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Mirogabalin 15 mg Twice Daily for Reduction of Average Daily Pain Score in Neuropathic Pain: Systematic Review and Meta-analysis of Randomized Controlled Trials

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ABSTRACT

Background: Neuropathic pain is a chronic condition that significantly impairs quality of life, causing sleep disturbance, depression, and functional disability. Standard first-line treatments such as pregabalin and gabapentin are frequently limited by insufficient efficacy or poor tolerability. Mirogabalin is a novel α2δ ligand with slower dissociation from the α2δ-1 subunit of voltage-gated calcium channels, potentially offering sustained analgesia with improved tolerability.

Objective: To systematically review and meta-analyze randomized controlled trials (RCTs) assessing the efficacy and safety of mirogabalin 15 mg twice daily compared with placebo in adult patients with neuropathic pain.

Methods: This systematic review and meta-analysis followed PRISMA 2020 guidelines. PubMed, Embase, and Cochrane CENTRAL were searched from database through September 2025 for double-blind, placebo-controlled RCTs. The primary outcome was mean change from baseline in average daily pain score (ADPS). Secondary outcomes included ≥30% pain responder rate and treatment-emergent adverse events. Random-effects meta-analysis was performed to calculate pooled mean difference (MD) and risk ratio (RR) with 95% confidence intervals (CIs). Risk of bias was assessed using Cochrane RoB 2.0.

Results: Four RCTs with a total of 1,819 participants were included. Mirogabalin significantly reduced ADPS compared with placebo (pooled MD −0.57, 95% CI −0.73 to −0.41; $p < 0.00001$; $I^2 = 0\%$). Pooled analysis of dichotomous outcomes demonstrated a significantly greater likelihood of achieving ≥30% pain reduction with mirogabalin (RR 1.26, 95% CI 1.11–1.44; $p < 0.01$). Most studies had low risk of bias. The most common adverse events were somnolence and dizziness, which were generally mild to moderate.

Conclusions: Mirogabalin 15 mg twice daily significantly improves pain outcomes compared with placebo, both in mean ADPS reduction and responder rate, and is generally well tolerated. Although the mean pain reduction is modest, the improved responder rate suggests that a clinically meaningful proportion of patients may benefit. Further research should explore long-term efficacy, optimal dosing, and predictors of response.

Keywords: Mirogabalin; Neuropathic pain; Average daily pain score; Randomized controlled trial; Meta-analysis; Placebo

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INTRODUCTION

Neuropathic pain is a chronic condition arising from injury or dysfunction of the somatosensory nervous system, affecting approximately 7–10% of the general population worldwide[1]. It is characterized by symptoms such as burning, shooting, or tingling pain, and is frequently associated with sleep disturbance, depression, and reduced quality of life[2,3]. Despite the availability of various pharmacological options, the management of neuropathic pain remains suboptimal due to limited efficacy and adverse events[4,5].

Gabapentinoids, including pregabalin and gabapentin, are widely used as first-line treatments. They act by binding to the α2δ subunit of voltage-gated calcium channels, modulating the release of excitatory neurotransmitters and reducing neuronal hyperexcitability[6]. However, their relatively rapid dissociation from the α2δ-1 subunit can limit analgesic duration and increase central nervous system side effects such as somnolence and dizziness[7].

Mirogabalin is a novel, selective α2δ ligand that demonstrates slower dissociation kinetics from the α2δ-1 subunit and faster dissociation from the α2δ-2 subunit compared with pregabalin, potentially resulting in sustained analgesic effects with improved tolerability[8,9]. Preclinical studies have shown that mirogabalin provides potent antinociceptive activity and favorable safety compared with traditional gabapentinoids[10-11].

