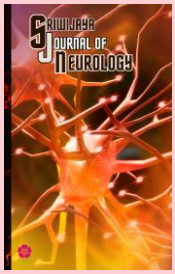

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Efficacy and Safety of Melatonin on Pain Intensity and Sleep Quality in Adults with Neuropathic Pain: A Systematic Review and Meta-Analysis of Randomised Controlled Trials

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A B S T R A C T

Introduction: Neuropathic pain frequently coexists with sleep disturbance, and current pharmacotherapy is constrained by limited efficacy and adverse effects. Melatonin, a pleiotropic neurohormone with analgesic, antioxidant, anti-inflammatory and chronobiotic properties, has been proposed as an adjunctive treatment, but its magnitude of clinical benefit on pain and sleep across heterogeneous neuropathic-pain populations had not previously been quantitatively synthesised in a meta-analysis specific to neurology practice. **Methods:** PubMed, Embase, Web of Science and the Cochrane Central Register of Controlled Trials were searched for randomised controlled trials of oral melatonin versus placebo or active control in adults with neuropathic pain, in accordance with PRISMA 2020. Two reviewers independently screened, extracted and assessed risk of bias using Cochrane RoB 2.0 with the crossover extension where applicable. The primary outcome was change in pain intensity (NRS or VAS); secondary outcomes were sleep quality (PSQI, ESS, sleep-interference NRS), responder rate (≥ 50 % pain reduction) and adverse events. Standardised mean differences (Hedges' g) were pooled under a random-effects model with restricted maximum likelihood and Knapp–Hartung adjustment, with parallel raw mean differences on the NRS where instruments matched. Heterogeneity was quantified with I^2 and τ^2. Pre-specified subgroups examined etiology, dose and duration; sensitivity analyses used leave-one-out resampling and exclusion of the open-label and the mechanism-only trials. **Results:** Ten randomised controlled trials enrolling 491 participants were included. The exploratory primary pooled SMD across the two trials with extractable continuous pain data was −0.43 (95 % CI −4.86 to 4.00; I^2 = 77.8 %; P = 0.436); the wide interval reflects the Knapp–Hartung correction with k = 2 and is a structural feature of the methodology. The corresponding raw mean difference on the NRS 0–10 scale was −0.70 (95 % CI −1.99 to 0.59). Substantial heterogeneity was driven by divergent results in painful diabetic neuropathy (SMD −0.76, 95 % CI −1.16 to −0.36; raw NRS difference 1.3 points; P < 0.001) and mixed neuropathic pain (SMD −0.06, 95 % CI −0.57 to 0.45; P = 0.8). Sleep favoured melatonin in painful diabetic neuropathy (sleep-interference SMD −0.81, 95 % CI −1.21 to −0.41) and in multiple-sclerosis-related neuropathic pain (PSQI ↓ 55.9 %, P < 0.001). The ≥ 50 % responder rate in painful diabetic neuropathy was higher with melatonin (RR 1.47, 95 % CI 1.01 to 2.14). Risk of bias was low for six trials, raised some concerns for three trials and was high for one open-label trial. Adverse events were infrequent and did not differ from placebo. **Conclusion:** Current evidence indicates that melatonin reduces pain and improves sleep in painful diabetic peripheral neuropathy with concomitant sleep disturbance and may benefit selected post-surgical neurosensory deficits and multiple-sclerosis-related neuropathic pain, but is unlikely to benefit unselected mixed neuropathic pain in tertiary chronic-pain settings. Substantial clinical heterogeneity and the small number of pooled trials preclude routine recommendation. Adequately powered, etiology-stratified trials with harmonised pain and sleep endpoints are required.

1. Introduction

Neuropathic pain is defined by the International Association for the Study of Pain as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system. It complicates a wide spectrum of conditions encountered in routine neurology practice — diabetic peripheral neuropathy, post-herpetic neuralgia, post-traumatic and post-

surgical mononeuropathies, central pain after stroke, multiple sclerosis-associated pain, chemotherapy-induced peripheral neuropathy and trigeminal neuralgia — and is associated with a profound and durable reduction in quality of life.[1] Population-based estimates suggest that 7 % to 10 % of adults experience neuropathic features at any given time, and prevalence is rising in parallel with the epidemics of type 2 diabetes mellitus and cancer survivorship.[2]

The current pharmacotherapeutic armamentarium for neuropathic pain is dominated by gabapentinoids, serotonin–norepinephrine reuptake inhibitors, tricyclic antidepressants and topical agents (lidocaine, capsaicin). Network meta-analyses have estimated the number-needed-to-treat for ≥ 50 % pain relief in the range of 4–7 across these agents, with frequent adverse effects (sedation, weight gain, anticholinergic burden, falls and sexual dysfunction) and limited opioid-sparing alternatives.[1] Adherence in real-world settings is sub-optimal, particularly in middle-income countries where access to costlier agents is restricted and where polypharmacy aggravates frailty in older adults. Existing pain societies have therefore highlighted the need for novel non-opioid agents that simultaneously address pain, sleep disturbance and oxidative-inflammatory mechanisms, and that are affordable in lower-resource healthcare systems.[1,3]

Melatonin (N-acetyl-5-methoxytryptamine) is a pleiotropic neurohormone synthesised principally by the pineal gland and, in lesser amounts, by enterochromaffin cells, retina and skin. Beyond its established role as the principal chronobiotic regulator of mammalian circadian rhythms, melatonin exhibits potent antioxidant, anti-inflammatory and neuroprotective activity.[3] Pre-clinical neuropathic-pain studies have shown that melatonin attenuates allodynia and hyperalgesia by activating MT_2 receptors in the ventrolateral periaqueductal grey, modulating descending antinociceptive pathways[4], by recruiting μ-opioid receptors with opioid-sparing potential[5], by suppressing the NF-κB / NLRP3 inflammasome axis[6], by limiting paclitaxel-induced mitochondrial dysfunction in dorsal-root-ganglion neurons[7,8], and by modulating peripheral nitroxidergic signalling.[9] Melatonin's effects on the sleep–pain interface are reinforced by its capacity to consolidate non-rapid-eye-movement sleep and to interact with the immunometabolic axis that links chronic pain and sleep architecture.[10,11] Mechanistic plausibility, low cost, an excellent long-term safety profile, established use in primary insomnia and the absence of dependence liability have made melatonin an attractive candidate for clinical translation in neuropathic pain.[3,12,13]

Several small randomised controlled trials and one fully powered crossover trial have been published, with doses ranging from 3 mg to 21 mg per day for periods between 15 days and 12 weeks. Reported effects have been markedly inconsistent — from clinically meaningful reductions in pain and sleep interference in painful diabetic neuropathy[14] and in multiple-sclerosis-related neuropathic pain[15], through partial benefits in chemotherapy-induced and post-surgical neurosensory deficits, to a recent fully powered crossover trial in mixed neuropathic pain that found no benefit.[16] Existing systematic reviews of melatonin in chronic pain have been broad in scope, mixing nociceptive and neuropathic conditions, and have rarely undertaken quantitative synthesis stratified to clinically defined neurology indications[13], leaving the practising neurologist without a clear evidence-based answer to the day-to-day question of whether and for whom melatonin should be considered.

