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Optimising the Therapeutic Window: A Systematic Review and Network Meta-Analysis of Pregabalin Dosing Strategies for Painful Diabetic Neuropathy

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ABSTRACT

Aims: Although pregabalin is a first-line therapy for painful diabetic polyneuropathy (PDPN), its optimal dose–response relationship remains unclear. We conducted a network meta-analysis to evaluate the efficacy and safety of fixed pregabalin dosages in PDPN patients.

Materials and Methods: We systematically searched major databases through October 2025 comparing various doses of pregabalin (75, 150, 300, and 600 mg/day) with placebo in adults with PDPN. The outcomes were short- and long-term changes in the average daily pain score, patient/clinician global impression of change, and adverse events (AEs) including dizziness, somnolence, headache, and peripheral oedema.

Results: Twelve RCTs were eligible. In the short term, pregabalin 300 (Standardised Mean Difference [SMD], 1.09; 95% CI, 0.69–1.50) and pregabalin 600 mg/day (SMD, 0.90; 95% CI, 0.24–1.55) produced significant pain reduction compared with placebo. In the long term, both pregabalin 300 (SMD, 0.12; 95% CI, 0.06–0.17) and 600 mg/day (SMD, 0.31; 95% CI, 0.23–0.38) remained effective, whereas pregabalin 75 and 150 mg/day did not demonstrate superiority over placebo. Regarding safety, both pregabalin 300 and 600 mg/day were associated with greater risks of dizziness, somnolence, and peripheral oedema compared with pregabalin 75 mg/day, pregabalin 150 mg/day, and placebo.

Conclusion: Pregabalin doses ≤ 150 mg/day demonstrated no clinical benefit over placebo. Conversely, both pregabalin 300 and 600 mg/day showed a pain reduction effect at short- and long-term follow-up. Given that pregabalin 600 mg/day was associated with a higher incidence of AEs, pregabalin 300 mg/day appears to offer a more favourable balance, aligning potent efficacy with a manageable safety profile.

Abbreviations: ADPS, average daily pain score; AEs, adverse events; CGIC, clinician global impression of change; CI, confidence interval; CINeMA, confidence in network meta-analysis; DM, diabetes mellitus; DPN, diabetic polyneuropathy; MPS, mean weekly pain score; NMA, network meta-analysis; OR, odds ratio; PDPN, painful diabetic polyneuropathy; PGB, pregabalin; PGIC, patient global impression of change; RCTs, randomised controlled trials; RoB, risk of bias; SMD, standardised mean difference; SUCRA, surface under the cumulative ranking.

Doyun Kwon and Hee-Jae Jung are equal contributors to this work and designated as co-first authors.

1 | Introduction

Diabetic polyneuropathy (DPN), clinically defined as a symmetrical, length-dependent sensorimotor polyneuropathy, is the most common complication in both type 1 and 2 diabetes, affecting up to 50% of DM patients [1, 2]. While the majority of DPN patients are asymptomatic, approximately one-third of the DPN population develops painful diabetic polyneuropathy (PDPN) [3]. Characterised by debilitating neuropathic pain (burning or electric shock-like sensations), PDPN significantly impairs quality of life, including physical functioning and sleep quality [3, 4].

Although glycaemic control is the primary strategy to prevent PDPN progression, management focuses on symptomatic pain relief [3, 4]. Clinical guidelines consistently recommend gabapentinoids as a first-line therapy for PDPN [3, 5, 6]. Beyond its primary analgesic effects, pregabalin has also been shown to provide meaningful improvements in critical comorbidities that profoundly affect quality of life, most notably pain-related sleep interference [7–11].

Despite established evidence supporting the efficacy of pregabalin in PDPN, uncertainty persists regarding the optimal dosage balancing pain relief and adverse events (AEs). The existing literature clearly establishes a dose-dependent relationship of pregabalin for both therapeutic effects and AEs [12–14]. However, there is a lack of large-scale, direct, head-to-head studies comparing the different therapeutic doses of pregabalin and placebo against one another. As a result, current knowledge is largely confined to regulatory-approved maximum daily dosages and insights from pharmacoepidemiologic studies on real-world prescribing patterns [2, 3, 5–7, 15]. These limitations highlight the necessity for a comprehensive network meta-analysis (NMA) that systematically accounts for these factors. NMA allows for the simultaneous comparison of multiple interventions, even in the absence of direct head-to-head trials, thereby providing a broader understanding of relative treatment effects [16].

This study employs an NMA to compare the effectiveness and safety of various dosages of pregabalin regimens (75, 150, 300, and 600 mg/day) and placebo in PDPN patients. Our objective is to establish a clinically actionable hierarchy of pregabalin dosages.

2 | Materials and Methods

2.1 | Protocol and Registration

Since this NMA is not a clinical study involving human subjects, the protocol for institutional review board approval was not needed. Instead, the authors registered the protocol in the International Prospective Register of Systematic Reviews (PROSPERO; https://www.crd.york.ac.uk/PROSPERO/) on October 18, 2025 (ID: CRD420251167031). This study was conducted and reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA; https://www.prisma-statement.org/prisma-2020) (Table S1).

2.2 | Search Strategy

The PICO (population, intervention, comparison, and outcome) of this study is as follows:

P: Patients (18 years or older) diagnosed with PDPN through physical, laboratory, and/or electrodiagnostic examinations.

I: fixed-dose pregabalin regimens (75, 150, 300, and 600 mg/day).

C: placebo.

O: changes in the average daily pain score (ADPS), patient global impression of change (PGIC), clinician global impression of change (CGIC), and AEs (headache, dizziness, somnolence, and peripheral edema).

A systematic literature search was conducted to identify relevant studies published up to October 2025 using PubMed, Embase, Cochrane Library, Google Scholar, and Scopus databases using key phrases (Table S2).

2.3 | Inclusion and Exclusion Criteria

Randomised controlled trials (RCTs) comparing the effect of pregabalin at any fixed dose with placebo in PDPN patients were included. For studies with an initial titration phase, only data from the fixed-dose period were included in the analysis. Studies enrolling patients with either type 1 or 2 DM were eligible. Crossover trials were included if data from the first period, prior to crossover, were available. Patients 18 years or older diagnosed as PDPN through physical examination, laboratory examinations and/or electrodiagnostic study were included.

Studies were excluded if they enrolled patients with neuropathic pain conditions other than PDPN (e.g., postherpetic neuropathy), employed a flexible-dose or "as-needed" regimen without a clearly defined stable-dose maintenance phase, investigated other gabapentinoids (e.g., gabapentin or mirogabalin), consisted of case reports, case series, protocols, overview or review articles, or laboratory experiments, commentaries or were published in a language other than English.

