

REVIEW

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# Safety, tolerability, and efficacy of a selective gabapentinoid mirogabalin in neuropathic pain—a topical review

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## Abstract

Gabapentin and pregabalin, known as gabapentinoids, have been used effectively as a monotherapy or in combination with other agents for managing chronic neuropathic pain due to various etiologies. These drugs act via  $\alpha 2\delta$ -1 and  $\alpha 2\delta$ -2 subunits of voltage-gated calcium channels (VGCCs) non-selectively. Due to its non-selective action, a certain group of patients reports central nervous system adverse effects like dizziness, drowsiness, somnolence, and cerebellar ataxia.

Mirogabalin besylate is an orally administered next-generation gabapentinoid approved for use in diabetic neuropathy and post-herpetic neuralgia. It binds selectively and with greater affinity to the  $\alpha 2\delta$ -1 and  $\alpha 2\delta$ -2 subunits of human VGCCs and thus has lesser central nervous system adverse events making it more tolerable. We reviewed all articles in various categories, published in reputed databases since 2014 where mirogabalin was used to treat chronic neuropathic pain. Case series and open-label studies have demonstrated the safety and efficacy of mirogabalin in cancer pain and lumbar spine disease. Pharmacokinetic/pharmacodynamic studies have cautioned using full dose in patients with renal/hepatic impairment and along with drugs that could lead to adverse effects like sedatives and opioids. Dose up to 30 mg/day when administered as a twice-daily divided dose has been tolerated quite well with adequate pain relief in diabetic neuropathy and post-herpetic neuralgia.

Mirogabalin appears to be a safe gabapentinoid in diabetic neuropathy and post-herpetic neuralgia. Further studies need to be conducted to explore the role of mirogabalin in cancer pain, postoperative pain, and neuropathic pain due to various other etiologies.

**Keywords:** Mirogabalin, Neuropathic pain, Diabetic neuropathy, Post-herpetic neuralgia, Chronic pain

## Background

Gabapentin and pregabalin are commonly used gabapentinoid anticonvulsants for managing neuropathic pain due to various etiologies including cancer pain (Derry et al., 2019; Wiffen et al., 2017; Bar, 2010). Several studies have shown that when gabapentinoids are used as monotherapy or as a part of a multimodal regimen, it has been successful in alleviating chronic neuropathic pain due to several etiologies (Moore et al., 2018).

Maladaptation and dysregulation of the  $\alpha 2\delta$ -1 subunits of voltage-gated calcium channels (VGCCs) are some of the causes of neuropathic pain. Both gabapentin and pregabalin bind to the  $\alpha 2\delta$ -1 and  $\alpha 2\delta$ -2 auxiliary subunits of VGCCs (Patel & Dickenson, 2016).

Dizziness, drowsiness, somnolence, and cerebellar ataxia were frequently reported with gabapentinoids. Other issues like visual blurring, ataxia, and weight gain were noticed by researchers with the use of pregabalin only (Shaheen et al., 2019). This is because of the binding of gabapentin and pregabalin to the  $\alpha 2\delta$ -1 and  $\alpha 2\delta$ -2 subunits of VGCCs non-selectively. There has been a concern with the use of gabapentinoids in the form of

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serious neuropsychiatric adverse drug reactions which has been discussed in several articles recently (Tambon et al., 2021). A review of pharmacovigilance data from France has shown serious hepatic and hematological adverse events with the use of gabapentinoids (Deeks, 2019).

### Introduction of mirogabalin besylate

Mirogabalin besylate is a new gabapentinoid that has been approved for use in diabetic neuropathic pain and post-herpetic neuralgia (Calandre et al., 2016). Mirogabalin selectively binds to and modulates the  $\alpha 2\delta$ -1 subunits of VGCCs and also has a unique binding profile and long duration of action (Fig. 1). This topical review discusses the various chronic pain indications in various doses where mirogabalin was used in humans only and also the adverse effects encountered in the published articles.

