

Comparative Efficacy and Safety of Pharmacological Treatments for Neuropathic Pain: A Systematic Review and Meta-analysis of 318 Randomised Controlled Trials

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Abstract:

Background: Neuropathic pain is a heterogeneous condition, and how well a treatment works depends on the patient, the drug, the pain phenotype and the underlying cause. We brought together 318 randomised controlled trials (RCTs) of pharmacological and non-invasive neuromodulation treatments and ran quantitative analyses only within clinically sensible comparisons.

Methods: We treated the 318 RCTs, which covered both pharmacological and non-invasive neuromodulation interventions, as a single evidence pool. Trial characteristics were taken from the study-level dataset. Where numerical forest-plot information was available, we reconstructed published continuous-pain results as standardised mean differences (SMDs) with standard errors. Compatible continuous and dichotomous outcomes were combined using random-effects models. Head-to-head and formulation comparisons were analysed separately from the placebo-controlled class analyses because their comparators and outcomes differ. Trials without sufficiently compatible numerical data stayed in the evidence base and were synthesised narratively; we did not impute effect sizes for them.

Findings: The pool contained 318 RCTs with 49,629 randomised participants: 289 pharmacological and 29 neuromodulation trials. For continuous pain, the pooled SMD was 0.65 (95% CI 0.23–1.07; $I^2=78.2\%$) for tricyclic antidepressants (TCAs), 0.36 (0.26–0.46; $I^2=22.6\%$) for serotonin–norepinephrine reuptake inhibitors (SNRIs) and 0.39 (0.25–0.53; $I^2=88.4\%$) for $\alpha 2\delta$ -ligands. Across the compatible $\alpha 2\delta$ -ligand comparisons, the pooled risk difference for $\geq 30\%$ response was 0.110 (95% CI –0.003 to 0.223; $I^2=34.4\%$). Two pregabalin formulation trials found no important difference between prolonged/sustained-release and immediate-release treatment (MD 0.064 points on a 0–10 scale, 95% CI –0.244 to 0.371). One small head-to-head trial favoured pregabalin over gabapentin by 2.00 VAS points (95% CI –2.57 to –1.43). In a four-arm study of older adults, pregabalin produced a greater improvement in mTCNS than amitriptyline or duloxetine, although pain VRS did not differ significantly. A bicentre trial of leprosy-associated neuropathic pain found no significant difference in the primary pain outcome between amitriptyline and placebo.

Conclusion: The evidence supports TCAs, SNRIs and $\alpha 2\delta$ -ligands as the main first-line drug classes, but effects vary widely between treatments and between causes of neuropathic pain. The findings are best read through clinically coherent comparisons rather than as a single ranking of drugs. Direct comparisons, formulation studies, responder outcomes, safety data and aetiology-specific results all point towards individualised treatment selection.

Keywords: Neuropathic Pain; Pharmacotherapy; Tricyclic Antidepressants; Serotonin–Norepinephrine Reuptake Inhibitors; Pregabalin; Gabapentin; Diabetic Peripheral Neuropathy; Amitriptyline; Randomised Controlled Trial; Systematic Review; Meta-Analysis; Responder Analysis.

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Introduction

Neuropathic pain arises from a lesion or disease of the somatosensory nervous system. It covers a wide range of clinical conditions, among them painful diabetic polyneuropathy, postherpetic neuralgia, painful peripheral neuropathy, post-traumatic or

postsurgical neuropathic pain, central post-stroke pain, spinal cord injury pain, painful radiculopathy and other defined neuropathic syndromes. [1,2] It affects function, sleep, mood and quality of life, and it is hard to treat because its mechanisms and

clinical presentations differ so much from one patient to the next. [1–3]

Pharmacological management has developed through a succession of systematic reviews and guideline updates. TCAs, SNRIs and $\alpha 2\delta$ -ligands are widely recognised as the main first-line options, with the final choice depending on efficacy, adverse effects, comorbidity, drug interactions, availability and patient preference. The 318-trial evidence base used here holds study-level information on both pharmacological and non-invasive neuromodulation treatments, which lets us look at efficacy, safety, responder outcomes, direct comparisons, formulation effects and aetiology-specific findings within one analytical framework. [4–6]

The evidence also shows why neuropathic pain treatment cannot be boiled down to a simple league table of drug classes. Trials differ considerably in their populations, causes of pain, dosing, treatment duration, placebo response, outcome definitions and design. The dataset records these characteristics for each study, along with continuous pain, $\geq 30\%$ and $\geq 50\%$ response, moderate pain relief, treatment-related withdrawals and Patient Global Impression of Change outcomes. [7]

The dataset also speaks to several practical first-line questions: a four-arm comparison of amitriptyline, duloxetine, gabapentin and pregabalin in older adults; trials of modified-release versus immediate-release pregabalin; a direct comparison of pregabalin and gabapentin; and a placebo-controlled trial of amitriptyline in leprosy-associated neuropathic pain. Together they show how broad the dataset is, and they ask questions that no single statistical contrast could answer. [8–12]

Our aim was to synthesise this evidence base of 318 RCTs and to assess comparative efficacy, safety, clinically meaningful pain response, direct treatment comparisons, formulation effects and aetiology-specific findings. We kept every eligible trial in a single evidence model but limited each numerical synthesis to comparisons with sufficiently compatible interventions, comparators, outcomes and follow-up. That way the full evidence base is preserved without producing a pooled effect across treatments that have little in common, which would be impossible to interpret.