2.4 | Data Extraction

All retrieved citations were imported into EndNote 21 (Clarivate Analytics, Philadelphia, PA, USA), where duplicate records were identified and removed. Two review authors (DYK and SGK) independently screened the titles and abstracts of the deduplicated records to identify potentially relevant studies. Subsequently, the full texts of all articles deemed potentially eligible were retrieved. The same two authors (DYK and SGK) independently assessed these full-text articles against the pre-specified inclusion and exclusion criteria to determine final eligibility. Any discrepancies encountered at either the title/abstract screening or the full-text assessment stage were resolved through discussion to reach consensus. If consensus could not be achieved, other reviewers (HJJ and JHK) were consulted to arbitrate and make the final decision.

Extracted variables included study characteristics, demographics, baseline characteristics, intervention details (dosage of pregabalin and follow-up period), and outcomes of interest. The ADPS was employed as the primary efficacy endpoint to quantify pain intensity. Since ADPS values were averaged over each 7-day period to obtain a mean weekly pain score (MPS), both terms were used interchangeably throughout the analysis. Pain reduction was analysed as the change from baseline (baseline minus follow-up) within each group. The primary treatment effect therefore represents the between-group difference in mean change (Δpregabalin − Δplacebo), where positive values indicate greater pain reduction in the pregabalin group.

If the pooled standard deviation (SD_{pooled}) between two groups was not obtainable, SD_{pooled} was calculated with sample size (n), mean and p value using the following formula.

$$SD_{pooled} = \frac{\left(Mean_{Group1} - Mean_{Group2}\right) \times \sqrt{n}}{\Phi^{-1}\left(1 - \frac{p-value}{2}\right)}$$

where $\Phi^{-1}(\,)$ *is the inverse function of a standard normal distribution.*

The values of ADPS were collected in chronological order. Short-term follow up ADPS and long-term follow up ADPS were respectively defined as a change in ADPS from baseline to ≤4 weeks and >4 weeks after pregabalin administration [17, 18]. For studies reporting pain scores at multiple intervals, we extracted all available data to comprehensively assess treatment effects.

The following formulas were used to calculate mean ($Mean_{change}$) and standard deviation of change (SD_{change}) between short- and long-term follow up. Correlation derived from another study which presented the standard deviation for change was used in this study. In the absence of reported data, a conservative correlation of 0.5 was imputed, in accordance with the Cochrane Handbook [19].

$$Mean_{change} = Mean_{baseline} - Mean_{follow-up}$$

$$SD_{change} = \sqrt{SD^2_{baseline} + SD^2_{follow-up} - 2 \times Correlation \times SD_{baseline} \times SD_{follow-up}}$$

When numerical data were available only in figures, they were extracted using a digital plot extraction software (PlotDigitizer; https://plotdigitizer.com/). To assess the robustness of our findings to this assumption, we conducted sensitivity analyses by varying the correlation coefficient to 0.25 and 0.75. Furthermore, additional sensitivity analyses were performed by sequentially excluding studies with a high risk of bias, those utilizing derived standard deviations, and those where data were digitised via PlotDigitizer. A difference in the SMD between the primary and sensitivity analyses (|Δ SMD|) <0.20 was pre-specified as the threshold for small impact on the results [20, 21].

PGIC and CGIC were analysed as dichotomous outcomes, with 'responders' defined as achieving a score of ≤3 [22]. Detailed definitions and scoring scales are provided in the Supporting Information. The incidence of AEs, including headache, dizziness, somnolence, and peripheral oedema, was also assessed. Sensitivity analyses were performed by calculating the ratio of odds ratios (ORs) defined as the OR from the sensitivity analysis divided by the OR from the primary analysis ($OR_{Sensitivity}/OR_{Primary}$).

2.5 | Risk of Bias Assessment & Certainty of Evidence

The methodological quality of the included studies was assessed using the revised Cochrane risk of bias tool (RoB 2.0, https://www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2). This tool evaluates potential bias across five distinct domains: Bias arising from the randomisation process (D1), Bias due to deviations from intended interventions (D2), Bias due to missing outcome data (D3), Bias in measurement of the outcome (D4), and Bias in selection of the reported result (D5). Based on the signalling questions within each domain, judgement of each study was assigned as 'Low risk', 'High risk', 'Some concerns', or 'No information' [23] (Figure 1).

To evaluate the overall certainty of the evidence for each outcome, we applied the Confidence in Network Meta-Analysis (CINeMA) web application (https://cinema.ispm.unibe.ch/) [24, 25]. The authors evaluated six key domains to determine the level of confidence in the effect estimates for each network comparison: (1) within-study bias (assessed by RoB 2.0); (2) reporting bias; (3) indirectness; (4) imprecision; (5) heterogeneity; (6) incoherence. The relative contribution of direct comparisons was weighted using the CINeMA-generated contribution matrix. The overall certainty of evidence for each outcome was rated as 'Very Low', 'Low', 'Moderate', or 'High' with reasons for the rating (Table S3).

2.6 | Network Assumption and Transitivity Assess

The validity of the network meta-analysis was predicated on the transitivity assumption, which assumes that potential effect modifiers are balanced across treatment comparisons. We assessed this plausibility by systematically examining the distribution of key clinical and demographic variables, including baseline pain severity (ADPS), duration of diabetes and PDPN, previous gabapentinoid use, and glycaemic control (HbA1c) (Table S4).

2.7 | Data Synthesis and Analysis

Continuous variables were analysed and reported as standardised mean differences (SMDs) with corresponding 95% confidence intervals (CIs) for changes in ADPS scores over short- and long-term follow-up periods. Categorical outcomes were compared between groups using ORs with 95% CIs. The I^2 statistic and Cochran's Q test were used to determine the heterogeneity of direct comparisons. Significant heterogeneity was defined as I^2 value >50% and p value <0.05, in which case a random-effects model was applied; otherwise, a common-effects model was used. Local inconsistency was further scrutinised via the node-splitting method, which compares direct and indirect evidence for each treatment comparison. Visual inspection of network consistency was performed using netheat plots. To establish a treatment hierarchy among the evaluated interventions, we utilised probability-based ranking

