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Systematic Review and Meta-analysis

Are Gabapentinoids Effective at Reducing Pain and Improving Sleep After Nerve Injury? A Systematic Review and Meta-analysis

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Abstract

Background Gabapentinoids are increasingly prescribed off-label to reduce the intensity of peripheral nerve injury–related pain and improve sleep. However, randomized controlled trials (RCTs) comparing gabapentinoids to placebo show differing results, and the crossover design used in some of these trials carries a significant risk of unblinding. Considering that side effects of gabapentinoids are common and misuse is increasing, we pooled the blinded data to provide the best available evidence on the efficacy of gabapentinoids compared with placebo.

Questions/purposes In this meta-analysis of RCTs of patients with peripheral nerve injuries, we asked: Are gabapentinoids superior to placebo in terms of (1) pain reduction or (2) mitigating sleep disruption?

Methods We searched PubMed, Embase, and Cochrane Library for RCTs from January 2000 up to January 2022. Only studies reporting on nerve injuries, measuring pain intensity with a VAS or numeric rating scale, were included. Our search yielded 1862 articles: 1218 from Embase, 559 from PubMed, and 85 from the Cochrane Library. We excluded 338 duplicate studies, leaving 1524 remaining studies. After an initial title and abstract screen, we excluded an additional 1512 studies. In all, 12 full texts were analyzed, and 4 studies were included in our meta-analysis, which involved 919 total patients: 402 were treated with either gabapentin or pregabalin, 394 with placebo, and 123 with both in two crossover trials. In the 3 of 4 studies wherein gender distribution of the patient populations was specified, women represented 57% (143 of 250) and 47% (118 of 250) of the patients in the treatment and placebo groups, respectively. The mean ± SD age was 52 ± 13 years for both the treatment and placebo groups. Risk of bias was assessed with the Cochrane Risk of Bias tool and was low for all included studies. We addressed the high risk of unblinding in the crossover trials by excluding the after crossover (unblinded) results. Certainty of evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was moderate. All included studies lacked an objective consensus reference test to diagnose peripheral nerve injury, therefore leading to indirectness of available results.

Results Gabapentinoids did not reduce pain compared with placebo at 1 month (-0.21 [95% confidence interval (CI) -0.72 to 0.29]; p = 0.40) nor at 2 to 4 months (-0.38 [95% CI -0.76 to 0.00]; p = 0.05) after treatment. Additionally, gabapentinoids showed no clinically important difference in sleep interference compared with placebo

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at 2 to 4 months (-0.56 [95% CI -0.91 to -0.22]; $p < 0.01$), with a minimum clinically important difference of -1.5.
Conclusion The best available evidence, now consisting of four RCTs, suggests that gabapentinoids should not be used to reduce pain intensity or sleep disruption in patients with peripheral nerve injuries, especially given their substantial side effects and potential for misuse.
Level of Evidence Level I, therapeutic study.

Introduction

About 2.8% of all patients with trauma presenting to a Level 1 trauma center have a peripheral nerve injury [26], and about one-half of these patients report experiencing substantial pain > 6 months after injury [23]. Pain and sleep are thought to have a bidirectional relationship [14]; pain can lead to poor sleep quality in up to 80% of patients [22], while poor sleep quality can lead to reduced pain tolerance [31]. Gabapentinoids such as gabapentin and pregabalin are increasingly prescribed to reduce pain intensity and improve sleep in patients with peripheral nerve injuries [3, 9], which represents off-label use of these drugs. Gabapentinoids have substantial side effects like dizziness, somnolence, and gait disturbance [24, 36], and reports of its misuse are increasing [17]. The number of patients to take gabapentinoids for one patient to experience side effects ranges from 3 to 11 depending on the adverse effect, with approximately 33% of patients experiencing somnolence and dizziness with higher dosages [24, 36].

To justify prescribing drugs with such substantial side effect profiles amidst a background of increasing misuse, these medications must consistently and substantially outperform placebo alternatives. Several randomized controlled trials (RCTs) have examined the effects of gabapentinoids on pain intensity and sleep disruption in patients with peripheral nerve injuries [10, 13, 21, 33]. However, some of these trials were small and the effect directions varied. Additionally, some trials used a crossover design [10, 13], which carries a significant risk of unblinding and subsequent overestimation of any positive effect ascribed to gabapentinoids.

