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# A critical appraisal of gabapentinoids for pain in cancer patients

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## Abstract

*Purpose of review:* Gabapentinoids are frequently used in the management of cancer pain. In recent Cochrane systematic reviews, whilst there was an abundance of evidence relating to non-cancer pain, only a few studies related to cancer pain. This review summarises recent randomised controlled trials evaluating the use of gabapentinoids for tumour-related (as monotherapy or part of combination therapy) and treatment-related pain.

*Recent findings:* For tumour-related pain, 10 out of 13 studies showed statistically significant benefits in favour of gabapentinoids. When used, as part of monotherapy or combination therapy,

benefits were observed in 5 out of 6 studies evaluating gabapentin, and in 6 out of 8 studies evaluating pregabalin. For treatment-related pain, none of the 4 studies (2 gabapentin, 2 pregabalin) showed statistically significant benefits in favour of gabapentinoids. Unfortunately many of the studies included were limited by small sample size, lack of blinding and inadequate follow-up.

*Summary:* More and better quality studies are required, although this may be challenging to accomplish in this patient population. Gabapentinoids may offer benefits to cancer patients with pain but careful titration and monitoring of adverse effects is necessary.

*Keywords: pregabalin; gabapentin; cancer pain*

# Introduction

The prevalence of pain in patients with cancer is over 50% [1]. Pain is often of moderate-to-severe intensity [2] and can be related to the tumour itself, cancer treatments or comorbid conditions [3]. The World Health Organisation 3-step analgesic ladder recommends the use of escalating analgesics (non-opioids to mild then strong opioids) with the use of adjuvants at each stage to achieve optimal pain control [4].

Gabapentinoids (gabapentin and pregabalin) are a type of adjuvant and anti-epileptic. They bind to the α2δ subunit of pre-synaptic N, P/Q type voltage-gated calcium channels [5] in the spinal dorsal horn [6], causing reduced cell-surface expression [7], and subsequent reduction in calcium influx and neurotransmitter release [6, 8]. α2δ subunits upregulation has been found in neuropathic pain and persistent inflammatory states [9, 10, 11]. Gabapentinoids also affect descending inhibitory pathways by reducing GABA transmission in the locus coeruleus [6, 12, 13]. Table 1 provides further details about their pharmacokinetics and information for prescribing.

Gabapentinoids have an established evidence base for use in the treatment of non-cancer neuropathic pain, including diabetic neuropathy, post-herpetic neuralgia and central neuropathic pain, comparable with antidepressants [15, 16, 17, 18, 19, 20, 21]. Recent Cochrane reviews of the management of neuropathic pain and gabapentinoids demonstrate a lack of studies investigating their use in cancer pain. No studies were identified for pregabalin use in acute and chronic pain in adults with cancer neuropathic pain [20]. Only three studies related to cancer pain management in a systematic review evaluating gabapentin in the management of chronic neuropathic pain in adults [21].

We have included evidence for the use of gabapentinoids in tumour- and treatment-related cancer pain in adult patients, focusing on randomised controlled trials (RCTs) within the last five years to demonstrate the most recent and highest quality of evidence. We have only included English-language papers.

## Tumour-related pain

The specific nature of pain is not always well-defined but most studies involve neuropathic or bone pain. Gabapentinoids have largely been evaluated in combination with other analgesics but a few studies evaluate their use as monotherapy. For the purposes of this review, monotherapy was defined as the use of gabapentin/pregabalin alone with no other regular analgesic, adjuvant or disease modifying treatment. Studies allowing 'as required' short-acting opioids as rescue medication were still classified as monotherapy studies as the overall daily consumption is often inconsistent and poorly defined. Combination therapy was defined as the use of gabapentin/pregabalin in combination with an alternative analgesic, adjuvant or disease modifying treatment. Controls were either placebo, an alternative analgesic, adjuvant or disease modifying treatment. Table 2 summarises and provides further detail about included tumour-related pain studies.

