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# The Effectiveness of Pregabalin in the Treatment of Neuropathic Pain in Cancer Patients: A Systematic Review and Meta-analysis of Randomised Controlled Trials

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## Abstract

**Background**: Neuropathic pain is a common medical condition among cancer patients, which might lead to deterioration in patients' health and their quality of life. It is caused by nerve damage which caused by different reasons such as chemotherapy side effects or cancer itself. Recently, treating such types of pain in cancer patients became problematic for healthcare providers since some analgesics such as opioids, antiepileptics and antidepressants have been reported to have an insufficient effect on treating this type of pain in some patients.

**Aims and objectives**: The aim of this review is to evaluate the efficacy and safety of pregabalin in treating neuropathic cancer pain and inform decision making for all healthcare providers by establishing new clinical policies. Also, to reduce the publication's bias and unnecessary relevant studies.

**Selection criteria**: The studies included in this review were only randomised controlled trials conducted on adult cancer patients with neuropathic pain (male or female >18 years). The outcomes are pain severity, sleep disturbance, side effect and quality of life.

**Data collection and analysis**: Relevant studies were collected and evaluated according to PRISMA. The Cochrane Criteria was used to assess the risk of bias in each included study. Eight of the included trials were evaluated narratively, while six studies were included in the meta-analysis.

**Results**: Fourteen studies met inclusion criteria. The results indicate that pregabalin had significantly reduced pain severity ($p>0.0001$) and sleep disturbance compared to placebo. However, there was no significant improvement in the quality of life compared to either placebo or other analgesics.

**Conclusion**: Pregabalin was an effective analgesic in relieving neuropathic cancer pain compared to placebo. However, more research might be needed in the future to compared pregabalin to more other analgesics.

**Keywords:** Cancer; Oncology; Palliative care; Analgesics; Pregabalin; Anticonvulsant; Antiepileptic; Tumour; Malignant disease; Neuropathic pain

## Abbreviations:

AEDs: Antiepileptics drugs; AT: Amitriptyline; DAAC: The Duration Adjusted Average Change; Du: Duloxetine; ECOG: Eastern Cooperative Oncology Group; EMEA: The European Medicines Agency; GB: Gabapentin; GSDS: General Sleep Disturbance Scale; GSDS: General Sleep Disturbance Scale; mg: Milligram; MOS-SSS: Social Support Scale; NCP: Neuropathic Cancer Pain; NPSI; Neuropathic Pain Symptom Inventory; NSAIDs: Non-steroid Anti-inflammatory Drugs; NSCLC: Non-small Cell Lung Cancer; NSR: Numerical Scale Rating; PG: Pregabalin; PICO: Population, Intervention, Comparison and Outcome; PL: Placebo; PRISMA: Systematic Reviews and Meta-Analyses; QoL: Quality of life; SD: Standard Deviation; VAS: Visual Analogue Rating; WHO: World Health Organisation; WHOQOL: The World Health Organisation Tool

## Introduction

Neuropathic pain is a very common medical condition that might affect approximately 60-90% of cancer patients [1,2]. It is a pain that is caused by nerve damage in the somatosensory nervous system [1,2]. Neuropathic pain is characterised by numbness, prickling or tingling in the feet or hands that can spread to the legs and arms [2]. Patients may also experience other symptoms such as burning, squeezing, pricking, and shooting pain that might seriously affect patients' quality of life [3]. Neuropathic pain in cancer patients could be caused due to different aetiology such as side effects of some chemotherapy, radiation or tumour itself.

Treating neuropathic pain in cancer patients remains challenging, as some analgesics might have a limited response rate, in addition to their side effects [4,5]. Although opioids are still the mainstay analgesic in the treatment of neuropathic cancer pain (NCP), they have been reported to have an insufficient effect on NCP in some cases compared to nociceptor pain. Therefore, using or adding other analgesics such as anticonvulsants (e.g. pregabalin) or antidepressants might give better effect.

Although it was first approved for the treatment of seizure, pregabalin has been reported to have an analgesic effect on neuropathic pain [6,7]. In 2007, pregabalin has been officially approved by the European Medicines Agency (EMEA) for the treatment of neuropathy [6].

The exact mechanism of the analgesic effect of pregabalin is unclear. However, it has been observed that the analgesia of pregabalin is caused by antagonising the voltage gate of the $Ca^{+}$ channel by

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selectively binding to α-2-δ subunit; and thereby causes a reduction in some neurotransmitter levels such as serotonin, glutamate, dopamine and noradrenaline [6,8]. Pregabalin, therefore, has an inhibitory effect on these neurotransmitters (i.e. serotonin, glutamate, dopamine and noradrenaline) that can reduce the intracellular calcium level and relieve nerve pain [6].

Since its approval, a few randomised control trials (RCTs) have been trying to illustrate the effectiveness of pregabalin in the management of NCP. Until now, however, there is no strong evidence for the actual effectiveness of pregabalin in treating NCP [6,9]. Therefore, further studies might be needed to show a strong evidence for pregabalin effectiveness on treating NCP [10-12].