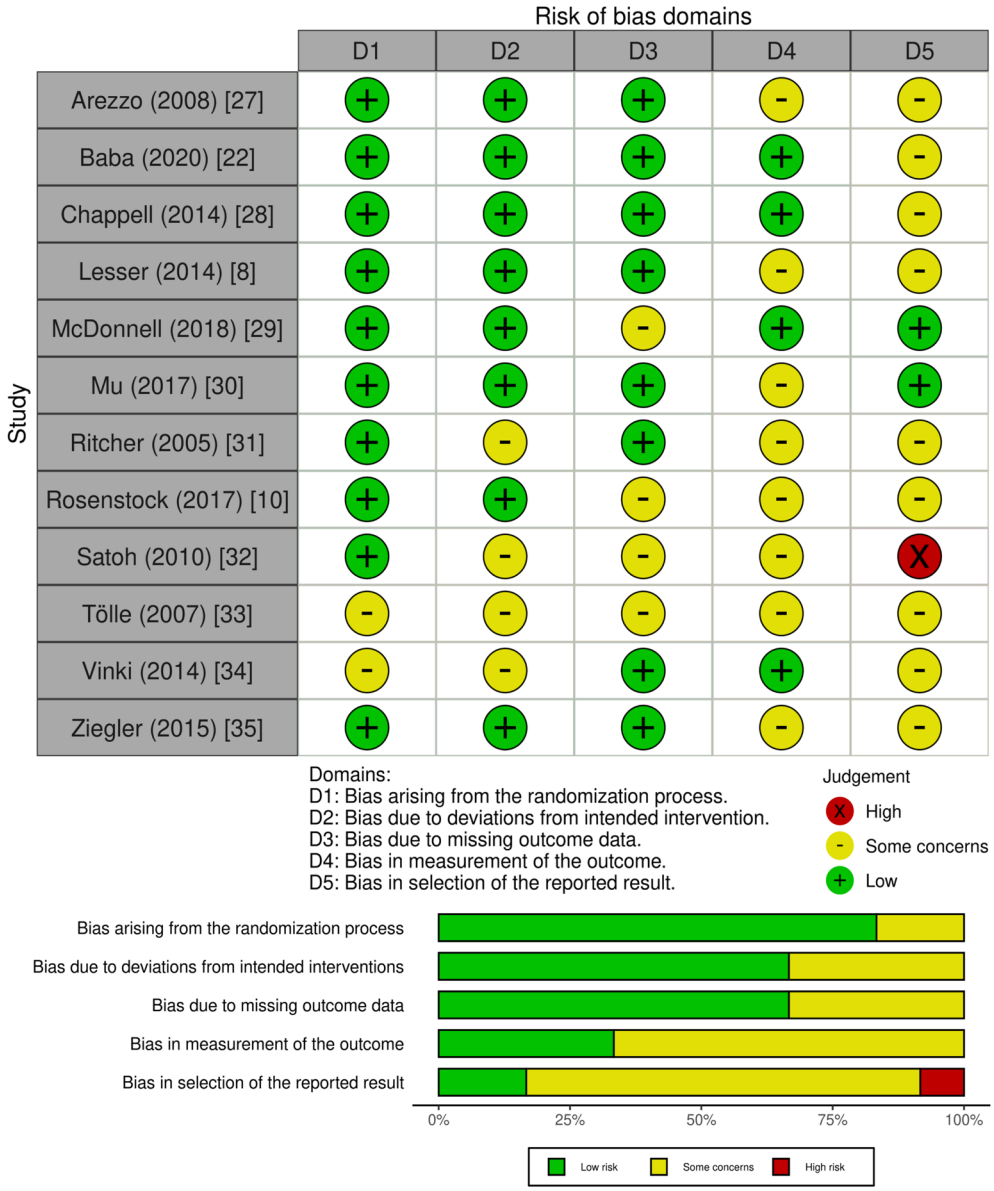

FIGURE 1 | Summary of risk of bias (RoB 2.0) of included studies.

metrics, summarised by the surface under the cumulative ranking (SUCRA) curve. SUCRA values range from 0 to 1, with higher values indicating a greater probability of being a superior option. This metric can be interpreted as the percentage of effectiveness a treatment achieves relative to an idealised intervention that would consistently rank first [26]. Publication bias was assessed using Egger's regression test with visual inspection of the funnel plots. All statistical analyses were performed using the 'netmeta' package (version 3.2–0) implemented in R 4.3.3 software (R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/); p value <0.05 was considered statistically significant.

3 | Results

A total of 1988 records were identified through database searches. After removal of 873 duplicate records, 1115 records remained for title and abstract screening, of which 1042 records were excluded. These excluded records comprised case reports, case series, study protocols, animal or in vitro studies, non-clinical studies, and studies employing inappropriate comparators (Supplementary Figure S1).

After screening of title and abstract for eligibility, 73 articles underwent full-text review, after which 61 articles were excluded. The final analysis included 12 RCTs [8, 10, 16, 27–35] with a total of 2717 patients. The placebo ($n=1125$), PGB75 ($n=77$), PGB150 ($n=178$), PGB300 ($n=1044$), and PGB600 groups ($n=293$) were included in 11, 1, 2, 10, and 4 RCTs, respectively (Table 1). Key trial design characteristics that may influence treatment exposure are summarised in Table S5.

3.1 | Risk of Bias Assessment

Overall, one study [32] was judged to be at high risk of bias in at least one domain (D5: bias in selection of the reported result). The remaining studies were rated as either low risk or some

TABLE 1 | Characteristics of included studies.

First author (year)	Study design	Interventions	Follow up period	Outcomes				
				ADPS/MPS		PGIC	CGIC	AEs
				Short	Long			
Arezzo (2008) [27]	RCT	PGB 600 Placebo	13 weeks	O	O	O	O	O
Baba (2020) [22]	RCT	PGB 300 Placebo	7 weeks	O	O	O		O
Chappell (2014) [28]	RCT	PGB 300 Placebo	8 weeks		O			O
Lesser (2014) [8]	RCT	PGB 75 PGB 300 PGB 600 Placebo	5 weeks		O	O	O	O
McDonnell (2018) [29]	RCT, crossover	PGB 300 Placebo	4 weeks	O				O
Mu (2017) [30]	RCT	PGB 300 Placebo	9 weeks	O	O			O
Richter (2005) [31]	RCT	PGB 150 PGB 600 Placebo	6 weeks		O	O	O	O
Rosenstock (2017) [10]	RCT	PGB 300 Placebo	8 weeks			O	O	O
Satoh (2010) [32]	RCT	PGB 300 PGB 600	8 weeks	O	O			O
Tölle (2007) [33]	RCT	PGB 150 Placebo	12 weeks			O	O	O
Vinki (2014) [34]	RCT	PGB 300 Placebo	5 weeks	O	O			O
Ziegler (2015) [35]	RCT	PGB 300 Placebo	6 weeks	O	O			O

Abbreviations: ADPS: average daily pain score, AEs: adverse events, CGIC: clinician global impression of change, MPS: mean weekly pain score, PDPN: painful diabetic polyneuropathy, PGB75: pregabalin 75 mg/day, PGB150: pregabalin 150 mg/day, PGB300: pregabalin 300 mg/day, PGB600: pregabalin 600 mg/day, PGIC: patient global impression of change, RCT: randomised controlled trial.

concerns across all five risk-of-bias domains. Ten of the twelve trials were judged to be at low risk of bias for D1. Eight trials were rated as low risk of bias in D2. Seven studies were assessed as low risk of bias in D3. Only four trials were judged to be at low risk of bias in D4. Two studies were rated as low risk of bias in D5. Nine trials were judged as having some concerns of bias in D5. One study was rated as high risk due to the absence of a prospectively registered protocol or prespecified analysis plan, combined with unclear outcome prioritisation and the potential for selective reporting of efficacy outcomes. According to the CINeMA assessment for the 66 pairwise comparisons, the confidence in the evidence was rated as 'Moderate' for 45 comparisons and "Very Low" for 20 comparisons (Table S3).

