Systematic Review

Pregabalin Combined With Opioids for Managing Neuropathic Pain in Patients With Cancer: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Background: Cancer-related neuropathic pain significantly affects patients' quality of life. Despite existing treatments, pain control remains inadequate for many of these patients. There is a lack of strong evidence for the efficacy of the combination of pregabalin, which is often used to treat neuropathic pain, and opioids for treating cancer-related neuropathic pain.

Objective: This study aimed to evaluate the analgesic effects and safety of pregabalin combined with opioids for managing cancer-related neuropathic pain through high-quality evidence analysis.

Study Design: A systematic review and meta-analysis of pregabalin combined with opioids for cancer-related neuropathic pain.

Methods: We systematically searched the PubMed, Web of Science, Embase, Cochrane Library and Cochrane Central Register of Controlled Trials databases from their inception through October 5, 2023. Two reviewers independently selected studies and extracted articles that met the inclusion and exclusion criteria. Quality assessments of the included studies were performed using the modified Cochrane Collaboration tool; data analysis was performed using RevMan 5.4 (The Nordic Cochrane Centre for The Cochrane Collaboration).

Results: A total of 8 studies were included in our qualitative synthesis, and 6 studies were included in the meta-analysis (6 studies with 757 patients, including 342 in the experimental group and 415 in the control group). The results showed a significant difference between the pregabalin combined with opioids group and the opioids alone group in terms of Numeric Rating Scale (NRS-11) pain scores (weighted mean difference [WMD] = -1.00; 95% CI, -1.29 to -0.70; $P < 0.001$). However, no significant difference in the NRS-11 score was observed between the pregabalin combined with opioids group and active comparator combined with opioids group (WMD = -0.47; 95% CI, -1.05 to 0.11; $P = 0.11$). There was a significant difference between the pregabalin combined with opioids group and the active comparator combined with opioids group in terms of extra morphine milligram equivalents (relative risk [RR] = 0.37; 95% CI, 0.20 to 0.70; $P = 0.002$). No significant difference was observed in quality of life (WMD = -2.01; 95% CI, -5.29 to 1.27; $P = 0.23$). In general, the frequency of adverse events in the pregabalin combined with opioids group was greater than that in the opioids alone group, but the frequency of adverse events between the pregabalin combined with opioids group and the active comparator combined with opioids group was unclear.

Limitations: The limited number of articles and sample size are the limitations of this meta-analysis

Conclusions: Pregabalin combined with opioids reduces cancer-related neuropathic pain but increases dizziness, somnolence, and peripheral edema, thus supporting its use in the clinic for treating cancer-related neuropathic pain. However, further high-quality randomized controlled trials are needed to confirm these findings.

Key words: Pregabalin, cancer pain, meta-analysis, systematic review

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Cancer is increasing as the population ages, with an estimated 19.3 million new cancer cases occurring in 2020 (1). Cancer-related neuropathic pain is frequently diagnosed in patients with cancer (2). Cancer-related neuropathic pain causes include local effects on tumor growth and local invasion and side effects of cancer treatment; chemotherapy-induced peripheral neuropathy occurs in 90% of patients receiving neurotoxic chemotherapy (3). This pain can have physical, psychological, and social effects, affecting patients' quality of life and functioning and even reducing survival rates (4).

Uncontrollable pain remains a problem for many patients with cancer (5). Inadequate analgesic treatment for pain has been identified in approximately 40% of patients with cancer (6). Since 1986, the World Health Organization's 3-step cancer pain relief ladder has recommended opioids for moderate to severe pain. However, opioids are often accompanied by adverse events, with half of patients experiencing drowsiness, constipation, and dry mouth (7,8). Evidence-based pharmacotherapies for cancer-related neuropathic pain include anticonvulsant drugs (mainly pregabalin and gabapentin) and tricyclic antidepressants (mainly nortriptyline and amitriptyline) (9). Evidence has emerged indicating that 2 or more analgesics with different mechanisms could have additive or synergistic effects when used together, thus reducing the dose of each and alleviating their respective side effects (10). For patients who have an incomplete response to opioids, a combination of adjuvant analgesics such as antiepileptics or antidepressants is usually recommended (11).

