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ORIGINAL ARTICLE

Pregabalin efficacy in painful diabetic peripheral neuropathy: A focused analysis of optimal dosing and the relationship of baseline glycemic control

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ABSTRACT

Introduction: Diabetic neuropathy, the most common long-term complication of diabetes, frequently presents as painful diabetic peripheral neuropathy (pDPN), significantly impairing patients' quality of life. Pregabalin is an established treatment for pDPN, but optimal dosing and the influence of glycemic control on efficacy remain uncertain.

Aims: To evaluate (1) the efficacy of different pregabalin doses for pDPN, and (2) the impact of baseline glycemic control, measured by glycosylated hemoglobin levels (HbA1c), on pregabalin's efficacy in reducing pain score.

Methods: Data from three randomized, double-blind, placebo-controlled trials involving 729 pDPN patients were pooled. Of these, 477 received pregabalin (75, 150, 300, or 600 mg/day) and 252 received placebo over 5–8 weeks. Pain scores were recorded at baseline, weekly, and at the endpoint. Patients were stratified by HbA1c: ≤8% (n = 377) and >8% (n = 346). Analysis of covariance (ANCOVA) assessed changes in endpoint pain scores; MMRM evaluated changes over time.

Results: Pregabalin 300 mg/day and 600 mg/day significantly reduced mean pain scores versus placebo ($P < 0.0001$), while 75 mg/day and 150 mg/day did not. In HbA1c subgroups, pregabalin maintained efficacy at 300 mg/day and 600 mg/day regardless of baseline glycemic control. Among patients with HbA1c ≤8%, pain reductions versus placebo were −1.69 and −1.71 for the 300 mg/day and 600 mg/day groups, respectively ($P < 0.0001$). In patients with HbA1c >8%, reductions were −1.04 and −1.09 ($P \leq 0.001$), demonstrating efficacy independent of glycemic control.

Conclusions: Pregabalin at 300 and 600 mg/day provides significant pain relief in pDPN, regardless of HbA1c levels, supporting dose optimization to achieve maximal benefit.

INTRODUCTION

The global prevalence of diabetes mellitus continues to grow rapidly. An estimated 589 million adults were living with diabetes in 2024, and by 2050, this number is projected to increase by a staggering 45%, reaching 852 million[1]. As the prevalence of diabetes rises, so will its complications, of which painful diabetic peripheral neuropathy is one of the most common. Painful DPN affects approximately one-third of patients with diabetes and manifests as chronic pain in the extremities, particularly the feet and lower limbs[2]. Painful DPN has a dramatic impact on its sufferers and can lead to poor sleep quality,

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decreased work efficiency, reduced quality of life, and psychological problems such as anxiety and depression[3–6]. Despite its high prevalence and significant health burden, pDPN remains an underdiagnosed and undertreated condition[4].

The management of pDPN remains challenging, with recommended first-line pharmacological treatments including tricyclic antidepressants (e.g., amitriptyline, nortriptyline), serotonin norepinephrine reuptake inhibitors (SNRIs) (e.g., duloxetine, venlafaxine), and α2δ-ligands (pregabalin, gabapentin, mirogabalin)[7]. In the current clinical landscape, patient comorbidities, the physician's discretion, and adverse event profile usually dictate the choice of drugs in a patient with pDPN. Among the first-line drugs, pregabalin, an α2-δ ligand that modulates calcium channel activity in the central nervous system, has demonstrated consistent efficacy in multiple randomized controlled trials[8].

Pregabalin is approved for the treatment of pDPN at doses ranging from 150 to 600 mg per day, administered in two or three divided doses[9]. Despite this established dosing range, evidence from real-world clinical practice suggests that many patients receive subtherapeutic doses that may fail to provide adequate pain relief[10]. Well-characterized dose-related adverse events of pregabalin are the main concerns leading to underdosing, and they often lead clinicians and patients to hesitate before titrating to the upper end of the therapeutic range[9].