3.2 | Pain Reduction Effectiveness

Seven studies compared the short-term ADPS among the placebo, PGB300, and PGB600 groups. Figure 2A illustrates the network geometry of the included treatment. A random-effects model was used due to study heterogeneity ($\tau^2 = 0.58$, $I^2 = 96.5\%$). Compared with the placebo group, the PGB300 (SMD: 1.09, 95% CI [0.69, 1.49]) and PGB600 groups (SMD: 0.90, 95% CI [0.24, 1.55]) showed significantly lower ADPS (Figure 3A). The PGB600 group had significantly lower ADPS than the PGB300 group (SMD: 0.24, 95% CI 0.05, 0.44) (Figure S4). The long-term ADPS were compared among the placebo, PGB75, PGB150, PGB300, and PGB600 groups in nine studies. Figure 2B illustrates the network geometry of the included treatment. A common-effects model was used ($\tau^2 = 0$, $I^2 = 0\%$). There were non-significant differences in the ADPS between the placebo and PGB75 groups and between the placebo and PGB150 groups. In contrast, the ADPS was lower in the PGB300 (SMD: 0.12, 95% CI [0.06, 0.17]) and PGB600 groups (SMD: 0.31, 95% CI [0.23, 0.38]) than in the placebo group (Figure 3B). The PGB600 group showed lower ADPS compared to the PGB300 group (SMD: 0.12, 95% CI [0.01, 0.22]) (Figure S5). The specific timepoints selected for short-term and long-term efficacy assessments are detailed in Table S6.

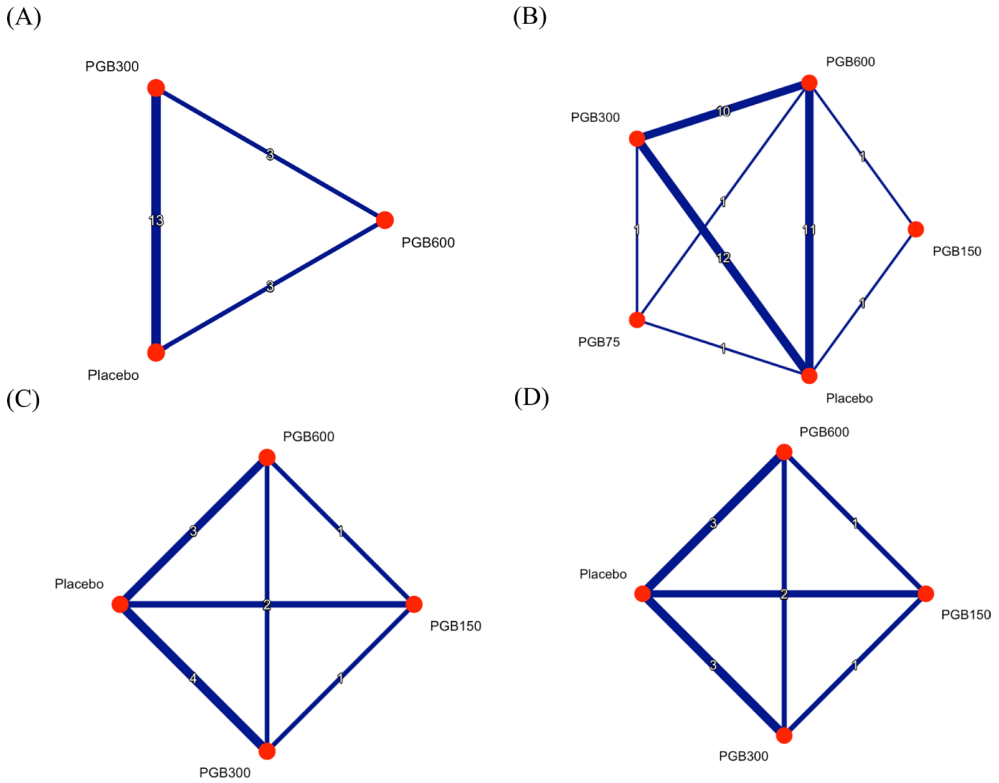

FIGURE 2 | Network plot of short term (A) and long term (B) follow up of pain scale (ADPS), PGIC (C), and CGIC (D). ADPS; average daily pain score, CGIC; clinician global impression of change, PGB; pregabalin, PGIC; patient global impression of change.

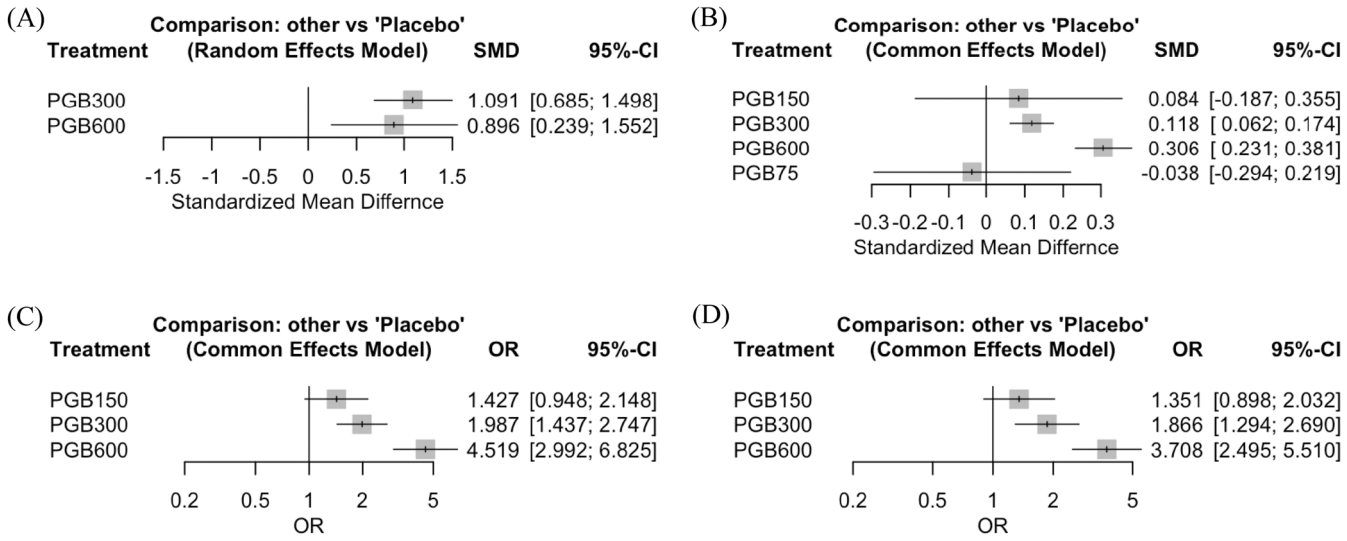

FIGURE 3 | NMA summary forest plot of short term (A) and long term (B) follow up of pain scale (ADPS), PGIC (C) and CGIC (D). Numerical labels (75, 150, 300, and 600) indicate PGB daily doses in mg/day. ADPS; average daily pain score, CGIC; clinician global impression of change, NMA; network meta-analysis, PGB; pregabalin, PGIC; patient global impression of change.