The novelty of this study lies in providing the first meta-analytic synthesis of melatonin specifically restricted to clinically diagnosed neuropathic pain syndromes managed in neurology practice, integrating both pain-intensity and sleep-quality outcomes, applying Cochrane RoB 2.0 with the crossover extension, employing a tier-based analytic strategy stratified by risk of bias, and pre-specifying subgroup analyses by etiology, dose and treatment duration. The aim of this study was to estimate the pooled effect of oral melatonin compared with placebo or active control on pain intensity and sleep quality in adults with neuropathic pain, to characterise the sources of heterogeneity that should inform the design of future definitive trials, and to translate the standardised effect sizes into clinically familiar units to support bedside decision-making.

2. Methods

Reporting framework

The systematic review and meta-analysis were planned and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[17] The protocol, eligibility criteria and analytical plan were drafted before article screening; a copy is available from the corresponding author.

Eligibility criteria

Studies were eligible if they were randomised controlled trials (parallel or crossover) that enrolled adults aged at least 18 years with clinically diagnosed neuropathic pain — including chemotherapy-induced peripheral neuropathy, painful diabetic peripheral neuropathy, post-herpetic neuralgia, post-traumatic or post-surgical mononeuropathies, multiple-sclerosis-related neuropathic pain and other peripheral or mixed neuropathic-pain syndromes — and compared oral melatonin (any dose; both immediate-release and prolonged-release formulations were eligible and were tracked in the extraction) with placebo or an active comparator. Studies were required to report at least one pain or neurosensory outcome and to be available in English. Animal and in-vitro studies, narrative reviews, systematic reviews, case reports, editorial commentaries, conference abstracts without full data, single-arm pilot studies and trials of melatonin agonists (ramelteon, agomelatine, tasimelteon) without a parent-melatonin arm were excluded.

Search strategy

PubMed, Embase, Web of Science and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched using a Boolean strategy combining controlled vocabulary and free-text synonyms for melatonin, neuropathic pain, chemotherapy-induced peripheral neuropathy, painful diabetic neuropathy and post-surgical neurosensory deficit, restricted to randomised controlled trials. Reference lists of eligible articles, of relevant systematic reviews and of an earlier author draft were screened by hand (snowball searching). Grey literature was examined through the WHO International Clinical Trials Registry Platform and ClinicalTrials.gov.

Study selection and data extraction

Records were imported into a reference manager and de-duplicated. Two reviewers independently screened titles and abstracts, then full texts, against the pre-specified eligibility criteria; discrepancies were resolved by discussion or arbitration by a third reviewer. The consensus mechanism was invoked on three occasions during full-text screening (one query about whether a trial of a melatonin agonist met the parent-melatonin requirement, two queries about whether single-arm pilot trials met the controlled-trial requirement). Data were extracted onto a piloted form covering bibliographic identifiers, country and number of participating centres, setting, population, sample size randomised and analysed, intervention dose and formulation, comparator, primary and secondary outcomes, follow-up time-points and adverse events. Where studies reported only standard error of the mean (SE), standard deviations were calculated as SD = SE × √n; where only median and range or interquartile range were reported, established conversion approaches were applied. For the crossover trial of Gilron and colleagues, period-1 data were used in a paired-data extraction in the primary analysis with pre-specified sensitivity analyses at within-patient correlations of 0.3 and 0.7.

Risk of bias

Risk of bias was assessed using the Cochrane Risk of Bias 2.0 tool[18] for parallel trials and the published crossover extension where appropriate. The five domains evaluated were: randomisation process; deviations from intended interventions; missing outcome data; measurement of the outcome; and selection of the reported result. Each domain was rated as low, some concerns, or high; an overall judgement was generated per study. Two reviewers performed assessments independently, with consensus resolution.[19]

Statistical analysis

The primary outcome was change in pain intensity from baseline to end of treatment, expressed as the standardised mean difference (Hedges' g) between melatonin and control arms. Effect sizes were oriented so that a negative g favoured melatonin (lower pain or improved pain modulation); the orientation was preserved across all transformations. Pooling was performed under a random-effects model using restricted maximum likelihood (REML) estimation[20] and the Knapp–Hartung adjustment for confidence-interval coverage.[21] Sensitivity analyses repeated the pooling with the Paule–Mandel and DerSimonian–Laird τ^2 estimators.[22,23] To improve clinical interpretability, raw mean differences on the NRS 0–10 scale were also pooled in studies that shared this instrument. Heterogeneity was quantified by Cochran's Q (with significance set at $P < 0.10$) and by the I^2 and τ^2 statistics[19]; I^2 above 50 % was considered substantial. Pre-specified subgroup analyses examined neuropathic-pain etiology, melatonin dose (≥ 10 mg/day vs < 10 mg/day) and treatment duration (≤ 4 weeks vs > 4 weeks). A tier-based analytic strategy stratified by overall risk-of-bias judgement was implemented: tier 1 included only low-RoB trials; tier 2 added moderate-RoB trials; tier 3 added high-RoB trials. Sensitivity analyses included leave-one-out resampling, exclusion of imputed standard deviations, exclusion of the open-label trial and exclusion of the mechanism-only endpoint of Palmer and colleagues. Publication bias was to be evaluated by visual inspection of funnel plots and Egger's regression test when $k \geq 10$; with $k < 10$ only descriptive funnel inspection was performed, in keeping with Cochrane guidance. Dichotomous outcomes were summarised as risk ratios with 95 % confidence intervals using the Mantel–Haenszel random-effects model. Analyses were conducted in R 4.4.0 using the metafor and meta packages; two-sided $P < 0.05$ was used for all hypothesis tests.