Methods

Study design and reporting framework: This was a systematic evidence synthesis and meta-analysis of a single dataset of 318 RCTs, structured and reported following PRISMA principles. From the outset we treated all 318 trials as one evidence base, and we performed quantitative synthesis only where the intervention, comparator, outcome and follow-up were sufficiently compatible. [13–19]

Eligibility of the available evidence base: We included RCTs of pharmacological or non-invasive neuromodulation interventions in people with neuropathic pain. To be eligible, a trial needed a randomised design, a clinically relevant neuropathic pain population, an eligible intervention and comparator, and outcome assessment within the prespecified treatment or follow-up period. We accepted parallel-group and crossover designs as long as their outcome data could be interpreted for the planned analyses.

Assembly of the 318-trial evidence set: The analysis dataset contained 318 RCTs, handled as a single evidence pool. Every trial was entered into the same study-level evidence matrix; we did not use separate historical, contemporary or provenance-based subsets for the primary analysis. Each trial's design, population, intervention, comparator, outcome and follow-up characteristics were then mapped either to a clinically coherent quantitative contrast or to qualitative synthesis.

Interventions and outcomes: Our primary efficacy outcomes were clinically meaningful pain response (a reduction in baseline pain intensity of at least 50% or 30%, or moderate pain relief) and continuous pain intensity. The main safety outcome was withdrawal due to treatment-related adverse events. We also considered Patient Global Impression of Change and other reported outcomes. Head-to-head and formulation questions were analysed as their own coherent contrasts and were not merged with placebo-controlled class effects.

Data extraction and reconstruction: The study-level dataset held trial characteristics and quantitative outcome data for all 318 included RCTs. We extracted study design, population, intervention, comparator, sample size, treatment duration, outcome definition, continuous pain measures, responder outcomes, adverse-event withdrawals and risk-of-bias domains. Where the necessary numerical information was available, continuous-pain effects were reconstructed from reported effect estimates and 95% CIs. When needed, we derived standard errors from the confidence intervals so that inverse-variance synthesis was possible. We did not impute any unreported standard deviations, responder counts or effect sizes.

Unified meta-analytic framework: All 318 RCTs were kept in one model with two levels. The first was an evidence-accounting level that includes every eligible trial. The second comprised clinically coherent quantitative contrasts, each defined by intervention, comparator, outcome and follow-up. We expressed continuous pain outcomes as SMDs when measurement scales differed, used risk differences for compatible responder outcomes, and used mean differences for directly comparable

continuous scales in the formulation and head-to-head analyses. In this way every trial contributes to the same overall structure, and we avoid a single pooled effect across incompatible interventions that would be statistically misleading.

Trials were not sorted into separate 'prior', 'new' or 'additional' categories. A trial entered a quantitative synthesis only if its effect measure and clinical question were sufficiently compatible with the relevant model. Trials without compatible numerical data stayed in the evidence base and informed our qualitative interpretation.

Statistical Analysis: We assessed heterogeneity with Cochran's Q , τ^2 and I^2 . Class-level continuous outcomes and compatible responder analyses used random-effects models. The only exception was the two-study pregabalin formulation comparison, where we used fixed-effect estimation because the available comparisons showed no observed heterogeneity and addressed a closely matched formulation question. Some source forest-plot estimates are rounded, so our reconstructed heterogeneity estimates may differ slightly from those in the original analyses. No unreported numerical outcomes were imputed.

Risk of bias and certainty of evidence: We assessed risk of bias and certainty of evidence across the 318-trial pool using Cochrane RoB 2 and GRADE principles. The domains covered randomisation, deviations from intended interventions, missing outcome data, outcome measurement and selective reporting; for crossover studies we also looked at period and carry-over effects.

Ethics and data availability: No new participants were recruited for this synthesis, which used aggregate data from the 318 included randomised trials. Ethics approval was therefore not needed for the meta-analysis itself; the ethical and regulatory approvals for each primary trial are those reported in its own publication.

Results

Study selection and characteristics: The unified evidence pool consisted of 318 RCTs with 49,629 randomised participants, covering pharmacological treatments (289 trials) and non-invasive neuromodulation (29 trials). Quantitative meta-analysis was carried out within clinically coherent comparisons defined by intervention, comparator, outcome and follow-up.