Sensitivity analyses employing correlation coefficients of 0.25 and 0.75 demonstrated that |ΔSMD| values remained small (< 0.20) for the majority of outcomes, with only short-term ADPS at $r = 0.75$ exceeding this threshold (Table S7). Further sensitivity analyses were performed by excluding studies with a high risk of bias ($n = 1$), those using derived standard deviations ($n = 3$), and those involving digitised data ($n = 3$); notably, the latter two categories consisted of the same three trials. While these exclusions resulted in non-trivial shifts (|ΔSMD| < 0.20) in the short-term estimates for 300 and 600 mg doses, all long-term |ΔSMD| values remained small (< 0.20) (Table S8).

3.3 | Global Impression of Change

The odds of being a treatment responder based on the PGIC score from six studies was compared among the placebo,

PGB150, PGB300, and PGB600 groups ($\tau^2 = 0.09$, $I^2 = 42.1\%$). Figure 2C illustrates the network geometry of the included treatment. The ORs were non-significant between the placebo and PGB150 groups. In contrast, the ORs of PGB300 (OR: 1.99, 95% CI [1.44, 2.75]) and PGB600 groups (OR: 4.52, 95% CI [2.99, 6.83]) to the placebo group were significant (Figure 3C). No significant OR was observed between PGB300 and PGB600 (Figure S6).

Five studies reported CGIC and the odds of being a treatment responder for each group were calculated based on the CGIC scores ($\tau^2 = 0$, $I^2 = 0\%$). Figure 2D illustrates the network geometry of the included treatment. The OR of the PGB150 group to the placebo group was non-significant. However, the ORs of the PGB300 (OR: 1.87, 95% CI [1.29, 2.69]) and PGB600 groups (OR: 3.70, 95% CI [2.50, 5.51]) to the placebo group were significant (Figure 3D). The OR of the PGB600 group to the PGB300 group was also significant (Figure S7).

3.4 | Adverse Events

Detailed network plots and summary forest plots illustrating the comparative analysis of AEs are provide in the Figures S2, S3, S8–S11.

None of the pregabalin doses demonstrated a statistically significant increase in risk of headache compared with placebo ($\tau^2 = 0$, $I^2 = 0\%$). Dose-dependent increase in risk was observed in dizziness ($\tau^2 = 0$, $I^2 = 0\%$), somnolence ($\tau^2 = 0.08$, $I^2 = 19.4\%$), and peripheral oedema ($\tau^2 = 0.30$, $I^2 = 67.7\%$). Regarding dizziness, both PGB300 (OR: 3.67, 95% CI [2.53, 5.33]) and PGB600 (OR: 8.38, 95% CI [5.34, 13.16]) were associated with significantly higher risks compared to placebo. Regarding somnolence, PGB300 (OR: 3.75, 95% CI [2.52, 5.56]) and PGB600 (OR: 6.24, 95% CI [3.91, 9.94]) significantly increased risk compared to placebo. Regarding peripheral oedema, PGB300 (OR: 3.35, 95% CI [2.02, 5.56]) and PGB600 (OR: 2.58, 95% CI [1.64, 4.07]) were associated with significantly increased risk compared to placebo. In addition, absolute risk metrics and number-needed-to-harm (NNH) values for each AE and treatment discontinuation were calculated, revealing a marked dose-dependent increase in the burden of dizziness, somnolence, and peripheral oedema (Table S9). Sensitivity analysis was conducted by excluding trials with a follow-up duration shorter than 8 weeks. The observed OR ratios for AEs and treatment discontinuation ranged from 0.62 to 1.99. The most pronounced OR fluctuations were observed in the 150 mg dose group compared to placebo (Table S10).

3.5 | SUCRA and Rankogram

Compared with the PGB150 and placebo groups, the PGB300 and PGB600 groups tended to show higher probabilities of effectiveness across ADPS, PGIC, and CGIC. Notably, however, PGB300 was estimated to have the highest probability of being the most effective for short-term ADPS (87%) (Figure 4A). Regarding AEs, PGB600 was associated with the lowest probability of tolerability for headache, dizziness, and somnolence, while PGB300 showed a higher likelihood of risk for peripheral oedema (5%). Placebo demonstrated the most favourable profile for dizziness and oedema but performed poorly for headache (37%). Conversely, PGB75 exhibited the most promising estimated profile for headache (71%) and somnolence (94%) (Figure 4B). Detailed rankograms illustrating the ranking probability distributions for all outcomes are provided in Figures S12–S19.

3.6 | Publication Bias

No publication bias indicated by the symmetrical funnel plots and egger's test was found in most of the outcomes except for the short-term ADPS (Figure S20) and peripheral oedema (Figure S21).

3.7 | Network Consistency and Validity

Robust internal consistency was demonstrated for short-term ADPS, PGIC, CGIC, headache, dizziness, and somnolence, with no significant discrepancies between direct and indirect evidence. Significant global inconsistency was limited to long-term ADPS and peripheral oedema.

Node-splitting analysis indicated that these discrepancies were primarily driven by localised differences in specific dose comparisons against placebo (Table S11). Visual inspection of the net heat plots confirmed that inconsistency was confined to specific nodes rather than being systemic across the network (Figures S22 and S23).

4 | Discussion

This study presents a comprehensive systematic review and NMA focused exclusively on patients with PDPN. Previous landmark guidelines and systematic reviews have established the efficacy of pregabalin at doses of 300 mg and 600 mg/day against placebo [1, 3–5, 7, 17, 18, 36]. Existing analyses lack dose-specific comparisons and pool heterogeneous neuropathic conditions, such as postherpetic neuralgia, with PDPN, hindering direct clinical translation [7, 18, 37]. By focusing on PDPN-specific RCTs and fixed-dose pregabalin regimens, this NMA provides a more clinically relevant and disease-specific estimate of treatment effects, thereby offering a more precise evaluation of dose–response relationships and informing optimal dose selection for the management of PDPN.

PDPN is a debilitating complication of DM, characterised by distal symmetric neuropathic pain [38]. Pathophysiologically, hyperglycaemia-induced metabolic and microvascular disturbances drive axonal degeneration and demyelination [39, 40]. Diagnosis of PDPN relies on clinical evaluation assessing both small- and large-fibre involvement [27, 41, 42]. As glycaemic control alone is often insufficient for symptom relief, pharmacological intervention is required, and major international guidelines recommend pregabalin as first-line therapy [1, 3, 5, 6].