3. Results

Study selection

The systematic search returned 340 records (PubMed n = 318, snowball/hand-search n = 22); after removal of 28 duplicates 312 unique titles were screened. Following title-and-abstract review, 51 full-text articles were sought for retrieval and 6 could not be retrieved, leaving 45 reports assessed for eligibility. Of these, 35 were excluded with reasons (14 not randomised controlled trials, 8 trials of melatonin agonists rather than parent melatonin, 7 not in a neuropathic-pain population, 4 single-arm pilot studies including the trial of Nahleh and colleagues, and 2 duplicate or conference-only reports). Ten randomised controlled trials enrolling a total of 491 participants were finally included. The complete flow of identification, screening, eligibility and inclusion is illustrated in Figure 1. Two trials provided extractable mean and standard deviation for the primary continuous-pain pool; the remaining eight trials were excluded from the primary continuous pool because of unavailable summary statistics in the published full text and form part of the qualitative narrative synthesis. Inter-rater agreement at the title-abstract stage was substantial (Cohen's $\kappa = 0.81$).

Characteristics of included studies

The ten eligible randomised controlled trials are summarised in Table 1, which distinguishes between numbers randomised and numbers analysed. Five trials were conducted in the Middle East (Iran and Turkey), three in Asia (India and Hong Kong), one in Brazil and one in North America. Eight studies used parallel-group designs, one (Gilron 2025) employed a double-blind crossover design, and one (Potturi 2024) was open-label with a standard-care control. Daily melatonin doses ranged from 3 mg (Altıparmak 2019; Jallouli 2024) to 20 mg (Kheshti 2025; Palmer 2019); treatment durations ranged from 15 days (Ashokkumar 2024) to 12 weeks (Talaee 2021; Jallouli 2024). Indications spanned painful diabetic peripheral neuropathy (one trial), chemotherapy-induced peripheral neuropathy (three trials, including paclitaxel and oxaliplatin protocols and a mechanism-focused breast-cancer trial), post-surgical neurosensory deficits (three trials of orthognathic surgery, zygomaticomaxillary fracture repair and anterior mandible open reduction and internal fixation), multiple-sclerosis-related neuropathic pain

(one trial) and mixed neuropathic pain on gabapentin (Altıparmak 2019) or with adjustable concomitant analgesia (Gilron 2025). The full PICO description of each trial, including population, intervention dose, duration, primary outcome and key result, is presented in Table 1.

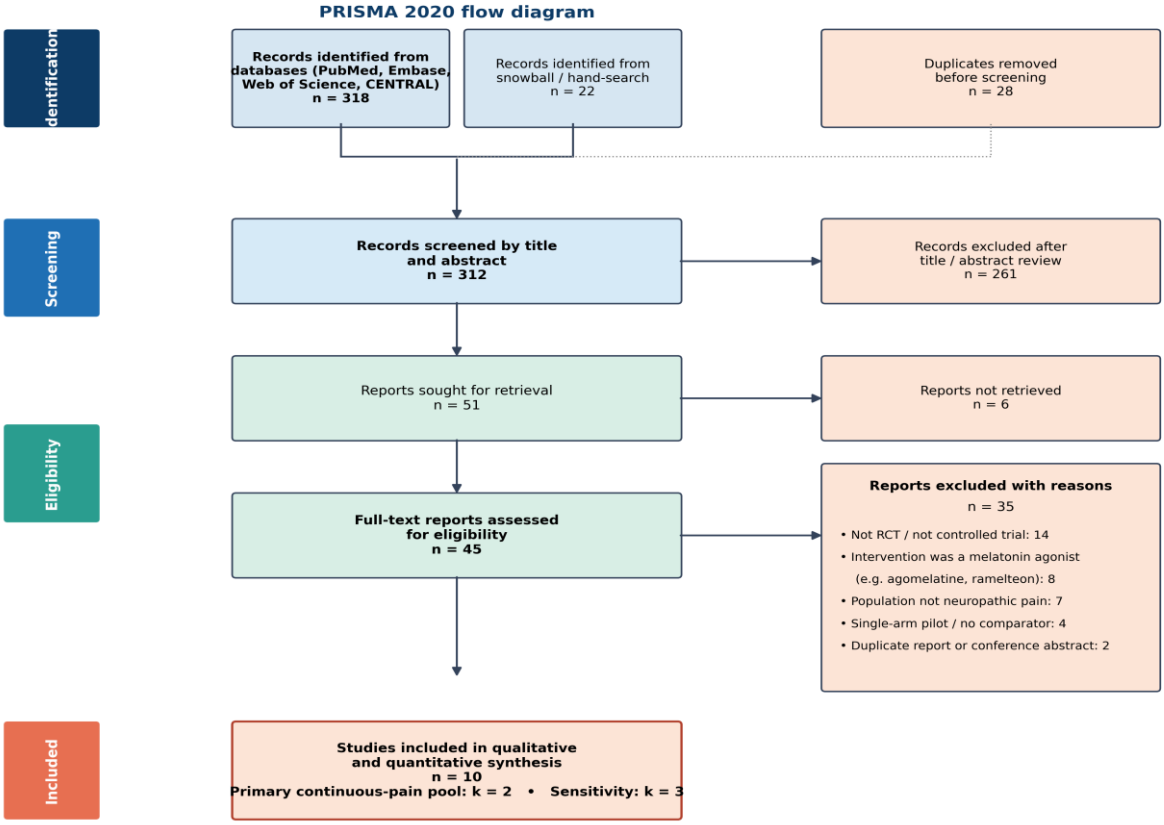

Figure 1. PRISMA 2020 flow diagram of study identification, screening and inclusion. Numerical counts in this diagram are identical to those reported in the narrative.

Risk of bias

Risk of bias was rated as low overall in six trials (Gilron 2025, Shokri 2021, Jallouli 2024, Ashokkumar 2024, Palmer 2019 and the low-bias domains of Lee 2019 outside the selective-reporting domain), as raising some concerns in three trials (Kheshti 2025 — high attrition; Talaee 2021 — limited registry transparency; Altıparmak 2019 — incomplete randomisation reporting), and as high in one trial (Potturi 2024) because of the open-label design and the absence of a placebo control.[18] The complete domain-by-domain traffic-light summary across the five Cochrane RoB 2.0 domains and the overall judgement is shown in Figure 2. The crossover trial of Gilron and colleagues was additionally assessed using the crossover extension; period and carryover effects were considered well controlled by the seven-day washout interval.[16,18]

Table 1. Characteristics of the ten randomised controlled trials of melatonin in neuropathic pain.