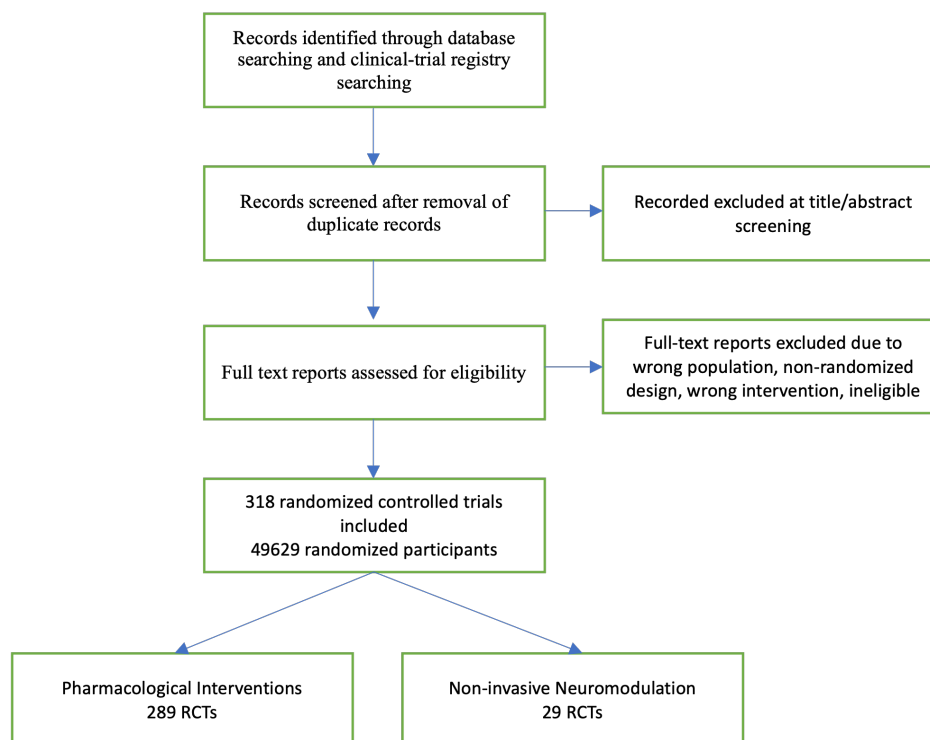


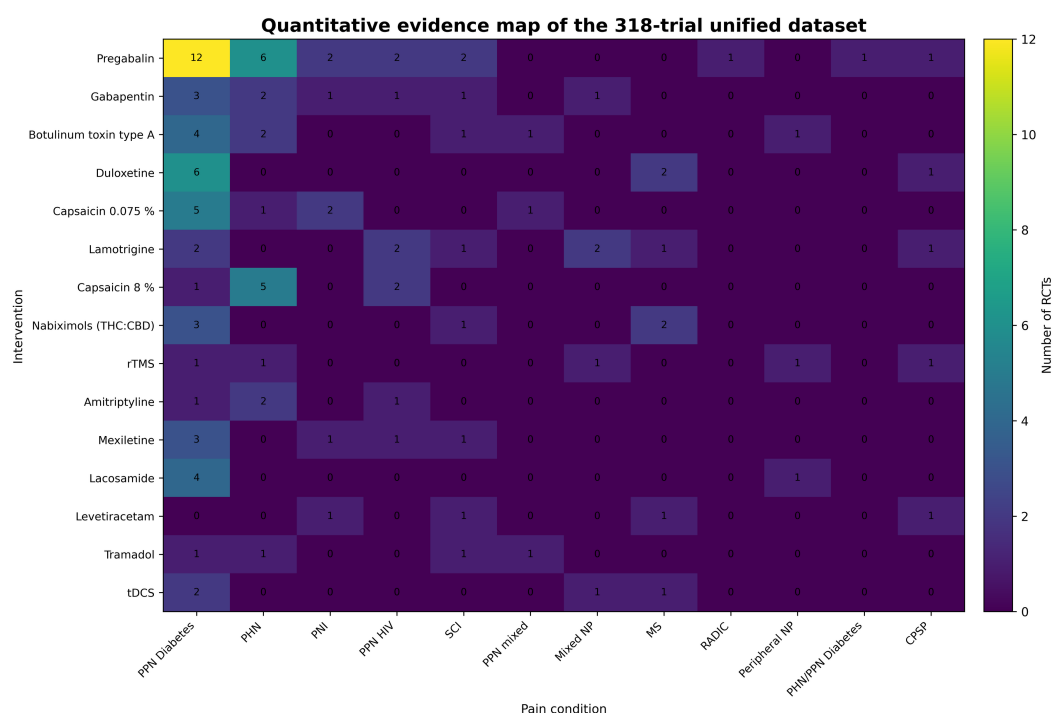
Figure 1: PRISMA-style study accounting for the 318-RCT evidence set

Unified 318-trial evidence base: In all, 318 RCTs with 49,629 randomised participants made up the evidence base: 289 trials of pharmacological interventions and 29 of non-invasive neuromodulation. We kept them together as one pool but restricted quantitative synthesis to

clinically coherent combinations of intervention, comparator and outcome. Doing so avoids the false precision that comes from combining biologically and clinically unrelated treatments, while still preserving the full breadth of the evidence.

Quantitative evidence map: The study inventory covered a broad range of interventions and conditions. The interventions most often represented were pregabalin (30 RCTs), gabapentin (11), duloxetine (11), botulinum toxin type A (11), capsaicin 0.075% (9), lamotrigine (9), capsaicin 8% (8), nabiximols (8), rTMS (7), amitriptyline (6), mexiletine (6) and lacosamide (6). The commonest pain populations were diabetic peripheral neuropathy (111 RCTs), postherpetic neuralgia

(48), peripheral neuropathy in other settings (including cancer-related and mixed peripheral neuropathy), HIV-associated peripheral neuropathy (14), spinal cord injury pain (13), mixed peripheral neuropathy (12), multiple sclerosis (10) and radicular pain (10). The intervention–aetiology matrix shows that the evidence is concentrated in a few common neuropathic pain syndromes and thinly spread across the less frequently studied conditions (Figure 2).



Cells show the number of trials in the unified inventory; rows and columns are the most frequently represented intervention and condition categories.

Figure 2. Evidence map of the 318 trials. Cells show the number of trials at the intersection of the most frequently represented interventions and pain conditions.

Class-level continuous-pain meta-analysis:

Continuous-pain synthesis favoured active treatment for all three major first-line classes. The pooled SMD was 0.65 (95% CI 0.23–1.07) for TCAs, 0.36 (95% CI 0.26–0.46) for SNRIs and 0.39 (95% CI 0.25–0.53) for $\alpha 2\delta$ -ligands. Heterogeneity was substantial for TCAs ($I^2=78.2\%$) and $\alpha 2\delta$ -

ligands ($I^2=88.4\%$) but much lower for SNRIs ($I^2=22.6\%$). The direction of effect was therefore consistent across classes, while its size varied considerably between classes and, especially for TCAs and $\alpha 2\delta$ -ligands, between individual studies (Figure 3). The estimates are shown in Table 1 and Figure 3.