Therefore, using a meta-analysis of RCTs of patients with peripheral nerve injuries, we asked: Are gabapentinoids superior to placebo in terms of (1) pain reduction or (2) mitigating sleep disruption?

Materials and Methods

This study was conducted in concordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [28].

Eligibility Criteria

We searched for RCTs comparing gabapentinoids with placebo using the following inclusion criteria: (1) studies pertaining to nerve injuries and (2) studies measuring pain intensity using either the VAS or numeric rating scale (NRS). We excluded studies if patients were diagnosed with diabetic neuropathy, postherpetic neuralgia, carpal tunnel syndrome, traumatic spinal cord injury, or any other nerve damage not related to a traumatic event. We also excluded gray literature (for example, preprint server papers, abstracts from annual meetings).

Information Sources and Search Strategy

We searched PubMed, Embase, and the Cochrane Library from January 2000 up to January 2022. We used the following keywords and Boolean operators: ('nerve injury' OR 'nerve repair' OR 'nerve grafting' OR 'nerve trauma' OR 'sciatica' OR 'carpal tunnel syndrome' OR 'complex regional pain syndrome') AND (gabapentin OR neurontin OR gralise OR horizant OR pregabalin OR lyrica). The search was restricted to studies either written in or translated to English. We hand-searched the references of the included articles to identify additional articles for inclusion.

Selection and Data Collection Process

Two independent authors (EKA, SNS) performed the initial title and abstract screen of all studies generated by our search and the full-text analysis on the remaining studies. Discrepancies were mediated by the senior author (TT). Data collection was done by two independent reviewers (EKA, NAK), and discrepancies were solved through discussion until a consensus was reached.

Data Items: Primary and Secondary Outcomes

All studies measured pain intensity with either the VAS or NRS, on a scale of 0 to 10, with higher scores corresponding to greater pain intensity. In studies that measured VAS on a scale of 0 to 100, we divided values by 10 to align with the 0 to 10 scale. The minimum clinically important difference (MCID) of VAS pain has been reported to range from 1.6 to 3.0; we chose an MCID of 2.0 for this study because of the high risk of side effects of gabapentinoids [16, 29].

Three studies [10, 21, 33] measured the daily sleep interference score, an 11-point score measuring how pain impacts sleep (0 indicating no interference and 10 indicating being completely unable to sleep because of pain).

Although no previous studies have determined the MCID for the daily sleep interference score, one study concluded that 1- to 2-point changes could be deemed clinically important [35]. Therefore, for the sake of our analysis, we assumed an MCID of -1.5 for the daily sleep interference score.

Two included studies reported outcomes at or around 1 month [10, 13], and two other studies reported outcomes between 2 to 4 months [21, 33]. We regarded the difference between a few weeks and 4 months after treatment too large to pool all studies. Therefore, both time points were used to analyze our primary and secondary outcomes. However, as only one study reported outcomes on sleep interference around 1 month [10], we could not pool results for our secondary outcome at 1 month. We decided to report the blinded and unblinded results from this one study for this time point.

Risk of Bias Assessment

Risk of bias was assessed by two authors (EKA, TT) using the Cochrane Risk of Bias tool [11]. Discrepancies were solved through discussion. All included studies were at low risk for bias in the randomization process, deviation from the intended intervention, missing outcome, measurement of the outcome, and selection of the reported results (Supplemental Fig. 1; http://links.lww.com/CORR/B388).

We used funnel plots to assess the publication bias of our outcomes of interest. The funnel plots indicate a lack of explicit publication bias but are unreliable with only four relevant studies.

Effect and Synthesis Measures

To assess differences in the effect of the treatment and placebo groups on pain intensity and sleep interference, we calculated the mean difference and 95% confidence intervals (CIs) of the mean score change from baseline between the two groups, with negative numbers indicating greater reduction in gabapentinoids than in the placebo group. For our meta-analysis, we used a random-effects model instead of a fixed-effects model because it was less likely to result in a spurious difference between treatments attributed to unobserved heterogeneity (a lower likelihood of a Type 1 error). Mean differences were considered statistically significant when $p < 0.05$. We assessed the heterogeneity with the I^2 statistic, and studies were considered statistically heterogeneous when $p < 0.1$ and $I^2 > 50\%$ [12]. For all endpoints, studies were relatively homogeneous (0% to 48%).