Pregabalin is an $\alpha 2\delta$ ligand that has analgesic, anxiolytic, and anticonvulsant effects (12). Pregabalin is among the new drugs commonly used to treat neuropathic pain. Neuropathic pain manifestations are extensive, such as postherpetic neuralgia, painful diabetic neuralgia, and phantom limb pain (13). Pregabalin has been widely used in the management of neuropathic pain worldwide (14). Compared with gabapentin, pregabalin has favorable pharmacokinetic characteristics (15). According to previous studies, pregabalin is 3 to 10 times more effective as an antiepileptic than gabapentin and 2 to 4 times more effective as an analgesic for neuropathic pain (16).

Previous studies and systematic reviews have reported the pregabalin's effect on managing neuropathic pain in adults with cancer (17,18). However, few articles were included, and most of them were observational studies or case reports. Strong evidence to support pregabalin's effectiveness in cancer pain management is lacking. Because of this, we decided to integrate high-quality evidence in order to evaluate and analyze the analgesic effects and safety of pregabalin combined with opioids in cancer-related neuropathic pain.

Methods

Search Strategy

Our investigation was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This research was also conducted in accordance with a predesigned protocol that was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42023481742). We systematically searched the PubMed, Web of Science, Embase, Cochrane Library and Cochrane Central Register of Controlled Trials (CENTRAL) databases from inception through October 5, 2023.

Two researchers (C.B. and M.Y.) independently evaluated study eligibility in 2 phases. Disagreements between researchers were resolved through discussion and consensus; if necessary, the senior author (S.L.) was consulted to make a final decision. To avoid omission, subject terms and key words, such as "pregabalin," "pain," "cancer," "neoplasm," "tumor," "RCT." and "random," were included as part of the structured search strategy.

Eligibility Criteria

We undertook a systematic review and meta-analysis of randomized controlled trials (RCTs). If an RCT met the following inclusion criteria, it was included in the meta-analysis: 1) the patients' ages were at least 18; 2) neuropathic pain had to be due to cancer or cancer treatment; 3) the experimental group took pregabalin combined with opioids and the control group took either a placebo or other drugs combined with opioids. The exclusion criteria were as follows: the reason for excluding any given study was that it was not an RCT.

Data Extraction

Data extraction was completed by two researchers (C.B. and M.Y.) and a standardized data extraction form on Microsoft Excel version 2019 (Microsoft Corp.) was adapted for this study. The following data were extracted: study design; the name of the first author; year of publication; study drug combination and compara-

tors; dosages; pain control; primary outcomes reported; and the incidence of adverse events. We consulted the corresponding authors for any inaccessible articles, but received no response.

Risk of Bias Assessment

Two reviewers (C.B. and M.Y.) independently performed the risk-of-bias assessment on all included RCTs using the criteria outlined in the modified Cochrane Collaboration tool (RoB 2 [(The Nordic Cochrane Centre for The Cochrane Collaboration]) (19). If there were disagreements, the original text was reviewed, and a consensus was reached via discussion. Studies were categorized as having a high risk of bias, some concerns, or a low risk of bias in the following 6 domains: 1) randomization process and timing of identification or recruitment of patients; 2) deviations from the intended interventions; 3) missing outcome data; 4) outcome measurement; 5) selection of the reported result; and 6) overall bias.

Outcome Data Analysis

The primary outcome data were the mean pain score at baseline and at final assessment as well as the corresponding SDs (mean change in pain from baseline). The pain score included outcomes reporting an assessment of pain intensity using a recognized pain scale (e.g., Visual Analog Scale [VAS] or Numeric Rating Scale [NRS-11]). We converted all pain scores into straight lines ranging from 0 to 10 cm in length (0 means no pain, 10 means maximum pain).

Statistical Analysis

RevMan 5.4 (The Nordic Cochrane Centre for The Cochrane Collaboration) was used for data analysis. All medians, ranges, and/or interquartile intervals are converted to mean and SDs. When dealing with continuous data, weighted mean differences (WMD) and 95% CIs were used to process the data. For dichotomous data, risk ratios (RRs) and 95% CIs were calculated. The changes in pain scores between the experimental group and the control group were compared. The coefficient I2 was calculated to assess heterogeneity and thresholds were predefined for low (25%–49%), medium (50%–74%), and high (≥ 75%) levels. In cases of moderate or high heterogeneity, a random effects model was applied; otherwise a fixed effects model was employed. The statistical significance was set at a level of $P < 0.05$.