### Pharmacology and clinical uses of mirogabalin besylate

Mirogabalin is an orally administered gabapentinoid developed by Daiichi Sankyo, Japan, for the treatment of peripheral neuropathic pain like diabetic peripheral neuropathic pain, post-herpetic neuralgia, lumbar spine disease, and cancer pain. Mirogabalin tablets (Tarlige®; 2.5, 5, 10, and 15mg) were approved in Japan in January 2019 for the treatment of peripheral neuropathic pain based on the results of trials conducted in patients with diabetic peripheral neuropathic pain or post-herpetic neuralgia (Domon et al., 2018).

Mirogabalin binds selectively and with greater affinity to the  $\alpha 2\delta$ -1 and  $\alpha 2\delta$ -2 subunits of human VGCCs in vitro (Kd 13.5 and 22.7 nmol/L). Mirogabalin takes considerably longer to dissociate from  $\alpha 2\delta$ -1 (dissociation half-life 11.1 h) than  $\alpha 2\delta$ -2 in vitro (dissociation

half-life 2.4 h) compared to pregabalin which required 1.4 h to dissociate from both  $\alpha 2\delta$ -1 and  $\alpha 2\delta$ -2 subunits of VGCCs. Mirogabalin has a tendency of greater affinity to and slow dissociation from the  $\alpha 2\delta$ -1 subunits which leads to its longer duration of action. At the same time, it has demonstrated a low affinity to and fast dissociation from the  $\alpha 2\delta$ -2 subunits in the cerebellum leading to lesser incidence of ataxia and other central nervous system adverse events. Mirogabalin is rapidly absorbed after when taken orally (median time to maximum plasma concentration (Tmax) of 0.5–1.5 h) single or multiple doses. With daily dosing, a steady-state plasma concentration gets achieved by day 3 (Brown et al., 2018). The adverse effects commonly encountered with the use of mirogabalin are dizziness (8–16%), somnolence (6–24%), and headache (6–14%). Issues like constipation, nausea, diarrhea, vomiting, edema, fatigue, and weight gain have rarely been encountered (Burgess et al., 2020).

### Main text

#### Materials and methods

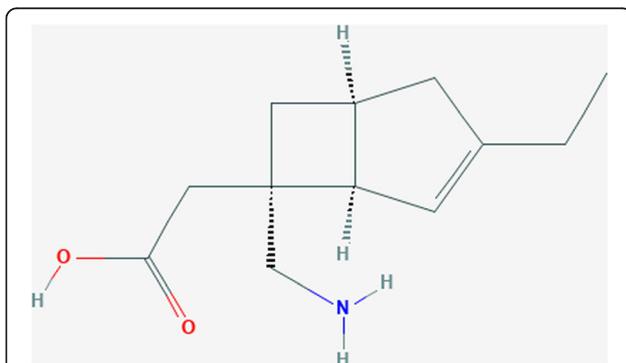
We used the keywords mirogabalin, chronic pain, neuropathic pain, cancer pain, and neuropathy to search MEDLINE, Embase, Web of Science, and Google Scholar databases. We included only those articles in the review where mirogabalin was used in human patients and volunteers. The full text of all articles was reviewed, and details like type of study, indication for which mirogabalin was used, number of patients, the dose of mirogabalin used, and key points of the articles were summarized in a tabular form. Animal studies, experimental studies like induced neuropathic pain, and review articles were excluded. However, those articles were used in the discussion for citing wherever necessary.