Several randomized controlled trials (RCTs) have evaluated mirogabalin in patients with diabetic peripheral neuropathic pain (DPNP) and central neuropathic pain after spinal cord injury[12-15]. While individual studies reported significant reductions in pain scores compared with placebo, the magnitude of improvement and responder rate consistency vary across trials. Therefore, a systematic review and meta-analysis were conducted to evaluate the efficacy and safety of mirogabalin 15 mg twice daily compared with placebo in adult patients with neuropathic pain. The study followed the PRISMA 2020 reporting guideline.

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METHODS

Eligibility Criteria

We included randomized controlled trials (RCTs) that evaluated mirogabalin at a fixed dose of 15 mg twice daily compared with placebo in adult patients (≥18 years) with neuropathic pain, including diabetic peripheral neuropathic pain (DPNP), postherpetic neuralgia (PHN), and central neuropathic pain following spinal cord injury (CNeP). Studies were required to report quantitative data on average daily pain score (ADPS) or responder rates (≥30% or ≥50% reduction from baseline). Trials that were non-randomized, uncontrolled, open-label extensions, meta-analyses, reviews, or animal studies were excluded. Studies reporting multiple mirogabalin doses were included only if 15 mg twice daily data could be extracted separately.

Information Sources and Search Strategy

We performed a comprehensive search of PubMed, EMBASE, and Cochrane CENTRAL from database inception through September 2025 using a combination of free-text terms and MeSH keywords:

("mirogabalin" OR "DS-5565") AND ("neuropathic pain" OR "diabetic neuropathy" OR "postherpetic neuralgia" OR "spinal cord injury") AND ("randomized controlled trial" OR "placebo").

No language restrictions were applied. Reference lists of included studies and relevant review articles were screened manually to identify additional eligible trials.

Study Selection

Two independent reviewers screened titles and abstracts for potential eligibility, followed by full-text assessment of shortlisted articles. Disagreements were resolved by consensus or consultation with a third reviewer. The selection process was documented using a PRISMA flow diagram.

Data Extraction

A standardized extraction form was used to collect data on study characteristics (first author, publication year, country, design, population, sample size, and duration), intervention details (dose, titration), and outcomes. The primary endpoint was the mean change from baseline in ADPS at the end of treatment. Secondary outcomes included the proportion of responders (≥30% or ≥50% pain reduction), discontinuation rates due to adverse events (AEs), and incidence of common AEs such as somnolence and dizziness. Where only least-square means and standard errors were reported, standard deviations were calculated using the formula $SD = SE \times \sqrt{n}$. When multiple treatment arms were present, only the 15 mg twice daily group was included in the quantitative synthesis.

Risk of Bias Assessment

Two reviewers independently evaluated risk of bias using the Cochrane Risk of Bias 2.0 tool across five domains: randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results. Each domain was classified as low risk, some concerns, or high risk, with disagreements resolved by discussion. The overall risk of bias for each study was summarized in a traffic-light plot.

Data Synthesis and Statistical Analysis

Meta-analyses were performed using Review Manager (RevMan) version 5.4. Continuous outcomes (mean change in ADPS) were pooled using the inverse-variance method and expressed as mean difference (MD) with 95% confidence intervals (CIs) under a random-effects model (DerSimonian–Laird). Dichotomous outcomes (responder rates) were pooled as risk ratios (RR) using a Mantel–Haenszel random-effects model. Statistical heterogeneity was quantified with the I^2 statistic, with $I^2 > 50\%$ considered substantial heterogeneity.