Results

A total of 336 trials were initially identified in our literature search; ultimately, 8 studies involving a total of 837 patients met the inclusion criteria (8 studies were included in our qualitative synthesis and 6 studies were included in the meta-analysis) (20-27). (Fig. 1)

Included Studies Characteristics

Our review included 8 RCTs with a total of 10 comparisons. In a double-blind study by Mishra, et al (25), which examined pregabalin versus common neuropathic analgesics (gabapentin and amitriptyline)

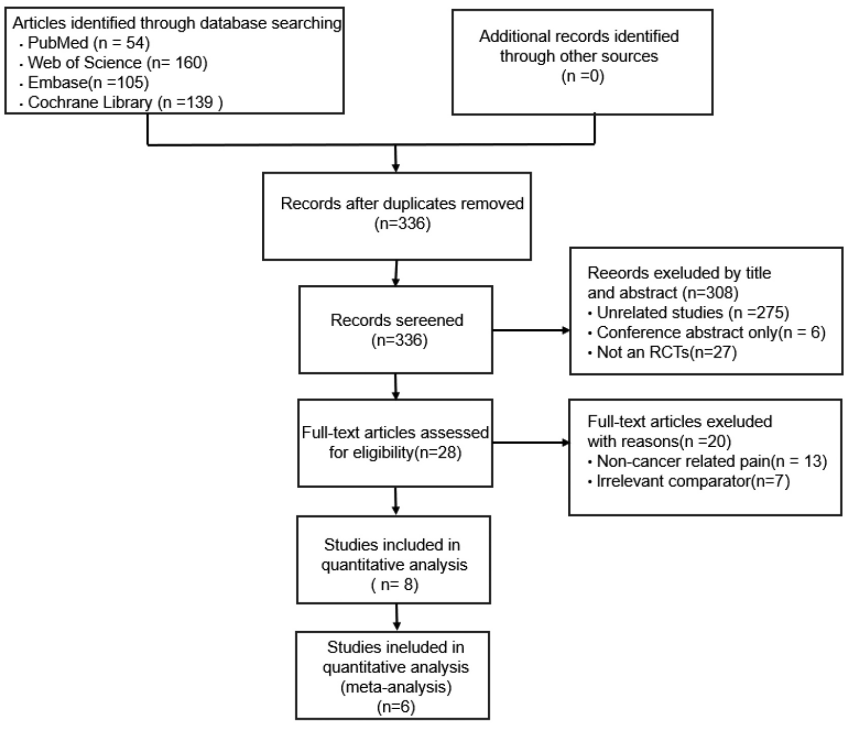

Fig. 1. *Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram.*

and placebo, we included each of the 3 sets of data from their study in our meta-analysis. The experimental group received pregabalin combined with opioids. For the control groups, 6 studies used opioids alone, and 4 studies used an active comparator (amitriptyline, gabapentin, duloxetine) combined with opioids. Doses of pregabalin varied from 25 mg to 600 mg daily; the lowest recommended dose is 300 mg. The features of the included studies are summarized in Table 1.

Risk-of-Bias and Quality-of-Evidence Assessment

The RoB 2 tool (Fig. 2) revealed that the majority of trials had a low risk of bias. Seven trials demonstrated a low risk of bias, one trial demonstrated some concerns of bias, and no trials demonstrated a high risk of bias.

Primary Outcome

We excluded 2 trials from the meta-analysis. The study by Mercadante, et al (23) could not be included in the meta-analysis because they used a low dose of pregabalin (25 mg–150 mg) while the rest of the articles used 150 mg–600 mg of pregabalin. Additionally, the study by Dou, et al (24) could not be included in our meta-analysis because their primary endpoint was the decrements in morphine dose without data on pain scores. Ultimately, 6 studies were included in the meta-analysis, encompassing 757 patients (342 patients in the experimental group and

Table 1. *Included studies characteristics*.