Initially developed as an antiepileptic agent, pregabalin was recognised for its analgesic efficacy for neuropathic pain [11, 43]. Its analgesic effects are mediated by selective binding to the α2δ

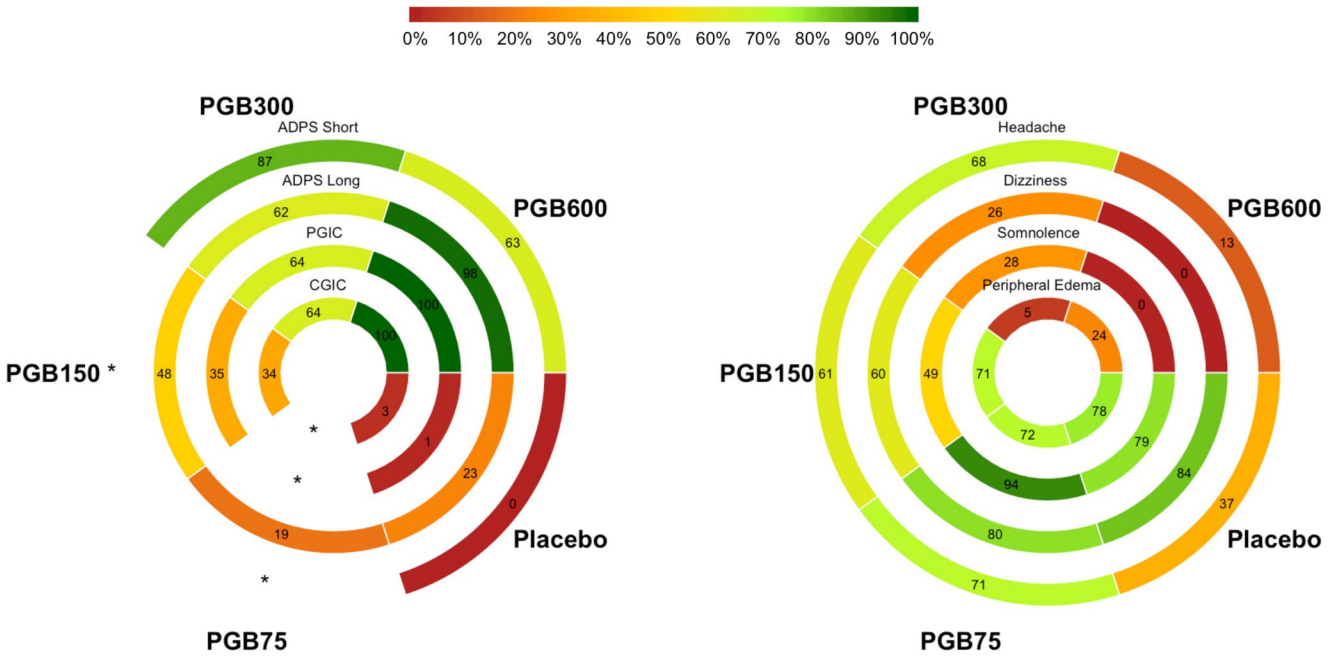

FIGURE 4 | Surface under the cumulative ranking curve (sucra) heatmap for efficacy and safety outcome. The circular heatmap illustrates the comparative hierarchy of pregabalin doses and placebo. The colour gradient ranges from red to green, where higher SUCRA values indicate a higher probability of being the most effective treatment for efficacy outcomes or the best tolerated (safest) treatment for safety outcomes. Asterisks (*) or blank segments indicate that the specific intervention-outcome pair was not available in the network. (A) Efficacy outcomes: Rings represent (from outer to inner) CGIC, PGIC, ADPS (long-term), and ADPS (short-term). (B) Safety outcomes: Rings represent (from outer to inner) headache, dizziness, somnolence, and peripheral oedema. ADPS; Average Daily Pain Score, CGIC; Clinician Global Impression of Change, PGB; pregabalin, PGIC; Patient Global Impression of Change.

subunit of voltage-gated calcium channels (VGCCs), reducing excitatory neurotransmitter release [4, 11, 37, 42].

Pregabalin exhibits linear, dose-proportional pharmacokinetics with high bioavailability, ensuring predictable systemic exposure [44, 45]. This profile supports a clear dose–response relationship, where higher doses are associated with greater analgesic efficacy mediated across both small and large afferent fibre pathways [7, 46, 47]. While pooled analyses of pivotal RCTs show significant pain reduction for 150–600 mg/day [46], lower doses (e.g., 150 mg/day) often fail to achieve statistical significance in smaller trials [46–49]. Current guidelines and prescribing information recommend titration to an effective dose, typically 300–600 mg/day, for the treatment of PDPN [1, 5, 18, 50, 51]. However, clinical observation and utilisation studies suggest many patients are maintained on doses as low as 150 mg/day [51, 52]. In one simulation-based analysis, dose escalation up to 300 mg/day consistently improved pain reduction across simulated patients [37]. Our NMA reinforces this hierarchy: doses ≤150 mg/day showed no significant benefit over placebo, whereas both 300 and 600 mg/day were associated with greater pain reduction relative to placebo, with magnitudes that may be clinically relevant. To provide a clinical perspective on these findings, treatment effects expressed as SMDs can be interpreted using the original 0–10 pain scale based on representative SD reported in PDPN trials. Assuming a typical SD of approximately 2 points, an SMD of 0.5 corresponds to a between-group difference of roughly 1 point. While a reduction of approximately 2 points (or a 30% reduction from baseline) is often cited as a minimal clinically important improvement at the individual level, a between-group difference of approximately 1 point in randomised trials is generally considered clinically relevant [17, 53, 54]. Consequently, our results suggest that titration to a dose of at least 300 mg/day should be considered. In addition, pregabalin 600 mg/day exhibited slightly greater analgesic efficacy than pregabalin 300 mg/day although the absolute difference was modest. The reliance on estimated SD_{pooled} may have potentially attenuated the observed magnitude of pain reduction, since p values reported as inequalities were approximated by applying a marginal decrement commensurate with the reporting precision (e.g., $p < 0.05$ was approximated as 0.049). Despite this potential underestimation, a statistically significant dose-dependent relationship for pregabalin was evident, underscoring the robustness of our findings.

