# Therapeutic Advantages of Mirogabalin and Pregabalin Over Current Treatments for Chemotherapy-Induced Peripheral Neuropathy

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## Abstract

Chemotherapy-induced peripheral neuropathy (CIPN) is a side effect of chemotherapy among cancer patients. In 2020, the cancer incidence in the United States was over 1.8 million. As cancer remains one of the prominent causes of death in the U.S., the incidence of CIPN poses concerning issues in cancer patients. Understanding the CIPN-induced neurodegeneration that occurs in cancer patients allows for treatments to be developed to reduce neuropathic pain. Compounds such as gabapentin, magnesium and calcium, vitamin B12, and goshajinkigan, have been used to treat CIPN; however, these drugs have displayed little to no effectiveness. Duloxetine is an effective treatment, but new drugs such as mirogabalin and pregabalin have also been evaluated for efficacy in cancer patients with CIPN. This literature review was conducted using two databases, Google Scholar and PubMed, to summarize the history, pharmacokinetics, pharmacodynamics, and effect of pregabalin, mirogabalin, and current treatments used in cancer and diabetic patients with peripheral neuropathy. Studies of pregabalin and mirogabalin on CIPN patients demonstrate their effectiveness in decreasing neuropathic pain; however, mirogabalin had a higher rate of improvement for neuropathic pain than pregabalin.

## Introduction

Peripheral neuropathy (PN) is a category of neurodegeneration that occurs as a result of nerve damage within the peripheral nervous system (1). The peripheral nervous system is comprised of nerves that branch outside the brain and spinal cord. These nerves control the motor and sensory divisions while contributing to the critical functions of the autonomic and somatic nervous systems (2). In the United States, the total percentage of existing cases of PN in adults age 40 and older without diabetes is 11.8%, with prevalence being higher in older adults with diabetes (28.4%) (3). Patients suffering from PN generally present with symptoms that are subclassified as "neuropathic pain." Such symptoms include but are not limited to severe pain (hyperalgesia and allodynia), numbness, tingling in the hands or feet, and burning sensations (paresthesia) (4). Many factors contribute to PN. The most common type is diabetic PN. As indicated in its name, diabetic peripheral neuropathy (DPN) is a diabetes-induced type of nerve damage in the hands and feet resulting from higher-than-normal blood glucose and triglyceride levels (5). Recent epidemiologic research has revealed that DPN prevalence was 34% in a community study of approximately 15,000 diabetic patients from varying ethnic backgrounds (6). Despite the prevalence of DPN, nondiabetic forms of PN also exist. Since cancer remains one of the prominent causes of death in the U.S., both the prevalence and incidence of PN pose concerning issues in cancer patients (7–9). Specifically, patients who have received chemotherapy as a general treatment for various cancers have developed a more specific type of PN known as chemotherapy-induced peripheral neuropathy (CIPN) (10–12).

CIPN is peripheral neuropathy in cancer patients that occurs as an adverse effect of chemotherapy. Concerning cancer-related deaths, pancreatic cancer (PC) is the fourth most common cause (13). The U.S. cancer incidence was over 1.8 million in 2020 (14). PC has one of the lowest survival rates, at 9% (13). One of the reasons for the low rate is because PC presents itself later in patients when the tumor has reached an advanced stage, which makes it challenging to resect. Therefore, only 15–20% of patients can undergo surgical interventions (13). Surgical interventions are determined based on a high-resolution CT scan of the PC to analyze the stage. A study examining patients with PC revealed more prolonged survival after receiving chemoradiotherapy (13). As cancer mortality and incidence continue to increase worldwide, further research has been conducted to observe the effects of current cancer treatments, such as chemotherapy (13). The development of CIPN is a limiting factor in chemotherapy. Chemotherapeutic drugs affect normal cells by damaging the nervous system's structure, thus creating adverse effects such as CIPN (15). An example of this is evident in taxane-induced peripheral neuropathy (TIPN) cases (16). Taxanes are a class of chemotherapeutic drugs used to treat metastatic breast cancer and have been linked to multiple TIPN cases (16). Provided that chemo drugs are neurotoxic agents, finding the proper treatment for CIPN becomes imperative (16).

Following the studies of PC patients, multiple treatment mechanisms have been utilized to treat CIPN. Such treatments include duloxetine, acupuncture, opioids, anti-seizure medications, and many more (17). Novel methods have considered using mirogabalin and pregabalin (18). However, since cancer types are not limited to PC, it becomes essential to assess the effectiveness of both drugs and apply these implications in future treatments of CIPN. This paper focuses on reviewing and exploring the efficacy of mirogabalin and pregabalin as potential alternative treatments to prevent and reduce the progression of CIPN in cancer patients. The pharmacology, response, and efficacy assessment of pregabalin and mirogabalin in CIPN will be further discussed.

## Methods

A literature review of mirogabalin and pregabalin as potential treatments for CIPN in cancer patients was conducted using PubMed and Google Scholar. The following key terms were used: "chemotherapy-induced peripheral neuropathy," "taxane-induced peripheral neuropathy," "peripheral neuropathy," "mirogabalin," and "pregabalin." The literature review included articles published between 2002 and 2023, except for one published in 1997. Meta-analyses, reviews, clinical trials, randomized controlled trials, and systematic reviews were included in this literature review. The chemical structures were derived from the ChemSpider software (19-20).

## Discussion

### Current Treatments for CIPN

Several previously identified substances have been used to attempt to treat the effects of CIPN. Some such substances include duloxetine, gabapentin, magnesium and calcium, vitamin B12, and goshajinkigan. Goshajinkigan is an herbal medicine from Japan commonly used to relieve general pain (21). Due to these therapeutic properties, a systematic review of five trials examined whether goshajinkigan effectively alleviated CIPN symptoms. Among these trials, it was found that while goshajinkigan was tolerated well, it was ineffective at preventing the effects of CIPN (21). Additionally, this herb was ineffective in reducing the risk of CIPN (22). Interestingly, though goshajinkigan did not prevent CIPN, it has been found effective at preventing acute PN induced by oxaliplatin (OXA) in rats (23).