#### Study selection

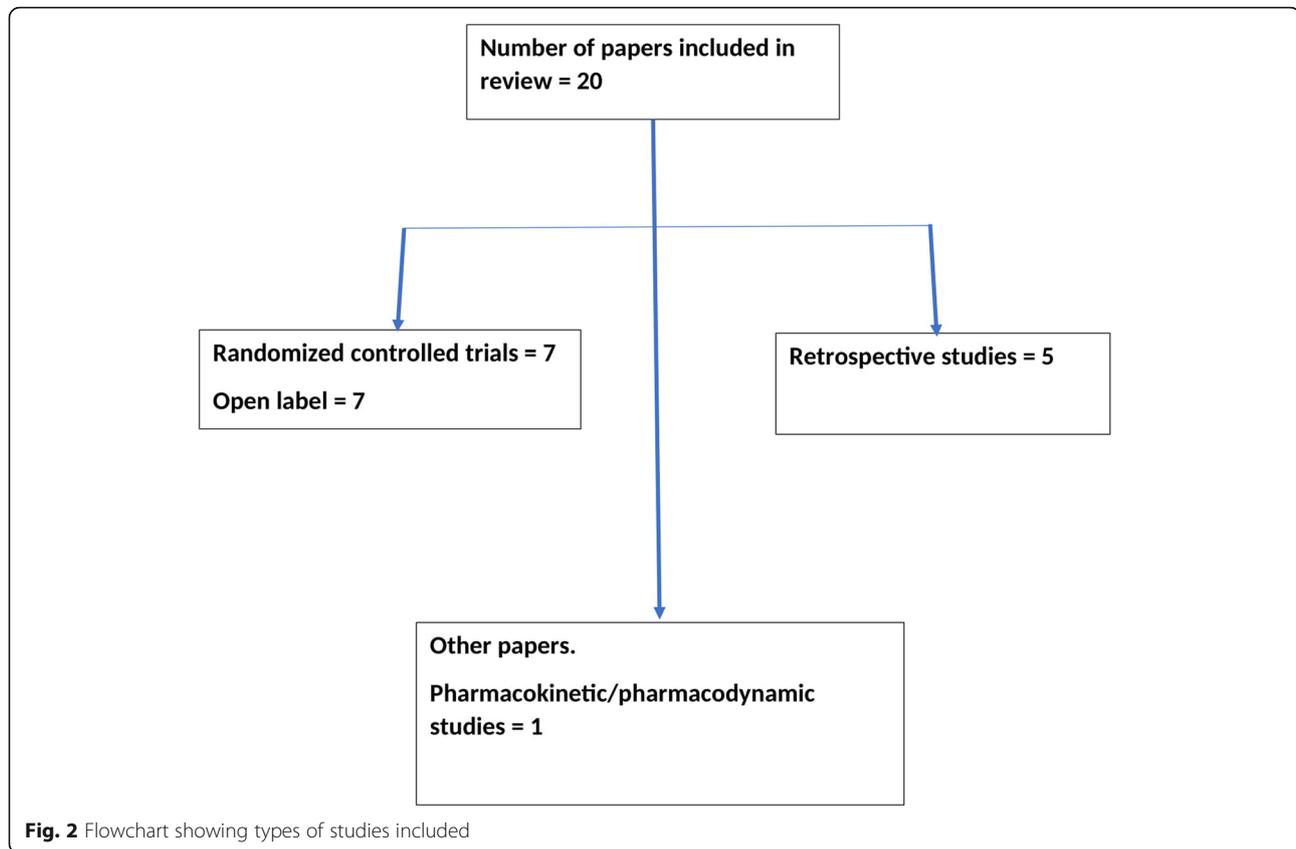
Starting from the year 2014 till date, we retrieved 20 full-text articles in which mirogabalin was used by researchers for various indications like diabetic neuropathy, post-herpetic neuropathic pain, lumbar spine disease, fibromyalgia, and cancer pain (Fig. 2). The dose of mirogabalin ranged from 10 to 30 mg/day.