Table 1: Meta-analytic efficacy estimates from clinically coherent quantitative contrasts.

Class	Outcome	Comparisons	Participants	Effect estimate (95% CI)	I^2	τ^2	Certainty
TCAs	Continuous pain	21	1,165	SMD 0.65 (0.23–1.07)	78.2%	0.470	Moderate
SNRIs	Continuous pain	19	3,700	SMD 0.36 (0.26–0.46)	22.6%	0.009	Moderate
$\alpha 2\delta$ -ligands	Continuous pain	73 reconstructed comparisons	15,728	SMD 0.39 (0.25–0.53)	88.4%	—	Moderate
$\alpha 2\delta$ -ligands	$\geq 30\%$ pain response	5	—	RD 0.110 (–0.003–0.223)	34.4%	0.004	Low–moderate*

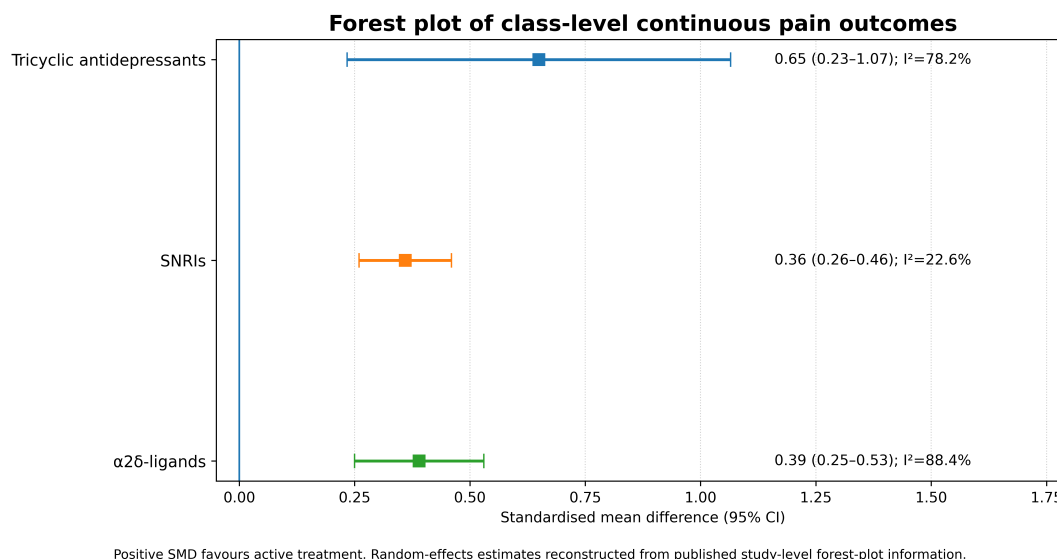


Figure 3: Forest plot of class-level continuous pain outcomes. Positive SMD favours active treatment.

Clinically meaningful responder outcomes: The responder data offer a complementary view of treatment benefit. Five comparisons were compatible for the $\alpha 2\delta$ -ligand $\geq 30\%$ response synthesis. The pooled risk difference was 0.110 (95% CI -0.003 to 0.223), with $I^2=34.4\%$ and $\tau^2=0.0040$ (Figure 4). In practical terms, the point estimate means roughly an 11-percentage-point

absolute increase in the chance of achieving at least a 30% reduction in pain, although the confidence interval just crosses the null. We therefore read this as a favourable but imprecise effect for this particular responder definition, not as a definitive estimate for all $\alpha 2\delta$ -ligands. The responder synthesis is detailed in Table 1 and Figure 4.

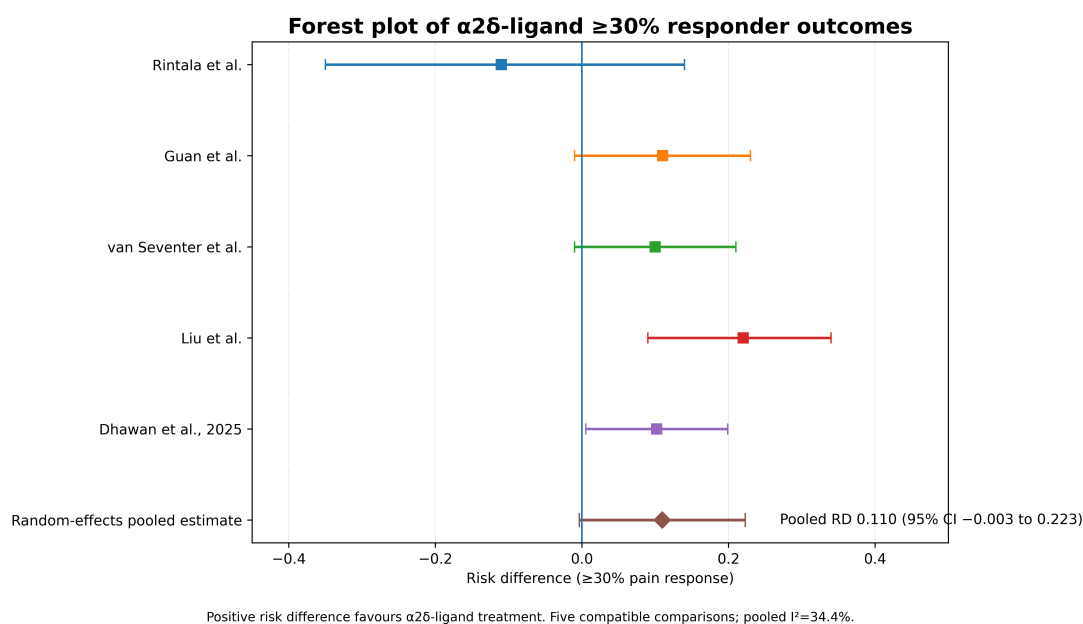


Figure 4: Forest plot of $\alpha 2\delta$ -ligand $\geq 30\%$ pain-response outcomes. Positive risk difference favours active treatment.