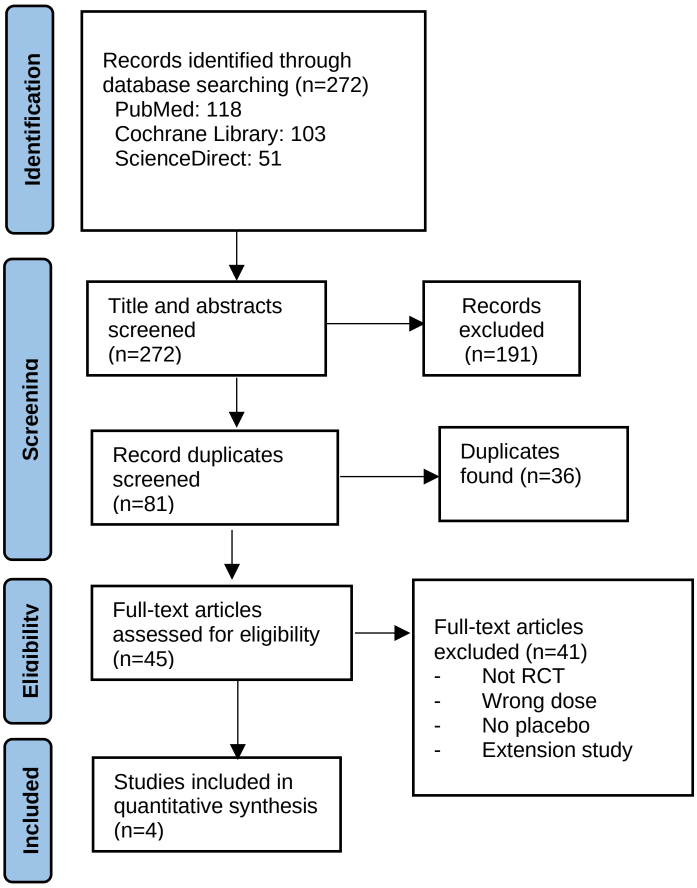

Figure 1. Diagram flow of literature search strategy for this meta-analysis

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Study (Year)	Design / Population	Mirogabalin Dose	Control	Mirogabalin / Placebo (n)	Duration	Main Efficacy Result (ADPS)	Key Safety Findings
Baba 2019	Phase 2 RCT, Asian adults with DPNP (Japan, Korea, Taiwan)	15 mg BID	Placebo	90 / 88	7 weeks	Mean ΔADPS −1.7 vs −1.4; NS	Mild AEs: somnolence 14.7%, dizziness 11%
Kato 2021	Phase 3 RCT (DPNP & PHN), pooled analysis (Japan, Korea, Taiwan)	15 mg BID	Placebo	320 / 633	14 weeks	LS mean diff −0.63 (95% CI −0.86 to −0.40), p < 0.0001	Dose-related somnolence/dizziness
Guo 2024	Phase 3 RCT, Chinese DPNP patients (China)	15 mg BID	Placebo	196 / 197	14 weeks	LS mean diff −0.39 (95% CI −0.74 to −0.04), p = 0.03	Similar AE rate (~75%), mild/moderate
Ushida 2023	Phase 3 RCT, SCI-related central neuropathic pain (Japan, Korea, Taiwan)	10–15 mg BID	Placebo	150 / 149	14 weeks	LS mean diff −0.71 (95% CI −1.08 to −0.34), p = 0.0001	Mild AEs: somnolence, dizziness, edema