Magnesium and calcium have also been proposed as CIPN treatments. The rationale behind this is that both molecules are involved with neuron excitability and the contraction of muscles (24). A longitudinal study was conducted regarding lifestyles and nutrition among 196 patients with colorectal cancer (CRC) (24). OXA is a cytotoxic chemotherapy used for treating CRC (25). CIPN is a common side effect of OXA in this subset of cancer patients (25). Magnesium consumption in the diet was associated with a lower prevalence of CIPN among CRC patients (prevalence ratio = 0.53) and higher magnesium intake during (ß = -1.08) and after (ß = -0.93) OXA chemotherapy treatments were associated with lower severity of symptoms caused by CIPN (24). Due to magnesium's role in the neuromuscular system, magnesium was found to be an effective treatment, whereas surprisingly, calcium was ineffective (24).

Due to the high demand for vitamin B12 in the nervous tissue, vitamin B12 deficiencies have been attributed to neuropathy manifestations (26). Therefore, the administration of vitamin B12 for CIPN treatment has been explored. Data from a clinical survey of oncology specialists was collected regarding the administration of certain pharmacotherapies, such as vitamin B12, for treating CIPN symptoms such as numbness and pain. Vitamin B12 was ineffective for CIPN, but some clinicians propose its use as placebo to alleviate symptoms due to its limited adverse effects (27).

Rather than taking a pharmacological approach, some investigators have found benefits in classic exercise for treating CIPN. A secondary analysis of a randomized controlled trial investigated how fatigue symptoms in breast cancer patients who received neurotoxic chemotherapy responded to exercise (28). The exercise regimen consisted of a progressive walking prescription for six weeks, followed by a therapeutic resistant band prescription that was individually tailored to each patient (28). The findings suggested that exercise effectively reduced the severity and prevalence of CIPN in cancer patients (28). Additional results have determined how sensorimotor and other resistance training has reduced the perceived sensory symptoms in the feet of cancer patients with CIPN (29).

Various investigations about gabapentin for CIPN have shown contradictory results. Gabapentin's use as an anti-neuropathic is associated with many adverse effects, such as lethargy, dizziness, and convulsions (30). In an effort to avoid some of these side effects, studies have been done using a topical administration of gabapentin and found therapeutic effects without those side effects (30).

While many currently proposed treatments for CIPN have shown little to no effectiveness, duloxetine is a drug that has demonstrated the opposite (31). Duloxetine belongs to the serotonin and norepinephrine reuptake inhibitors class of drugs (32). Its therapeutic use in treating neuropathies is by activating serotonergic and noradrenergic neurons in the spinal pain pathway (32). Duloxetine as a treatment for CIPN and DPN has been studied extensively and has been recommended as a first-line treatment for DPN (33). In 2022, researchers wanted to investigate tapentadol's efficacy as an analgesic for CIPN management (34). Tapentadol is a μ-opioid receptor agonist as well as a norepinephrine reuptake inhibitor (34). Due to its action as an opioid analgesic, tapentadol was cultivated for chronic pain management and thought to be beneficial for treating PN (34). To analyze tapentadol's impact on CIPN, a randomized, double-blind trial was conducted where patients either received tapentadol alone, or tapentadol plus duloxetine, as duloxetine is a common current treatment supported by the American Society of Clinical Oncology (34-35). Based on this comparison, it was found that tapentadol alone was an effective analgesic and improved the quality of life for CIPN patients (34).

### Patients Treated with Pregabalin and Mirogabalin

According to a retrospective report published in 2021 in Japan, 163 patients diagnosed with PC who were administered either gemcitabine plus nab-paclitaxel (GnP) or a combination of 5-fluorouracil, oxaliplatin, irinotecan, and leucovorin (FOLFIRINOX) as their chemotherapy regimens, were enrolled in a study testing the effectiveness of mirogabalin and pregabalin in treating those who developed CIPN (18). While FOLFIRINOX and GnP are successful treatments for PC, CIPN is often a side effect of these chemotherapy regimens. Comparisons were made between pretreatment severity scores and then again at two, four, and six weeks after treatment (18). In the mirogabalin-treated group, significant improvements in CIPN grade were shown at two, four, and six weeks compared to the pretreatment grade with $P<0.01$ (18). In the pregabalin group, significant improvements in CIPN grade were shown at two, four, and six weeks compared to the pretreatment grade with $P<0.05$ (18). At two weeks (84.6% vs. 33.3%), four weeks, and six weeks (92.3% vs. 33.3%), mirogabalin showed significantly higher rates of improvement in CIPN than the pregabalin group with $P<0.01$ (18). This study concluded that mirogabalin generated a higher rate of CIPN improvement than pregabalin in patients treated with GnP and FOLFIRINOX,

although both drugs had therapeutic improvement effects (18). Due to this being a retrospective study, having a small sample size, and varying treatment doses, further investigation into the effectiveness of mirogabalin and pregabalin would be informative for future CIPN patients (18).

While pregabalin and mirogabalin have been found effective treatments for PC patients, many other cancer patients also develop CIPN. A report involving lung cancer patients who have developed neuropathic pain looked at the efficacy of duloxetine and pregabalin as potential therapies (36). Positive and negative symptoms associated with neuropathic pain were evaluated before and after treatment, and pregabalin showed statistically significant reductions ($P<0.001$) in pain symptoms in these lung cancer patients. However, the results may not reveal clinical significance due to the relatively moderate sample size (N=42) (36). Paclitaxel is a type of chemotherapy and is known to have the common side effect of paclitaxel-induced peripheral neuropathy (PIPN). The vast majority (97%) of all urological and gynecological cancer patients have developed PIPN (37). Although pregabalin is often prescribed as a treatment for PIPN in patients with breast and gynecologic cancers, even more research is needed to test its effectiveness (38). Mirogabalin has been found effective in alleviating symptoms in patients suffering from postherpetic neuralgia and diabetic peripheral neuropathic pain (39). Due to its success in treating DPN, in Japan, mirogabalin became covered by insurance to treat CIPN (18).