Two studies used a crossover design [10, 13]. Because gabapentinoids have substantial potential side effects, such as drowsiness and headache, the concern arose that a crossover design might result in unblinding after the crossover. Namely, patients taking placebo who switched to gabapentinoids would start to experience side effects and patients taking gabapentinoids would no longer experience side effects and realize that they had switched to placebo. This concern was substantiated by the finding that there was no difference in pain intensity favoring gabapentinoids before crossover, while there was a difference after crossover in both trials [1, 10]. We therefore decided to only use before-crossover data for the primary analysis. We report a separate sensitivity analysis that includes before- and after-crossover data. One crossover study did not report data before and after crossover separately [13], and we used its results as reported on ClinicalTrials.gov [1].

Certainty Assessment

We assessed certainty of evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. For both research questions, quality of evidence was moderate, meaning that the true effect is likely to be close to the effect estimate, but there is a possibility of substantial difference (Supplemental Table 1; http://links.lww.com/CORR/B388). All included studies were at a serious risk for indirectness (potentially not addressing the research question of interest directly) as none used a consensus reference test, or provided interpretation of such test, to diagnose peripheral nerve injuries. Therefore, all included patients had "suspected" but not confirmed nerve injuries.

Study Selection

We found 1862 articles with our search strategy: 1218 from Embase, 559 from PubMed, and 85 from Cochrane Library. We excluded 338 studies after deduplication, leaving 1524 remaining studies. After the initial title and abstract screen, we excluded an additional 1512 studies. In all, 12 full texts were analyzed, and 4 studies [10, 13, 21, 33] were included in our meta-analysis (Fig. 1).

Study Characteristics

All included studies were placebo RCTs, two of which were crossover studies. All but one study reported the confirmation of nerve injuries by pain specialists or neurologists, although no specific designations were given as to how to diagnose or grade nerve injuries (such as neuropraxia, axonotmesis, and neurotmesis). Two studies noted sporadic use of electrodiagnostic and/or sensibility tests but did not disclose specific cutoffs to determine presence or absence of a nerve injury [10, 21] (Table 1).