## Monotherapy studies

In their open-label study, Raptis *et al* [22] identified 120 patients with moderate-severe neuropathic cancer pain (NCP), uncontrolled on mild opioids. 60 patients were randomised to pregabalin and 60 patients to transdermal fentanyl. 73.3% of the pregabalin group achieved at least a 30% reduction in the visual analogue score (VAS) for pain, in comparison to 36.7% in the fentanyl group ($p<0.0001$). Other statistically significant outcomes in favour of pregabalin were mean change in VAS score from

baseline and final VAS score. This study shows some evidence of the benefit of pregabalin over fentanyl. It included patients with chemotherapy-induced neuropathy and tumour-related pain and the extent to which findings can be extrapolated to either group is unknown.

Mishra *et al* [23] compared pregabalin with gabapentin, amitriptyline and placebo in groups of 30 patients with severe NCP for 4 weeks. Results favoured pregabalin over all other groups with a reduction in mean VAS score from 7.77 to 2.5, and significantly lower scores in comparison with amitriptyline by week 3, and gabapentin and placebo by week 4. Scores were comparable at baseline and final VAS scores were 3.07, 3.23 and 3.4 for gabapentin, amitriptyline and placebo respectively. The pregabalin group also showed the greatest improvements in dysesthesia, burning and lancinating pain (statistically significant), but not allodynia. Gabapentin showed favourable outcomes over amitriptyline and placebo for burning and lancinating pain. However, there was no comparison of the differences between baseline and final outcomes. Therefore, the data is limited and it is unclear if pregabalin is superior.

## Combination therapy studies

RCTs have evaluated gabapentinoids in combination with opioids alone, and opioids in conjunction with both radiotherapy and antidepressants.

## Combination with opioids alone

In 2004 Caraceni *et al* [24] reported on the first placebo-controlled study of gabapentin in combination with opioids for NCP. 79 patients received gabapentin and 41 patients received placebo over 10 days. Both groups had comparable and stable opioid dosing (~100mg/day oral morphine equivalent). Gabapentin combined with opioid showed lower global pain scores compared to placebo (4.6 vs. 5.4 respectively on 0-10 numerical rating scale (NRS)). The proportion of patients

with ≥33% reduction in pain showed more responders in the gabapentin group on day one (24% versus 15%), however, by day five the group differences converged. There were no differences in common neuropathic pain symptoms and signs reported between the groups. In the Gabapentin group, 70% of patients required the maximum daily dose (1800mg), and one third still reported pain >5/10 on the final follow-up day. Although there is some evidence of additional benefit using gabapentin-opioid combination therapy, it may be minimal and may be offset by drug-related adverse events.

In 2007, Keskinbora *et al* [25] conducted an open label study of gabapentin for NCP. 75 patients were randomised to receive gabapentin plus opioid or to continue on opioid therapy alone. The authors reported significantly lower mean pain scores after 2 weeks (compared to baseline) for both groups; however, the drop in pain scores was significantly greater for the gabapentin plus opioid group. In contrast to Caraceni et al. [24], Keskinbora et al. [25] demonstrated a clear therapeutic effect of gabapentin when used in combination with 140mg/day oral morphine equivalent dose.

In an open-label study, Mercadante *et al* [26] compared opioid monotherapy to a combination of opioid and adjuvant pregabalin in 70 advanced cancer patients with unclassified cancer pain. Over an eight week follow-up period there were no differences in pain intensity, medication side-effects, pain interference with daily activities or quality of life between the two groups. The authors concluded that their flexible approach to dosing pregabalin, the small sample and between group heterogeneity (pain aetiology and pain mechanisms) may account for the negative findings. Nevertheless, the doses of pregabalin used were much lower than other pregabalin studies and may reflect cautious prescribing.

Garassino *et al* [27] compared two escalating strategies for pregabalin and oxycodone combination therapy for NCP in a multicentre RCT. 38 patients were allocated to fixed oxycodone dose with

increasing titration of pregabalin (Group A); and 37 patients were allocated to fixed pregabalin dose with increasing titration of oxycodone. Follow-up was 2 weeks, after which 77% of patients in Group A achieved at least 33% reduction in pain intensity (compared to baseline) versus 64% in Group B. The difference was not significant. There were fewer side effects and rescue doses for breakthrough pain reported in Group A. The authors concluded that both titration strategies resulted in adequate pain relief, and indicated a preference for a pregabalin titration strategy (Group A), reasonable given the secondary outcomes.