As previously discussed, due to the neurotoxic identity of chemotherapeutic drugs, CIPN represents a common disabling effect. Chemotherapeutic drugs exert their neurotoxic effects through myelinopathy, neuronopathy, and axonopathy (40). Additionally, multifactorial mechanisms such as oxidative stress, increased apoptosis, calcium imbalance, and immunologic neuropathy are among the many associated pathophysiologies (40). Patients receiving chemotherapy bear a high risk of CIPN chronicity and impairments in their quality of life (41–44). Considering the severity and progression of CIPN symptoms, the pursued use of chemotherapy in cancer treatment may negatively affect patient prognosis (42, 44–45). Limited CIPN treatment options exist. Current targeted therapies mainly focus their pharmacokinetic dispositions on reducing and preventing further symptoms in affected patients (46). However, despite the limited treatment options, many efforts have been made to assess the efficacy of three main drugs: duloxetine, pregabalin, and mirogabalin (47–52). The pharmacokinetics and pharmacodynamics of pregabalin and mirogabalin in CIPN will be further discussed.

### Response to Pregabalin: Pharmacokinetics/ Pharmacodynamics

Pregabalin, depicted in Figure 1, has been approved by the FDA since 2004 for use in the United States (19, 53). Like mirogabalin, pregabalin is a gabapentinoid primarily used in treating neuropathic pain associated with DPN, spinal cord injuries, various forms of neuralgia, and multiple forms of PN (55). Pregabalin is referred to as an analog of the neurotransmitter gamma-aminobutyric acid (GABA) due to its structural similarity. Although its pharmacological profile resembles gabapentin, neither compound binds to $GABA_A$ or $GABA_B$ receptors (55–57). After oral administration, like mirogabalin, pregabalin functions as a ligand that selectively binds to the $\alpha_2\delta$ subunit of presynaptic voltage-gated calcium channels (VGCCs), with high affinity (56). The analgesic effects of pregabalin are attributed to the decreased neuronal calcium influx and lessened release of excitatory neurotransmitters induced by depolarization (57). In healthy fasting patients without renal impairments, rapid absorption is typically observed after administration, with average maximum plasma concentrations achieved within 0.5–1.5 hours (58). Steady-state concentrations are achieved within two days. The bioavailability of pregabalin is greater than or equal to 90%, and its volume of distribution is 42.1 L (57–58). Renally excreted in the urine, pregabalin is mainly 98% eliminated as an unchanged drug, with an elimination half-life of approximately 6 hours (55–58). Though pregabalin is well-tolerated in treating neuropathic pain, some patients have reported dose-dependent adverse symptomatic events. Adverse effects include weight gain, drowsiness, dizziness, edema, xerostomia, ataxia, euphoria, and hyperhidrosis (59).

### Response to Mirogabalin: Pharmacokinetics/ Pharmacodynamics

Mirogabalin besylate (mirogabalin), shown in Figure 2, was manufactured in Japan and gained its first marketing approval in 2019 after phase 3 clinical trials were completed (20, 54). FDA considerations for approval are still undergoing as U.S.

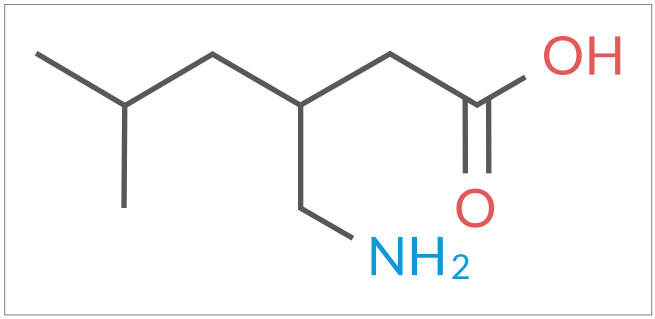


**Figure 1.** Pregabalin chemical structure (19). Pregabalin Molecular Formula: C8H17NO2, PubChem CID: 5486971, IUPAC Name: (3R)-3-(Aminomethyl)-5-methylhexanoic acid (53).

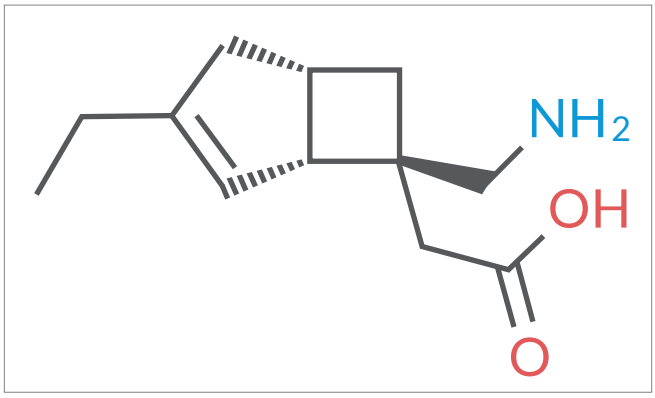


**Figure 2.** Mirogabalin chemical structure (20). Mirogabalin Molecular Formula: C12H19NO2, PubChem CID: 59509752, IUPAC Name: [(1R,5S,6S)-6-(Aminomethyl)-3-ethylbicyclo[3.2.0]hept-3-en-6-yl] acetic acid (54).