The uncertainty surrounding the dose–response relationship in heterogeneous patient populations, particularly those with comorbidities or suboptimal glycemic control, may further complicate dose optimization[9, 11]. Importantly, while glycemic control itself is predictive of the progression and severity of DPN, the factors that predict progression of pDPN are more uncertain[12]. Furthermore, there is a paucity of data to determine if poor glycemic control might attenuate treatment response.

Therefore, this analysis aimed to address two clinically relevant questions through a post hoc evaluation of three clinical trials of pregabalin: (1) The effect of various doses of pregabalin on endpoint mean pain scores in patients with pDPN, and (2) the influence of baseline glycemic control, as measured by HbA1c levels, on the efficacy of pregabalin in reducing neuropathic pain.

METHODS

Study selection and patient population

This post hoc analysis pooled data from three randomized, double-blind, placebo-controlled trials of pregabalin in patients with pDPN[13–15]. We selected company-sponsored studies with fixed pregabalin dosing, similar design, and published primary efficacy data covering all approved pregabalin doses (150–600 mg/day), enabling a consistent and clinically relevant evaluation of short-term efficacy (≤8 weeks) (Table 1).

Design of included studies

The full details of the trials are included in the primary publications; however, in brief, the individual studies had a similar design: a 1-week baseline period, after which patients were randomized to receive a placebo or pregabalin at doses of 75, 150, 300, or 600 mg per day with a three-times daily (TDS) dosing regimen.

The inclusion criteria of the trials are- patients ≥18 years of age, diagnosed with pDPN, an average pain score ≥4 (on an 11-point, Likert-like numeric rating scale [NRS]: 0 = "no pain" to 10="worst possible pain") over a 7-day baseline period, and a score ≥40 mm on the 0- to 100-mm visual analog scale of the Short-Form McGill Pain Questionnaire (SF-MPQ) at screening and randomization. All patients in each trial were required to have HbA1c levels ≤11%. Common exclusion criteria were prior therapeutic failure of gabapentin and participation in any other pregabalin clinical trial.

Outcome measures

The trials included in this post hoc analysis assessed the efficacy (in terms of endpoint mean pain score, weekly mean pain

Table 1 | Pregabalin clinical studies considered for pooled analysis

Trial[†]	Phase	Study population (*N*)[‡]	Treatment arms	Dosing	Study design
Lesser et al (1008–029)[13]	III	337	PBO, PGB 75 or 300, or 600 mg/day	TDS	1-week baseline phase, 5-week (1-week titration/4-week fixed dose) DB treatment phase
Richter et al (1008–014)[14]	III	246	PBO, PGB 150 or 600 mg/day	TDS	1-week baseline, 6-week (2-week titration/4-week fixed dose) DB treatment phase
Rosenstock et al (1008–031)[15]	III	146	PBO, or PGB 300 mg/day	TDS	1-week baseline phase and an 8-week, fixed dose, DB treatment phase

DB, double-blind; PBO, placebo; TDS, three-times daily. [†]Studies considered in this pooled analysis were based on the clinical trials by Lesser *et al.*, Richter *et al.*, and Rosenstock *et al.* [‡]Total number of patients in the ITT population (randomized patients who received at least one dose of study medication).

score, sleep interference score, patient global impression of change, clinical global impression of change, SF-MPQ, and multiple domains of the SF-36 Health Survey) and tolerability of various doses of pregabalin (75, 150, 300, 600 mg/day) vs placebo in patients with pDPN. In this analysis, the primary efficacy endpoint was the change in mean pain score from baseline to endpoint. Pain was assessed using an 11-point numerical rating scale (0 = no pain, 10 = worst possible pain) recorded daily in patient diaries. Mean pain scores were assessed at baseline (last seven available scores before taking study medication, up to and including Day 1), weekly, and at the endpoint (last seven available scores while on study medication, up to and including the day after the last dose).

For the analysis of glycemic control, HbA1c values obtained during screening were used to categorize patients into two subgroups: HbA1c ≤8% (n = 377) and HbA1c >8% (n = 346). The cut-off of 8% was chosen to ensure adequate patient numbers in each subgroup for meaningful analysis and based on available literature[16, 17].