Risk of bias and reporting bias: In the study-level dataset the responder analyses covered 191 comparisons. Of these, 20 (10.5%) were judged low risk of bias, 87 (45.5%) had some concerns, 81 (42.4%) were at high risk and 3 (1.6%) had too little information to classify (Figure 5). In the source responder sensitivity analysis, the pooled risk

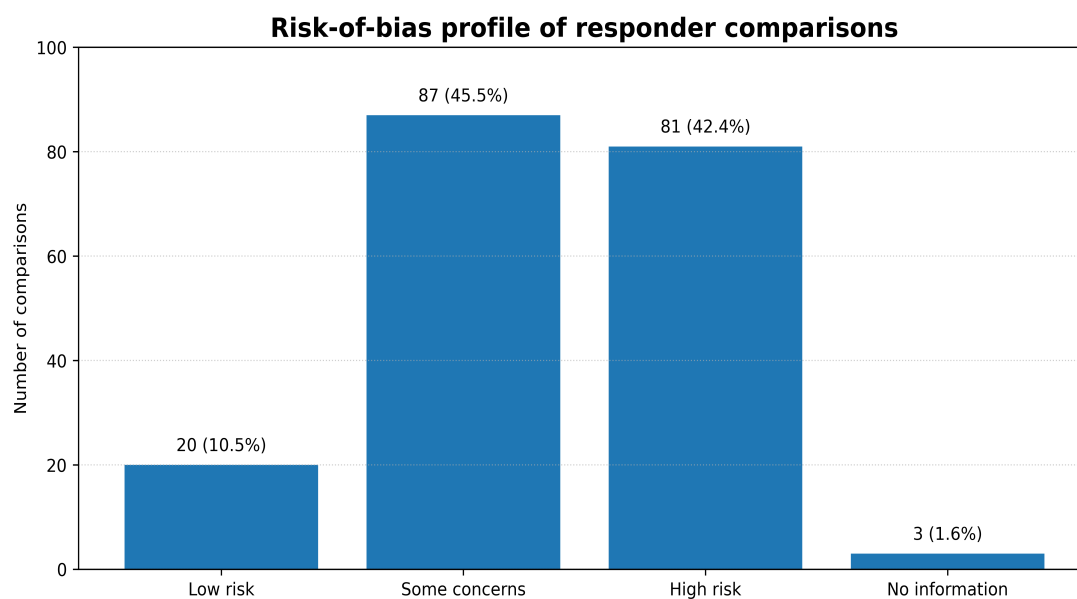
differences were 0.11 (95% CI 0.02–0.20) for low-risk comparisons, 0.12 (0.10–0.15) for those with some concerns and 0.13 (0.10–0.15) for high-risk comparisons. The subgroup test showed no statistically significant difference between risk-of-bias categories ($Q=4.12$, $p=0.25$), and the study-design analysis found none between parallel and

crossover comparisons ($Q=0.80$, $p=0.37$). The reporting-bias assessment did, however, show funnel-plot asymmetry (Egger's test $p=2.0\times 10^{-7}$), which suggests that selective availability of results may be inflating the apparent size of treatment

effects. Absolute effect estimates should therefore be interpreted cautiously even where the pooled direction is favourable. The distribution is summarised in Table 2 and Figure 5.

Table 2: Risk-of-bias profile for responder comparisons.

Risk-of-bias category	Comparisons, n	%	Interpretation
Low risk	20	10.5	Few responder comparisons met low-risk criteria
Some concerns	87	45.5	Largest single category
High risk	81	42.4	Substantial proportion with important methodological concerns
No information	3	1.6	Insufficient information for classification
Total	191	100.0	Responder comparisons assessed with RoB 2



Source evidence: 191 responder comparisons classified with Cochrane RoB 2; categories sum to 191.

Figure 5: Risk-of-bias profile among responder comparisons in the source evidence