researchers continue to assess the applications of the drug's mechanisms of action in different types of PN pain (60). As a category of gabapentinoids, mirogabalin functions to provide analgesia by lessening dorsal horn sensitivity (61–62). Upon oral administration, mirogabalin serves as a ligand that selectively binds to the $\alpha_2\delta$-1 and $\alpha_2\delta$-2 subunits of VGCCs (60–62). In an investigation examining the activity of human VGCCs in vitro, upon exposure to mirogabalin, it was discovered that mirogabalin binding differed for both subunits. For the $\alpha_2\delta$-1 subunit, the dissociation half-life of mirogabalin was approximately 11.1 hours, compared to 2.4 hours for the $\alpha_2\delta$-2 subunit (62). Due to its longer dissociation half-life in the $\alpha_2\delta$-1 subunit, mirogabalin is considered to have a more potent effect, with a greater affinity for that subunit, thus producing a longer duration (62–63). As per the pharmacokinetics of mirogabalin, the drug is absorbed rapidly, and renal elimination occurs at a maximum of 72% through urine. Dosage measurements are determined based on renal function, with renal-impaired patients receiving lower doses. Mirogabalin volume of distribution ranges from 64 L to 88 L, with steady-state plasma concentrations achieved three days after initial administration (61, 63). Patients who have received mirogabalin to treat PN pain have reported moderate adverse effects. Adverse effects include dizziness, drowsiness, and headaches (61, 63-64).

### Applications of Pregabalin and Mirogabalin in Cancer Patients

Many symptoms are associated with CIPN, most of which start in the fingers and toes and then progress to the body. Several symptoms related to this condition were reported, including tingling or pins-and-needles sensations, pain, burning, numbness, temperature sensitivity, and difficulty with fine motor skills, such as writing and picking up small items (65). These symptoms have been analyzed using pregabalin and mirogabalin in cancer patients to further observe how these treatments would work for CIPN in cancer patients.

In chemotherapy, CIPN is one of the most common adverse effects caused by OXA and paclitaxel (39). OXA is a drug given to cancer patients through chemotherapy. It has been reported that patients with colorectal cancer develop acute and chronic pain related to oxaliplatin-induced peripheral neuropathy (66). OXA-related neuropathies have different pathophysiological bases, both acute and chronic. Several causes lead to neuropathic pain, including central sensitization of nociceptive neurons, causing the somatosensory system to have increased sensitivity, namely hyperalgesia and allodynia (66). Physiological sensations of pain are due to peripheral stimuli of enough intensity to trigger or threaten the activation of nociceptive pathways that result in acute nociceptive pain in patients (67). Peripheral sensitization represents the function of the nociceptor, which occurs from an injury that releases inflammatory mediators (68). Nociceptors are crucial in restoring the body's overall function; they are the peripheral pathway to nociceptive pain. This contributes to the hypersensitivity pain experienced in patients (68).

In a double-blind, randomized, placebo-controlled trial, neuropathic pain was measured daily in cancer patients via the 100-mm visual analogue scale, with 0 mm indicating no pain and 100 mm indicating unbearable pain, and averaged over seven days (69). Pregabalin significantly decreased neuropathic pain in cancer patients from 7.77 mm to 2.5 mm on the visual analogue scale compared to the placebo group, which decreased from 7.47 mm to 3.4 mm (69). On the fourth visit, 100% of the patients from the placebo group required rescue morphine dosage compared to 16.7% of patients in the pregabalin group (69). Pregabalin provided a decrease in neuropathic pain in patients with cancer. After the administration of OXA, patients treated with 150 mg/day pregabalin for two to six weeks displayed neuropathy improvements (66). This further highlights the function of pregabalin used to control neuropathic pain (17). As a result of pregabalin's improvement in neuropathic pain, morphine dosages can be significantly reduced in combination therapy. Pregabalin is the recommended first choice in the Neuropathic Pain Special Interest Group Guidelines (70).

Pregabalin was also used as a treatment for breast cancer patients with TIPN. Research shows that TIPN has a negative impact on the quality of life in patients with breast cancer (51). After the completion of chemotherapy, patients could suffer from neuropathic pain and paresthesia, obstructing the daily activities of the patients. This may affect their mental health leading to anxiety, depression, and cognitive impairment (52). The quality of life and the overall well-being of patients were impacted for those who needed breast cancer surgery. Acute postoperative pain after breast cancer surgery must be managed (71). In breast cancer patients who received pregabalin postoperatively, there was a decrease in tramadol consumption in the pregabalin group of 92.86 mg in comparison to the placebo group with a consumption of 162.50 mg ($P=0.029$) (71). Additionally, in patients with pronociceptive pain who underwent surgery, administration of pregabalin perioperatively reduced analgesic consumption by 16% (71).

A selective $\alpha_2\delta$ ligand, mirogabalin, was approved to treat peripheralπ neuropathic pain in Japan (72). In a study to determine the symptomatic grade changes before and after mirogabalin for patients who underwent chemotherapy for breast cancer, five mg of mirogabalin was administered twice daily, yielding stable symptoms for about six weeks; thus, the dosage was increased to 22.5 mg per day (73). The effect of mirogabalin decreased the numerical rating scale for numbness from 5/10 to 3/10 and pain from 8/10 to 5/10, further confirming the positive impact mirogabalin has on neuropathy (73). The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Chemotherapy-Induced Peripheral Neuropathy assesses the sensory neuropathy, autonomic neuropathy, and motor function of CIPN patients. The efficacy of patients introduced with mirogabalin controls the worsening of CIPN and improved sensory neuropathy (74). Mirogabalin did not further progress CIPN in patients with PC. As a result, it has been demonstrated to be a suitable treatment for patients with sensory neuropathy, including tingling and numbness symptoms (74). The cumulative toxicity of mirogabalin may not be a hindrance because it slows down the progression of CIPN and significantly improves sensory neuropathy. Dosing and titration should be carefully monitored due to the high rate of adverse events (74). Overall, the mirogabalin and pregabalin groups displayed significant progress upon treatment compared to the pretreatment grade (18). However, the rate of improvement was higher in the mirogabalin group.