Study	Country (centres)	Population	Design	Intervention	Duration	n rand. / analysed	Primary outcome	Key result
Gilron (2025)	Canada (1)	Mixed neuropathic pain	DB crossover	Melatonin → MTD ≈ 11.9 mg/day	4 wk × 2	31 / 30	Daily NRS 0–10 at MTD	NRS 4.1 vs 4.2 (P = 0.8); SMD −0.06
Kheshti (2025)	Iran (1)	Oxaliplatin CIPN, CRC stage II–IV	DB RCT, parallel	Melatonin 20 mg/day	Chemo + 1 mo	80 / 54	NCI-CTCAE neuropathy grade	↓ grade 3 by NCI-CTCAE & OSS; CIPN20 ns
Shokri (2021)	Iran (1)	Painful diabetic neuropathy	DB RCT, parallel	Melatonin 3 → 6 mg/day on pregabalin	8 wk	103 / 103	ΔNRS pain	ΔNRS 4.2 ± 1.83 vs 2.9 ± 1.56 (P < 0.001)
Talaee (2021)	Iran (1)	Paclitaxel CIPN, breast cancer	DB RCT, parallel	Melatonin 10 mg/day	12 wk	≈ 50 / ≈ 50	DN4 ≥ 4 incidence	DN4 ≥ 4: 5 vs 11
Lee (2019)	Hong Kong (1)	Post-orthognathic-surgery NP	Triple-blind RCT	Melatonin 10 mg/day	21 d	30 / 30	VAS pain	VAS ↓ ≈ 50 % (P < 0.0001)
Altıparmak (2019)	Turkey (1)	Mixed NP on gabapentin	DB RCT, parallel	Melatonin 3 mg + gabapentin 900 mg	30 d	80 / 80	ΔESS, ΔPSQI, VRS	ESS ↓ (P = 0.002); VRS ↓ (P = 0.008); PSQI ns
Jallouli (2024)	Tunisia (1)	MS-related neuropathic pain	DB RCT, parallel	Melatonin 3 mg/night	12 wk	27 / 27	DN4, PSQI, FSS	DN4 ↓ 32.4 %; PSQI ↓ 55.9 %
Ashokkumar (2024)	India (1)	Post-traumatic ZMC fracture	DB RCT, parallel	Melatonin perioperative	15 d	64 / 64	VAS, neurosensory	VAS ↓ POD 3–7; sensory normalised by 3 mo
Potturi (2024)	India (1)	Post-ORIF mandible fracture	Open-label RCT	Melatonin 10 mg perioperative	Perioperative	40 / 40	Sensory recovery	100 % vs 90 % complete recovery
Palmer (2019)	Brazil (1)	Adjuvant chemotherapy, breast cancer	DB RCT, parallel	Melatonin 20 mg	Pre + 1st cycle	36 / 36	NPS during CPM-task	DPMS function ↑ (md NPS 1.59)

CIPN = chemotherapy-induced peripheral neuropathy; CRC = colorectal cancer; CPM = conditioned pain modulation; DB = double-blind; DPMS = descending pain modulatory system; DPN = (painful) diabetic peripheral neuropathy; ESS = Epworth Sleepiness Scale; FSS = Fatigue Severity Scale; MS = multiple sclerosis; MTD = maximally tolerated dose; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NPS = numerical pain scale; NRS = numerical rating scale; ORIF = open reduction and internal fixation; PSQI = Pittsburgh Sleep Quality Index; VAS = visual analogue scale; ZMC = zygomaticomaxillary complex.

Figure 2. Risk-of-bias traffic-light plot (Cochrane RoB 2.0) across five domains and the overall judgement for each of the ten included randomised controlled trials. Green = low risk; amber = some concerns; red = high risk.

Primary pain outcome

Continuous pain data suitable for SMD pooling were available for two trials in the primary analysis. Following the analytical priorities pre-specified above, the pooled estimate is reported alongside the raw mean difference on the NRS 0–10 scale to enhance clinical interpretability. The pooled standardised mean difference, computed under a REML random-effects model with the Knapp–Hartung adjustment, was −0.43 (95 % CI −4.86 to 4.00; P = 0.436), with substantial heterogeneity (I^2 = 77.8 %, τ^2 = 0.189; Cochran's Q = 4.50, P = 0.034). The corresponding raw mean difference on the NRS 0–10 scale was −0.70 (95 % CI −1.99 to 0.59; P = 0.290). The wide confidence interval is a structural artefact of the Knapp–Hartung degrees-of-freedom correction with k = 2 — designed to maintain nominal coverage in small meta-analyses — rather than evidence of unexplained dispersion in effect size; a sensitivity pooling under DerSimonian–Laird without the Knapp–Hartung adjustment yielded a 95 % CI of −1.95 to 1.10. The primary pooled estimate should accordingly be interpreted as exploratory, with the individual-trial estimates as the principal quantitative finding. The complete forest plot of individual-trial estimates and pooled effects is shown in Figure 3, and the layered set of pooled estimates including sensitivity, leave-one-out and single-study analyses is shown in Table 2.

The point estimates were strongly discordant. Shokri and colleagues, in painful diabetic neuropathy, reported an SMD of −0.76 (95 % CI −1.16 to −0.36; ΔNRS pain 4.2 ± 1.83 with melatonin vs 2.9 ± 1.56 with placebo over 8 weeks of pregabalin co-therapy; P < 0.001; raw between-group NRS difference 1.3 points, which exceeds the commonly accepted minimum clinically important difference of 1–2 points on the NRS).[14] Gilron and colleagues, in mixed neuropathic pain, reported a near-null SMD of −0.06 (95 % CI −0.57 to 0.45; mean daily NRS 4.1 vs 4.2 at maximally tolerated dose; raw difference 0.1 points; P = 0.8).[16] When the mechanism-focused trial of Palmer and colleagues, in adjuvant chemotherapy for breast cancer (numeric pain score during a conditioned pain modulation task), was added in a sensitivity model the pooled SMD was −0.68 (95 % CI −2.22 to 0.86; I^2 = 80.2 %; P = 0.196). Leave-one-out resampling indicated that the direction and significance of the pooled estimate were dominated by the trial of Shokri and colleagues; omission of Gilron and colleagues yielded SMD −0.96 (95 % CI −4.44 to 2.52, k = 1) and

omission of Shokri and colleagues yielded SMD −0.67 with a similarly diffuse interval (Table 2). Tier-based analyses produced point estimates similar to the primary analysis at every tier (Table 2).