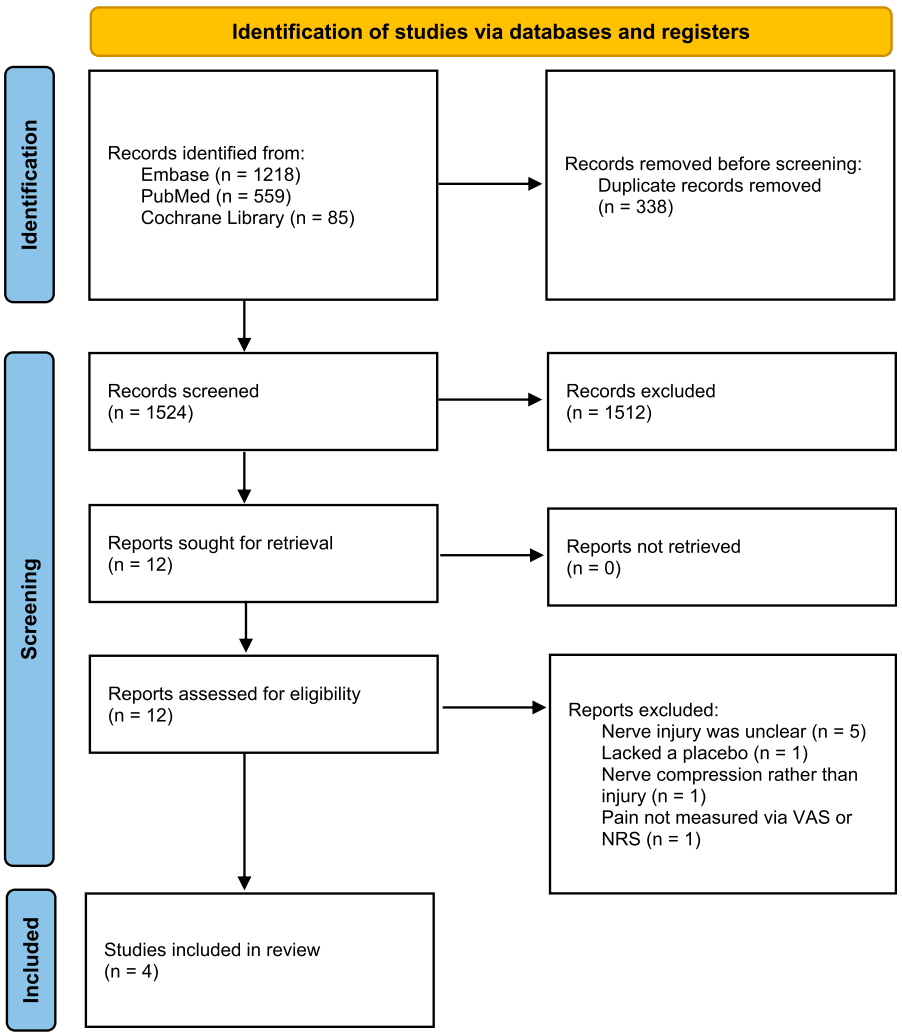

Fig. 1 This PRISMA flow diagram shows the study selection.

Of the 919 total patients, 402 were treated with either gabapentin or pregabalin, 394 were given a placebo, and 123 took part in both treatment groups. The gender distribution of the patient populations was specified in 3 of 4 studies we examined. In these studies, women represented 57% (143 of 250) and 47% (118 of 250) of the patients in the treatment and placebo groups, respectively. The mean ± SD age was 52 ± 13 years for both the treatment and placebo groups (Table 1).

Results

Difference in Pain Reduction

We found no difference between gabapentinoids and placebo in reduction in pain intensity (-0.21 [95% CI -0.72 to 0.29]; p = 0.40) 1 month after treatment (Supplemental Fig. 2; http://links.lww.com/CORR/B388). Including the unblinded data (Supplemental Fig. 3; http://links.lww.com/CORR/B388), there was no clinically important difference favoring gabapentinoids (-0.44 [95% CI -0.74 to -0.13]; p = 0.01) (Table 2). After 2 to 4 months, we found no difference in pain intensity (-0.38 [95% CI -0.76 to 0.00]; p = 0.05) (Supplemental Fig. 4; http://links.lww.com/CORR/B388).

Difference in Mitigating Sleep Disruption

We found no clinically important difference between gabapentinoids and placebo in reduction in sleep interference (-0.56 [95% CI -0.91 to -0.22]; p < 0.01) 2 to 4 months after treatment (Supplemental Fig. 5; http://links.lww.com/CORR/B388). After 1 month, a single study [10] reported no difference in sleep interference before (-0.39

Table 1. Study characteristics

Author [ref].	Study type	Drug studied	Drug dosage per day	Nerve injury diagnosis	Participants		Age in years		Women	
					Gabapentinoids	Placebo	Gabapentinoids	Placebo	Gabapentinoids	Placebo
Markman et al. [21]	RCT	Pregabalin	150 mg to 600 mg	Mostly subjective criteria[a]	51 (275)	49 (267)	53 ± 13	54 ± 13	NR	NR
van Seventer et al. [33]	RCT	Pregabalin	150 mg to 600 mg	Subjective criteria	50 (127)	50 (127)	52 ± 14	51 ± 13	61 (77)	41 (52)
Gordh et al. [10]	Quasi-RCT: crossover[b]	Gabapentin	300 mg to 2400 mg	Subjective criteria	100 (98)	100 (98)	49 ± NR	49 ± NR	53 (52)	53 (52)
Jenkins et al. [13]	Quasi-RCT: crossover[b]	Pregabalin	300 mg	Subjective criteria	100 (25)	100 (25)	50 ± 14	50 ± 14	56 (14)	56 (14)

Data presented as % (n) or mean ± SD. NR = not reported.
[a]Mostly subjective because nerve conduction studies confirming neuropathy were optional.
[b]Patients were randomized to receive either gabapentinoids or placebo in the first period, followed by a washout period, then switched to the alternate treatment in the second period.

[95% CI -0.95 to 0.17]; p = 0.17) and after unblinding (-0.33 [95% CI -0.72 to 0.062]; p = 0.10) (Table 3).