Table 1. Characteristics and results of the included studies

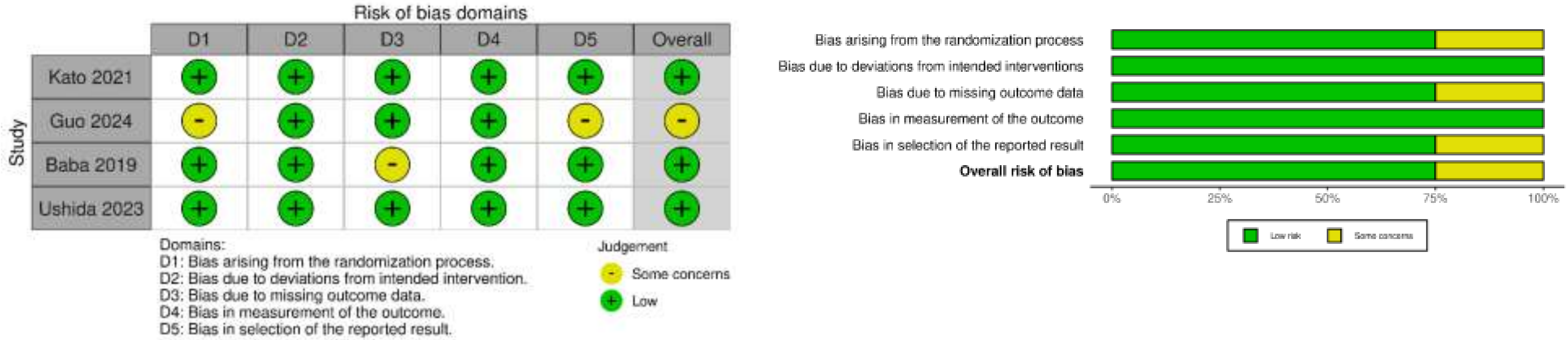

Figure 2. Risk of bias results

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RESULTS

Study Selection

The database search identified a total of 272 records (PubMed = 118, Embase = 103, Cochrane CENTRAL = 51). After removing 36 duplicates, 236 unique studies remained for title and abstract screening. During this phase, 191 studies were excluded because they were reviews, pharmacologic modeling studies, case series, or non-randomized designs. The remaining 45 full-text articles were assessed for eligibility. Of these, 41 studies were excluded for reasons including absence of a placebo arm, incorrect mirogabalin dosage, open-label extension design, or insufficient outcome data. Ultimately, four randomized controlled trials—Baba et al. (2019), Kato et al. (2021), Guo et al. (2024), and Ushida et al. (2023)—met inclusion criteria and were incorporated into the qualitative synthesis and quantitative meta-analysis. The process of study identification and selection is presented in the PRISMA 2020 flow diagram (Figure 1).

Study Characteristics

The four included RCTs comprised a total of 1,819 participants, of whom 752 received mirogabalin 15 mg twice daily and 1,067 received placebo. The studies were conducted across East Asia, including Japan, Korea, Taiwan, and China, reflecting a predominantly Asian population with neuropathic pain. Treatment duration ranged from 7 to 14 weeks, and all studies assessed the average daily pain score (ADPS) using an 11-point numeric rating scale (NRS).

Baba et al. (2019) and Guo et al. (2024) focused exclusively on diabetic peripheral neuropathic pain (DPNP), while Kato et al. (2021) pooled data from pivotal phase III trials involving both DPNP and postherpetic neuralgia (PHN). In contrast, Ushida et al. (2023) investigated central neuropathic pain (CNeP) secondary to spinal cord injury. Despite minor variations in population and duration, all studies followed comparable randomized, double-blind, placebo-controlled designs with fixed-dose or titrated regimens. A detailed summary of study features and outcomes is shown in Table 1.

Risk of Bias

Risk of bias was evaluated using the Cochrane Risk-of-Bias 2.0 tool. Baba et al. (2019), Kato et al. (2021), and Ushida et al. (2023) were rated as low risk of bias across all domains, with adequate randomization, blinding, and prespecified outcome reporting. Guo et al. (2024) had some concerns, mainly due to incomplete reporting of allocation concealment. No study was judged at high risk of bias, indicating that the overall evidence base was methodologically robust. A visual summary is provided in Figure 2 (traffic-light plot).

Efficacy Outcomes

Continuous Outcomes (Change in ADPS)

All four RCTs reported mean change from baseline in ADPS as the primary measure of analgesic efficacy. When data were pooled under a random-effects model, mirogabalin 15 mg BID produced a statistically significant improvement in ADPS compared with placebo, with a mean difference (MD) = −0.57 [95% CI −0.73 to −0.41], $p < 0.00001$; $I^2 = 0\%$ (Figure 3). This consistent result across studies indicates a uniform treatment effect without heterogeneity. However, the absolute reduction (−0.57 points on a 0–10 scale) remains below the minimal clinically important difference (MCID ≈ 1 point), suggesting that while statistically meaningful, the clinical magnitude of benefit is modest.