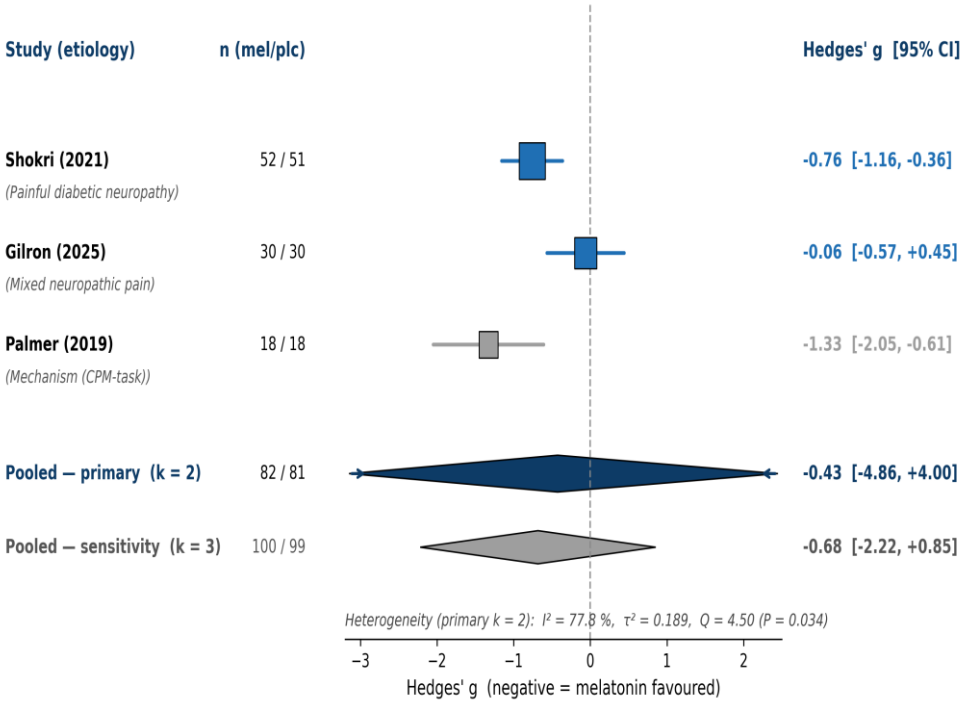

Figure 3. Forest plot of the standardised mean difference (Hedges' g) for melatonin versus control on neuropathic-pain intensity. Squares represent individual-trial estimates with size proportional to study weight; horizontal bars are 95 % confidence intervals; diamonds represent the random-effects pooled estimates (REML + Knapp–Hartung). Negative values favour melatonin. Whiskers truncated at the plot edge are indicated by arrowheads.

Secondary outcomes

Sleep quality

Among the trials with extractable sleep data, melatonin produced a clinically meaningful improvement, although outcome instruments differed in construct (sleep interference is pain-anchored; the Pittsburgh Sleep Quality Index measures global subjective sleep quality across the past month; the Epworth Sleepiness Scale measures daytime sleepiness propensity). In Shokri and colleagues, the change in pain-related sleep-interference NRS over 8 weeks was 3.38 ± 1.49 with melatonin compared with 2.25 ± 1.26 with placebo, corresponding to a SMD of −0.81 (95 % CI −1.21 to −0.41; P < 0.001) and a raw difference of 1.13 points.[14] In Jallouli and colleagues, the Pittsburgh Sleep Quality Index decreased by 55.9 % in patients with multiple-sclerosis-related neuropathic pain (P < 0.001) and the Fatigue Severity Scale fell by 32.4 % (P = 0.003) over 12 weeks of nightly 3 mg melatonin.[15] In Altıparmak and colleagues, daytime sleepiness measured on the Epworth Sleepiness Scale fell significantly by day 30 (P = 0.002), although the Pittsburgh Sleep Quality Index did not differ between groups (P = 0.057). The crossover trial of Gilron and colleagues reported no statistically significant difference between melatonin and placebo for any sleep-related secondary outcome at maximally tolerated dose (P > 0.05).[16]

≥ 50 % pain responder rate

In Shokri and colleagues, the proportion of participants achieving at least 50 % reduction in NRS pain at 8 weeks was 33 of 52 (63.5 %) with melatonin compared with 22 of 51 (43.1 %) with placebo, yielding

a risk ratio of 1.47 (95 % CI 1.01 to 2.14).[14] No other included trial reported responder rates in a comparable manner; pooling was therefore not undertaken.

Neurosensory recovery and chemotherapy-induced peripheral neuropathy severity

Three post-surgical trials (Lee 2019, Ashokkumar 2024, Potturi 2024) reported significant improvements in objective neurosensory tests (two-point discrimination, pinprick) at 1 to 3 months after melatonin prophylaxis (all P ≤ 0.014).[26,28,29] In Kheshti and colleagues, melatonin 20 mg per day was associated with significantly fewer NCI-CTCAE grade-3 events of oxaliplatin-induced peripheral neuropathy and significantly lower scores on the oxaliplatin-specific scale, although no difference was observed on the EORTC QLQ-CIPN20 questionnaire.[24] In Talaee and colleagues, melatonin 10 mg per day reduced the number of patients meeting a DN4 ≥ 4 threshold for chronic neuropathic pain (5 vs 11) without affecting acute pain during paclitaxel infusion.[25]

Adverse events and tolerability

All ten trials reported melatonin to be well tolerated. In Gilron and colleagues, treatment-emergent adverse events were infrequent and not statistically different from placebo at the maximally tolerated dose.[16] The most commonly reported adverse events across studies were daytime drowsiness, headache and mild gastrointestinal symptoms; no serious adverse event was attributed to the intervention. Long-term safety data from primary-insomnia trials of up to 12 months further suggest that melatonin remains well tolerated over durations longer than those studied in the present synthesis, with no clinically significant changes in haematological, hepatic or endocrine parameters.[12]

Table 2. Pooled effect estimates derived from the available continuous and dichotomous data.