Discussion

Pain and poor sleep quality after nerve injury are common [6, 8, 22]. Gabapentinoids are increasingly prescribed for pain in general, and specifically—off label—for pain and sleep disruption after nerve injury [2, 9, 20, 30], although side effects are common. RCTs comparing gabapentinoids to placebo in peripheral nerve injuries show variable effects or are at substantial risk of unblinding. Accounting for appropriate blinding, our meta-analysis found no difference in pain intensity between gabapentinoids and placebo after suspected nerve injury and no clinical benefit in sleep mitigation. Given the lack of effectiveness, substantial side effects with a low number needed to harm, and increase in misuse, we recommend against the use of gabapentinoids to reduce pain intensity and sleep disruption after peripheral nerve injury.

Limitations

The findings of this study should be interpreted in light of some limitations. First, none of the studies consistently used a consensus reference test, such as surgical exploration, or electrodiagnostic studies to diagnose peripheral nerve injuries. Even if they had, peripheral nerve injuries are often accompanied by other injuries, such as fractures and lacerations. There currently is no consensus reference test to differentiate pain caused by a nerve injury from pain caused by concomitant injuries—a reason that we generally avoid the label "neuropathic pain." This means that our findings apply to suspected nerve injuries but not confirmed nerve injuries. We, and others [9], commonly encounter patients taking gabapentinoids for suspected nerve injury, so our findings do apply to actual clinical practice.

Second, we analyzed pregabalin and gabapentin together. There is a possibility that one drug is somewhat effective and the other is not. Separating them in a sensitivity analysis, excluding unblinded data, showed overlapping CIs, indicating no difference in effect on pain at 1 month (mean difference gabapentin -0.030 [95% CI -0.69 to 0.63] versus pregabalin -0.47 [95% CI -1.3 to 0.31]) [10, 13]. Only pregabalin was used for the other study endpoints, precluding further comparison. In clinical practice, gabapentinoids are often used interchangeably, legitimizing their combined analysis in our study.

Third, the change in daily sleep interference score that patients with peripheral nerve injury would deem clinically relevant is unknown. We used the suggested clinically relevant change based on patients with diabetic peripheral

Table 2. Meta-analysis of reported outcomes

Variable	Number of participants	Mean difference (95% CI)	Effect p value	Number of studies
Pain intensity				
After 1 month of treatment, appropriate blinding only	123	-0.21 (-0.72 to 0.29)	0.40	2
After 1 month of treatment, including unblinding	123	-0.44 (-0.74 to -0.13)	0.01	2
After 2 to 4 months of treatment	796	-0.38 (-0.76 to 0.00)	0.05	2
Sleep interference				
After 2 to 4 months of treatment	796	-0.56 (-0.91 to -0.22)	< 0.01	2

A negative number means greater reduction in gabapentinoid than placebo group. Both pain intensity and sleep interference were measured on a scale from 0 to 10. The MCID was assumed to be -2 for pain intensity and -1.5 for sleep interference.

neuropathy and postherpetic neuralgia [35]. Because an MCID is likely disease specific, the actual MCID might be different for patients with peripheral nerve injuries than the one we used. Still, we do not expect that a disease-specific MCID for nerve injury would be substantially small enough to result in a clinically relevant difference in sleep disturbance at 2 to 4 months.

Fourth, all studies excluded missing patients from their intention-to-treat analyses. This is likely to result in an overestimation of the apparent benefit of the intervention being studied, which strengthens our findings of the lack of a difference in pain intensity and a clinically relevant effect on sleep disturbance with gabapentinoids.

Fifth, some might regard the difference between 1 month of treatment and 2 to 4 months of treatment small enough to pool all studies. Because the 95% CI is outside the MCID for all endpoints, pooling all studies would not substantially change our results.

Sixth, this meta-analysis encompasses a relatively large number of patients (n = 919) but only four RCTs. Sensitivity analyses that omit studies to assess the stability of the findings result in a substantial decrease in sample size and are not as reliable with only four studies. Therefore, we did not perform additional sensitivity analyses because we did not expect that they would substantially change the interpretation of our findings.

Finally, some people advocate increasing the dosage when the patient experiences a limited effect on pain intensity. The daily dosage used in the studies included in this review ranged from 150 to 2400 mg. Side effects increase proportionally with increased dosage [17]. We find it unlikely that there is a threshold effect that was not reached in the included studies, and we are not sure that the increase in side effects outweighs such a currently unproven threshold effect.