### Applications of Pregabalin and Mirogabalin in DPN and Adverse Effects

Pregabalin has been shown to be very effective when treating patients with neuropathic pain, most notably diabetic neuropathy (75). One of the advantages of using pregabalin as a treatment option for DPN is its tolerability. A recent study investigated the dosage for individuals taking pregabalin to manage diabetic neuropathy and concluded that patients exhibited several signs of improvement (76). The dosage ranged from 150 mg/kg to 600 mg/kg and was taken between 4 weeks and 14 weeks. The results indicated that taking 600 mg of pregabalin daily significantly reduced the average pain score by more than 50% (77). Pain relief typically occurred in the first two weeks of treatment for DPN and was sustained throughout the study. When comparing the different doses of pregabalin (daily doses of 150 mg/kg, 300 mg/kg, and 600 mg/kg), there was a positive correlation between the dosage and the rate of pain reduction (78, 55). Using pregabalin to treat DPN also comes with mild to moderate side effects, including dizziness, edema, weight gain, fatigue, epigastric pain, and motor incoordination (77).

Mirogabalin was intended to treat pain associated with fibromyalgia and neuropathic pain (80). Patients who were generally administered mirogabalin either once or twice daily, with a dosage range between 5 and 30 mg, produced average daily pain scores that were significantly reduced when compared to patients who were given a placebo (81). An investigation was conducted to compare the effects of mirogabalin that were administered to patients with DPN (15 mg/day, 20 mg/day, and 30 mg/day) and determined that mirogabalin provided greater pain relief than pregabalin (82). Patients who initially took pregabalin to treat DPN and eventually switched to mirogabalin reported improved sleep (52). Patients who discontinued their mirogabalin treatment experienced a lower incidence of somnolence and a higher incidence of edema and dizziness, resulting in the cessation of that treatment (84–86). Overall, mirogabalin is an alternative treatment for DPN due to its comparable effectiveness to pregabalin (79).

## Conclusion

The incidence of cancer was over 1.8 million in 2020 in the U.S. CIPN is peripheral neuropathy in cancer patients that occurs as an adverse effect of chemotherapy. Since 30–40% of patients treated with neurotoxic chemotherapy develop CIPN, CIPN needs to be assessed to discover and develop therapies (43). While many potential substances have been attempted to treat CIPN symptoms, few have significantly impacted symptom severity and prevalence in cancer patients. Though duloxetine has been previously shown to be an effective treatment, pregabalin and now mirogabalin have shown greater efficacy at treating CIPN in retrospective studies. Provided that mirogabalin was a preliminary treatment for DPN and has now been concluded to be more efficacious than pregabalin for treating CIPN, the potential for new drug discoveries as well as repurposing current drugs as therapies for CIPN is of critical importance for improving the quality of life of these cancer patients. Mirogabalin demonstrated more significant pain relief and rate of improvement in comparison to pregabalin in patients with peripheral neuropathy.

In terms of limitations, the primary limitation of this literature review that could be addressed with future research was the inclusion of some outdated articles. With our methodology, we included articles published between 2002 and 2023, except for one published in 1997. Although current and future research focuses on novel treatments of CIPN, these older articles were included in this review to provide foundational insight into the past treatments of CIPN. While there has been some discovery of effective treatments for CIPN, much more information can be gained by conducting further analyses. Administering future investigations of the effectiveness of pregabalin, mirogabalin, and any other potential new drugs, such as venlafaxine, would be beneficial with much larger sample sizes to obtain stronger statistical and clinical significance. Duloxetine has been used as a first-line treatment for CIPN. Both duloxetine and venlafaxine are serotonin and norepinephrine reuptake inhibitors that have been recognized to be effective in treating CIPN (87). Consequently, applying the use of these drugs to treat the side effects of CIPN in other cancers, such as breast and colorectal cancers, and diabetic neuropathy patients will increase the discoveries of pharmacotherapies for CIPN.

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## References

1. DiAntonio A. Axon degeneration: Mechanistic insights lead to therapeutic opportunities for the prevention and treatment of peripheral neuropathy. *Pain*. 2019;160(1):17-22.
2. Sternini C. Organization of the peripheral nervous system: Autonomic and sensory ganglia. *J Investig Dermatol Symp Proc*. 1997;2(1):1-7.
3. Hicks CW, Wang D, Windham BG, Matsushita K, Selvin E. Prevalence of peripheral neuropathy defined by monofilament insensitivity in middle-aged and older adults in two US cohorts. *Sci Rep*. 2021;11(1):19159.
4. Reichling DB, Levine JD. Pain and death: Neurodegenerative disease mechanisms in the nociceptor. Ann Neurol. 2011;69(1):13-21.Izenberg A, Perkins BA, Bril V. Diabetic neuropathies. *Semin Neurol*. 2015;35(4):424–430.
5. Iqbal Z, Azmi S, Yadav R, Ferdousi M, Kumar M, Cuthbertson DJ, et al. Diabetic peripheral neuropathy: Epidemiology, diagnosis, and pharmacotherapy. *Clin Ther*. 2018;40(6):828-849.
6. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin*. 2022;72(1):7-33.