The last systematic review which had evaluated the effectiveness of pregabalin in the treatment of NCP was conducted by Bennett et al. in 2013. However, the authors had not drawn a clear conclusion for their study due to limitations in the published data [11]. Thus, this study will try to find a clear evidence for pregabalin effectiveness.

The aim of this review is to evaluate the effectiveness of pregabalin in the management of NCP regarding quality of life, side effect and sleep disturbance. Also, it aims to draw a clear and useful conclusion and inform decision making for all healthcare providers.

## Method

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

### Inclusion and exclusion criteria

Only randomised controlled studies were included in this systematic review. All these trials should be in English languages only. All participants were adult patients with NCP (male and female aged ≥ 18). The exposed groups only contained patients who used pregabalin; while control groups only included patients who used other analgesics, placebo or no treatment at all. Moreover, the duration of treatment, type of dosage form and the regimen dose were not restricted to a certain level.

### Type of outcomes

The primary outcome in this review is severity of the NCP pain. Pain severity in the included trials was measured using scale tools such as Visual Analog Scale (VAS), Verbal Numerical Rating Scale (VNRS), Verbal Descriptor Scale (VDS) and Numerical Rating Scale (NRS). The secondary outcomes are quality of life (QoL), sleep disturbance and severity of the side effects caused by the interventions.

### Searching strategies and identification of relevant studies

Electronic search tools were the main search approaches used to search for relevant articles. Different search methods including PUBMED, Ovid, EMBASE, CINHAL and the US National Library of Medicine (NIH) were used to search for relevant trials. In addition, the Cochrane Library, Web of Science and "Find it" search tool on University of Birmingham website were also used in searching for trials.

In addition, a hand search had been conducted to search for relevant articles in different journals in the University of Birmingham Libraries, including the main library and Barnes library in the medical school. A wide range of different terms had been used to find all the relevant studies on different journals as much as possible.

### Data selection and analysis

The process of study selection was conducted by two reviewers. In addition, a third reviewer was identified to check and resolve any disagreement between the primary reviewer and the second reviewer. All the identified articles were downloaded and saved on a personal computer. Then, Mendeley Software (version 1.19.1.0) was used as a referencing tool to save and organise the selected references. The titles and abstracts of all studies were carefully read and added to Mendeley Software. First screening process was conducted by screening the titles and abstracts only of all identified studies to check for their eligibility.

A screening form was used to help in checking for eligibility in this screening process. For a study to be included in this systematic review, the answers in each section in such screening form should be "Yes". Otherwise, the study would be excluded from this review. A further full-text screening process was conducted by the primary reviewer to assess and extract the required data in each selected study using the same screening form previously stated previously. Finally, required data were extracted from eligible studies from 4 areas (population, methods, intervention and outcomes) using data extraction form.

Data were analysed using qualitative (narrative) and quantitative (meta-analysis) approaches. The effectiveness of pregabalin in reducing pain severity was tested narratively and quantitatively using meta-analysis. While quality of life (QoL), sleep disturbance and common side effects were only narratively evaluated as these outcomes were measured differently in different trials.

Only trials that compared pregabalin to placebo were included in meta-analysis as they are homogenous in term of their intervention, population and outcomes. However, it was not appropriate to include trials that compared pregabalin against other analgesics as such trials were heterogeneous in term of their intervention. Therefore, a forest plot was only established in ordered to make a comparison between pregabalin and placebo in terms of pain reduction. The difference in the mean and standard deviation in pain reduction score was used to establish this meta-analysis.

## Results

### Result of search

Initially, 387 relevant articles were identified during the search process in this systematic review, using both electronic and hand search approaches described previously in the methodology section. Nine articles were excluded due to duplication during the collections process; and thereby, only 378 articles remained after excluding duplicated articles.

After excluding 326 articles during the title and abstract screening process, both reviewers have found that only 52 studies remained, and they should be processed to a full-text screening to check for their eligibility in depth (i.e. checking their population, method, intervention and outcomes). After such full-text screening, only 14 studies were eligible for this review after excluding 38 studies.

Thirty eight references were excluded during the full-text screening due to different reasons such as non-relevant population, intervention (e.g. not pregabalin) or non-randomised controlled trials (Figure 1).

### Description of the studies

At the end of the screening, according to the inclusion criteria, only 14 randomised controlled trials were eligible to be included in this review. Eight trials of these studies compared pregabalin to placebo; while 6 compared it to other analgesics. In all such included trials, the used outcomes were reduction in pain, severity of the side effects, improving sleep quality and quality of life. Six of these 14 trials are homogeneous; and thereby, included in the meta-analysis. The