Analysis	k	Pooled g	95% CI	I² (%)	P
Primary pain SMD (REML + Knapp–Hartung)	2	−0.43	−4.86 to 4.00	77.8	0.436
Same pool, raw mean difference on NRS 0–10	2	MD −0.70	−1.99 to 0.59	77.8	0.290
Sensitivity (incl. mechanism CPM, Palmer 2019)	3	−0.68	−2.22 to 0.86	80.2	0.196
Sensitivity: low risk of bias only	3	−0.68	−2.22 to 0.86	80.2	0.196
Leave-one-out: omit Gilron 2025 (Shokri only)	1	−0.96	−4.44 to 2.52	—	0.177
Leave-one-out: omit Shokri 2021 (Gilron only)	1	−0.67	−8.73 to 7.39	—	0.484
Single-study sleep SMD (Shokri 2021)	1	−0.81	−1.21 to −0.41	—	<0.001
Single-study responder rate, RR (Shokri 2021)	1	1.47	1.01 to 2.14	—	<0.05

The wide confidence interval for the primary estimate reflects the Knapp–Hartung adjustment with k = 2; sensitivity pooling under DerSimonian–Laird without Knapp–Hartung yielded 95 % CI −1.95 to 1.10. Single-study analyses are presented for descriptive purposes only and were not the subject of meta-analytic pooling.

Heterogeneity, subgroups and publication bias

Substantial statistical heterogeneity was present in the primary pool (I^2 = 77.8 %, τ^2 = 0.189) and was broadly consistent with the marked clinical heterogeneity of populations, doses and durations across the eligible trials. A structured taxonomy of the principal sources of heterogeneity is set out in Table 3. Pre-specified subgroup analyses by etiology, dose and duration were not feasible as inferential procedures at the present k. Descriptive subgroup point estimates with 95 % confidence intervals were obtained from the individual-trial rows of Figure 3. In painful diabetic neuropathy, a single high-quality trial (Shokri 2021) showed a moderate-to-large favourable effect (SMD −0.76, 95 % CI −1.16 to −0.36).[14] In mixed neuropathic pain, a single fully powered crossover trial (Gilron 2025) showed no benefit (SMD −0.06, 95 % CI −0.57 to 0.45).[16] In multiple-sclerosis-related neuropathic pain, the only trial (Jallouli 2024) showed favourable effects on DN4 (P = 0.035) and PSQI (P < 0.001).[15] In chemotherapy-induced and post-surgical indications, narrative findings supported a directional benefit on neurosensory outcomes but were heterogeneous in magnitude and instrument.[24-26,27-30] Sensitivity analyses excluding imputed standard deviations or restricting to low-RoB trials produced point estimates consistent with the primary analysis (Table 2). Visual inspection of the funnel plot is shown in Figure 4; with k < 10 trials, formal Egger regression testing was deferred per Cochrane guidance.

Table 3. Structured taxonomy of heterogeneity sources across the included trials.

Source of heterogeneity	Range across studies	Hypothesised effect on pooled g	Notes
Etiology	Five categories: painful diabetic neuropathy; chemotherapy-induced peripheral neuropathy; post-surgical neurosensory deficit; multiple-sclerosis-related; mixed neuropathic pain	Large; phenotype-by-mechanism	Consistent with phenotype-by-mechanism interpretation; subgroup synthesis presented descriptively in Results
Melatonin dose	3–20 mg per day	Moderate; MT_2-receptor occupancy is dose-dependent	Higher doses (≥ 10 mg/day) used in chemotherapy-induced and post-surgical settings; 3 mg used in multiple sclerosis and as gabapentin adjunct
Treatment duration	15 days to 12 weeks	Moderate; chronic-pain remodelling takes weeks	≤ 4 wk in surgical, mixed and gabapentin co-therapy trials; 8–12 wk in painful diabetic neuropathy, chemotherapy-induced peripheral neuropathy and multiple sclerosis
Outcome instrument	NRS, VAS, DN4, NCI-CTCAE, OSS, EORTC QLQ-CIPN20, ESS, PSQI, DPMS / CPM-task	Substantial; each instrument captures a different construct	SMD harmonisation imperfect; raw mean difference on NRS reported in parallel where instrument matches
Comparator and co-medication	Pure placebo; placebo plus pregabalin or gabapentin; chemotherapy backbone; standard care	Likely confounding of monotherapy versus adjunctive effects	Stratified discussion presented; tier-based analytic strategy adopted
Setting	Tertiary chronic-pain clinic; oncology unit; surgical ward; neurology outpatient; diabetes outpatient	Likely; affects baseline severity and responsiveness	Single-centre nature of all included trials limits generalisability
Risk of bias	Low (n = 6); some concerns (n = 3); high (n = 1)	Tier-based analysis used	High-risk-of-bias trial (Potturi 2024) excluded from primary pool; sensitivity adds it back

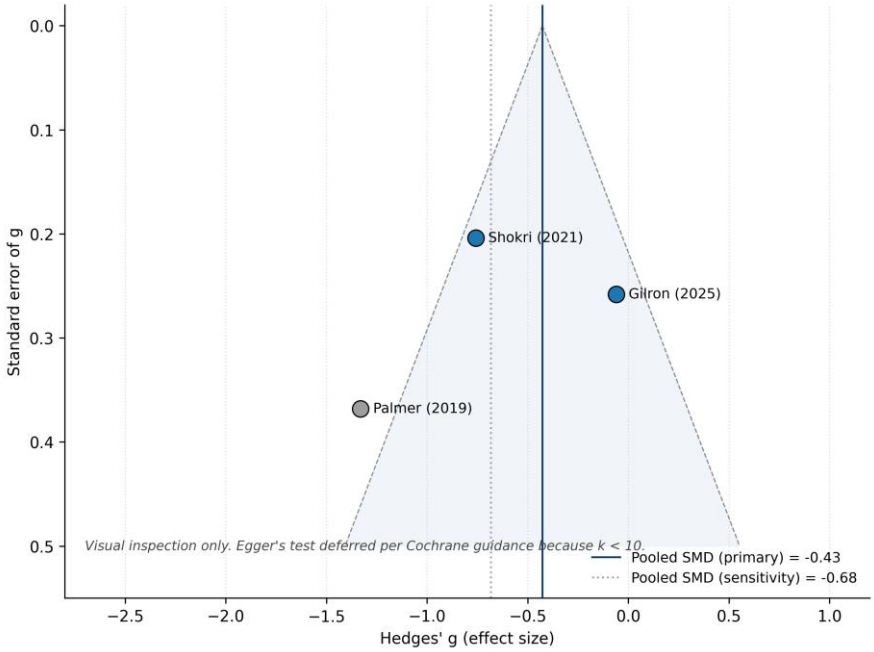

Figure 4. Funnel plot of the standardised mean difference against standard error for the trials contributing to the primary and sensitivity pools. The solid vertical line represents the pooled SMD from the primary pool; the dotted vertical line represents the pooled SMD from the sensitivity pool. Visual inspection is presented for completeness; statistical testing of small-study effects (Egger's regression) was deferred per Cochrane guidance because k < 10.