7. Selvy M, Kerckhove N, Pereira B, Barreau F, Nguyen D, Busserolles J, et al. Prevalence of chemotherapy-induced peripheral neuropathy in multiple myeloma patients and its impact on quality of life: A single center cross-sectional study. *Front Pharmacol*. 2021;12:637593.
8. Seretny M, Currie GL, Sena ES, Ramnarine S, Grant R, MacLeod MR, et al. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis. *Pain*. 2014;155(12):2461-2470.
9. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68:394–424.
10. Quasthoff S, Hartung HP. Chemotherapy-induced peripheral neuropathy. *J Neurol*. 2002;249(1):9-17.
11. Gordon-Williams R, Farquhar-Smith P. Recent advances in understanding chemotherapy-induced peripheral neuropathy. *F1000Res*. 2020;9:F1000.
12. Fogel EL, Shahda S, Sandrasegaran K, DeWitt J, Easler JJ, Agarwal DM, et al. A multidisciplinary approach to pancreas cancer in 2016: A review. *Am J Gastroenterol*. 2017;112:537-554.
13. Siegel RL, Miller KD, Goding Sauer A, Fedewa SA, Butterly LF, Anderson JC, et al. Colorectal cancer statistics, 2020. *CA Cancer J Clin*. 2020;70(3):145-64.
14. Zajączkowska R, Kocot-Kępska M, Leppert W, Wrzosek A, Mika J, Wordliczek J. Mechanisms of chemotherapy-induced peripheral neuropathy. *Int J Mol Sci*. 2019;20(6):1451.
15. Rivera E, Cianfrocca M. Overview of neuropathy associated with taxanes for the treatment of metastatic breast cancer. *Cancer Chemother Pharmacol*. 2015;75(4):659-70.
16. Zhang S. Chemotherapy-induced peripheral neuropathy and rehabilitation: A review. *Semin Oncol*. 2021;48(3):193-207.
17. Sugimoto M, Takagi T, Suzuki R, Konno N, Asama H, Sato Y, et al. Mirogabalin vs pregabalin for chemotherapy-induced peripheral neuropathy in pancreatic cancer patients. *BMC Cancer*. 2021;21(1):1319.
18. CSID:3902475, http://www.chemspider.com/Chemical-Structure.3902475.html (accessed 22:28, May 10, 2023)
19. CSID:32701007, http://www.chemspider.com/Chemical-Structure.32701007.html (accessed 23:05, May 10, 2023)
20. Kuriyama A, Endo K. Goshajinkigan for prevention of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis. *Support Care Cancer*. 2018;26(4):1051-1059.
21. Hoshino N, Ganeko R, Hida K, Sakai Y. Goshajinkigan for reducing chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis. *Int J Clin Oncol*. 2018;23(3):434-442.
22. Mizuno K, Kono T, Suzuki Y, Miyaji C, Omiya Y, Miyano K, et al. Goshajinkigan, a traditional Japanese medicine, prevents oxaliplatin-induced acute peripheral neuropathy by suppressing functional alteration of TRP channels in rat. *J Pharmacol Sci*. 2014;125(1):91-98.
23. Wesselink E, Winkels RM, Van Baar H, Geijsen AJ, Van Zutphen M, Van Halteren HK, et al. Dietary intake of magnesium or calcium and chemotherapy-induced peripheral neuropathy in colorectal cancer patients. *Nutrients*. 2018;10(4):398.
24. Kang L, Tian Y, Xu S, Chen H. Oxaliplatin-induced peripheral neuropathy: Clinical features, mechanisms, prevention and treatment. *J Neurol*. 2021;268(9):3269-3282.
25. Pavlov CS, Damulin IV, Shulpekova YO, Andreev EA. Neurological disorders in vitamin B12 deficiency. *Ter Arkh*. 2019;91(4):122-129.
26. Hirayama Y, Yoshida Y, Mori M, Tamura K. Effects of the publication of clinical guidelines for the management of chemotherapy-induced peripheral neuropathy on the administration preferences of oncology specialists: Japanese association of supportive care in cancer. *Jpn J Clin Oncol*. 2020;50(8):897-902.
27. Kleckner IR, Kamen C, Gewandter JS, Mohile NA, Heckler CE, Culakova E, et al. Effects of exercise during chemotherapy on chemotherapy-induced peripheral neuropathy: A multicenter, randomized controlled trial. *Support Care Cancer*. 2018;26(4):1019-1028.
28. Müller J, Weiler M, Schneeweiss A, Haag GM, Steindorf K, Wick W, et al. Preventive effect of sensorimotor exercise and resistance training on chemotherapy-induced peripheral neuropathy: A randomised-controlled trial. *Br J Cancer*. 2021;125(7):955-965.
29. Shahid M, Subhan F, Ahmad N, Sewell RDE. Efficacy of a topical gabapentin gel in a cisplatin paradigm of chemotherapy-induced peripheral neuropathy. *BMC Pharmacol Toxicol*. 2019;20(1):51.
30. Sugimoto M, Takagi T, Suzuki R, Konno N, Asama H, Sato Y, et al. Drug treatment for chemotherapy-induced peripheral neuropathy in patients with pancreatic cancer. *Fukushima J Med Sci*. 2022;68(1):1-0.
31. Dhaliwal JS, Spurling BC, Molla M. Duloxetine. *StatPearls*. 2023.
32. Battaglini E, Park SB, Barnes EH, Goldstein D. A double blind, placebo controlled, phase II randomised cross-over trial investigating the use of duloxetine for the treatment of chemotherapy-induced peripheral neuropathy. *Contemp Clin Trials*. 2018;70:135-138.
33. Sansone P, Giaccari LG, Aurilio C, Coppolino F, Passavanti MB, Pota V, et al. Comparative efficacy of tapentadol versus tapentadol plus duloxetine in patients with chemotherapy-induced peripheral neuropathy (CIPN): A randomized non-inferiority clinical trial. *Cancers (Basel)*. 2022;14(16):4002.