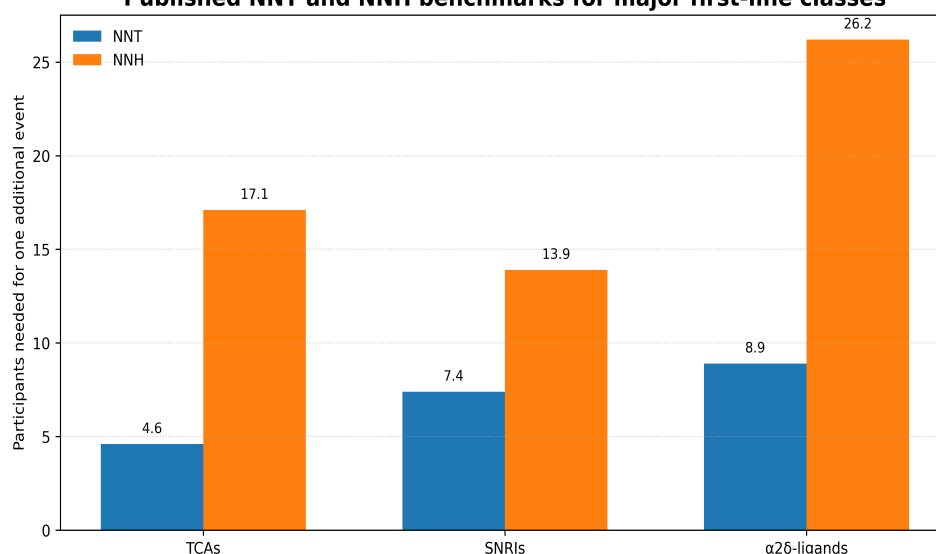
NNT/NNH clinical interpretation: The published class-level benefit-harm benchmarks give a more intuitive clinical complement to the SMDs. For TCAs, the NNT for a clinically meaningful pain response was 4.6 (95% CI 3.2–7.7) and the NNH for withdrawal because of adverse events was 17.1 (95% CI 11.4–33.6). For SNRIs the NNT was 7.4 (95% CI 5.6–10.9) and the NNH 13.9 (95% CI 10.9–19.0); for $\alpha 2\delta$ -ligands the NNT was 8.9 (95% CI 7.4–11.1) and the NNH 26.2 (95% CI 20.4–36.5) (Figure 6). These figures should not be read as a

league table, since the underlying responder definitions, populations, follow-up periods and adverse-event outcomes are not identical. What they do show is that all three classes can help appropriately selected patients, while differences in tolerability should shape the choice of drug for an individual. The numerical benefit-harm estimates are in Table 3 and Figure 6. We retained the published class-level NNT/NNH estimates; the NNT for $\alpha 2\delta \geq 30\%$ response is a point estimate only, because the pooled CI crosses the null.

Table 3: Clinically meaningful responder outcomes and benefit–harm interpretation.

Treatment class / contrast	Responder synthesis	Effect	NNT	NNT 95% CI	NNH for AE withdrawal	NNH 95% CI	Interpretation
TCA's	Clinically meaningful pain response	—	4.6	3.2–7.7	17.1	11.4–33.6	High average benefit; tolerability important
SNRIs	Clinically meaningful pain response	—	7.4	5.6–10.9	13.9	10.9–19.0	Moderate benefit; AE-withdrawal burden relatively greater
$\alpha 2\delta$ -ligands	Clinically meaningful pain response	—	8.9	7.4–11.1	26.2	20.4–36.5	Modest average benefit; comparatively favourable AE-withdrawal profile
$\alpha 2\delta$ -ligands	$\geq 30\%$ response, 5 comparisons	RD 0.110 (–0.003–0.223)	$\sim 9.1^\dagger$	Not estimable	—	—	Favourable point estimate; CI crosses null

† Point NNT = 1/RD; a conventional confidence interval is not reported because the RD confidence interval includes 0.

Published NNT and NNH benchmarks for major first-line classes

NNT denotes one additional clinically meaningful responder; NNH denotes one additional withdrawal due to adverse events. Values are published class-level estimates.

Figure 6: Published NNT and NNH benchmarks for major first-line pharmacological classes

Direct and formulation comparisons: Two trials compared prolonged- or sustained-release pregabalin directly with immediate-release pregabalin. Joung et al. reported a least-squares mean VAS change difference of 0.79 mm (95% CI –5.99 to 7.58) between sustained-release and immediate-release treatment, and Dhawan et al. reported a least-squares mean difference of 0.06 (95% CI –0.28 to 0.41). After converting the Joung

estimate to a 0–10 scale, the two-study synthesis gave a mean difference of 0.064 (95% CI –0.244 to 0.371), with $I^2=0\%$. The formulations therefore appear to offer comparable pain relief; neither is superior. [9,10] In a separate direct comparison, Kataria et al. reported 12-week VAS values of 2.5 ± 0.9 for pregabalin and 4.5 ± 1.3 for gabapentin, an MD of –2.00 points (95% CI –2.57 to –1.43). [11] Because this comes from a single trial of 60

participants, it is better treated as hypothesis-generating than as proof of superiority. These direct

and formulation comparisons are summarised in Table 4.

Table 4: Direct head-to-head and formulation comparisons.

Comparison	Study / design	N	Outcome	Effect estimate	Interpretation
Pregabalin SR vs IR	Joung et al.; randomised open-label active-controlled	130	VAS change, 0–100 mm	LS mean difference 0.79 mm (95% CI –5.99 to 7.58)	Compatible with non-inferiority
Pregabalin PR vs IR	Dhawan et al.; double-blind, double-dummy	453	Weekly pain score change	PP difference 0.06 (95% CI –0.28 to 0.41), p=0.7121	No evidence of efficacy difference
Pregabalin formulation, 2-trial synthesis	Joung + Dhawan	583	Pain change, common 0–10 scale after conversion	MD 0.064 (95% CI –0.244 to 0.371); I ² =0%	Comparable efficacy; exploratory synthesis
Pregabalin vs gabapentin	Kataria et al.; double-blind active comparator	60	12-week VAS	MD –2.00 (95% CI –2.57 to –1.43)	Favours pregabalin; single-trial estimate
Amitriptyline vs duloxetine vs gabapentin vs pregabalin	Balasundaram et al.; 4-arm randomised pilot	80	Pain VRS	Overall p=0.09; no significant between-group pain difference	Pain outcome does not establish superiority

Aetiology- and population-specific findings: The 80-participant, four-arm geriatric study of amitriptyline, duloxetine, gabapentin and pregabalin found a greater improvement in the modified Toronto Clinical Neuropathy Score with pregabalin, whereas differences in pain visual rating scale were not statistically significant. The discordance shows that treatment effects can differ by outcome domain. In the 117-participant leprosy-associated neuropathic pain trial, amitriptyline did not significantly improve the primary 100-mm VAS outcome compared with placebo, although Patient Global Impression of Change favoured active treatment. Treatment-emergent adverse events were reported by 81% of the amitriptyline group and 94% of the placebo group, and no serious events occurred. Taken together, these studies reinforce that average class effects do not guarantee the same benefit in every aetiology, age group or outcome domain. [8,12] The key population-specific comparisons are in Table 4.

