), allodynia (2,455; 22.0%), and intolerance to temperature (1,053; 9.4%). Many patients presented with multiple overlapping symptoms.

Comorbidities

Comorbid conditions were common in this population. Diabetes mellitus was the most prevalent comorbidity (39.8%), closely followed by anxiety disorder (39.6%) and diabetic peripheral neuropathy (38.8%). Depression was noted in 32.4% of patients. Other comorbidities included hypertension (9.8%), autoimmune disorders (9.7%), spinal cord injury (9.2%), postherpetic neuralgia (8.3%), stroke (3.4%), and cardiovascular diseases (2.4%).

Treatment Allocation

The most commonly prescribed dose was pregabalin 75 mg/duloxetine 20 mg, used in 7,434 patients (66.7%), followed by pregabalin 50 mg/duloxetine 20 mg in 2,894 patients (25.9%), and pregabalin 75 mg/duloxetine 30 mg in 824 patients (7.4%). Regarding dosing frequency, 7,569 patients (67.9%) received once-daily dosing, while 3,583 patients (32.1%) received twice-daily dosing.

Efficacy Outcomes

The mean NRS pain intensity score decreased significantly from 6.79 ± 2.45 at baseline to 4.19 ± 2.32 at 3 months, representing an absolute mean reduction of 2.60 ± 3.24 points ($p < 0.001$; paired t-test). The percentage reduction in NRS score was approximately 38.3%.

Similarly, DSIRS sleep interference scores improved significantly from 6.65 ± 2.38 at baseline to 4.15 ± 2.41 at 3 months, with an absolute mean reduction of 2.50 ± 3.31 points ($p < 0.001$). The percentage reduction in DSIRS score was approximately 37.6%.

Table 2. Summary of Efficacy Outcomes

Outcome	Baseline	Post 3 Months	p-value
NRS Score (mean ± SD)	6.79 ± 2.45	4.19 ± 2.32	< 0.001
NRS Reduction (mean ± SD)	—	2.60 ± 3.24	< 0.001
DSIRS Score (mean ± SD)	6.65 ± 2.38	4.15 ± 2.41	< 0.001
DSIRS Reduction (mean ± SD)	—	2.50 ± 3.31	< 0.001

Safety and Tolerability

Treatment was well tolerated in 10,108 of 11,152 patients (90.6%). Adverse drug reactions (ADRs) were absent in 11,103 patients (99.6%), and only 49 patients (0.4%) reported any ADR, predominantly mild in nature. No serious or life-threatening ADRs were documented.

Physician Global Assessment rated the treatment outcome as Excellent in 3,428 patients (30.7%) and Good in 7,160 patients (64.2%), yielding a combined Excellent or Good rating of 94.9%. Average and Poor ratings were reported in 535 (4.8%) and 29 (0.3%) patients, respectively.

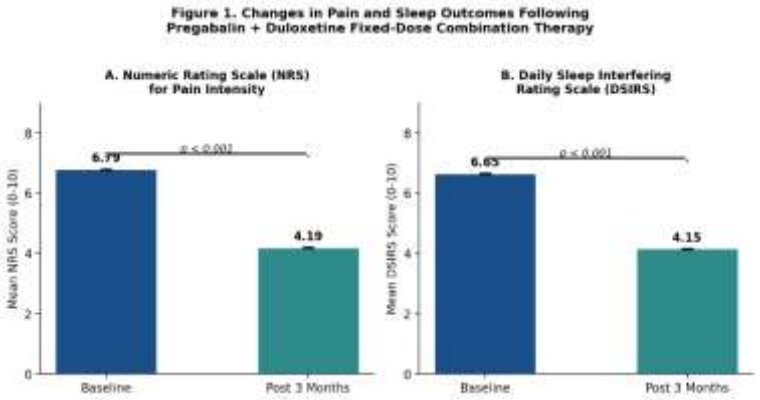

Figure 1. Mean NRS and DSIRS scores at baseline and post-3 months treatment with pregabalin–duloxetine FDC. Error bars represent standard error of the mean. ***p < 0.001 (paired t-test).