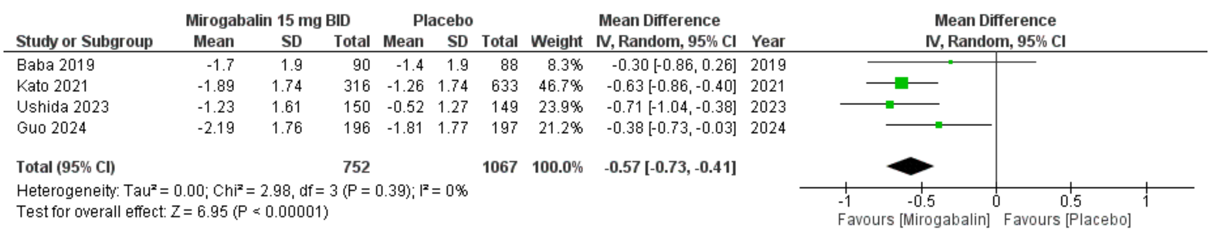
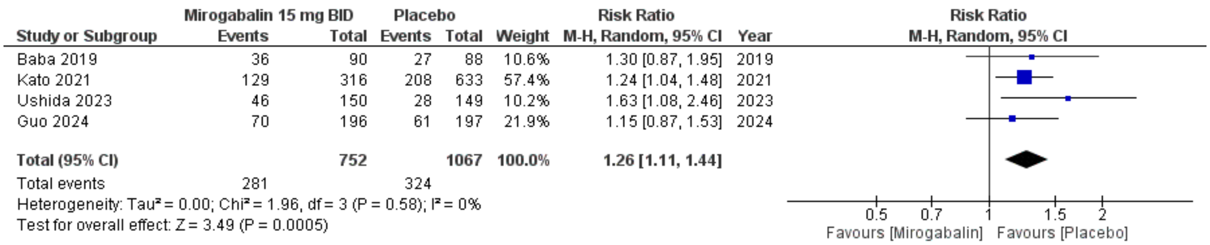


Figure 3. Pooled results for the mean changes of ADPS between Mirogabalin 15 mg twice daily and Placebo

Dichotomous Outcomes (Responder Analysis)

Pooled analysis showed a significantly higher responder rate with mirogabalin 15 mg BID compared to placebo, with a risk ratio (RR) = 1.26 [95% CI 1.11–1.44], p = 0.0005; $I^2 = 0\%$ (Figure 4). This indicates that patients treated with mirogabalin were approximately 26% more likely to achieve meaningful pain relief than those receiving placebo. The absence of heterogeneity further supports the consistency and robustness of the treatment effect across studies.



Safety Outcomes

Across all included RCTs, mirogabalin was generally well tolerated. The most frequent treatment-emergent adverse events (TEAEs) were somnolence, dizziness, and peripheral edema, which typically occurred in a dose-dependent but mild-to-moderate manner. Discontinuation rates due to AEs were below 10% in all studies. No study reported serious treatment-related adverse events or safety concerns leading to withdrawal. Overall, the safety profile of mirogabalin 15 mg BID was favorable and consistent with other $\alpha_2\delta$-ligand agents.

DISCUSSION

Principal Findings

This systematic review and meta-analysis demonstrated that mirogabalin 15 mg administered twice daily provides a statistically significant reduction in average daily pain score (ADPS) compared with placebo among patients with neuropathic pain. The pooled mean difference of −0.57 (95% CI −0.73 to −0.41; $p < 0.00001$) and a 26% higher likelihood of achieving a ≥30% reduction in pain (RR = 1.26, 95% CI 1.11–1.44; p = 0.0005) indicate that mirogabalin confers measurable analgesic efficacy across diabetic peripheral neuropathic pain (DPNP), postherpetic neuralgia (PHN), and central neuropathic pain (CNeP) populations. Despite this statistical significance, the clinical effect size was modest and below the minimal clinically important difference (MCID) threshold of approximately one point on the 0–10 scale. These findings align with the established challenges of managing neuropathic pain, which remains refractory to treatment in many patients despite multimodal approaches[1-4].