Sjolund *et al* [28] compared flexible-dose pregabalin with placebo, both in combination with stable opioid therapy in 152 patients with cancer-induced bone pain (CIBP). After 28 days follow-up the mean change from baseline in worst pain score favoured pregabalin over placebo (-1.53 *vs* -1.23). There were similar changes in average pain and sleep interference in favour of pregabalin. The frequency of side effects was higher in the pregabalin group compared to the placebo group. The authors did not undertake statistical comparisons due to early termination of the trial due to positive effects in the pregabalin-opioid combination arm. Therefore, definitive conclusions cannot be drawn.

In 70 cancer patients with unspecified severe pain, Chen *et al* [29] randomised patients to receive gabapentin in combination with oxycodone, or oxycodone alone. The authors describe the primary outcome pain intensity on 0-100mm VAS but no data are reported in the results. Baseline daily average oxycodone doses (DAOD) were not reported; however at week 1 follow-up the DAOD was 23.4 mg/d and 25.3 mg/d for intervention and control groups respectively. Between group differences in DAOD were not significant at week 1 or 1 month follow-up but were significantly different (in favour of gabapentin) at 3 and 6 month follow-ups. Nevertheless, poor reporting of outcome measures and their results prevents meaningful interpretation of the study findings which should be interpreted with caution.

In a crossover study, Dou *et al* [30] evaluated the efficacy of pregabalin in combination with morphine. 40 patients with severe NCP were randomised to receive pregabalin-morphine combination followed by morphine-placebo combination, or vice versa. The two week treatment periods were separated by a one week washout period. Mean minimally effective morphine dose was significantly lower during the pregabalin-morphine combination period (184.4 ± 69.9 mg/day) compared to the placebo-morphine combination period (228.7 ± 66.9 mg/day), with greater improvements in sleep and reduction in constipation (both significant) but higher rates of dry mouth and drowsiness. The authors concluded that equivalence pain relief can be achieved with lower dose of morphine following the addition of pregabalin treatment.

## Other combination therapies

Arai *et al* [31] compared low-dose gabapentin in combination with imipramine, with low-dose gabapentin, high-dose gabapentin, and imipramine, all in combination with opioids in 52 patients with NCP. Some patients in all groups continued regular NSAIDs. The gabapentin/imipramine/opioid group's final total pain score was significantly lower than both the low-dose gabapentin/opioid and imipramine/opioid groups alone, but not the high-dose gabapentin/opioid group. However, the sample sizes were very small (n of 12-14), NSAID/varying opioid use may have confounded the result, and 7 days of follow-up is unlikely to be sufficient to demonstrate full effect. There is insufficient evidence to support one intervention over another.

In their open-label RCT, Banerjee *et al* [32] evaluated gabapentin in combination with tramadol versus amitriptyline and tramadol in 88 patients with NCP over 6 months. Patients were excluded during the study if they used a stronger opioid. No statistical differences in VAS pain score, percentage of pain relief and global pain score were found throughout the study period. Both groups

improved overall with VAS score, with the most significant improvements in the first month however this is difficult to interpret without further information about the titration schedule. This study shows no benefit of gabapentin over amitriptyline when used in combination with tramadol. It is unclear if the findings can be extrapolated to populations requiring stronger opioids.

In 2016, Fallon *et al* [33▪], recruited 233 patients scheduled for radiotherapy with moderate-severe CIBP in 5 cancer centres. 116 patients were randomised to pregabalin and 117 patients to placebo, both in combination with palliative radiotherapy and a regular opioid, for 4 weeks. There was no difference between proportion of each group achieving treatment response (defined as a reduction of ≥2 points in worst pain NRS from baseline, and stable/reduced opioid dose), average and worst pain, pain intensity and interference or number of breakthrough episodes. The study was underpowered given the dropout of study participants, and opioid use between groups was poorly described. However, this is an otherwise well conducted study showing no evidence of additional benefit with pregabalin.