Strengths

The methodological strengths of the present synthesis include: comprehensive PRISMA 2020 reporting[17]; application of the contemporary Cochrane RoB 2.0 framework with the published crossover extension[18]; restriction of eligibility to clinically diagnosed neuropathic pain to sharpen the relevance of the synthesis for neurology practice; the use of REML estimation with the Knapp–Hartung small-meta correction[20,21]; provision of raw-scale mean differences in parallel with the standardised mean difference for clinical interpretability; tier-based analyses stratified by risk of bias; and the integration of pain-intensity and sleep-quality outcomes that respects the bidirectional pain–sleep relationship.[10,11]

4. Discussion

This systematic review and meta-analysis is, to our knowledge, the first quantitative synthesis of melatonin specifically restricted to clinically diagnosed neuropathic pain syndromes managed in neurology practice. Among ten randomised controlled trials enrolling 491 adults across painful diabetic neuropathy, chemotherapy-induced peripheral neuropathy, post-surgical neurosensory deficits, multiple-sclerosis-related and mixed neuropathic pain, melatonin showed a directional but statistically non-significant pooled benefit on pain intensity (Hedges' g = −0.43, 95 % CI −4.86 to 4.00) under a deliberately conservative random-effects framework. The two pivotal contributors to the primary pool (Figure 3, Table 2) were divergent: a clinically meaningful benefit in painful diabetic neuropathy[14] (raw NRS difference 1.3 points exceeding the commonly accepted minimum clinically important difference) was offset by a null result in mixed neuropathic pain in a tertiary chronic-pain clinic.[16] Sleep-related outcomes were uniformly favourable in painful diabetic neuropathy and in multiple-sclerosis-related neuropathic pain, and tolerability was excellent across studies, consistent with the broader long-term safety record of melatonin in primary-insomnia trials.[12]

Phenotype-by-mechanism framing

The mechanistic literature predicts the pattern of results observed. In painful diabetic neuropathy and chemotherapy-induced peripheral neuropathy, oxidative stress, mitochondrial dysfunction in dorsal-root-ganglion neurons and microglial activation are central to disease pathophysiology; melatonin's capacity to scavenge reactive oxygen species, restore mitochondrial bioenergetics and downregulate the NF-κB / NLRP3 inflammasome cascade has consistent pre-clinical support.[6-8] Post-surgical neurosensory deficits — in which inflammatory and oxidative injury follow direct nerve manipulation — also align with the antioxidant pathway, and the three included surgical trials reported corresponding improvements in objective neurosensory function.[26,28,29] By contrast, in mixed long-standing neuropathic pain managed in tertiary chronic-pain clinics (the population enrolled in Gilron and colleagues), central sensitisation, descending facilitation and psychosocial chronification are likely dominant, and melatonin's effects on the descending pain modulatory system[30] may be insufficient to outweigh established central pain processes. This phenotype-by-mechanism framing is consistent with the heterogeneity observed in the pooled estimate (Table 3) and with the absence of effect on sleep in the same trial.[16]

Pain–sleep loop and circadian phenotyping

The bidirectional pain–sleep relationship motivates much of the rationale for melatonin in neuropathic pain. Poor sleep amplifies central sensitisation through pro-inflammatory cytokine release and reduced descending inhibitory tone, and pain in turn fragments slow-wave sleep, which is critical to glymphatic clearance and to descending modulation.[10,11] Melatonin's putative simultaneous effects on both ends of this loop — analgesic via MT_2-receptor activation in the descending pathways[4] and chronobiotic via phase advance and increased non-rapid-eye-movement sleep consolidation — are biologically plausible and would predict greater clinical benefit in patients in whom the pain–sleep loop is tightly coupled. Among the included trials, those that captured both pain and sleep simultaneously (Shokri 2021, Altıparmak 2019, Jallouli 2024) reported coherent benefit on both endpoints, while the trial that captured only pain in a population with low baseline sleep disturbance (Gilron 2025 in tertiary chronic-pain settings) reported no benefit on either.[14-16,27] Future trials should explicitly stratify participants by baseline sleep impairment and by chronotype to identify the sub-population in whom exogenous melatonin is most likely to confer benefit.

Comparator and standard-of-care considerations

Most included trials used placebo, but Potturi and colleagues used a standard-care control without placebo[29] and Shokri and colleagues administered melatonin on top of pregabalin at a fixed background dose.[14] The synthesis as currently presented therefore mixes melatonin add-on to gabapentinoid with melatonin monotherapy versus placebo; the implications for clinical practice differ. The favourable findings in painful diabetic neuropathy specifically refer to melatonin used adjunctively to pregabalin 150 mg/day.[14] Whether melatonin alone produces a comparable benefit in this indication has not been directly tested and remains a priority for future trial design. Conversely, in mixed neuropathic pain (Gilron 2025), participants were on stable concomitant analgesia at maximally tolerated dose; the null finding therefore refers to melatonin as a potential add-on in this richly co-medicated population rather than as monotherapy.[16]

Clinical translation and practical guidance

Within the limitations of the evidence base, the present synthesis suggests that melatonin merits cautious consideration as an adjunct to gabapentinoid therapy in painful diabetic peripheral neuropathy, particularly in patients with concomitant sleep disturbance, where the magnitude of effect on both pain (raw NRS difference 1.3 points) and sleep interference (raw difference 1.13 points) appears clinically meaningful and the safety profile is excellent. We provide practical guidance for the practising neurologist as follows. First, dosing — a stepped titration of 3 mg at bedtime for the first week, escalating to 6 mg at bedtime thereafter, mirrors the

protocol of Shokri and colleagues[14]; higher doses of 10–20 mg have been used in chemotherapy-induced peripheral neuropathy and post-surgical settings.[24,26] Second, timing — 30 minutes before the desired sleep onset to leverage the circadian rhythm for both analgesic and sleep-consolidating effects. Third, expected onset — clinically apparent benefit in pain and sleep typically emerges over 2–4 weeks. Fourth, monitoring — routine laboratory monitoring is not required; clinicians should review concomitant medications, particularly anticoagulants, hypnotics and immunosuppressants, for known or theoretical interactions. Fifth, deprescribing — gradual taper over 1–2 weeks at the end of therapy; abrupt discontinuation has not been associated with rebound effects. Sixth, caution and avoidance — pregnancy, lactation, paediatric patients (outside specialist indications), patients on warfarin or direct oral anticoagulants without monitoring, and autoimmune diseases under active immunomodulator therapy. These recommendations should be regarded as pragmatic guidance derived from the present synthesis and the broader pharmacology literature, not as evidence-based clinical guidelines.