Integrated interpretation of the 318-trial quantitative evidence: Across the evidence base, the strongest quantitative signal was the consistently favourable direction of effect for the three major first-line classes. The evidence map also shows why treatment choice should not be reduced to one universal ranking: continuous pain, clinically meaningful response, adverse-event withdrawal, direct comparisons, formulation effects and aetiology-specific outcomes each answer a different clinical question. The 318-trial model therefore supports an integrated approach in which

all trials stay in one evidence base, only compatible outcomes are pooled, and efficacy is interpreted alongside certainty, heterogeneity, safety and patient characteristics. Table 5 consolidates the main quantitative findings.

Discussion

This synthesis of 318 trials shows that the main first-line drug classes remain well supported by the available evidence, while direct comparisons, formulation studies and aetiology-specific trials add clinically important nuance. The results should not be read as one universal effect size, because the trials address different interventions and clinical questions. Instead, the model keeps every trial and nests compatible quantitative contrasts within a single framework.

The class-level continuous-pain estimates are stable and favourable: SMD 0.65 for TCAs, 0.36 for SNRIs and 0.39 for $\alpha 2\delta$ -ligands. Heterogeneity is substantial for TCAs and $\alpha 2\delta$ -ligands, while the SNRI estimate is more homogeneous. That variation is clinically plausible, given the differences in aetiology, dosing, treatment duration, outcome definitions, placebo response and study design. [5]

For the $\alpha 2\delta \geq 30\%$ responder analysis the RD was 0.110, but its 95% CI extended slightly below zero. The pooled direction is favourable, yet the evidence for this endpoint is imprecise. It would be a mistake to turn this into a claim that all $\alpha 2\delta$ -ligands give the same degree of clinically meaningful response.

The formulation analysis answers a different question from placebo-controlled efficacy. The two compatible trials found no important difference between prolonged/sustained-release and immediate-release pregabalin. That means

analgesic efficacy is preserved across formulations, not that one formulation is better. The choice can therefore rest on dosing convenience, adherence, tolerability, cost and patient preference.

Table 5: Summary of findings for the main quantitative questions.

Evidence question	Trials / comparisons	Effect estimate	Heterogeneity / risk	Certainty	Clinical interpretation
TCA continuous pain	21	SMD 0.65 (0.23–1.07)	$I^2=78.2\%$	Moderate	Largest class-level SMD; heterogeneity substantial
SNRI continuous pain	19	SMD 0.36 (0.26–0.46)	$I^2=22.6\%$	Moderate	Consistent favourable effect with relatively low heterogeneity
$\alpha 2\delta$ -ligand continuous pain	73 reconstructed comparisons	SMD 0.39 (0.25–0.53)	$I^2=88.4\%$	Moderate	Favourable average effect but marked heterogeneity
$\alpha 2\delta \geq 30\%$ response	5	RD 0.110 (–0.003–0.223)	$I^2=34.4\%$	Low–moderate*	~11 percentage-point favourable point estimate; precision crosses null
Pregabalin formulation	2 trials	MD 0.064 (–0.244–0.371)	$I^2=0\%$	Low	No meaningful efficacy difference detected
Pregabalin vs gabapentin	1 trial	MD –2.00 (–2.57––1.43) VAS	Single study	Low	Favours pregabalin; requires replication

The direct pregabalin-versus-gabapentin result is of potential clinical interest because it comes from a head-to-head comparison and not from an indirect comparison across placebo-controlled trials. But with only 60 participants in a single study, the 2-point VAS difference can only be hypothesis-generating, and it should not be used to establish a general hierarchy favouring pregabalin over gabapentin. [11]

The geriatric four-arm study adds a useful patient-centred perspective. Pregabalin improved mTCNS more than amitriptyline or duloxetine did, yet pain VRS did not differ significantly. This divergence shows that treatment effects can vary across outcome domains, and it underlines the need to choose outcomes that reflect what matters most to the patient.

The leprosy-associated neuropathic pain trial is a useful aetiology-specific counterpoint to the class-level TCA evidence. Amitriptyline did not significantly improve the primary pain-intensity endpoint compared with placebo, although Patient Global Impression of Change favoured active treatment. This does not overturn the broader TCA evidence. It illustrates that average class effects across heterogeneous neuropathic conditions do not guarantee uniform benefit within every aetiology. [12]

The main methodological lesson of the 318-trial model is that being comprehensive and pooling statistically are two different things. All eligible trials belong in the evidence base, but pooling should follow clinical and measurement compatibility. Merging unrelated treatments, comparators and outcomes just to obtain a single number would create false precision and hide clinically meaningful differences.