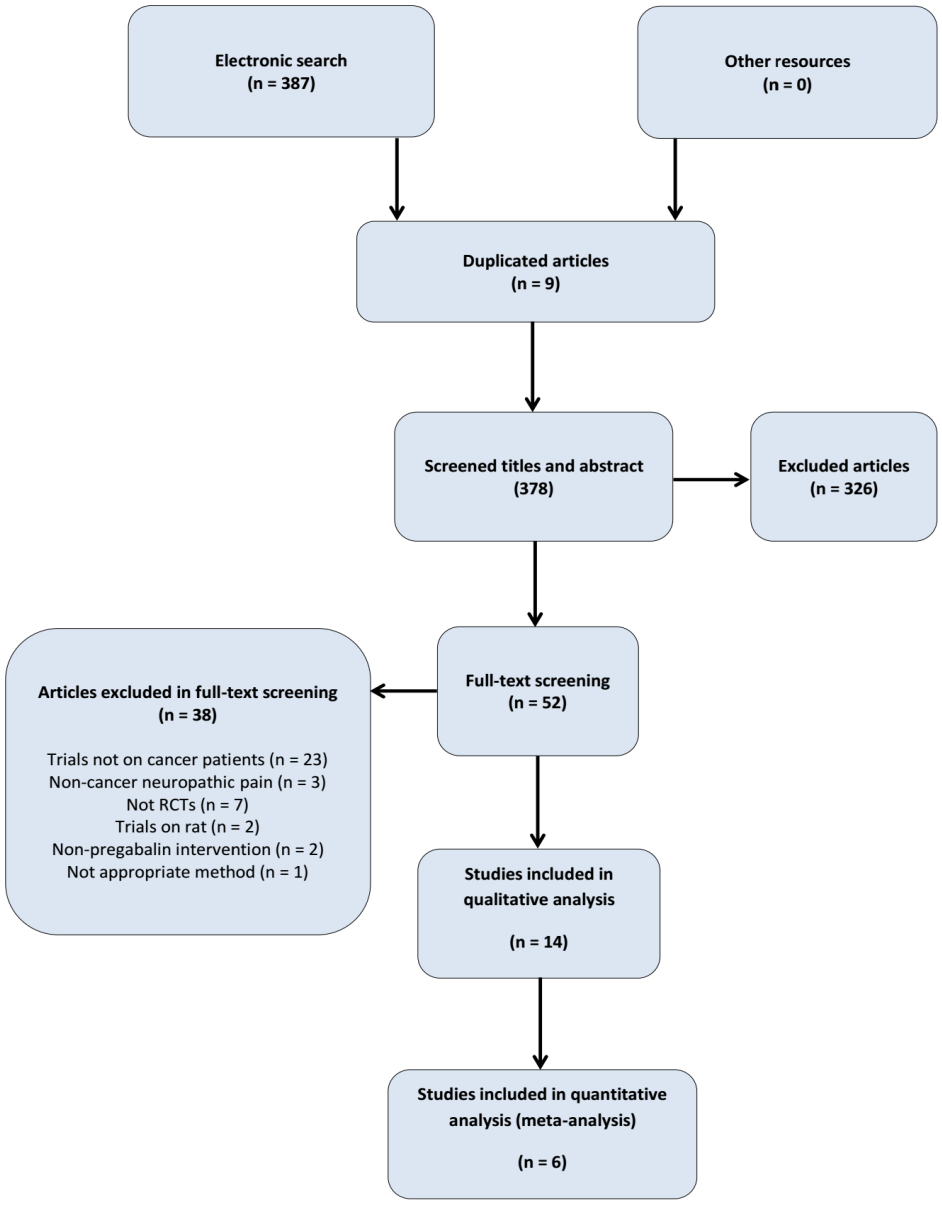


**Figure 1:** Flow of information through the procedures of this review.

characteristics and descriptions of the included studies were explained in Table 1 below.

## Effect of intervention

Totally, 14 trials were identified in evaluating the effectiveness of pregabalin in relieving neuropathic pain in cancer patients. Eight of these 14 trials have compared the effectiveness of pregabalin to placebo; while there were only six studies compared pregabalin to other analgesics including antiepileptic (gabapentin), antidepressant (amitriptyline), opioids (oxycodone) and non-opioids analgesics (paracetamol and NSAIDs). The results of the included trials were explained in the Tables 2-4 below.

In term of quality of life, 9 studies indicate that pregabalin gave a positive result compared to opioids only. However, there was not any significant difference in improvement in QoL between pregabalin and either placebo or the other analgesics.

On the other hand, 10 studies show that pregabalin had a beneficial effect on sleep quality compared to placebo and duloxetine. The improvement in sleep quality might be because of the sedation effect and the reduction in pain severity that were caused by pregabalin.

Different side effects were observed during the interventions in such 14 trials. However, the most common side effects noticed during pregabalin therapy were determined. Somnolence, nausea, vomiting and dizziness were the most common side effects noticed during pregabalin therapy in 9 trials.

## Meta-analysis

Meta-analysis in this review only includes trials that compared pregabalin to placebo as they are homogenous in term of PICO homogenous ($\lambda^2$=5.49; df=5; $I^2$=9%). In this review, 8 trials had