Reference	Setting	Pain Origin	Groups		Number of Patients Completed		Primary Outcome	Adverse Events Reported
			Experimental	Control	Experimental	Control		
Sjölund, et al (2013)	Kingdom of Sweden	Cancer-induced bone pain	Pregabalin (100 mg-600 mg)	Opioids	72	80	DAAC	Yes
Jiang, et al (2019)	People's Republic of China	Radiotherapy-related NP (head and neck cancer)	Pregabalin (150 mg-600 mg)	Opioids	64	64	NRS-11 scores	Yes
Fallon, et al (2016)	United Kingdom of Great Britain and Northern Ireland	Cancer-induced bone pain	Pregabalin (150 mg-600 mg)	Opioids	116	117	improvement in cancer-induced bone pain	Yes
Mercadante, et al (2013)	Italian Republic	Advanced cancer	Pregabalin (25 mg-150 mg)	Opioids	16	28	Pain intensity	Yes
Dou, et al (2017)	People's Republic of China	Cancer NP	Pregabalin (75 mg-300 mg)	Opioids	18	18	The decrements in morphine dose (MMEs)	Yes
Mishra, et al (2012) (A)	Republic of India	Cancer NP	Pregabalin (150 mg-600 mg)	Opioids	30	30	NRS-11 scores	Yes
Mishra, et al (2012) (B)	Republic of India	Cancer NP	Pregabalin (150 mg-600 mg)	Amitriptyline	30	30	NRS-11 scores	Yes
Mishra, et al (2012) (C)	Republic of India	Cancer NP	Pregabalin (150 mg-600 mg)	Gabapentin	30	30	NRS-11 scores	Yes
Gül, et al (2020)	Republic of Turkey	Lung cancer NP	Pregabalin (300 mg)	Duloxetine	20	22	VAS scores	No
Avan, et al (2018)	Islamic Republic of Iran	Chemotherapy-induced NP (breast cancer)	Pregabalin (150 mg)	Duloxetine	40	42	Mean global health status/ QoL, pain, insomnia, and emotional functioning scores	Yes

NP, neuropathic pain; DAAC, duration-adjusted average change; MMEs, morphine milligram equivalents; NRS-11, Numeric Rating Scale; VAS, Visual Analog Scale; QoL, quality of life.

415 patients in the control group). The studies recorded pain scores at baselineand at final assessment, and the difference in scores between baseline and final assessment. Six studies reported the NRS-11 scores. Studies using pregabalin combined with opioids (n = 282) versus opioids alone (n = 291) were pooled using a fixed effects model. The pooled WMD was -1.00 (95% CI, -1.29 to -0.70; $I^2 = 0\%$; $P < 0.001$), thus indicating a statistically significant difference (Fig. 3). Studies using pregabalin combined with opioids (n = 90) versus an active comparator combined with opioids (n = 124) were pooled using a random effects model. The pooled WMD was -0.47 (95% CI, -1.05 to 0.11; $I^2 = 78\%$; $P = 0.11$), indicating a nonsignificant difference (Fig. 3). Due to the limited number of included articles, publication bias was not assessed.

Secondary Outcomes

Mishra, et al (25) reported the use of extra morphine (morphine milligram equivalents [MMEs}) as a rescue drug in their groups; the control group was treated with an active comparator combined with opioids. The studies using pregabalin combined with opioids (n = 30) versus an active comparator combined with opioids (n = 60) were combined using a fixed effects model. The RR of the combined data was 0.37 (95% CI, 0.20 to 0.70; $I^2 = 0\%$; $P = 0.002$. This difference was statistically significant (Fig. 4).

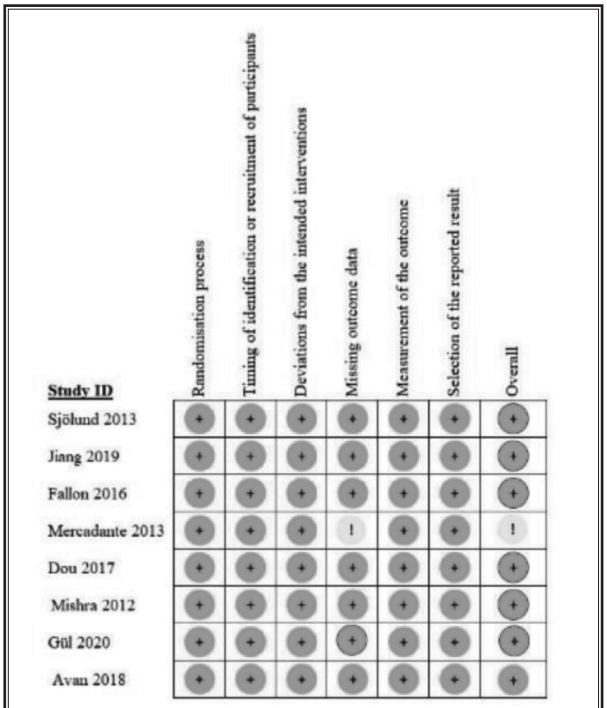

Fig. 2. *Risk of bias summary of included trials: evaluation of bias risk items for each included study. Green circle, low risk of bias; yellow circle, unclear risk of bias.*