Nishihara *et al* [34] also evaluated the use of pregabalin as a combination therapy in CIBP. 12 patients were randomised to high-dose pregabalin (group 1). The two comparator groups had pregabalin at a lower dose with group 2 (12 patients) also given imipramine, and group 3 (13 patients) also given mirtazapine. All patients were given a regular opioid, an NSAID and a bisphosphonate. Some patients in each group were also given paracetamol. Groups 2 and 3 both had statistically significant reductions in total pain score and daily paroxysmal pain episodes in comparison with the group 1 throughout the study period of 7 days. However, as the sample sizes are small with very short follow-up, the findings may not demonstrate the full effect. Therefore this study's findings are inconclusive regarding the role of gabapentinoids in combination with antidepressants.

## Treatment-related pain

Gabapentin and pregabalin have both been evaluated in RCTs to prevent or manage treatment-related cancer pain. In this section, treatment-related pains are defined as pains arising from specific cancer treatments such as chemotherapy and radiotherapy. Table 3 summarises and provides further detail about included treatment-related pain studies. We have not discussed cancer surgery and post-operative pain due to the crossover with mechanisms of pain in non-cancer post-operative pain. A recent systematic review evaluating the use of pre-operative gabapentinoids in patients undergoing breast cancer surgery found improvements in acute post-operative pain in comparison with patients receiving placebo/active controls [35].

## Gabapentin studies

Rao *et al* [36] used a cross-over study to compare gabapentin with placebo in chemotherapy-induced neuropathic pain over a 3 week duration. No significant differences were found between gabapentin and placebo. However, the study was underpowered. Furthermore, eligible patients were those with pain, sensory loss or paraesthesia. This approach might have lacked sensitivity to detect any analgesic efficacy.

Kataoka *et al* [37] evaluated the effect of gabapentin or placebo added to opioids and paracetamol in 22 patients with head and neck cancer with mucositis as a result of chemo-radiotherapy. Higher pain scores and opioid doses were found in the gabapentin arm but these were not significantly different from placebo. This was partly a feasibility study enabling data collection for future sample size calculations. It is very unlikely that the study was powered well enough to detect a possible difference.

## Pregabalin studies

The effectiveness of pregabalin in preventing oxaliplatin-induced painful neuropathy was evaluated by de Andrade *et al* [38]. Of 199 colorectal cancer patients who were pain free and chemotherapy naiive randomised, 56 were subsequently excluded from analysis. Of those that were analysed, 78 received pregabalin and 65 received control 3 days before and 3 days after each oxaliplatin infusion. Follow up lasted up to 6 months post chemotherapy. Average pain intensity and neuropathic pain symptoms assessed using the Douleur Neuropathique-4 (DN4) and the Neuropathic pain Symptom Inventory showed no differences between groups. This was corroborated by nerve conduction studies which also failed to show any protective effect of pregabalin.

Another smaller study evaluating the protective effects of pregabalin was conducted by Shinde *et al* [39]. Patients who were about to receive paclitaxel chemotherapy were randomised to pregabalin or placebo. Forty six patients were recruited and no differences in pain intensity were found between arms.

## Conclusion

For tumour-related pain, 10 out of 13 studies showed statistically significant benefits in favour of gabapentinoids. When used, as part of monotherapy or combination therapy, benefits were observed in 5 out of 6 studies evaluating gabapentin, and in 6 out of 8 studies evaluating pregabalin. For treatment-related pain, none of the 4 studies (2 gabapentin, 2 pregabalin) showed statistically significant benefits in favour of gabapentinoids. Unfortunately many of the studies included were limited by small sample size, lack of blinding and inadequate follow-up, considering the need to titrate treatments. This review is in agreement with systematic reviews within the last 5 years [40, 41, 42, 43, 44]. More and better quality studies are required, although this may be challenging to

accomplish in this patient population. Gabapentinoids may offer benefits to cancer patients with pain but careful titration and monitoring of adverse effects is necessary.

## Key points

- Gabapentinoids act by reducing pain transmission in spinal pathways and modulating central descending inhibitory pathways.
- Statistically significant benefits using gabapentinoids as monotherapy or as part of combination therapies for tumour-related cancer pain have been found.
- Many existing RCTs have poor methodology due to small sample size, lack of blinding and insufficient follow-up to demonstrate full effect of interventions.
- More RCTs of better quality are needed, although this may be challenging to accomplish in this patient population.
- Gabapentinoids may offer benefits to cancer patients with pain but careful titration and monitoring of adverse effects is necessary.

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## Conflicts of interest

None declared

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