| Study | Title | Type/Method | Participants | Intervention | Duration |
|---|---|---|---|---|---|
| Moon et al. [13] | Efficacy and Tolerability of Pregabalin Using a Flexible, Optimized Dose Schedule in Korean Patients With Peripheral Neuropathic Pain: A 10-Week, Randomised, Double-Blind, Placebo-Controlled, Multicentre Study | Multicentre, randomised double-blind, placebo-controlled trial, phase III (2:1 ratio) | 241 Adult cancer patients (>18 yrs.) pregabalin (n=162) *vs* placebo (n=78) | Pregabalin (150-600 mg/day) *vs* placebo | 10 weeks |
| Shinde et al. [14] | Can pregabalin prevent paclitaxel-associated neuropathy? an ACCRU pilot trial | Multicentre, Randomised, double-blind, pilot controlled trial, phase III (2:1 ratio) | 46 Adult women with cancer (>18 yrs.) Life expectancy >6 months pregabalin (n=23) *vs* placebo (n=23) | pregabalin (150-600 mg/day) *vs* placebo | 12 weeks |
| Sjolund et al. [10] | Randomised Study of Pregabalin I Patients with Cancer-induced Bone Pain | Multicentre, Randomised, double-blind, parallel group, flexible dose, placebo-controlled trial (20 countries) | 152 Adult with metastatic solid tumour (>18 yrs.) pregabalin (n=72) *vs* placebo (n=80) | Pregabalin (150-600 mg/day) *vs* placebo | 2006-2010 |
| De Andrade et al. [15] | Pregabalin for the Prevention of Oxaliplatin Induced Painful Neuropathy: A Randomised, Double-Blind Trial | Randomised, double-blind trial (1:1 ratio) | 199 Adult patients with colorectal cancer (>18 yrs.) pregabalin (n=101) *vs* placebo (n=98) | Pregabalin (150-600 mg/day) *vs* placebo | 6 months |
| Dou et al. [16] | Efficacy and safety of pregabalin in patients with neuropathic cancer pain undergoing morphine therapy | Randomised, double-blind, placebo-controlled crossover trials | 40 Adult patients with neuropathic cancer pain (>18 yrs.) pregabalin (n=20) *vs* placebo (n=20) | Pregabalin (75-300 mg/day) *vs* placebo | 2 months |
| Fallon et al. [17] | Randomised Double-Blind Trial of Pregabalin Versus Placebo in Conjunction With Palliative Radiotherapy for Cancer-Induced Bone Pain | Multicentre, Randomised, double-blind, placebo-controlled trials | 233 Adult patients with cancer (>18 yrs.) pregabalin (n=116) *vs* placebo (n=117) | Pregabalin (75 mg/day) *vs* placebo | 2 weeks |
| Karthaus et al. [18] | A randomised, double blind, placebo-controlled trial for prevention of oxalipatin-induced peripheral neuropathy symptoms with pregabalin in patients with advanced colorectal cancer | Randomised, double-blind, placebo-controlled trials | 61 Adult patients with colorectal cancer (>18 yrs.) pregabalin (n=32) *vs* placebo (n=29) | Pregabalin *vs* placebo | Not stated |

**Table 1**: This table shows the characteristics of the 14 included studies.

| Pain intensity | | |
|---|---|---|
| **Study** | **Intervention** | **Results** |
| Moon et al. [13] | Pregabalin *vs* Placebo | Significant pain reduction in pregabalin group (LS mean difference: – 0.50; 95% CI, -1.00 to 0.00; $p$ = 0.041 |
| Shinde et al. [14] | Pregabalin *vs* Placebo | No significant different in worst pain score ($p$=0.56) |
| Sjolund et al. [10] | Pregabalin *vs* Placebo | Mean difference in NRS favoured pregabalin Pregabalin: -1.53 (SD=1.81) Placebo: -1.23 (SD=1.74) |
| Karthaus et al. [18] | Pregabalin *vs* Placebo | No significant difference in:<br>*Persistent pain:*<br>PG*=0/32(0%) PL*=2/29(6.9%)<br>*Persistent paraesthesia:*<br>PG=2/32(6.25%) PL=1/29(3.45%)<br>*Dysesthesia:*<br>PG=2/32(6.25) PL=2/29(6.9%) |
| Dou et al. [16] | Pregabalin *vs* Placebo | More pain reduction in pregabalin group ($p$>0.001)<br>PL=1.7 ± 0.6 PG=1.4 ± 1.1 |
| Fallon et al. [17] | Pregabalin *vs* Placebo | No significant difference in pain reduction<br>PG=45/116 (38.8%) PL=47/117 (40.2%) OR=1.07; (95% CI, 0.63-1.81) ($p$ = 816) |
| De Andrade et al. [16] | Pregabalin *vs* Placebo | No significant difference in pain intensity<br>PG=1.03 (95% CI, 50.79-1.26) PL=0.85 (95% CI, 50.64-1.06) |
| Yoshimura et al. [19] | Pregabalin *vs* (paracetamol +codeine) | Significant difference in VAS mean (reduction in pain intensity in PG)<br>Control=29.5(SD=21.9) PG=16.3(SD=15) $p$=0.02 |
| Raptis et al. [20] | Pregabalin *vs* Opioids (transdermal fentanyl) | 30% reduction in VAS in PG groups compared with the fentanyl group<br>PG=73.3% (95% CI: 60.3-83.93%). Fentanyl=36.7% (95% CI: 24.5-50.1%). $p$<0.0001 |
| Miyazaki et al. [21] | Pregabalin *vs* NSAIDs | No significant difference in NRS between two groups ($p$=0.72)<br>No significant difference in number of NSAIDs doses added ($p$=0.78) |
| Mishra et al. [9] | Pregabalin *vs* Amitriptyline *vs* Gabapentin *vs* Placebo | Pregabalin was efficacious compared to AT, GB and PL<br>AT= VAS mean decreased from 7.77 (SD=1.0) to 3.23 (SD=0.70).<br>GB=VAS mean decreases from 7.5 (SD=1.1) to 3.07 (SD=0.80).<br>PG=VAS mean decreased from 7.77 (SD=0.81) to 2.5 (SD=0.70).<br>PL=VAS mean decreased from 7.47 (SD=1.0) to 3.4 (SD=0.66). |
| Garassino et al. [22] | Pregabalin *vs* Oxycodone | A slight increase in pain reduction in pregabalin group<br>PG=76% achieved ≥ 1/3 reduction in pain.<br>Oxycodone=only 64% achieved ≥ 1/3 reduction in pain. OR=1.84 (95% CI: 0.65-5.22) ($p$=0.25) |
| Avan et al. [23] | Pregabalin *vs* Duloxetine | More pain reduction in pregabalin than in duloxetine ($P$ < 0.001) |
| Abdelfattah et al. [24] | Pregabalin *vs* Placebo | Significant reduction in VAS in pregabalin group ($p$<0.001).<br>Number of opioids added were significantly lower in pregabalin group ($p$<0.001) |
| *PG: Pregabalin; PL: Placebo; GB: Gabapentin; AT: Amitriptyline. | | |