Interestingly, the magnitude of pain reduction for pregabalin 300 and 600 mg/day was larger in the short-term ADPS analysis than in the long-term assessment. This pattern appears to be driven by the short-term trial by McDonnell et al. [29], in which pregabalin 300 mg/day demonstrated a markedly greater separation from placebo than that observed in the other included studies. This may have contributed to the comparatively elevated short-term treatment estimates for the higher pregabalin doses. In addition, only one study [27] evaluated pregabalin 600 mg/day in both short- and long-term follow-up, and several timepoints in that trial showed no meaningful difference in SMD between pregabalin 600 mg/day and placebo

during the long-term assessment. This attenuation in long-term effect may explain the smaller pooled estimates observed for pregabalin 600 mg/day when short- and long-term outcomes are compared.

Dose-dependent AEs remain the principal barrier to pregabalin titration [10, 31, 44, 47, 48]. Somnolence and dizziness are a direct pharmacological extension of pregabalin's therapeutic mechanism [3, 7, 48, 50]. By dampening neuronal hyperexcitability, pregabalin modulates CNS pathways beyond nociception [47, 48]. Our findings showed no significant increase in somnolence and dizziness for pregabalin doses ≤150 mg/day compared with placebo. In contrast, both pregabalin 300 and 600 mg/day were associated with a significantly higher risk, with the higher dose demonstrating a clearly greater burden of AEs. This confirms a steep trade-off between incremental analgesia and tolerability. Headache was frequently reported, despite the off-label use of pregabalin in migraine prophylaxis, suggesting a complex effect on headache pathways [37, 47, 55]. In this study, headache did not differ from placebo across pregabalin doses. This absence of a dose–response pattern may reflect unmeasured patient-level factors—such as a history of migraine or tension-type headache—or could represent a masking effect related to pregabalin's glutamatergic modulation. Peripheral oedema appears to be mediated by α2δ-independent off-target effects on L-type calcium channels, resulting in vasodilation and fluid extravasation [46, 48]. In this study, both pregabalin 300 and 600 mg/day significantly elevated the risk of peripheral oedema. However, direct comparison showed no significant difference, indicating that dose escalation from 300 to 600 mg/day does not significantly exacerbate the risk of oedema. Reflecting these AE profiles, treatment discontinuation (acceptability) exhibited a clear dose–response pattern. Compared to placebo, the risk of discontinuation was significantly higher for pregabalin 300 mg/day (OR 2.02) and 600 mg/day (OR 3.27), whereas lower doses (75 and 150 mg/day) showed no significant difference. Notably, the NNH for discontinuation at 600 mg/day was nearly twice as low as that for 300 mg/day (13 vs. 27), highlighting a substantial decrease in patient adherence at the highest dosage.

By strictly isolating PDPN from heterogeneous neuropathic conditions, this study seeks to provide a high-resolution comparison of fixed-dose regimens that was previously obscured in broader analysis. These efficacy estimates remained generally robust to varying correlation assumptions and were further supported by a sensitivity analysis restricted to trials of at least 8 weeks. Although numerical fluctuations were observed in the short-term ADPS across sensitivity analyses, the overall treatment hierarchy and statistical significance remained largely unaffected. In addition, while the OR ratios for certain AEs—most notably in the 150 mg/day group—showed some variability, the overall safety profiles and treatment effect estimates for primary AEs and discontinuation remained stable, confirming the robustness of our findings across different follow-up durations and statistical assumptions. Our findings suggest that whilst doses of ≤150 mg/day—common in clinical practice—offered limited benefit, 300 mg/day appears to provide more meaningful efficacy. The 600 mg/day regimen provided only marginal incremental relief relative to the disproportionate increase in AEs. By highlighting the dose–response profile of pregabalin, this study offers a rationale for aiming towards 300 mg/day to optimise outcomes, whilst acknowledging that a 600 mg/day regimen remains a potential option tailored specifically for tolerant responders.

Regarding the internal validity of the network, it is worth mentioning that most efficacy and safety outcomes showed high levels of consistency. Statistical inconsistency was observed in long-term ADPS and peripheral oedema, which suggests that these specific results should be approached with caution. Although statistical inconsistency was identified, the net heat plots demonstrate that this 'heat' is highly localised to a few specific nodes rather than representing a systemic issue across the entire network. This suggests that the overarching internal validity of the network remains intact, with discrepancies being confined to specific comparisons where evidence is particularly sparse or clinical reporting is more variable.

This study has several limitations. First, the lack of direct head-to-head comparisons between pregabalin doses resulted in a weakly connected network, with most evidence derived from placebo-controlled trials, thereby limiting the precision and robustness of dose-to-dose estimates, particularly for lower and intermediate doses. Given the predominance of placebo-controlled trials, the estimated dose hierarchy relies substantially on indirect comparisons and should therefore be interpreted cautiously. Second, the included trials exhibited significant heterogeneity in trial design, including titration schedules, maintenance durations, and rescue medication policies. Although we attempted to standardise outcome windows by defining short- and long-term periods, these trial-level variances may have introduced confounding factors. The localised statistical inconsistency in certain outcomes means those specific hierarchies should be interpreted with a degree of caution. Third, several included RCTs were judged to have 'Some Concerns' or 'High' risk of bias, which contributed to the 'Moderate to 'Very Low' certainty of evidence as assessed by the CINeMA framework. Fourth, emerging evidence suggests that glycaemic variability, independent of mean HbA1c, may influence neuropathy progression and treatment response [56, 57]; however, the absence of continuous glucose monitoring-derived metrics in the included studies precluded evaluation of this potential effect modifier. Finally, although observational studies have reported an association between gabapentinoid use and suicidal ideation [58, 59], such events were not systematically captured in the included RCTs, limiting safety assessment.

5 | Conclusion

This NMA demonstrates a dose–response relationship of pregabalin for both analgesic efficacy and AEs exclusively within the PDPN population. Doses ≤150 mg/day appear to offer negligible benefits over placebo, whereas clinically relevant pain reductions emerge from 300 mg/day. Although pregabalin 600 mg/day yields the greatest long-term efficacy, it is associated with a marked increase in AEs. Accordingly, pregabalin 300 mg/day may offer a favourable balance between efficacy and tolerability; however, this should be viewed as an evidence-informed estimate contingent on trial-level constraints and the inherent

uncertainty in both efficacy and safety outcomes. These findings provide a framework to support individualised titration and shared decision-making in PDPN.

Author Contributions

Design: Do Yun Kwon, Jonghae Kim, Sang Gyu Kwak. Conduct/data collection: Do Yun Kwon, Sang Gyu Kwak, Hee-Jae Jung, Junho Nam. Analysis: Sang Gyu Kwak, Junho Nam. Writing manuscript: Do Yun Kwon, Hee-Jae Jung, Junho Nam, Jonghae Kim, Eonju Jeon, Sang Gyu Kwak.

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Ethics Statement

Since this meta-analysis is not a clinical study involving human subjects, a protocol for IRB approval or patient consent statement was not needed.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data used for all analyses, and analytic code can be provided by authors with a reasonable request.