Safety analyses assessed the frequently reported adverse events (AEs) across all the treatment arms.

Statistical analysis

All efficacy analyses were based on the ITT population, which contained all subjects who received at least one dose of study medication as per the randomization. All statistical analyses were performed using SAS 9.4. No correction for multiplicity was applied.

The primary analysis of the pooled data used analysis of covariance (ANCOVA) on the endpoint mean pain scores, with treatment and study as factors and baseline mean pain score as a covariate, using the last observation carried forward (LOCF) approach to deal with missing postbaseline scores. Treatment differences were expressed as least squares mean (LS Means) differences vs placebo, with 95% confidence intervals (CI) and P-values. A treatment by study interaction term was added to the ANCOVA model to check for homogeneity of treatment effects.

Responders were defined as patients achieving a reduction in mean pain score from baseline to endpoint with a clinically meaningful threshold of ≥30%, ≥50%, and ≥70% reduction. A greater than 30% reduction and 50% reduction were selected as they are well-recognized thresholds for moderate/substantial clinically meaningful improvements, respectively, in chronic pain trials[18]. Greater than 70% change in pain is less frequently used but represents extensive improvement in pain[19].

A mixed model repeated measures (MMRM) analysis was conducted to evaluate the changes over time in the weekly mean pain scores, with terms for study, visit, treatment group, interaction between visit and treatment group, and baseline score as a covariate. A treatment by study interaction term was added to the MMRM model to check for homogeneity of treatment effects.

To assess the impact of glycemic control on treatment response, patients were stratified by baseline HbA1c (≤8% or >8%), and separate ANCOVA analyses were performed for each of the two subgroups to evaluate the treatment effects. An interaction term of treatment by baseline HbA1c stratum was added to the overall ANCOVA model to see if it indicated different treatment effects depending on baseline HbA1c levels.

RESULTS

Patient demographics and baseline characteristics

A total of 729 patients were involved in this pooled analysis (ITT). Baseline demographic and clinical characteristics were generally comparable across treatment groups (Table 2). The overall population was predominantly male (59.4%) and white (89.4%), with a mean (±SD) age of 58.9 (±10.49) years. A total of 31.3% of patients were aged ≥65 years. The mean (±SD) body weight was 96.87 (±19.99) kg. The mean (±SD) estimated creatinine clearance at baseline was 104.77 (±36.65) mL/min. The majority of patients had type 2 diabetes (90%), with a

Table 2 | Pooled patient demographics and baseline characteristics

Characteristic	Placebo (N = 252)	Pregabalin 75 mg (N = 77)	Pregabalin 150 mg (N = 79)	Pregabalin 300 mg (N = 157)	Pregabalin 600 mg (N = 164)	Total Pregabalin (N = 477)	All Patients (N = 729)
Sex, n (%)							
Male	145 (57.5)	43 (55.8)	57 (72.2)	90 (57.3)	98 (59.8)	288 (60.4)	433 (59.4)
Female	107 (42.5)	34 (44.2)	22 (27.8)	67 (42.7)	66 (40.2)	189 (39.6)	296 (40.6)
Ethnicity, n (%)							
White	222 (88.1)	74 (96.1)	74 (93.7)	140 (89.2)	142 (86.6)	430 (90.1)	652 (89.4)
Black	15 (6.0)	1 (1.3)	3 (3.8)	9 (5.7)	12 (7.3)	25 (5.2)	40 (5.5)
Hispanic	12 (4.8)	1 (1.3)	2 (2.5)	6 (3.8)	10 (6.1)	20 (4.2)	32 (4.4)
Other	3 (1.2)	1 (1.3)	–	1 (0.62)	–	2 (0.4)	5 (0.7)
Age (years)							
Mean ± SD	58.3 ± 10.85	61.3 ± 10.51	56.3 ± 9.36	59.1 ± 10.82	59.9 ± 9.85	59.3 ± 10.29	58.9 ± 10.49
Range	26–79	34–85	33–74	21–83	29–80	21–85	21–85

Intent-to-Treat (ITT) population, defined as all randomized patients who received at least one dose of study medication. SD, standard deviation.

mean duration of diabetes of 9.9 (±8.9) years. The mean baseline pain score ranged from 6.33 to 6.66 across treatment groups.