**Table 2**: A summary of the results of the included trials that show the effect of pregabalin use on relieving neuropathic pain.

| Quality of life | | |
|---|---|---|
| **Study** | **Intervention** | **Results** |
| Moon et al. [13] | Pregabalin *vs* Placebo | No significance difference<br>3.50 (95% CI, -1.18-8.18) ($p$=0.142) |
| Shinde et al. [14] | Pregabalin *vs* Placebo | Not measured |
| Sjolund et al. [10] | Pregabalin *vs* Placebo | Not measured |
| Dou et al. [16] | Pregabalin *vs* Placebo | No significance difference in mean difference<br>PL=37.1 ± 6.3 PG=39.6 ± 4.6 |
| Fallon et al. [17] | Pregabalin *vs* Placebo | No significance difference in mean difference<br>PG=60.1 (SD=24.1) PL=60.2 (SD=23.0) |
| De Andrade et al. [16] | Pregabalin *vs* Placebo | No difference in QoL score mean between two groups<br>PL=76.9 (SD=23.1) PG = 79.4 (SD=20.6) |
| Yoshimura et al. [19] | Pregabalin *vs* (paracetamol +codeine) | Not measured |
| Raptis et al. [20] | Pregabalin *vs* Opioids (transdermal fentanyl) | More patients' satisfaction in pregabalin group ($p$<0.0001)<br>PG=53.3% patients' satisfaction.<br>Fentanyl=21.7% patients satisfaction. |
| Miyazaki et al. [21] | Pregabalin *vs* NSAIDs | No significant difference in NRS ($p$=0.13) |
| Mishra et al. [9] | Pregabalin *vs* Amitriptyline *vs* Gabapentin *vs* Placebo | No significant difference in ECOG mean<br>AT=2.07 GB=2.90 PG=2.77 PL=2.43<br>(p=0.680) |
| Garassino et al. [22] | Pregabalin *vs* Oxycodone | Slightly better performance status in Oxycodone<br>PG=32 (84.2%) Oxycodone=35 (94.6%) |
| Avan et al. [23] | Pregabalin *vs* Duloxetine | No significant difference between pregabalin and duloxetine in improving quality of life ($P$=0.54)<br>PG=mean 61 (SD: 5.11)<br>DU=mean 60.28 (SD: 5.44) |
| Abdelfattah et al. [24] | Pregabalin *vs* Placebo | Not measured |
| *PG: Pregabalin; PL: Placebo; GB: Gabapentin; AT: Amitriptyline. | | |

**Table 3**: A summary of the results of the included trials that show the effect of pregabalin use on patients' quality of life.

| Sleep disturbance | | |
|---|---|---|
| **Study** | **Intervention** | **Results** |
| Moon et al. [13] | Pregabalin *vs* Placebo | Improvement in sleep disturbance in pregabalin group (mean difference -0.65; $p$=0.018) |
| Shinde et al. [14] | Pregabalin *vs* Placebo | Not measured |
| Sjolund et al. [10] | Pregabalin *vs* Placebo | Improvement in the mean difference of sleep interference NRS in pregabalin group.<br>Pregabalin: -1.37 (SD=2.02)<br>Placebo: -0.63 (SD=1.78) |
| Dou et al. [16] | Pregabalin *vs* Placebo | Using MOS-SS, significant improvement in PG group<br>Lower sleep disturbance: ($p$<0.001).<br>Lower sleep problems: ($p$<0.001).<br>Longer hours for sleep: ($p$<0.001)<br>PG=7.7 ± 1.2 h PL=6.5 ± 1.4 h |
| Fallon et al. [17] | Pregabalin *vs* Placebo | Not measured |
| De Andrade et al. [15] | Pregabalin *vs* Placebo | Not measured |
| Yoshimura et al. [19] | Pregabalin *vs* (paracetamol +codeine) | Significant reduction in sleep disturbance (VAS) after 2 weeks in pregabalin group<br>PL=62.2(SD=27.9) PG=83.5(SD=21.2)<br>Mean difference -21.3 ($p$<0.01) |
| Raptis et al. [20] | Pregabalin *vs* Opioids (transdermal fentanyl) | Not measured |
| Miyazaki et al. [21] | Pregabalin *vs* NSAIDs | Not measured |
| Mishra et al. [9] | Pregabalin *vs* Amitriptyline *vs* Gabapentin *vs* Placebo | Not measures |
| Garassino et al. [22] | Pregabalin *vs* Oxycodone | Not measured |
| Avan et al. [23] | Pregabalin *vs* Duloxetine | Significant insomnia improvement in pregabalin than in duloxetine group ($P$<0.001) |
| Abdelfattah et al. [24] | Pregabalin *vs* Placebo | Not measured |
| *PG: Pregabalin; PL: Placebo; GB: Gabapentin; AT: Amitriptyline. | | |