Peer Review

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Flowchart of search results. **Figure S2:** Network plot of adverse events including headache (A), dizziness (B), somnolence (C) and peripheral oedema (D). Numerical labels (75, 150, 300, and 600) indicate PGB daily doses in mg/day. PGB; pregabalin. **Figure S3:** NMA summary forest plot of adverse events including headache (A), dizziness (B), somnolence (C), and peripheral oedema (D). Numerical labels (75, 150, 300, and 600) indicate PGB daily doses in mg/day. NMA; network meta-analysis, PGB; pregabalin. **Figure S4:** Forest plots of pairwise comparison of short term follow up of pain scale (ADPS). Numerical labels (75, 150, 300, and 600) indicate pregabalin daily doses in mg/day. ADPS; average daily pain score, PGB; pregabalin. **Figure S5:** Forest plots of pairwise comparison of long term follow up of pain scale (ADPS). Numerical labels (75, 150, 300, and 600) indicate pregabalin daily doses in mg/day. ADPS; average daily pain score, PGB; pregabalin. **Figure S6:** Forest plots of pairwise comparison of patient global impression of changes (PGIC). Numerical labels (75, 150, 300, and 600) indicate PGB daily doses in mg/day. PGB; pregabalin. **Figure S7:** Forest plots of pairwise comparison of clinician global impression of changes (CGIC). Numerical labels (75, 150, 300, and 600) indicate PGB daily doses in mg/day. PGB; pregabalin. **Figure S8:** Forest plots of pairwise comparison for the incidence of headache. Numerical labels (75, 150, 300, and 600) indicate PGB daily doses in mg/day. PGB; pregabalin. **Figure S9:** Forest plots of pairwise comparison for the incidence of dizziness. Numerical labels (75, 150, 300, and 600) indicate PGB daily doses in mg/day. PGB; pregabalin. **Figure S10:** Forest plots of pairwise comparison for the incidence of somnolence. Numerical labels (75, 150, 300, and 600) indicate PGB daily doses in mg/day. PGB; pregabalin. **Figure S11:** Forest plots of pairwise comparison for the incidence of peripheral oedema. Numerical labels (75, 150, 300, and 600) indicate PGB daily doses in mg/day. PGB; pregabalin. **Figure S12:** Ranking probability plots (rankograms) for short term follow up of pain scale (ADPS). Numerical labels (75, 150, 300, and 600) indicate pregabalin daily doses in mg/day. ADPS; average daily pain score, PGB; pregabalin. **Figure S13:** Ranking probability plots (rankograms) for long term follow up of pain scale (ADPS). Numerical labels (75, 150, 300, and 600) indicate pregabalin daily doses in mg/day. ADPS; average daily pain score, PGB; pregabalin. **Figure S14:** Ranking probability plots (rankograms) for patient global impression of changes (PGIC). Numerical labels (75, 150, 300, and 600) indicate PGB daily doses in mg/day. PGB; pregabalin. **Figure S15:** Ranking probability plots (rankograms) for clinician global impression of changes (CGIC). Numerical labels (75, 150, 300, and 600) indicate PGB daily doses in mg/day. PGB; pregabalin. **Figure S16:** Ranking probability plots (rankograms) for the incidence of headache. Numerical labels (75, 150, 300, and 600) indicate PGB daily doses in mg/day. PGB; pregabalin. **Figure S17:** Ranking probability plots (rankograms) for the incidence of dizziness. Numerical labels (75, 150, 300, and 600) indicate PGB daily doses in mg/day. PGB; pregabalin. **Figure S18:** Ranking probability plots (rankograms) for the incidence of somnolence. Numerical labels (75, 150, 300, and 600) indicate PGB daily doses in mg/day. PGB; pregabalin. **Figure S19:** Ranking probability plots (rankograms) for the incidence of peripheral oedema. Numerical labels (75, 150, 300, and 600) indicate PGB daily doses in mg/day. PGB; pregabalin. **Figure S20:** Funnel plots for pain scale changes [ADPS short (A) and ADPS long(B)] and global impression of changes [PGIC (C) and CGIC (D)]. Numerical labels (75, 150, 300, and 600) indicate PGB daily doses in mg/day. ADPS; average daily pain score, CGIC; clinician global impression of change, PGB; pregabalin, PGIC; patient global impression of change. **Figure S21:** Funnel plots for adverse events; headache (A), dizziness (B), somnolence (C), and peripheral oedema (D). PGB; pregabalin. **Figure S22:** Netheat plots for efficacy outcomes. The netheat plots visualise the internal consistency of the network meta-analysis for (A) short-term ADPS, (B) long-term ADPS, (C) PGIC, and (D) CGIC. Axis labels are formatted as "Comparison (Design)" to identify the specific treatment pair and its source trial structure. Within the matrix, the area of each grey square is proportional to the contribution of the design-specific evidence to the overall network estimate. Cooler colours (blue to purple) represent negative values on the inconsistency scale, indicating designs where direct and indirect evidence are in high agreement, thereby reinforcing the stability of the network. Conversely, warmer colours (yellow to red) indicate positive inconsistency, reflecting a discrepancy between different sources of evidence ADPS; average daily pain score, CGIC; clinician global impression of change, PBO; placebo, PGB; pregabalin, PGIC; patient global impression of change. **Figure S23:** Netheat plots for adverse events. The netheat plots visualise the internal consistency for adverse events: (A) headache, (B) dizziness, (C) somnolence, and (D) peripheral oedema. Axis labels are formatted as "Comparison (Design)" to identify the specific treatment pair and its source trial structure. Within the matrix, the area of each grey square is proportional to the contribution of the design-specific evidence to the overall network estimate. Cooler colours (blue to purple) represent negative values on the inconsistency scale, indicating designs where direct and indirect evidence are in high agreement, thereby reinforcing the stability of the network. Conversely, warmer colours (yellow to red) indicate positive inconsistency, reflecting a discrepancy between different sources of evidence. PBO; placebo, PGB; pregabalin. **Table S1:** PRISMA extension statement for reporting systematic reviews incorporating network meta-analyses checklist. **Table S2:** Detailed Search Strategy and Syntax for PubMed, Embase, Cochrane Library, Google Scholar, and Scopus Database. **Table S3:** Granular Assessment of Certainty of Evidence for Pairwise Comparisons Using the CINeMA Framework. **Table S4:** Distribution of Potential Effect Modifiers across Included Trials. **Table S5:** Summary of Trial Design and Intervention Protocols of the Included Trials. **Table S6:** Summary of timepoints extracted for short-term and long-term ADPS. **Table S7:** Sensitivity Analysis of Correlation Coefficients in ADPS. **Table S8:** Clinical of Safety and Acceptability Profiles Across Pregabalin Doses. **Table S9:** Sensitivity analysis for clinical safety and treatment acceptability in trials with ≥ 8 weeks of follow-up period. **Table S10:** Summary of Network Consistency and Homogeneity Assessments of Outcomes.