34. Hou S, Huh B, Kim HK, Kim KH, Abdi S. Treatment of chemotherapy-induced peripheral neuropathy: Systematic review and recommendations. *Pain Physician*. 2018;21(6):571-592.
35. Gül ŞK, Tepetam H, Gül HL. Duloxetine and pregabalin in neuropathic pain of lung cancer patients. *Brain Behav*. 2020;10(3):e01527.
36. Klein I, Lehmann HC. Pathomechanisms of paclitaxel-induced peripheral neuropathy. *Toxics*. 2021;9(10):229.
37. Hiramoto S, Asano H, Miyamoto T, Takegami M, Kawabata A. Risk factors and pharmacotherapy for chemotherapy-induced peripheral neuropathy in paclitaxel-treated female cancer survivors: A retrospective study in Japan. *PLoS One*. 2021;16(12):e0261473.
38. Kim JY, Abdi S, Huh B, Kim KH. Mirogabalin: Could it be the next generation gabapentin or pregabalin? *Korean J Pain*. 2021;34(1):4-18.
39. Miltenburg NC, Boogerd W. Chemotherapy-induced neuropathy: A comprehensive survey. *Cancer Treat Rev*. 2014;40(7):872–882.
40. Maihöfner C, Diel I, Tesch H, Quandel T, Baron R. Chemotherapy-induced peripheral neuropathy (CIPN): Current therapies and topical treatment option with high-concentration capsaicin. *Support Care Cancer*. 2021;29(8):4223-4238.
41. Boyette-Davis JA, Hou S, Abdi S, Dougherty PM. An updated understanding of the mechanisms involved in chemotherapy-induced neuropathy. *Pain Manag*. 2018;8(5):363–375.
42. Staff NP, Grisold A, Grisold W, Windebank AJ. Chemotherapy-induced peripheral neuropathy: A current review. *Ann Neurol*. 2017;81(6):772–781.
43. Starobova H, Vetter I. Pathophysiology of chemotherapy-induced peripheral neuropathy. *Front Mol Neurosci*. 2017;10:174.
44. Gießen-Jung C, von Baumgarten L. Chemotherapie-induzierte periphere neuropathie [Peripheral neuropathy as a side effect of chemotherapy and targeted therapy]. *Dtsch Med Wochenschr*. 2018;113(13):970–978.
45. Jordan B, Jahn F, Sauer S, Jordan K. Prevention and management of chemotherapy-induced polyneuropathy. *Breast Care (Basel)*. 2019;14(2):79-84.
46. Mezzanotte JN, Grimm M, Shinde NV, Nolan T, Worthen-Chaudhari L, Williams NO, et al. Updates in the treatment of chemotherapy-induced peripheral neuropathy. *Curr Treat Options Oncol*. 2022;23(1):29-42.
47. Staurengo-Ferrari L, Bonet IJM, Araldi D, Green PG, Levine JD. Neuroendocrine stress axis-dependence of duloxetine analgesia (anti-hyperalgesia) in chemotherapy-induced peripheral neuropathy. *J Neurosci*. 2022;42(3):405-415.
48. Smith EM, Pang H, Cirrincione C, Fleishman S, Paskett ED, Ahles T, et al. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: A randomized clinical trial. *JAMA*. 2013;309(13):1359-67.
49. Avan R, Janbabaei G, Hendouei N, Alipour A, Borhani S, Tabrizi N, et al. The effect of pregabalin and duloxetine treatment on quality of life of breast cancer patients with taxane-induced sensory neuropathy: A randomized clinical trial. *J Res Med Sci*. 2018;23:52.
50. Salehifar E, Janbabaei G, Hendouei N, Alipour A, Tabrizi N, Avan R. Comparison of the efficacy and safety of pregabalin and duloxetine in taxane-induced sensory neuropathy: A randomized controlled trial. *Clin Drug Investig*. 2020;40(3):249-257.
51. Baba M, Matsui N, Kuroha M, Wasaki Y, Ohwada S. Mirogabalin for the treatment of diabetic peripheral neuropathic pain: A randomized, double-blind, placebo-controlled phase III study in Asian patients. *J Diabetes Investig*. 2019;10(5):1299-1306.
52. PubChem [Internet]. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; 2004-. PubChem Compound Summary for CID 5486971, Pregabalin.
53. PubChem [Internet]. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; 2004-. PubChem Compound Summary for CID 59509752, Mirogabalin.
54. Frampton JE, Scott LJ. Pregabalin: In the treatment of painful diabetic peripheral neuropathy. *Drugs*. 2004;64(24):2813-20.
55. Cross AL, Viswanath O, Sherman AL. Pregabalin [Internet]. Treasure Island, FL: StatPearls Publishing; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470341/
56. Tassone DM, Boyce E, Guyer J, Nuzum D. Pregabalin: A novel gamma-aminobutyric acid analogue in the treatment of neuropathic pain, partial-onset seizures, and anxiety disorders. *Clin Ther*. 2007;29(1):26-48.
57. Chew ML, Alvey CW, Plotka A, Pitman VW, Alebic-Kolbah T, Scavone JM, et al. Pregabalin controlled-release pharmacokinetics in healthy volunteers: Analysis of four multiple-dose randomized clinical pharmacology studies. *Clin Drug Investig*. 2014;34(9):627-37.
58. Onakpoya IJ, Thomas ET, Lee JJ, Goldacre B, Heneghan CJ. Benefits and harms of pregabalin in the management of neuropathic pain: A rapid review and meta-analysis of randomized clinical trials. *BMJ Open*. 2019;9(1):e023600.
59. Kim JY, Abdi S, Huh B, Kim KH. Mirogabalin: Could it be the next generation gabapentin or pregabalin? *Korean J Pain*. 2021;34(1):4-18.
60. Deeks ED. Mirogabalin: First global approval. *Drugs*. 2019;79(4):463-468.
61. Tetsunaga T, Tetsunaga T, Nishida K, Misawa H, Takigawa T, Yamane K, et al. Short-term outcomes of mirogabalin in patients with peripheral neuropathic pain: A retrospective study. *J Orthop Surg Res*. 2020;15(1):191.
62. Nair A. Mirogabalin, a selective gabapentinoid for managing neuropathic pain - A curtain raiser. *J Anaesthesiol Clin Pharmacol*. 2022;38(4):691-692.