Difference in Pain Reduction

We found no difference in change in pain intensity after suspected nerve injury between gabapentinoids and placebo at 1 month and 2 to 4 months after initiation of treatment. Our findings are in line with two Cochrane reviews that also found limited or no effect of

Table 3. Reported outcomes per study

Author [ref.]	Time of outcome assessment in weeks	Pain intensity, mean difference (95% CI)	p value	Sleep interference, mean difference (95% CI)	p value
Markman et al. [21]	15	-0.22 (-0.54 to 0.10)	0.18	-0.43 (-0.71 to -0.14)	0.0031
van Seventer et al. [33]	8	-0.62 (-1.1 to -0.15)	0.010	-0.79 (-1.3 to -0.34)	0.001
Gordh et al. [10][a]	5	-0.030 (-0.69 to 0.63)	0.93	-0.39 (-0.95 to 0.17)	0.17
Gordh et al. [10][b]	5	-0.46 (-0.88 to -0.036)	0.036	-0.33 (-0.72 to 0.062)	0.10
Jenkins et al. [13][a]	2	-0.47 (-1.3 to 0.31)	0.25		
Jenkins et al. [13][b]	2	-1.1 (-2.0 to -0.15)	0.034		

A negative number means greater reduction in gabapentinoid than placebo group. Both pain intensity and sleep interference were measured on a scale from 0 to 10. The MCID was assumed to be -2 for pain intensity and -1.5 for sleep interference.
[a]Before unblinding.
[b]After unblinding.

gabapentinoids on pain intensity other than postherpetic and concomitant with diabetic neuropathy, but both reviews did not specifically assess suspected nerve injury [7, 36].

In contrast to our results, a recent systematic review that used the same studies on pregabalin as our review and specifically looked at pain intensity after suspected nerve injury reported a decrease in pain intensity compared with placebo [20]. However, the authors did not account for the unblinding after the washout period, which we found to have a significant effect on the perceived benefit of gabapentinoids. In addition, the reported difference was below the lower limit of the MCID, rendering the difference not meaningful to patients.

Interestingly, in addition to the prior systematic review, all included RCTs report favorably on the use of gabapentinoids in peripheral nerve injury. However, the combined data of these studies (n = 919 participants) shows that gabapentinoids do not outperform placebo and the 95% CI does not exceed the MCID, even if lower thresholds would be used. This makes it unlikely that further RCTs will substantially change this finding.

In 2022, gabapentinoids were the tenth-most prescribed drug in the United States [4], but < 1% of them were prescribed for an FDA indication [5]. The rationale for use in suspected nerve injury seems extrapolated from the FDA approval of gabapentinoids for the treatment of pain from herpes zoster and diabetic neuropathy [19, 25]. It is noteworthy that both the manufacturer of gabapentin and pregabalin paid penalties for improper marketing for off-label use, particularly related to pain [15, 27, 32]. Additionally, the manufacturer of gabapentin manipulated trials to inflate the drug's effectiveness in treating neuropathy-related pain [15, 34]. Considering the above, we recommend against off-label use of gabapentinoids for reducing pain intensity in patients with suspected peripheral nerve injury.

Difference in Mitigating Sleep Disruption

We found no clinically relevant improvement of sleep with gabapentinoids compared with placebo at 2 to 4 months after initiation of treatment. This was supported by the results of a single study assessing sleep quality at 1 month. The previously mentioned systematic review specifically assessing suspected nerve injury found a similar small, possibly clinically irrelevant effect [20]. A systematic review including any use of gabapentinoids (such as for fibromyalgia, menopause, alcohol dependence, bipolar disorder) reported a small, likely not clinically important improvement in sleep compared with placebo for any condition [18]. Considering that we found no effect on pain intensity and that sleep improves with the use gabapentinoids for any reason, we expect that the small, likely negligible effect on sleep disruption can be ascribed to the common adverse effect of drowsiness.

Conclusion

In our meta-analysis, consisting of four RCTs, we found no difference in pain intensity and no clinically relevant effect on sleep disruption favoring gabapentinoids in patients with suspected peripheral nerve injuries. Currently, based on the best available evidence, we recommend against the off-label prescription of gabapentinoids for this indication, especially given their substantial adverse effects and potential for misuse.

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