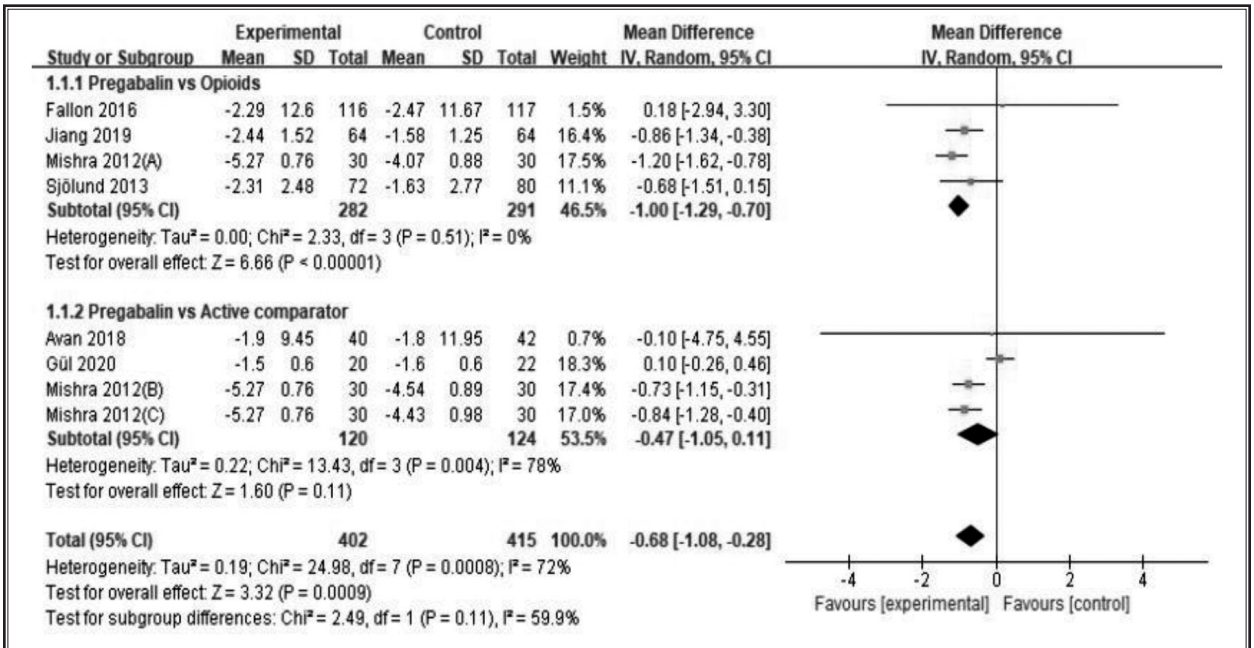

Fig. 3. *Forest plot of pain scale decline.*

Three studies reported the modified Brief Pain Inventory Short Form (mBPI-sf) (20-22); the control group was opioids alone. The studies using pregabalin combined with opioids (n = 252) versus opioids alone (n = 261) were pooled using a random effects model. The pooled WMD was -2.01 (95% CI, -5.29 to 1.27; I^2 = 79%; *P* = 0.23) indicating a nonsignificant difference (Fig. 5).

The Hospital Anxiety and Depression Scale (HADS) includes a 2-part assessment of "anxiety" and "depression." One study (20) reported the mean and SD HADS scores at rest. The results showed that scores on the HADS-A (anxiety) and HADS-D (depression) subscales were higher for patients who received pregabalin than for those who had received a placebo. However, another study (22) only mentioned the HADS scale without sorting out the data of the 2 subscales separately. There was a difference in HADS score between study arms (WMD -1.1; 95% CI, -2.1 to 0.1; *P* = 0.031).

Adverse Events

In addition to the study by Gül et al (26), all other studies reported adverse events (AEs), although the methods of reporting varied widely. The most commonly reported AEs associated with pregabalin treatment were dizziness, somnolence, peripheral edema, nausea, vomiting, fatigue, diarrhea, and headache.