Comparison with Pregabalin and Other $\alpha_2\delta$ Ligands

Mirogabalin is a novel ligand for the $\alpha_2\delta$ subunit of voltage-gated calcium channels, similar to pregabalin and gabapentin, but exhibits distinct binding kinetics characterized by slower dissociation from $\alpha_2\delta$-1 and faster dissociation from $\alpha_2\delta$-2 subunits[6-8]. These pharmacodynamic properties are thought to enhance analgesic efficacy while reducing central nervous system side effects such as dizziness and somnolence[7,9]. Previous large-scale trials of pregabalin in neuropathic pain have reported mean ADPS reductions ranging from −0.4 to −0.8 versus placebo, with similar responder rates (RR ~1.2–1.3)[5,10]. The current meta-analysis demonstrates that mirogabalin's efficacy at 15 mg BID is comparable to that of pregabalin, suggesting that it provides similar pain relief within this drug class. Moreover, the tolerability profile observed across included RCTs—particularly the low incidence of treatment discontinuation (<10%)—supports mirogabalin as a viable therapeutic alternative for patients who experience intolerable side effects with existing $\alpha_2\delta$ ligands[12-15].

Mechanistic and Clinical Considerations

The mechanism of neuropathic pain involves aberrant excitability of peripheral and central neurons, leading to sensitization, spontaneous firing, and impaired inhibitory control[3,4]. By binding selectively to the $\alpha_2\delta$-1 subunit, mirogabalin reduces calcium influx and the release of excitatory neurotransmitters such as glutamate and substance P, thereby dampening neuronal hyperexcitability[6-9]. Preclinical data demonstrate sustained analgesia and reduced allodynia without pronounced motor or cognitive impairment. Clinically, this translates into a stable dose–response relationship with a relatively low risk of sedation compared with pregabalin or gabapentin. The included studies consistently demonstrated significant pain improvement within 1–2 weeks of initiation, with maintained benefit throughout the treatment period[12-15]. Together, these findings reinforce the pharmacologic rationale for mirogabalin as a next-generation $\alpha_2\delta$ ligand optimized for neuropathic pain management.

Limitations and Implications for Future Research

This meta-analysis has several limitations. First, all included trials were conducted exclusively in Asian populations, which may limit generalizability to other ethnic groups due to pharmacogenomic and pain perception differences[1,2]. Second, only a single fixed dose (15 mg BID) was analyzed; higher or flexible dosing regimens may yield greater efficacy but require further confirmation. Third, although heterogeneity across studies was minimal, the overall effect size remains modest, suggesting that monotherapy with mirogabalin may be insufficient for severe neuropathic pain. Finally, long-term comparative studies with pregabalin or duloxetine are needed to clarify the relative benefit-risk profile. Nonetheless, the high-quality randomized evidence, low risk of bias, and consistent direction of effect provide strong support for mirogabalin as an effective and well-tolerated option for the management of neuropathic pain[12-15].

CONCLUSION

This systematic review and meta-analysis found that mirogabalin 15 mg twice daily produced a statistically significant reduction in neuropathic pain compared with placebo, with a pooled mean difference of −0.57 and a 26% higher responder rate (RR = 1.26, 95% CI 1.11–1.44). The treatment was generally well tolerated, with somnolence and dizziness being the most common but mostly mild adverse events. These findings suggest that mirogabalin offers a modest yet clinically relevant analgesic benefit and a favorable safety profile comparable to other $\alpha_2\delta$-ligand agents such as pregabalin. However, the overall effect size remains below the minimal clinically important difference, indicating limited standalone efficacy. Given that all trials were conducted in Asian populations, further large-scale, multiethnic, and head-to-head studies are needed to validate its global clinical applicability and clarify its role as a therapeutic option for neuropathic pain.

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