#### Review of literature and discussion

Table 1 depicts various studies published starting from 2014 till 2020 where mirogabalin was used in various doses for several chronic pain indications. The results of the first study were by Vinik et al. published in 2014 which was a randomized, double-blind, placebo- and active comparator-controlled, adaptive proof-of-concept phase 2 study (Vinik et al., 2014). The authors enrolled 452 patients in seven groups; patients in 5 groups received different doses of mirogabalin (5–30 mg/day), the 6th group received pregabalin 300 mg/day, and the 7th



**Fig. 1** Chemical structure of mirogabalin (figure source: PubChem [Internet]. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; 2004-. PubChem Compound Summary for CID 59509752, Mirogabalin; [cited 2021 Jan. 11]. Available from: <https://pubchem.ncbi.nlm.nih.gov/compound/Mirogabalin>)



group was placebo, for 5 weeks. In 20-mg and 30-mg arms, patients received mirogabalin twice daily in divided doses. At doses from 15 to 30 mg/day, mirogabalin provided statistically significant pain relief when compared to pregabalin, placebo, and fewer doses of mirogabalin and was well tolerated. Later, Hutmacher et al. analyzed central nervous system adverse events of single-dose versus twice-daily divided dosing of mirogabalin (in the group where the dose was 20 mg/day or more) from the article by Vinik et al. (Hutmacher et al., 2016). After analysis, the authors suggested that for a dose of 20 mg or more, a divided dosing results in lesser adverse effects thereby increasing tolerability.

Arnold et al. investigated the efficacy of mirogabalin in three 13-week, multicenter, double-blind, phase 3 studies in patients with fibromyalgia. Patients were randomized to receive placebo, pregabalin 150 mg twice daily, mirogabalin 15 mg once daily, or mirogabalin 15 mg twice daily. On analysis, authors concluded that although well tolerated the primary endpoint of significant pain reduction in patients on mirogabalin compared with placebo was not achieved in any of the three randomized controlled studies (Arnold et al., 2019). Later, Merante et al., (2017) published a commentary in which the author discussed the lessons learned from the negative

outcome of the mirogabalin ALDAY phase 3 clinical program in pain associated with fibromyalgia, i.e., the paper by Arnold et al. (Merante, 2020). The author emphasized the need for a comprehensive patient-focused strategy to identify the challenges of fibromyalgia based on the patient perspective and study complexity; the need for a harmonized, patient-centric, global regulatory guidance accepted by regulatory agencies; and the importance of a phase 2 proof-of-concept, dose-ranging study before starting any phase 3 program in fibromyalgia.

Kanbayashi et al. enrolled 159 patients with various chronic neuropathic etiologies and eventually analyzed retrospective data of 133 patients who received less than 20 mg/day of mirogabalin for 2 weeks. The authors found that mirogabalin was effective in 85 of 133 patients. The authors suggested avoiding mirogabalin with concomitant opioids but found that it can be safely used with neurotrophin (NTP) which is a non-protein extract isolated from the inflamed skin of rabbits inoculated with vaccinia virus and used for the treatment of neuropathic pain (Kanbayashi et al., 2020). Caution needs to be exercised when using other drugs like opioids, benzodiazepines with mirogabalin. In a pharmacokinetic/pharmacodynamic study, Jansen et al. enrolled healthy