Three studies (20,21,24) provided data on dizziness, somnolence, and peripheral edema. When comparing pregabalin plus opioids (n = 176) to opioids alone (n = 184), the pooled relative risk (RR) for dizziness was 2.34 (95% CI 1.26, 4.37; I^2 = 0%, *P* = 0.007), for somnolence was 3.78 (95% CI 2.12, 6.73; I^2 = 0%, *P* < 0.001), and for peripheral edema was 3.44 (95% CI 1.12, 10.51; I^2 = 6%, *P* = 0.03), all indicating statistically significant differences (Fig. 6).

Three studies (20,22,24) assessed nausea and vomiting. When comparing pregabalin plus opioids (n = 228) to opioids alone (n = 237), the pooled RR for nausea/vomiting was 0.95 (95% CI 0.65, 1.38; I^2 = 0%, *P* = 0.78), showing no significant difference (Fig. 6).

Two studies (20,21) reported rates of diarrhea and headache. In the comparison of pregabalin plus opioids (n = 136) with opioids alone (n = 144), the pooled RR for diarrhea was 2.67 (95% CI 0.85, 8.38; I^2 = 0%, *P* = 0.09), and for headache it was 1.73 (95% CI 0.65, 4.61;

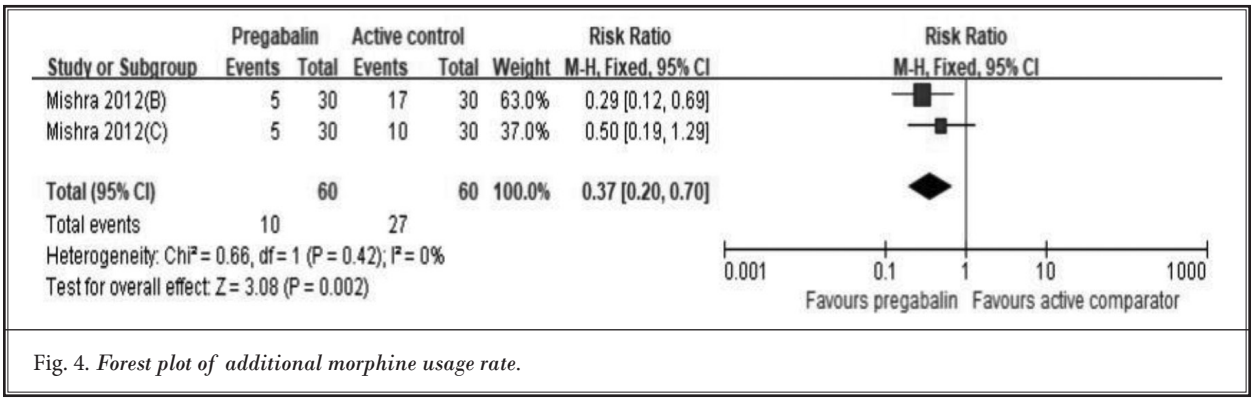

Fig. 4. *Forest plot of additional morphine usage rate.*

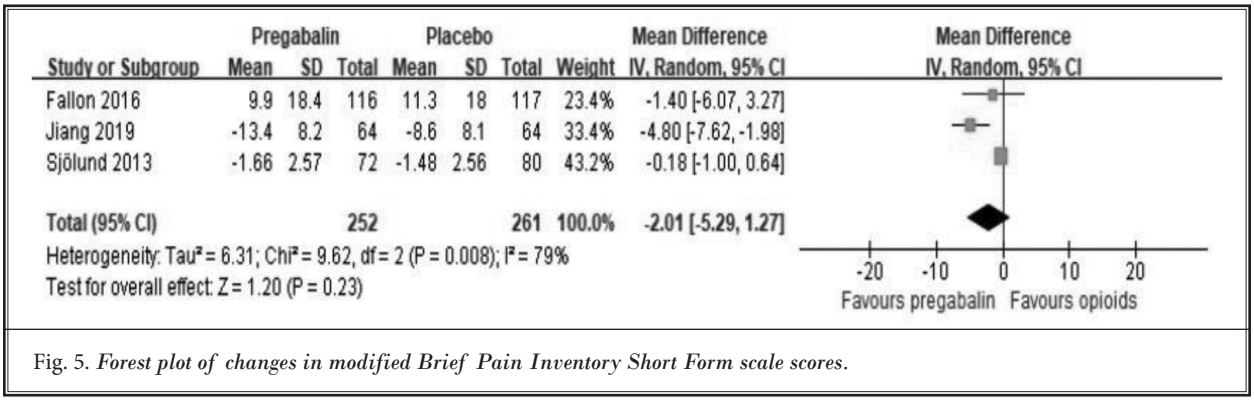

Fig. 5. *Forest plot of changes in modified Brief Pain Inventory Short Form scale scores.*