Efficacy of Pregabalin by dose (endpoint mean pain score)

All treatment groups, including placebo, showed more than 1 point reduction in the mean pain score at the study Endpoint. The treatment effects of pregabalin 75 mg ($P = 0.5051$; 95% CI: −0.75 to 0.37) and 150 mg ($P = 0.0711$; 95% CI: −1.13 to 0.05) were not statistically significant compared with placebo (ANCOVA). However, pregabalin 300 mg (−1.38) and 600 mg (−1.39) showed very similar effects, and both were statistically significant compared with placebo ($P < 0.0001$) (Table 3). The treatment by study interaction term ($P = 0.76$) added to the ANCOVA model supported homogeneous treatment effects across the studies.

MMRM

Testing for homogeneous treatment effects across the studies revealed that the treatment by study interaction term was statistically significant ($P < 0.01$), indicating that the treatment effects are not homogeneous. Further investigation revealed that pregabalin at a dose of 600 mg/day for one trial (1008–014) was the main source of this statistical significance. This finding was due to differences in the titration scheme for the 600 mg/day dose between studies, indicating that the data are not sufficiently similar for weeks 1 and 2, and therefore, *P*-values for both these timepoints for the 600 mg dose have to be interpreted carefully.

The analyses of the weekly pain scores showed a statistical change from baseline for pregabalin doses of 300 mg/day and 600 mg/day, and this difference was observed starting from week 1 onwards. With a pregabalin dose of 75 mg/day, there was no statistically significant difference in the pain scores between pregabalin and placebo at any of the weeks, and with a pregabalin dose of 150 mg/day, the difference was statistically significant starting from week 3 onwards (Table S1).

By Week 1, dose-related reductions were evident: the LSMeans change from baseline in the weekly mean pain score was −0.44 in the placebo group, −0.49 in pregabalin 75 mg, −0.79 in pregabalin 150 mg, −1.84 in pregabalin 300 mg, and − 1.31 in pregabalin 600 mg.

From Week 2 through Week 6, pregabalin 300 mg/day and 600 mg/day consistently demonstrated greater reductions in pain scores compared to the lower doses of pregabalin and placebo. At Week 6, the LSMeans change from baseline in the mean pain scores was highest with pregabalin 600 mg (−2.71), followed by pregabalin 300 mg (−2.40), pregabalin 150 mg (−1.85), but at Week 5 with pregabalin 75 mg (−1.72) as there's no analysis for Week 6 at this dose, whereas placebo showed a modest reduction (−1.07).

At endpoint, the LSMeans change from baseline in mean pain scores was very similar between pregabalin 600 mg (−2.49) and 300 mg (−2.48), and between pregabalin 150 mg (−1.64) and 75 mg (−1.29), when compared with placebo (−1.10).

Responder rates based on clinically meaningful pain reduction

As shown in Figure 1, a higher proportion of responders, defined as patients achieving ≥50% reduction in mean pain score from baseline to endpoint, was observed in the pregabalin 300 mg/day ($n = 67/157$; 42.7%) and 600 mg/day ($n = 69/164$; 42.1%) groups compared with placebo ($n = 37/252$; 14.7%). Both 75 mg/day (22.1%) and 150 mg/day (17.7%) show similar proportions as placebo.

Using a ≥30% reduction as a threshold for clinically important improvement shows a very similar pattern, with higher response rates in the 300 mg/day ($n = 89/157$; 56.7%) and 600 mg/day ($n = 98/164$; 59.8%) groups compared with placebo ($n = 78/252$; 31.0%) and 75 mg/day (36.4%) and 150 mg/day (34.2%) groups. Approximately 25% of patients treated with pregabalin 600 mg achieved a ≥70% reduction in endpoint mean pain scores, highlighting a meaningful subset of patients who experienced marked pain relief.