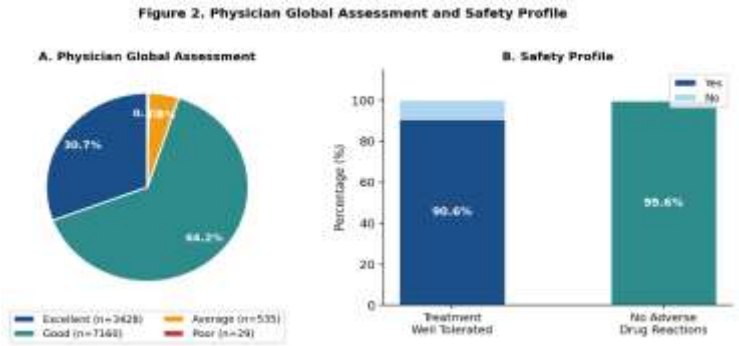

Figure 2. Physician Global Assessment distribution and safety profile of pregabalin–duloxetine FDC therapy. Left panel: PGA categorization; Right panel: treatment tolerability and ADR incidence.

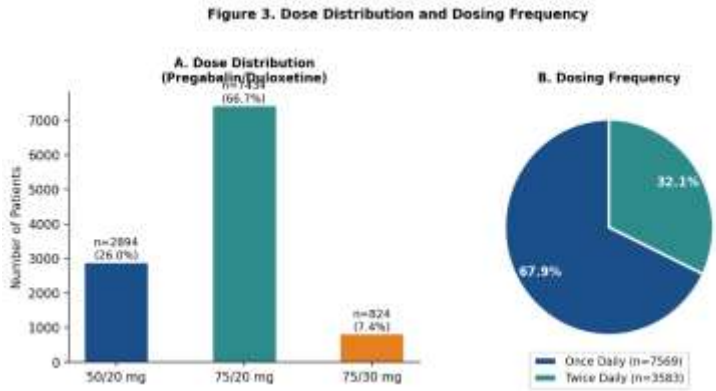

Figure 3. Dose distribution and dosing frequency of pregabalin–duloxetine FDC in the study population.

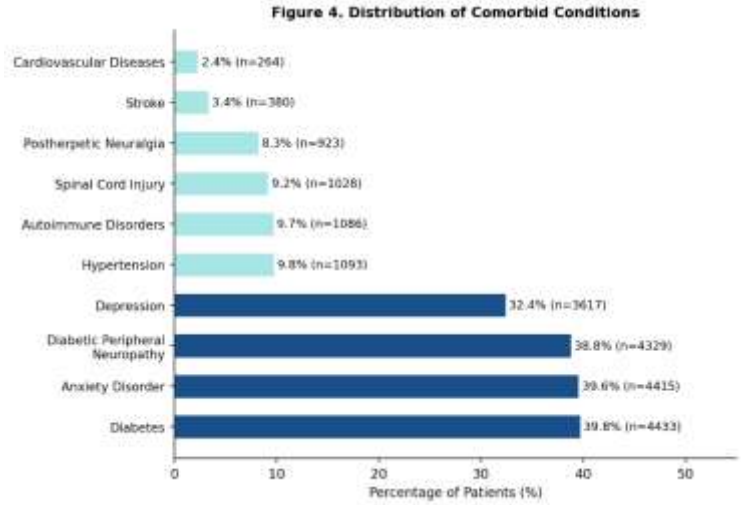

Figure 4. Prevalence of comorbid conditions in the study population. Percentages represent proportion of total patients.

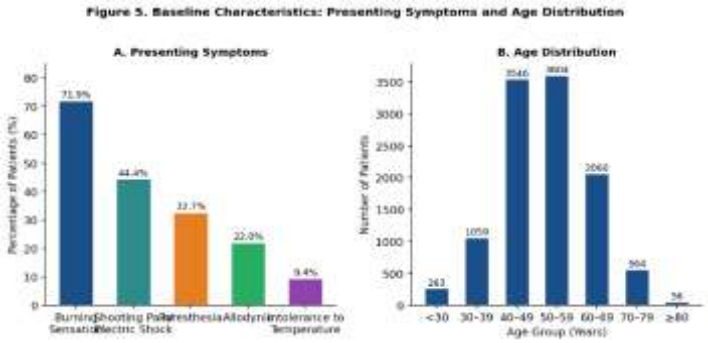

Figure 5. Baseline characteristics: A) presenting symptoms and their prevalence; B) age distribution of the study population.