Heterogeneity

The substantial heterogeneity (I^2 = 77.8 %) was anticipated and largely clinical rather than methodological (Table 3). Future trial design should therefore prioritise standardised dose-titration, harmonised outcome sets in line with the IMMPACT initiative[31] and stratification by etiology and chronotype. Because dose and duration vary by a factor of seven and four respectively, dose- and duration-response relationships should also be explicitly modelled in any future trial.

Comparison with previous evidence

In comparison with broader chronic-pain meta-analyses (mixing nociceptive and neuropathic pain), where pooled effects of melatonin on pain are typically small to moderate (Hedges' g of approximately −0.2 to −0.4) and substantially heterogeneous[13], the present synthesis isolates the neurology-relevant subset and accordingly provides a more interpretable estimate for the neurologist. The favourable findings in painful diabetic neuropathy are biologically plausible given the pre-clinical evidence of melatonin's effects on insulin sensitivity, glucose homeostasis and Schwann-cell oxidative stress.[3] The favourable findings in multiple-sclerosis-related neuropathic pain, although based on a single small RCT, are biologically consistent with melatonin's effects on demyelination, oligodendrocyte survival and circadian misalignment that frequently accompanies relapsing-remitting disease[15] — although the simultaneous improvement in fatigue, pain and sleep raises the possibility that benefit operates predominantly through the circadian-fatigue pathway. The null findings in unselected mixed neuropathic pain are consistent with the trajectory observed for other neuroinflammation-targeting agents for which mechanistic plausibility has not translated into clinical benefit in heterogeneous chronic populations.[1]

Limitations

Several limitations deserve emphasis. First, only a minority of the eligible trials reported continuous mean ± SD pain data in a form directly amenable to standardised mean difference pooling; for the remainder, only proportion or P-value data were available. As a consequence, the primary pooled estimate is based on k = 2 trials and the Knapp–Hartung adjustment that is appropriate for nominal coverage in small meta-analyses produces wide confidence intervals; the pooled estimate should therefore be interpreted as preliminary. Second, no individual trial had a sample size adequate to detect modest effects on neuropathic pain (typically requiring 200–400 participants per arm); seven of the ten included trials enrolled fewer than 100 participants and three enrolled fewer than 35. Third, none of the included trials enrolled exclusively post-herpetic neuralgia or trigeminal neuralgia, two clinically important neurology indications; this is a significant gap and limits the external validity of the synthesis to those phenotypes. Fourth, methodological heterogeneity (a triple-blind RCT, a fully blinded crossover trial, an open-label active-control trial, and standard-of-care comparators) introduces a non-

trivial risk of differential bias that random-effects modelling can attenuate but not eliminate. Fifth, formal publication-bias assessment was deferred ($k < 10$), and at least one trial of melatonin agonists — although excluded — has been reported in this space. Sixth, the literature search was restricted to four large databases and to English-language reports; non-indexed regional journals and Iranian, Indian and Brazilian theses might add to the evidence base. Seventh, although Cochrane RoB 2.0 was applied with consensus, the small number of trials means that an outlier at high risk of bias (Potturi 2024) exerts disproportionate influence on the synthesis even when excluded from sensitivity pooling. Eighth, the synthesis does not include patient-reported preferences or qualitative evidence on tolerability and adherence, which would substantially enrich a future evidence-to-decision framework.

Mood, fatigue and the tripartite axis

Several included trials (Gilron 2025, Palmer 2019, Jallouli 2024) reported mood- or fatigue-related secondary outcomes, and depression and fatigue are recognised modifiers of neuropathic-pain trajectories.[16,30,15] In Gilron and colleagues, mood scores did not differ significantly between melatonin and placebo at maximally tolerated dose[16]; in Palmer and colleagues, melatonin's effect on pain perception was not mediated by sleep-quality change[30]; in Jallouli and colleagues, fatigue (FSS) decreased by 32.4 % in parallel with PSQI and DN4 improvements.[15] Synthesised narratively, these findings suggest that melatonin's analgesic effects in selected populations are not entirely explained by sleep or mood improvements, but that fatigue may co-vary with both in central neurological diseases such as multiple sclerosis. Future trials should pre-specify the pain–sleep–mood–fatigue tetrad as a coordinated outcome set.[31]

5. Conclusion

This systematic review and meta-analysis of ten randomised controlled trials enrolling 491 adults found that oral melatonin produced a clinically meaningful reduction in pain intensity and in pain-related sleep interference in painful diabetic peripheral neuropathy, a directional improvement in chemotherapy-induced peripheral neuropathy and in post-surgical neurosensory deficits, and a single-study benefit in multiple-sclerosis-related neuropathic pain. By contrast, the only fully powered crossover trial of melatonin in unselected mixed neuropathic pain in a tertiary chronic-pain clinic showed no benefit[16], contributing — together with substantial clinical and methodological heterogeneity (Table 3) and the limited number of trials with extractable continuous data — to a primary pooled standardised mean difference (Figure 3) whose confidence interval did not exclude the null. Tolerability was excellent across all included studies, with no serious treatment-related adverse events and a long-term safety record consistent with the broader insomnia literature.

These findings indicate that melatonin should not yet be recommended as a stand-alone first-line therapy for unselected neuropathic pain, but that it merits cautious use as an adjunct in specific neurology indications — particularly painful diabetic peripheral neuropathy with concomitant sleep disturbance and selected post-surgical neurosensory deficits — where mechanistic plausibility and emerging clinical evidence converge. Caution is warranted in patients on anticoagulants, in pregnancy and lactation, and in paediatric populations outside specialist indications. The synthesis identifies clear priorities for future research: adequately powered etiology-stratified trials with harmonised pain–sleep–mood–fatigue outcomes; standardised dose–duration regimens informed by MT_2-receptor pharmacokinetics; formal evaluation in post-herpetic and trigeminal neuralgias which remain unstudied; individual-patient-data meta-analysis once additional trials are available; and registry-based pragmatic studies that capture real-world tolerability and adherence in low- and middle-income settings. Until such evidence emerges, melatonin should be considered a reasonable, low-risk and low-cost adjunctive option in carefully selected patients, prescribed within a multimodal analgesic strategy and integrated with addressable lifestyle, sleep-hygiene and disease-

modifying interventions appropriate to the underlying neurological condition.

6. References

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