**Table 4**: A summary of the results of the included trials that show the effect of pregabalin use on patients' sleep disturbance.

compared pregabalin to placebo. However, two of them were excluded due to various reasons. Karthaus et al. [18] paper was excluded as it was published in abstract form only; and thereby, the details of this trials were not fully known. Abdelfattah et al. [24] was excluded as the reduction in pain severity in such trial was measured differently compared to the other trials, since the authors in such trial had used the median and the range in measuring the reduction in pain severity

The result of the meta-analysis demonstrated that pregabalin had a significant positive effect on pain severity compared to placebo. The forest plot in Figure 2 demonstrates the effect of pregabalin on pain reduction (i.e. primary outcome). Generally, regardless the side effects and QoL, pregabalin might have a significant effective in relieving neuropathic cancer pain compared to placebo (p<0.0001).

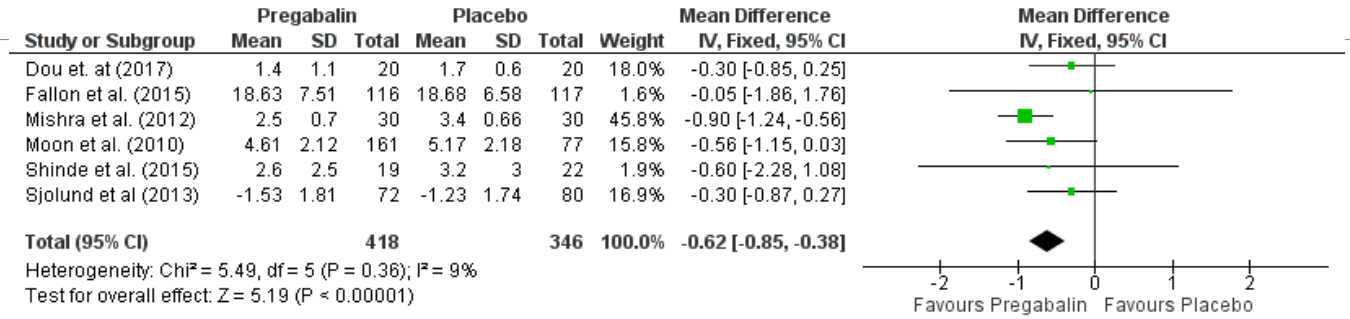


**Figure 1:** Forest plot shows pregabalin effectiveness in reducing NCP compared to placebo. Six randomised controlled trials show that pregabalin had a positive effect on reducing neuropathic pain in cancer patients compared to placebo.

## Discussion

### Quality of the evidence

Although evaluating the quality of the evidences in different trials might be difficult, The Cochrane Collaboration Tool was helpful in determining the location of risk of bias in each single study. Some systematic and random errors were identified during this review. According to The Cochrane Collaboration Tool, there was a high level of risk of bias in some trials especially in open-label trials. In addition, methods of selecting targeted patients were unclear in some studies, which might lead to a high risk of bias in such trials.

Moreover, one of the issues that might negatively affect the quality of the trials is that attrition large numbers of participants during the trials. This could affect the quality of the results, and thereby, lead to incomplete results. For example, Yoshimura et al. [19] had excluded > 60% of the enrolled participants which result in producing a small sample size.

### Strength of the review

One of the strengths of this systematic review is using meta-analysis in determining the effectiveness of pregabalin in relieving neuropathic cancer pain. According to hierarchy of evidence, meta-analysis is considered the highest level of medical evidence [25]. Therefore, using meta-analysis next to a narrative review could significantly support the results and give a strong medical evidence for the effectiveness of a specific intervention or treatment. However, conducting meta-analysis in a review depends on the heterogeneity of the included studies.

Another advantage is that this review is only restricted to randomised controlled trials. Randomised controlled trials are considered the gold standard to evaluate the effectiveness of any intervention or therapy compare to observational studies such as cohort, cross-sectional and case-control study [26]. They also can add or change current guidelines and practice. Therefore, systematic review and meta-analysis might give more reliable results if it is restricted to randomised control trials only.

In addition, this review had used 4 different outcomes to evaluate the effectiveness of pregabalin in treating neuropathic syndromes in cancer patients. One primary outcome plus three different secondary outcomes. It is better to evaluate the effectiveness of a drugs using more than one secondary outcomes such as side effects, quality of life and sleep disturbance. Identifying more than one secondary outcomes could help in determining the effectiveness of a drug in more than one area.