**Table 1** Table showing studies in which mirogabalin was used in various chronic pain conditions

S. no.	No. of patients	Type of study	Indication	Dose used	Key points	Author/ year/ reference
1	452	Randomized, double-blind, placebo and active comparator-controlled, adaptive proof-of-concept phase 2 study	Diabetic peripheral neuropathy	5–30 mg/day	Mirogabalin was effective and well tolerated in this patient population at doses ranging from 5 to 30 mg/day in titrated doses.	(Vinik et al., 2014)
2	436	Retrospective	Diabetic peripheral neuropathy	5–30 mg/day	Authors suggested twice daily dosing of mirogabalin instead of once daily to avoid adverse events.	(Hutmacher et al., 2016)
3	32	Open-label parallel-group study	Volunteers with varying degree of renal functions	5 mg/day	Reduction of mirogabalin dose by 50% in subjects with moderate renal impairment and by 75% in subjects with severe renal impairment was suggested.	(Yin et al., 2016)
4	452	Phase II Proof-of-concept study	Diabetic peripheral neuropathy	5–30 mg/day	Mirogabalin provided effective pain relief and better quality of sleep compared to placebo and 75–600 mg/day of pregabalin in a dose-dependent manner.	(Merante, 2020)
5	32	Open-label single-dose study	16 healthy controls and 16 subjects with hepatic impairment (8 mild and 8 moderate)	15 mg/day	A single 15-mg dose of mirogabalin was well tolerated by subjects with mild or moderate hepatic impairment.	(Duchin et al., 2018)
6	53	Randomized, placebo-controlled, double-blind study	Volunteers	10–40 mg/day	Mirogabalin had an acceptable safety and tolerability profile in Asian and white subjects at doses up to 15 mg twice a day for 7 days.	(Jansen et al., 2018b)
7	30	Multicenter open-label study	Volunteers	5 mg/day	Administration of a single oral 5-mg mirogabalin tablet was well tolerated in Japanese subjects with normal renal function and those with mild to severe renal impairment.	(Kato et al., 2018)
8	48/47/30	Three phase 1 pharmacokinetic (PK)/ pharmacodynamics (PD) studies	Healthy volunteers	3–75 mg/day	Mirogabalin 15 mg twice daily was selected as the highest target dose for further clinical development.	(Brown et al., 2018)
9	88	Four randomized, double-blind, placebo-controlled, 4-period drug-drug interaction studies	Healthy adults	30 mg/day	Increased CNS adverse events when mirogabalin co-administered with lorazepam or ethanol.	(Jansen et al., 2018c)
10	765	Multicenter, double-blind, placebo-controlled phase 3 study	Post-herpetic neuralgia	15–30 mg/day	Mirogabalin was superior to placebo in all groups for relieving PHN and appeared well tolerated.	(Kato et al., 2019)
11	494	Randomized, double-blind, placebo-controlled phase III study	Diabetic peripheral neuropathy	15–30 mg/day	All doses (between 15 and 30 mg/day) provided significant pain relief in a dose-dependent manner compared to placebo.	(Baba et al., 2019)
12	1934	Three 13-week randomized, double-blind, placebo and active-controlled, parallel-group studies and a 52-week open-label extension study	Fibromyalgia	15–30 mg/day	The primary endpoint of significant pain reduction in patients on mirogabalin compared with placebo was not achieved although well tolerated and showed potential for pain relief.	(Arnold et al., 2019)
13	74	Retrospective clinical investigation	Diabetic peripheral neuropathy	10 mg/day for 1 week, 20 mg/day after 2 weeks	A significant decrease in the temporal change of VAS for lower limb pain was observed before administration and 2 and 4 weeks after administration.	(Inage et al., 2020)
14	187	Retrospective	Peripheral neuropathic pain of different etiologies	5–10 mg/day	Mirogabalin was found safe and effective for reducing peripheral neuropathic pain.	(Tetsunaga et al., 2020)
15	274	Phase 2, double-blind, randomized, placebo-controlled study	Diabetic peripheral neuropathy	5–10 mg/day	Mirogabalin was well tolerated in the doses with good pain relief.	(Baba et al., 2020a)
16	60	Retrospective	Lumbar spine disease	10–30 mg/day	Mirogabalin was useful for the	(Kim et al.,

**Table 1** Table showing studies in which mirogabalin was used in various chronic pain conditions (Continued)

S. no.	No. of patients	Type of study	Indication	Dose used	Key points	Author/ year/ reference
				day	treatment not only of leg symptoms but also of LBP and sleep disturbance associated with lumbar spine disease.	(2020)
17	34	Observational	Cancer pain		Effectiveness was 88.2% with patients having reasonable pain control.	(Nakanishi et al., 2020)
18	133	Retrospective	Mixed	Less than 20 mg/day	Mirogabalin was effective in 85 of 133 patients.	(Kanbayashi et al., 2020)
19	172	52-week open-label extension study	Diabetic peripheral neuropathy	5–15 mg/day	Long-term flexible dosing of mirogabalin was safe and well tolerated.	(Baba et al., 2020b)
20	35	Phase III, open-label, 14-week study	Diabetic peripheral neuropathy or post-herpetic neuralgia	7.5 mg once or twice daily	Mirogabalin was well tolerated and significantly reduced pain levels when used at a fixed dose of 7.5 mg once or twice daily in patients with renal impairment.	(Baba et al., 2020c)