Effect of glycemic control on pregabalin efficacy

Impact of baseline HbA1c on glycemic parameters and treatment response

Across both subgroups of >8% ($n = 346$) and ≤8% ($n = 377$), all the treatment arms demonstrated similar glycemic stability,

Table 3 | Endpoint mean pain score inference: results of analysis of covariance

	Pooled Studies				
	PBO ($n = 248$)	PGB 75 ($n = 77$)	PGB 150 ($n = 79$)	PGB 300 ($n = 156$)	PGB 600 ($n = 163$)
Observed Mean (SE) Baseline	6.57 (1.56)	6.66 (1.34)	6.45 (1.31)	6.33 (1.52)	6.48 (1.60)
LS Means Endpoint (95% CI)[†]	5.40 (5.14, 5.65)	5.21 (4.70, 5.72)	4.86 (4.33, 5.39)	4.02 (3.67, 4.37)	4.00 (3.66, 4.35)
LS Means Difference (95% CI)[†]		−0.19 (−0.75, 0.37)	−0.54 (−1.13, 0.05)	−1.38 (−1.81, −0.95)	−1.39 (−1.82, −0.97)
P-value[†]		0.5051	0.0711	<0.0001	<0.0001

[†]LSMeans, differences and *P*-values derived from ANCOVA model including terms for study, treatment, and baseline score, and using last observation carried forward.

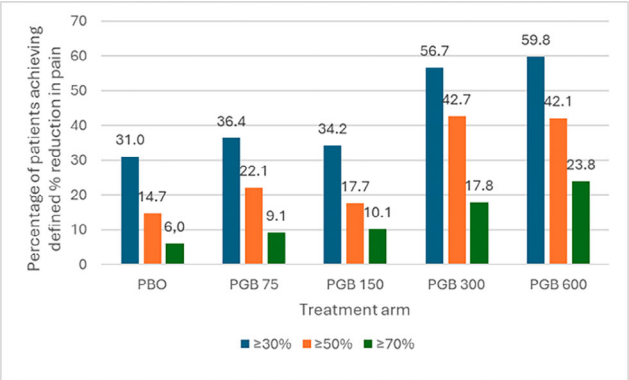

Figure 1 | Percentage of patients achieving a defined % reduction in Endpoint mean pain scores. Proportions of patients achieving ≥30%, ≥50%, and ≥ 70% reduction in Endpoint mean pain score are shown for each treatment group. PBO, placebo; PGB, pregabalin.

with no clinically significant changes in HbA1c observed from baseline to endpoint.

In the HbA1c >8% subgroup, the LS Means change from baseline in HbA1c ranged from −2.40 to −1.05 across all pregabalin doses, compared to −1.32 in the placebo group. Similarly, in the HbA1c ≤8% subgroup, mean changes ranged from −2.59 to −1.56 across pregabalin doses, compared to −0.89 in the placebo group.

Pregabalin at 300 and 600 mg/day consistently demonstrated greater pain reduction compared to placebo than the lower dosages in both HbA1c subgroups. This illustrates that the reduction of pain from Baseline to Endpoint is independent of baseline HbA1c levels (Table 4). This was supported by the non-statistically significant (P = 0.95) interaction term of treatment by HbA1c into the ANCOVA model.

Safety data

The safety profile of pregabalin observed in this study was consistent with that reported in previous pooled analyses across neuropathic pain populations. Consistent with the established dose-dependent tolerability profile of pregabalin, the overall incidence of adverse events was numerically higher at 300 mg/day and 600 mg/day compared with lower doses and placebo. The most frequently reported treatment-emergent adverse events were dizziness (17.8%), somnolence (11.1%), headache (8.9%), infection (7.8%), and peripheral edema (6.9%) (Table S2).