63. Jansen M, Warrington S, Dishy V, Ohwada S, Johnson L, Brown K, et al. A randomized, placebo-controlled, double-blind study of the safety, tolerability, pharmacokinetics, and pharmacodynamics of single and repeated doses of mirogabalin in healthy Asian volunteers. *Clin Pharmacol Drug Dev*. 2018;7(6):661-669.
64. Brown TJ, Sedhom R, Gupta A. Chemotherapy-induced peripheral neuropathy. *JAMA Oncol*. 2019;5(5):750.
65. De Andrade DC, Jacobsen Teixeira M, Galhardoni R, Ferreira KSL, Braz Mileno P, Scisci N, et al. Pregabalin for the prevention of oxaliplatin-induced painful neuropathy: A randomized, double-blind trial. *Oncologist*. 2017;22(10):1154-e105.
66. Latremoliere A, Woolf CJ. Central sensitization: A generator of pain hypersensitivity by central neural plasticity. *J Pain*. 2009;10(9):895-926.
67. Woolf CJ, Ma Q. Nociceptors--Noxious stimulus detectors. *Neuron*. 2007;55(3):353-64.
68. Mishra S, Bhatnagar S, Goyal GN, Rana SP, Upadhya SP. A comparative efficacy of amitriptyline, gabapentin, and pregabalin in neuropathic cancer pain: A prospective randomized double-blind placebo-controlled study. *Am J Hosp Palliat Care*. 2012;29(3):177-82.
69. Dworkin RH, O'Connor AB, Audette J, Baron R, Gourlay GK, Haanpää ML, et al. Recommendations for the pharmacological management of neuropathic pain: An overview and literature update. *Mayo Clin Proc*. 2010;85(3 Suppl):S3-14.
70. Rai AS, Khan JS, Dhaliwal J, Busse JW, Choi S, Devereaux PJ, et al. Preoperative pregabalin or gabapentin for acute and chronic postoperative pain among patients undergoing breast cancer surgery: A systematic review and meta-analysis of randomized controlled trials. *JPRAS*. 2017;70(10):1317-28.
71. Kato J, Matsui N, Kakehi Y, Murayama E, Ohwada S, Sugihara M. Mirogabalin for the management of postherpetic neuralgia: A randomized, double-blind, placebo-controlled phase 3 study in Asian patients. *Pain*. 2019;160(5):1175–85.
72. Saito Y, Takekuma Y, Oshino T, Sugawara M. Combination of mirogabalin and duloxetine attenuates peripheral neuropathy by eribulin: A novel case report. *Case Rep Oncol*. 2022;15(2):606-610.
73. Takasaki Y, Fujisawa T, Ushio M, Takahashi S, Yamagata W, Suzuki A, et al. Effect of mirogabalin on chemotherapy-induced peripheral neuropathy caused by gemcitabine plus nab-paclitaxel therapy in pancreatic cancer patients: A pilot study. *J Vasc Surg*. 2022;1(1):36-42.
74. Freynhagen R, Strojek K, Griesing T, Whalen E, Balkenohl M. Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible-and fixed-dose regimens. *Pain*. 2005;115(3):254-63.
75. Pachman DR, Barton DL, Watson JC, Loprinzi CL. Chemotherapy-induced peripheral neuropathy: Prevention and treatment. *Clin Pharmacol Ther*. 2011;90(3):377-87.
76. Verma V, Singh N, Singh Jaggi A. Pregabalin in neuropathic pain: Evidences and possible mechanisms. *Curr Neuropharmacol*. 2014;12(1):44-56.
77. Richter RW, Portenoy R, Sharma U, Lamoreaux L, Bockbrader H, Knapp LE. Relief of painful diabetic peripheral neuropathy with pregabalin: A randomized, placebo-controlled trial. *J Pain*. 2005;6(4):253-260.
78. Freeman R, Durso-Decruz E, Emir B. Efficacy, safety, and tolerability of pregabalin treatment for painful diabetic peripheral neuropathy: Findings from seven randomized, controlled trials across a range of doses. *Diabetes Care*. 2008;31(7):1448-1454.
79. Merante D, Rosenstock J, Sharma U, Feins K, Hsu C, Vinik A. Efficacy of mirogabalin (DS-5565) on patient-reported pain and sleep interference in patients with diabetic neuropathic pain: Secondary outcomes of a phase II proof-of-concept study. *Pain Med*. 2017;18(11):2198-2207.
80. Yokoyama T, Arakawa N, Domon Y, Matsuda F, Inoue T, Kitano Y, et al. Pharmacological, pharmacokinetics and safety profiles of DS-5565, a novel α2δ ligand. *Neurol Sci*. 2013;333:e535.
81. Vinik A, Rosenstock J, Sharma U, Feins K, Hsu C, Merante D. Efficacy and safety of mirogabalin (DS-5565) for the treatment of diabetic peripheral neuropathic pain: A randomized, double-blind, placebo - And active comparator-controlled, adaptive proof-of-concept phase 2 study. *Diabetes Care*. 2014;37(12):3253-3261.
82. Tetsunaga T, Tetsunaga T, Nishida K, Misawa H, Takigawa T, Yamane K, et al. Short-term outcomes of mirogabalin in patients with peripheral neuropathic pain: A retrospective study. *J Orthop Surg Res*. 2020;15(1):191.
83. Baba M, Matsui N, Kuroha M, Wasaki Y, Ohwada S. Long-term safety and efficacy of mirogabalin in Asian patients with diabetic peripheral neuropathic pain. *J Diabetes Investig*. 2020;11(3):693-698.
84. Alyoubi RA, Alshareef AA, Aldughaither SM, Aljaroudi AM, Alabdulwahed A, Alduraibi FM, et al. Efficacy and safety of mirogabalin treatment in patients with diabetic peripheral neuropathic pain: A systematic review and meta-analysis of randomised controlled trials. *Int J Clin Pract*. 2021;75(5):e13744.
85. Javed S, Alam U, Malik RA. Mirogabalin and emerging therapies for diabetic neuropathy. *J Pain Res*. 2018;11:1559-1566.
86. Aziz MT, Good BL, Lowe DK. Serotonin-norepinephrine reuptake inhibitors for the management of chemotherapy-induced peripheral neuropathy. *Ann Pharmacother*. 2014;48(5):626-32.