The study-level evidence also suggests that publication bias and small-study effects may influence the size of the observed treatment benefits. This matters most when interpreting small TCA studies and when comparing effect sizes across treatment eras. We have therefore given more weight to the direction, consistency, certainty and clinical applicability of the evidence than to numerical ranking alone. [7]

The evidence supports individualised treatment selection. Among first-line agents, the choice should take into account neuropathic pain phenotype and aetiology, age, renal function, cardiovascular and anticholinergic burden, sedation risk, concurrent medicines, cost, availability and patient preference. A clinically meaningful response target should be set in advance and treatment titrated appropriately, and if benefit is inadequate or adverse effects are unacceptable, an alternative first-line treatment should be considered. [20–22]

Direct comparisons should increasingly inform treatment selection, because indirect comparisons can be distorted by differences in placebo response, trial design and population. The pregabalin–gabapentin result illustrates both the value and the limits of head-to-head evidence: it is easy to interpret clinically but, for now, too small to support a general claim of superiority. [23,24]

The leprosy finding likewise argues against treating neuropathic pain as a biologically uniform condition. Aetiology, sensory phenotype, disease duration, co-treatment and outcome definition may all modify the response. Where enough trials exist, future syntheses should therefore prioritise aetiology-specific and phenotype-specific analyses.

Clinically, the most defensible reading of this evidence is a treatment-trial approach. Choose a first-line option to fit the patient's clinical profile and preferences, start and titrate it appropriately, and judge it against a predefined, clinically meaningful response target. If benefit is insufficient or adverse effects are unacceptable, switching to another first-line class is reasonable. Combination treatment can be considered selectively when the response is partial, but the evidence does not establish a universally preferred combination.

Strengths and limitations

Strengths: We kept all 318 eligible RCTs in one integrated evidence framework instead of analysing only a selected subset.

All 318 RCTs sit in the same evidence pool (318 trials, 49,629 randomised participants), and each is treated as a distinct record in the analysis dataset.

Where the necessary effect estimates and confidence intervals were available, we reconstructed published continuous-pain results quantitatively and checked the reconstructed class-level estimates against the class-level values reported in the source.

The analysis does not rely on a single efficacy metric. It includes clinically meaningful responder outcomes, continuous pain, direct comparisons, formulation comparisons and aetiology-specific findings.

Because the framework keeps evidence that cannot validly be combined numerically, and no unreported statistics were imputed, clinically important information is not lost.

We interpreted the evidence using the risk-of-bias and certainty information available for the included trials, together with the methodological characteristics reported for each one.

Limitations: We analysed the 318 trials as one evidence base. For some continuous-pain outcomes, effect estimates had to be reconstructed

from reported forest-plot estimates and 95% CIs, because machine-readable raw means and standard deviations were not available for every comparison. We checked these reconstructed estimates against the corresponding reported class-level estimates before including them in the synthesis.

The 318 trials are clinically and methodologically heterogeneous, and their interventions, comparators, outcomes and follow-up periods differ materially. A single pooled effect across all of them would therefore be inappropriate.

If this work is to be presented as a fully independent systematic review, it needs to be accompanied at submission by a complete, reproducible search strategy, a study-selection record and a deduplication audit.

Only quantitatively compatible outcomes were pooled. This protects validity, but it also means the 318-trial model is an integrated evidence framework with nested quantitative contrasts and not a single, mathematically homogeneous effect estimate.

The $\alpha 2\delta \geq 30\%$ responder analysis rests on only five comparisons and remains imprecise.

The pregabalin formulation analysis includes just two trials and addresses a narrowly defined question.

The pregabalin-versus-gabapentin estimate comes from one small trial and cannot establish general superiority.

Before submission, the domain-level RoB 2 assessments should be independently checked against the full reports of all 318 trials, and every extracted numerical value should be verified by a second person.

Conclusions

The 318-trial evidence pool, with 49,629 randomised participants, supports the continued role of TCAs, SNRIs and $\alpha 2\delta$ -ligands as the main first-line drug classes. Their class-level effects on continuous pain are favourable but heterogeneous, especially for TCAs and $\alpha 2\delta$ -ligands. Direct and formulation comparisons add clinically relevant information without supporting a rigid universal ranking of individual drugs. Modified-release pregabalin appears to give analgesia comparable to immediate-release treatment, and one small head-to-head trial favoured pregabalin over gabapentin. The geriatric evidence shows that neuropathy severity and pain outcomes can diverge, and the leprosy trial highlights how response to amitriptyline can vary by aetiology. Overall, the evidence supports individualised, patient-centred treatment selection guided by efficacy, safety,

acceptability, aetiology, comorbidity and patient preference.

Clinical implications of the 318-trial evidence

Table 6. Clinical implications

Treatment question	Evidence	Certainty	Clinical interpretation
TCA's	First-line class; published class-level NNT 4.6	Moderate	Useful efficacy, but a heavier anticholinergic and sedative burden; use caution in older adults. The leprosy RCT showed no significant primary pain benefit.
SNRIs	First-line class; published class-level NNT 7.4	Moderate	Duloxetine remains a well-supported first-line option. The geriatric study found no significant pain difference versus the other first-line agents.
$\alpha 2\delta$ -ligands	First-line class; published class-level NNT 8.9	Moderate	Pregabalin and gabapentin remain supported by evidence. The responder estimate is favourable but imprecise.
Pregabalin modified-release	Comparable to immediate-release in two contemporary trials	Not regraded	May offer convenience and adherence advantages, with no evidence of an important loss of analgesia.
Pregabalin vs gabapentin	Single-trial MD -2.00 VAS	Very uncertain	Possible signal favouring pregabalin, but it needs replication before class-level recommendations change.

Declarations

Ethics Approval: Not required, as the analysis used only published aggregate data.

Patient and public involvement: No new patient or public involvement was undertaken for this synthesis.

Funding: No dedicated external funding was received for preparing this synthesis.

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