DISCUSSION

This pooled analysis of three randomized, double-blind, placebo-controlled trials provides evidence for the dose-dependent efficacy of pregabalin in the management of pDPN. Pregabalin at doses of 300 mg/day and 600 mg/day resulted in statistically and clinically significant reductions in mean pain scores, compared with both placebo and lower doses of pregabalin (75 mg/day and 150 mg/day). These effects were consistent across patients with varying levels of baseline glycemic control, indicating pregabalin's therapeutic utility in a metabolically heterogeneous population.

The efficacy of pregabalin in pDPN has been demonstrated across several clinical trials[8, 14, 15] and reinforced by meta-analyses and real-world evidence[19, 20]. These findings are reflected in multiple international guidelines, which recommend pregabalin as a first-line agent for neuropathic pain, including the NeuPSIG, EFNS, ADA, and AAN guidelines[7, 21–23].

Despite this, real-world studies reveal that patients often receive subtherapeutic pregabalin doses due to concerns about tolerability, leading to insufficient pain control[10, 24]. In our analysis, more than 42% of patients receiving either pregabalin 300 mg/day or 600 mg/day achieved ≥50% pain reduction, a clinically meaningful threshold, compared with only 14.7% on placebo.

The early onset of analgesia, as demonstrated through MMRM analysis, is another critical aspect of pregabalin's clinical utility. Separation from placebo was observed as early as Week 1 in the 300 mg/day and 600 mg/day groups, with sustained benefit throughout the study duration. Rapid pain relief is not only clinically beneficial but may also enhance patient adherence, reduce dropout rates, and improve functional outcomes, such as sleep, mood, and quality of life[25].

Moreover, although treatment-emergent adverse events were generally more frequent at higher pregabalin doses, clinicians are advised to individualize therapy and maintain optimal dosing tailored to each patient's tolerability and therapeutic response.

Table 4 | Analysis of Covariance (ANCOVA) results Endpoint Mean Pain Scores by Baseline HbA1c category

HbA1c category		Placebo	75 mg	150 mg	300 mg	600 mg
≤8%	*N*	130	40	40	81	86
	LSMeans (SE)	−0.89 (0.18)	−1.56 (0.37)	−1.80 (0.39)	−2.57 (0.25)	−2.59 (0.25)
	Difference versus placebo	–	−0.68	−0.91	−1.69	−1.71
	P-value vs placebo	–	0.097	0.034	<0.0001	<0.0001
>8%	*N*	118	37	39	75	77
	LSMeans (SE)	−1.32 (0.18)	−1.05 (0.36)	−1.51 (0.38)	−2.36 (0.25)	−2.40 (0.25)
	Difference vs placebo	–	0.27	−0.19	−1.04	−1.09
	P-value vs placebo	–	0.50	0.65	0.0009	0.0004

One important consideration, as highlighted in real-world clinical observations, is that patients often present with greater clinical complexity than those in controlled trials. The publication by Freynhagen *et al.* (2021) underscores the need for a personalized, patient-centric titration 5strategy, advocating a "start low, go slow" approach to balance efficacy with tolerability, especially in populations with polypharmacy, multimorbidity, or advanced age[26]. Such practical insights are critical, particularly in contrast to the structured environment of phase 3 trials. However, our pooled analysis suggests reliable efficacy for pDPN is achieved with 300 mg/d doses and above, reinforcing the need to maintain cautious upward dose titration in routine clinical practice to optimize an individual patient's therapeutic response.

The study by Tesfaye *et al.* (2022) further supports this. It is reported that the mean maximum tolerated dose per day in the monotherapy arm was 397 mg, with 59 participants (55%) reaching the maximum dose by week 6[24]. These results support the clinical utility of titrating pregabalin dose to 300–600 mg/day in pDPN, challenging the traditional reluctance to titrate due to glycemic concerns or fear of adverse events.

Concerns often arise regarding whether patients with poor glycemic control (e.g., HbA1c >8%) experience reduced therapeutic benefit[9, 11]. Our subgroup analysis demonstrates that pregabalin's efficacy is not significantly influenced by baseline HbA1c, with comparable pain reductions observed in both glycemic strata. These findings are consistent with previous reports[24] and provide reassurance that effective analgesia can be achieved even in patients with suboptimal metabolic control.