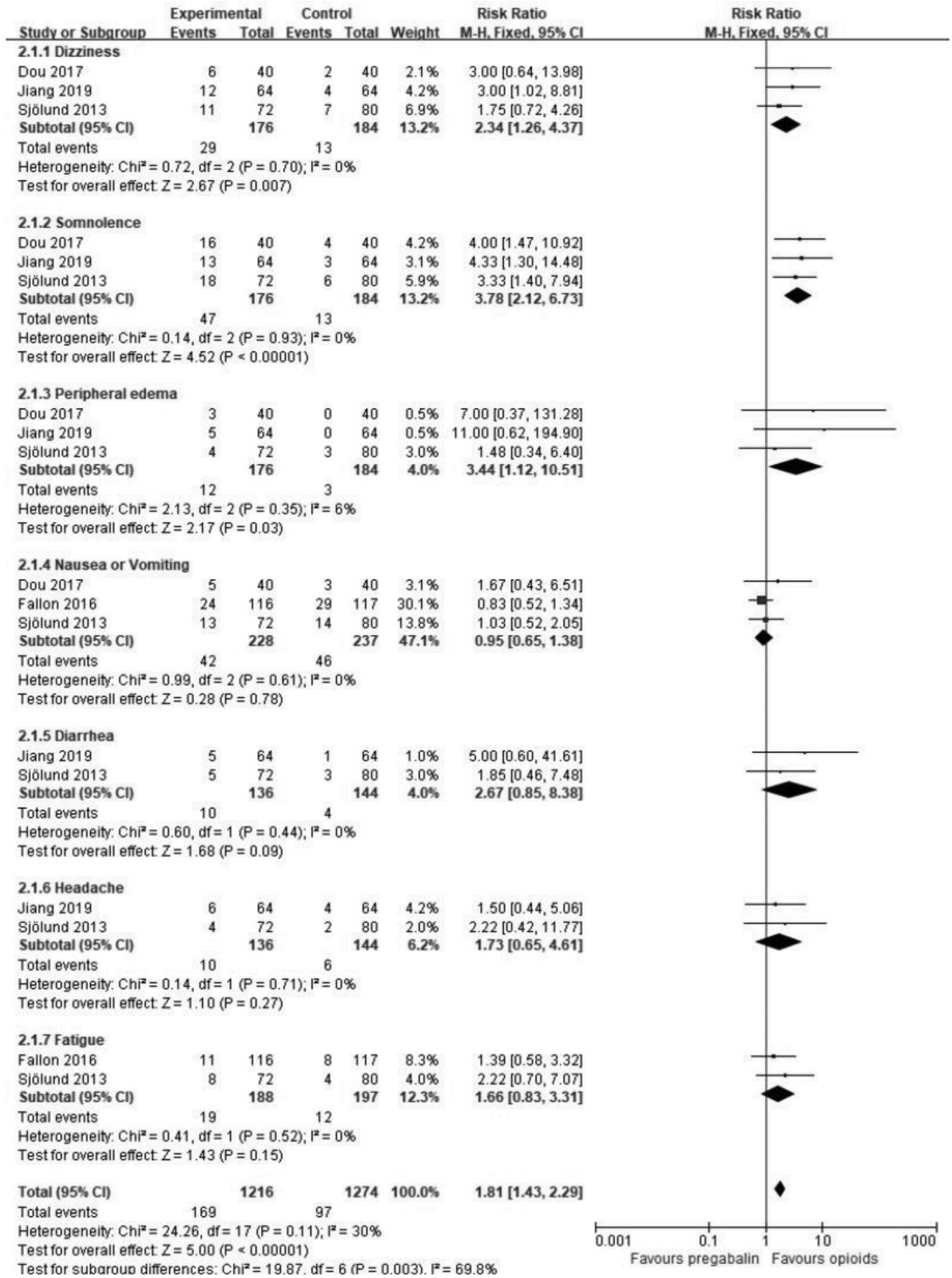

Fig. 6. *Forest plot of adverse events incidence.*

I^2 = 0%, *P* = 0.27). Neither difference was statistically significant (Fig. 6).