volunteers on 30 mg/day mirogabalin and co-administered ethanol, lorazepam, zolpidem, and tramadol. Although there were no major adverse events as they were all healthy volunteers, patients should be warned and monitored if drugs with sedative effects are co-administered (Jansen et al., 2018a). In a pharmacokinetic study designed to understand dosing in patients with renal impairment, Yin et al. concluded that although no dose adjustment is required in mild renal impairment, reduction by 50% or 75% in subjects is necessary for patients with moderate or severe renal impairment (Yin et al., 2016). Dose adjustment in moderate to severe renal impairment was further established by Kato et al. in their study involving 30 Japanese patients with mild, moderate, and severe renal impairment who received a 5-mg dose of mirogabalin (Kato et al., 2018). However, mild to moderate hepatic dysfunction did not interfere with the dosing of mirogabalin. A dose of 15 mg once daily was well tolerated without any adverse events (Duchin et al., 2018). Nakanishi et al. prescribed mirogabalin in 34 patients who were not having cancer pain under effective control despite opioid titration (Nakanishi et al., 2020). The rate of effectiveness of this addition as per the authors was 88.2%. Two patients experienced mild central nervous system adverse effects but the medication was not discontinued. Except for this article, to date, mirogabalin has not been explored in managing cancer neuropathic pain in the form of randomized studies.

In a critical appraisal of gabapentinoids for managing neuropathic pain in cancer patients performed by Jordan et al., authors felt that studies were not designed appropriately, had a small sample size, lacked blinding, and had an inadequate follow-up. Moreover, high doses although offered better pain relief, the use was associated with neurological adverse events due to which therapy

was discontinued or dosing changed. Well-designed, prospective, multicentric studies need to be planned to explore the unique properties of mirogabalin in managing cancer pain (Jordan et al., 2018). Alyoubi et al. performed a systematic review and meta-analysis of randomized controlled trials to investigate the analgesic efficacy of mirogabalin in diabetic peripheral neuropathic pain (Alyoubi et al., 2020). The authors concluded that mirogabalin treatment was superior to placebo and pregabalin in decreasing the average daily pain score over time and that mirogabalin was safe and associated with some adverse events that could be managed conservatively.

Current evidence suggests starting mirogabalin at a dose of 10 mg/day (preferably in divided doses, i.e., 5 mg twice daily and weekly increase by 10 mg/day every week to a maximum of 30 mg/day). The adverse effect profile and safety in renal and hepatic impairment makes it a viable option as an adjuvant in various chronic neuropathic pain conditions. From existing data, the neurological adverse effects appear mild and can be managed conservatively.

#### Limitations

This is a topical review and not a systematic review due to the type of data available, i.e., case series and a limited number of randomized controlled studies. Mirogabalin is not yet approved by the Food and Drug Administration (US-FDA) of the USA. This could be the reason behind limited data across other countries due to non-availability.

#### Conclusions

Mirogabalin appears to be a selective, well-tolerated, next-generation gabapentinoid which appears to be effective in managing chronic neuropathic pain due to

diabetes, post-herpetic neuralgia, lumbar spine disease, and to some extent cancer in combination with other drugs. Further research is warranted to establish its safety and efficacy in managing postoperative pain, cancer pain, and fibromyalgia.

#### Abbreviations

VGCCs: Voltage-gated calcium channels; NTP: Neurotrophin; US-FDA: Food and drug administration

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#### Authors' contributions

AN: literature review, manuscript preparation, concepts, design, and final draft. SK: manuscript review and data analysis. SS: literature review and manuscript editing. All authors read and approved the final version of the manuscript.

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#### Ethics approval and consent to participate

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#### Consent for publication

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#### Competing interests

The authors declare that they have no competing interests.

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