Moreover, this review aimed to includes previously reviewed randomised controlled trials. The clinical trial conducted by Mishra et al. [9] had been previously reviewed by Bennett et al. [11], and it is also included in this review. Including previously reviewed trials might have a clear advantage. It can increase the number of the included studies; and thus, this might give more reliable results and stronger medical evidence.

### Limitations of the review and risk of bias

Different limitations and risk of bias have been identified in this review. Firstly, as one of systematic review aims is the comprehensive search, advanced strategies of electronic and hand search should be used in each systematic review by the authors to collect as many as they can of clinical trials. In this review, however, the electronic and hand search strategies were performed precisely using highly specific and precise search strategy instead of sensitive search strategy. More variety of terms are used in sensitive search strategy than in precise search strategy which might lead to finding a large number of studies [27]. According to Cochrane Handbook 6.4.4, sensitive search strategy might be highly recall; however, it can retrieve irrelevant studies. While precise search strategy might only retrieve relevant trials; however, it might be considered an incomprehensive search strategy [27]. Therefore, regardless the limitation in the published trials, using precise search strategy in this review might lead to "zero search results" on some databases websites such as CINHAL, Web of Science and The Cochrane Library; and thereby, resulting in finding few relevant studies (387 articles) at the end of the search process. It has been recommended that using advanced and sensitive search strategy could lead to finding more trials; and thereby, fining large number of relevant trials in a review might give more reliable results. Also, it has been stated that the more trials included, the stronger evidence we found [28].

Secondly, since the main aim of this review is to determine whether pregabalin is an appropriate analgesic in relieving NCP, comparing the effectiveness of pregabalin to placebo could give unreliable results as placebo are not a pharmacological analgesic to compare with. In another meaning, comparing placebo to pregabalin could tell whether pregabalin can reduce pain severity or not. However, it might not determine whether pregabalin can reduce neuropathic cancer pain more than opioids or antidepressants as examples. Therefore, the results might be more reliable if the included trials were only restricted to pregabalin *vs* other analgesics. However, there are insufficient clinical trial publications comparing pregabalin to other analgesics, since pregabalin is a newly licensed analgesic for neuropathic cancer pain.

Thirdly, the actual effectiveness of pregabalin in treating neuropathic cancer pain might not be determined in this review due to

the limitation in the published trials since pregabalin is a newly licensed anti-neuropathic. Therefore, due to the limitation in the publication, it was difficult to compare pregabalin to another specific analgesic using meta-analysis. Therefore, meta-analysis was only restricted to placebo-controlled trials.

### Agreements and disagreement with other studies or reviews

In the last systematic review, Bennett et al. [11] had tried to evaluate the effectiveness of pregabalin in treating neuropathic pain in cancer patients. However, they had not found any clear result due to the limitation in the published studies. Although Bennett et al. [11] had not restrict their inclusion criteria to specific types of studies, they only included 5 studies in their review. These 5 studies consist of different types of studies such as observational, case report and single armed trial. However, only one of these 5 studies was a randomised controlled trial [9] which is included in this review as well.

In contrast, this review includes 14 relevant randomised controlled trials compared to last systematic review conducted by Bennett et al. [11]. This might indicate that an acceptable number of randomised controlled trials have been published between 2013 and 2018. Including more clinical trials in this review could lead to more reasonable results than in last systematic review. The result of this review claim the beneficial effect of pregabalin on improving neuropathic pain reduction and sleep quality in cancer patients.

## Conclusion

Although most of the trials included in this review claimed the positive role of pregabalin in treating NCP, it cannot be said that pregabalin is the drug of choice in the management of NCP as choosing the most appropriate analgesic for cancer patients still depends on different factors such patients' health, age or tolerability. However, this review can give a simple and useful evidence for the effectiveness of pregabalin on treating NCP. In addition, focusing on randomised controlled trials that compare two analgesics instead of those that compare analgesic to placebo could help in obtaining reliable and accurate results in the future.