Two studies (20,22) evaluated rates of fatigue. Comparing pregabalin plus opioids (n = 188) with opioids alone (n = 197), the pooled RR for fatigue was 1.66 (95% CI 0.83, 3.31; I^2 = 0%, *P* = 0.15), suggesting no significant difference (Fig. 6).

Overall, the incidence of AEs such as dizziness, somnolence, peripheral edema was higher in the pregabalin plus opioids group than the opioids alone group. However, there was no difference between the two groups for nausea, vomiting, diarrhea, headache. and fatigue.

Discussion

The evidence from published RCTs suggests that pregabalin combined with opioids reduces pain in patients with cancer compared to opioids alone, but this difference is not statistically meaningful compared to an active comparator combined with opioids. Compared with opioids alone, pregabalin combined with opioids significantly increased the risk of adverse events, including dizziness, somnolence, and peripheral edema, but had no effect on other adverse events. Compared with an active comparator, pregabalin reduces the use of additional MMEs. There was insufficient evidence to assess the effect on the Brief Pain Inventory Short Form. The analysis presented here demonstrates that pregabalin combined with opioids has additional benefits in treating cancer pain, but causes a higher incidence of dizziness, somnolence, and peripheral edema.

We identified several published reviews evaluating the effectiveness of pregabalin for the managing cancer pain; our results are partly consistent with these findings. Our results are consistent with previous research (10,28) supporting the use of adjuvant analgesics (antidepressants and gabapentanoids) to treat neuropathic pain, both for cancer and non-cancer pain. However, Kane et al (18) showed that the addition of adjuvant analgesia (antidepressants or antiepileptic drugs) to opioids for cancer pain had no additional benefit compared to the use of opioids alone and that it increased the incidence of adverse events. However, due to the heterogeneity of patients, benefits for those with definite neuropathic cancer pain cannot be excluded. Bennett, et al (17) showed that no conclusions have been drawn on the descriptive summary of pregabalin for the treatment of cancer pain due to limitations of their studies since only one RCT has been conducted.

We identified a number of guidelines that recommend the use of pregabalin for treating cancer-related neuropathic pain. Some of these guidelines are consistent with our results. The European Society for Medical Oncology (29) clinical practice guidelines state that pregabalin is a single agent for first-line neuropathic pain treatment and recommend that cancer-related neuropathic pain be treated using opioids in combination with anticonvulsants when opioids alone provide insufficient pain relief. Moreover, the guidelines point to a lack of high-quality RCTs in the context of cancer-related pain, and that future RCTs with large samples should be carried out. The National Comprehensive Cancer Network (30) clinical practice oncology guidelines indicate that adjuvant analgesics (e.g., gabapentin and pregabalin) can help patients manage bone pain, neuropathic pain, and visceral pain, reducing the need for opioids. Adjuvant analgesics can be helpful for patients whose pain is only partially responsive to opioids. Although improvements have been observed, undertreatment of pain remains a problem for a large group of patients with cancer.

The studies we included were generally of high quality; most were randomized controlled double-blind studies. However, there are several limitations. First, most of the included studies had small sample sizes, which led to a risk of bias. Second, due to the limited number of references included, we did not assess the extent to which different doses of pregabalin affected the outcome. In addition, the benefits and harms of pregabalin were not analyzed by specific cancer type. Third, only a few studies have evaluated the role of pregabalin in anxiety and depression, Patient Global Impression of Change and Clinical Global Impression of Change. Future trials should further evaluate the role of pregabalin in these outcomes. Finally, most of the included studies were single-center RCTs.

Conclusion

Our meta-analysis of 6 high-quality RCTs demonstrates that pregabalin combined with opioids reduces pain in patients with cancer compared to opioids alone but increases the risk of some adverse events, supporting its use in the clinic for the treatment of cancer-related pain. Because few studies are available in this field and current evidence remains limited, this conclusion should be further confirmed by RCTs with adequate methodological quality.

Acknowledgments

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Data Availability

All analyses were based on previously published studies; thus, no informed consent is required.

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