DISCUSSION

The RESET study constitutes one of the largest retrospective analyses evaluating the real-world effectiveness and safety of pregabalin–duloxetine FDC therapy in neuropathic pain, encompassing 11,559 patients across diverse clinical settings. Existing evidence supports the use of pregabalin and duloxetine as first-line agents and suggests that low-dose pregabalin–duloxetine FDC can provide clinically relevant analgesia in neuropathic pain **[5–7,10]**.

Our findings demonstrate statistically significant and clinically meaningful reductions in both pain intensity (NRS: 6.79 → 4.19; $\Delta = 2.60$; $p < 0.001$) and sleep interference (DSIRS: 6.65 → 4.15; $\Delta = 2.50$;

$p < 0.001$) following 3 months of FDC therapy. These improvements are particularly notable given the heterogeneous patient population with multiple comorbidities, including diabetes mellitus (39.8%), diabetic peripheral neuropathy (38.8%), anxiety disorder (39.6%), and depression (32.4%), which are known to influence neuropathic pain severity and treatment response.

The pharmacological rationale for combining pregabalin and duloxetine is well-founded. Pregabalin modulates central sensitization and ectopic neuronal discharge through calcium channel blockade at the α2δ subunit **[8]**, while duloxetine reinforces descending inhibitory pain control through dual monoamine reuptake inhibition **[9]**. This complementary mechanism may explain the sustained analgesic benefit observed in the present cohort **[10,11]**.

Previous studies have reported clinically meaningful pain reductions with pregabalin monotherapy and duloxetine monotherapy in diabetic peripheral neuropathy **[12,13]**. The mean NRS reduction of 2.60 points observed in the current study, while in a retrospective setting without a comparator arm, is consistent with the clinical rationale for combining mechanistically complementary first-line agents and suggests that FDC therapy may offer practical benefits, particularly in patients with complex, multi-mechanism neuropathic pain **[5,10,11]**.

The high tolerability rate (90.6%) and very low ADR incidence (0.4%) are noteworthy. ADRs were infrequently documented in medical records (0.4%), which may reflect underreporting inherent to retrospective real-world data. This safety profile may partly reflect the FDC formulation's potential to achieve therapeutic effects at lower individual component doses compared to monotherapy, thereby attenuating dose-dependent adverse effects such as pregabalin-associated dizziness, somnolence, and peripheral oedema **[8,10,12]**. The PGA rated as Good or Excellent in 94.9% of patients further corroborates the favourable clinical impression of treating physicians.

The predominance of male patients (66.2%) likely reflects the demographic characteristics of neuropathic pain secondary to diabetes and diabetic peripheral neuropathy, which were the most prevalent comorbidities in our cohort. The mean age of 52.9 years aligns with epidemiological data reporting higher neuropathic pain burden in middle-aged and older adults **[4]**.

Improvement in sleep interference is clinically meaningful, as sleep disturbance is both a consequence and amplifier of chronic neuropathic pain **[2,3]**. Beyond pain relief, better sleep quality contributes to enhanced daytime functioning, reduced fatigue, and overall quality of life, underscoring the multidimensional benefit of pregabalin–duloxetine FDC therapy.

Several limitations of this study warrant acknowledgment. As a retrospective observational analysis, it lacks a randomized comparator arm, and findings are subject to inherent selection bias. The absence of standardized disease severity criteria or etiological subgrouping limits the generalizability of conclusions to specific neuropathic pain subtypes. Additionally, data quality issues (implausible anthropometric entries) necessitated exclusion of a subset of records, potentially introducing bias. Long-term follow-up beyond 3 months would further clarify the durability of treatment response.

CONCLUSION

The RESET study demonstrates that pregabalin–duloxetine fixed-dose combination therapy is associated with statistically significant and clinically relevant improvements in pain intensity and sleep interference over 3 months in patients with neuropathic pain. The treatment exhibits an excellent tolerability and safety profile, with the large majority of patients achieving Good or Excellent outcomes per physician assessment. These real-world findings support the clinical utility of pregabalin–duloxetine FDC as an effective

therapeutic option for neuropathic pain, particularly in patients with concomitant diabetes, peripheral neuropathy, and comorbid psychiatric conditions, and are consistent with the mechanistic rationale and published clinical evidence for pregabalin–duloxetine combination therapy. Prospective randomized controlled trials with extended follow-up are warranted to establish comparative efficacy and long-term safety.

Declaration

Ethical Approval: Approved

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Conflict of Interest: The authors declare no conflict of interest.

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