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### References

1. Bennett M, Rayment C, Hjermstad M, Aass N, Caraceni A, et al. (2012) Prevalence and aetiology of neuropathic pain in cancer patients: A systematic review. Pain 153: 359-365.
2. Fallon MT (2013) Neuropathic pain in cancer. British Journal of Anaesthesia 111: 105-111.
3. Finnerup NB, Jensen TS (2007) Clinical use of pregabalin in the management of central neuropathic pain. Neuropsychiatr Dis Treat 3: 885-891.
4. Jongen J, Huijsman M, Jessurun J, Ogenio K, Schipper D, et al. (2013) The evidence for pharmacologic treatment of neuropathic cancer pain: beneficial and adverse effects. Journal of Pain and Symptoms Management 46: 581-591.
5. Kane CM, Mulvey MR, Wright S, Craigs C, Wright J, et al. (2018) Opioids combined with antidepressants or antiepileptic drugs for cancer pain: Systematic review and meta-analysis. Palliative Medicine 32: 276-286.
6. Gajraj NM (2007) Pregabalin: Its pharmacology and use in pain management. Anesth Analg 105: 1805-1815.
7. Naresh K, Andre L, Jonathan Y, Amelia L, Terence C (2010) Evidence that pregabalin reduces neuropathic pain by inhibiting the spinal release of glutamate. Journal of Neurochemistry 113: 552-561.
8. Verma V, Singh N, Jaggi AS (2014) Pregabalin in neuropathic pain: Evidences and possible mechanisms. Curr Neuropharmacol 12: 44-56.
9. Mishra S, Bhatnagar S, Goyal G, Rana S, Upadhya S (2012) A comparative efficacy of amitriptyline, gabapentin and pregabalin in neuropathic cancer pain: A prospective randomized double-blind placebo-controlled study. American Journal of Hospice & Palliative Medicine 29: 177-182.
10. Sjolund K, Yang R, Lee K, Resnick M (2013) Randomized study of pregabalin in patients with cancer-induced bone pain. Pain Ther 2: 37-48.
11. Bennett M, Laird B, Litsenburg C, Nimour M (2014) Pregabalin for the management of neuropathic pain in adults with cancer: A systematic review of the literature. Pain Medicine 14: 1681-1688.
12. Bar Ad (2010) Gabapentin for the treatment of cancer-related pain syndromes. Rev Recent Clin Trials 5: 174-178.
13. Moon D, Lee D, Lee S, Song S, Yoon D, et al. (2010) Efficacy and tolerability of pregabalin using a flexible, optimized dose schedule in korean patients with peripheral neuropathic pain: A 10-week, randomized, double-blind, placebo-controlled, multicenter study. Clinical Therapeutics 32: 2370-2385.
14. Shinde S, Seisler D, Soori G, Atherton P, Pachman D, et al. (2016) Can pregabalin prevent paclitaxel-associated neuropathy? An ACCRU pilot trial. Support Care Cancer 24: 547-553.
15. De Andrade D, Teixeira M, Galhardoni R, Ferreira K, Mileno P, et al. (2017) Pregabalin for the prevention of oxaliplatin-induced painful neuropathy: A randomized, double-blind trial. The Oncologist 22: 1154-e105.
16. Dou Z, Jiang Z, Zhong J (2017) Efficacy and safety of pregabalin in patients with neuropathic cancer pain undergoing morphine therapy. Asia-Pacific Journal of Clinical Oncology 13: e57–e64.
17. Fallon M, Hoskin P, Colvin L, Fleetwood-Walker S, Adamson D, et al. (2016) Randomized double-blind trial of pregabalin versus placebo in conjunction with palliative radiotherapy for cancer-induced bone pain. Journal of Clinical Oncology 34: 550-558.
18. Karthaus M, Karapetis C, Brown M, Pavlakis N, Trarbach T, et al. (2010) Randomised, double blind, placebo-controlled trial for prevention of oxalipatin-induced peripheral neuropathy symptoms with pregabalin in patients with advanced colorectal cancer. Journal of Clinical Oncology 28: e19573.
19. Yoshimura N, Iida H, Takenaka M, Tanabe K, Yamaguchi S, et al. (2015) Effect of postoperative administration of pregabalin for post-thoracotomy pain: A randomized study. J Cardiothorac Vasc Anesth 29: 1567-1572.
20. Raptis E, Vadalouca A, Stavropoulou E, Argyra E, Melemeni A et al. (2014) Pregabalin vs. opioids for the treatment of neuropathic cancer pain: A prospective, head-to-head, randomized, open-label study. Pain Practice 14: 32-42.
21. Miyazaki T, Sakai T, Sato S, Yamasaki N, Tsuchiya T, et al. (2016) Is early postoperative administration of pregabalin beneficial for patients with lung cancer? randomized control trial. J Thorac Dis 8: 3572-3579.
22. Garassino MC, Piva S, La Verde N, Spagnoletti I, Iorno V, et al. (2013) Randomised phase II trial (NCT00637975) evaluating activity and toxicity of two different escalating strategies for pregabalin and oxycodone combination therapy for neuropathic pain in cancer patients. PLOS ONE 8: e59981.
23. Avan R, Janbabaei G, Hendouei N, Alipour A, Borhani S, et al. (2018) The effect of pregabalin and duloxetine treatment on quality of life of breast cancer patients with taxane-induced sensory neuropathy: A randomized clinical trial. Journal of Research in Medical Sciences 23: 52.
24. Abdelfattah A, Rizk F, Hawash N, Hanafy A, El-kalla F et al. (2018) Randomized trial of preoperative administration of oral pregabalin for postoperative analgesia in patient As scheduled for radiofrequency ablation of focal lesions in the liver. International Journal of Hyperthermia 34: 1367-1371.
25. Haidich AB (2010) Meta-analysis in medical research. Hippokratia 14: 29-37.
26. Hannan E (2008) Randomized clinical trials and observational studies: Guidelines for assessing respective strengths and limitations. JACC Cardiovascular Interventions 1: 211-217.
27. Cochrane (2018) Cochrane methods bias.
28. Mallett R, Hagen-Zanker J, Slater R, Duvendack M (2012) The benefits and challenges of using systematic reviews in international development research. Journal of Development Effectiveness 4: 445-455.