These results support the clinical utility of dose titration to 300–600 mg/day in patients with pDPN, without concern for adverse glycemic impact. The findings reinforce that glycemic status should not limit the optimization of pregabalin dosing for pain management in this population.

From a clinical standpoint, these results support titration of pregabalin to optimal doses of 300–600 mg/day in patients with pDPN and challenge the traditional reluctance to titrate due to glycemic concerns or fear of adverse events. A personalized approach, focused on therapeutic response rather than metabolic exclusion criteria, is key to optimizing outcomes in this population[20].

LIMITATIONS

Despite the strengths of using pooled individual-level data from well-controlled studies, several limitations must be acknowledged. First, the analysis was post hoc in nature and not originally designed to detect subgroup differences based on HbA1c; also, no statistical correction for multiple testing was made. The trial durations (5 to 8 weeks) reflect short-term efficacy and safety, and longer-term effects remain to be investigated. In the Richter *et al.* study, the 600 mg/day group underwent dose titration during weeks 1–2, which may influence the interpretation of the pooled week 1–2 results for this dose. Additionally, the 75 mg/day and 150 mg/day treatment groups were each evaluated in only one clinical trial, resulting in smaller sample sizes and limited generalizability compared to the other dose groups.

CONCLUSION

In this pooled analysis, pregabalin at 300 mg/day and 600 mg/day demonstrated significant and clinically meaningful pain relief in patients with pDPN compared with lower doses, along with consistent efficacy observed across different levels of baseline glycemic control. These findings support a treatment strategy focused on titration to effective doses without being constrained by a patient's HbA1c status. Clinicians should be encouraged to pursue optimal pregabalin dosing to maximize therapeutic outcomes, thereby improving the quality of life for patients suffering from diabetic peripheral neuropathy.

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DISCLOSURE

The authors declare no other conflicts of interest related to this work.
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Informed consent: N/A.
Registry and the registration no. of the study/trial: N/A.
Animal studies: Primary data from research on human or animal subjects were not used in the analyses for this paper. Secondary, deidentified and anonymized data from previously conducted clinical trials were utilized in this paper. Hence ethics approval has been deemed not required.

AUTHOR CONTRIBUTIONS

Solomon Tesfaye, MB ChB, MD, reports grants or contracts paid from Withings, Viatris, and Procter & Gamble, outside the submitted work. Gordon Sloan, MB ChB, PhD, reports payments or honoraria for lectures, presentations, speakers bureaus, or educational events by Proctor and Gamble, Viatris and Eli Lily, outside the submitted work. He has also acted as a consultant or speaker for Angelini, Astra Zeneca, Bayer, Berlin-Chemie, Grunenthal, Medtronic, Merc, Merz, Nevro, Novo Nordisk, P&G, Viatris, and Worwag Pharma. Gavin Lyndon, PhD, is a Contracted Consultant with Viatris Inc., and reports holding stock or stock options with Pfizer Inc. and Viatris Inc. Ashish Bajaj, MD; Chris Walker, PhD; Egbert Biesheuvel, PhD;

and Sagar Suresh Kumbhar, MSc, are employees of Viatris Inc. No authors received personal remuneration for authorship or participation in this publication.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in PubMed at https://pubmed.ncbi.nlm.nih.gov/. These data were derived from the following resources available in the public domain: - PubMed, https://pubmed.ncbi.nlm.nih.gov/15596757/ - PubMed, https://pubmed.ncbi.nlm.nih.gov/15820913/ - PubMed, https://pubmed.ncbi.nlm.nih.gov/15288403/.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Weekly Mean Pain Scores: Results of MMRM for pooled studies (1008-014, 1,008-029, and 1,008-131).

Table S2. Summary of Adverse Events Occurring in ≥3% of Patients in Any Treatment Group by decreasing frequency.