



Mirogabalin as a Novel Gabapentinoid for the Treatment of Chronic Pain Conditions: An Analysis of Current Evidence

Eric Y. Chen¹, Sascha S. Beutler¹, Alan D. Kaye^{2,*}, Amber N. Edinoff³, Seyed-Hossein Khademi^{4, **}, Andrea E. Stoltz⁵, Nicole R. Rueb⁵, Elyse M. Cornett² and Winston J. Suh²

¹Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Boston, USA

²Department of Anesthesiology, Louisiana State University Shreveport, Shreveport, USA

³Department of Psychiatry and Behavioral Medicine, Louisiana State University Health Science Center Shreveport, Shreveport, USA

⁴Department of Anesthesiology, Mashhad University of Medical Sciences, Mashhad, Iran

⁵Louisiana State University Health Sciences Center, New Orleans, USA

*Corresponding author: Department of Anesthesiology, Louisiana State University Shreveport, Shreveport, USA. Email: alan.kaye@lsuhs.edu

**Corresponding author: Department of Anesthesiology, Mashhad University of Medical Sciences, Mashhad, Iran. Email: khademihs@mums.ac.ir

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Abstract

Neuropathic pain is a challenge for physicians to treat and often requires a multimodal approach with both pharmacologic and lifestyle interventions. Mirogabalin, a potent, selective ligand of the $\alpha 2\delta$ -1 and $\alpha 2\delta$ -2 subunits of voltage-gated calcium channels (VGCCs), provides analgesia by inhibiting neurotransmitter release at the presynaptic end of the neuron. Mirogabalin offers more sustained analgesia than its gabapentinoid counterparts in addition to a wider safety margin for adverse events. Recent clinical trials of mirogabalin have demonstrated both efficacy and tolerability of the drug for the treatment of diabetic peripheral neuropathic pain and postherpetic neuralgia, leading to its approval in Japan. While still not yet FDA approved, mirogabalin is still in its infancy and offers potential into the treatment of neuropathic pain and its associated comorbidities.

Keywords: Mirogabalin, Gabapentinoid, Diabetic Peripheral Neuropathic Pain, Postherpetic Neuralgia, Fibromyalgia, Anxiety

1. Context

Mirogabalin (Tarlige), a gabapentinoid developed by Daiichi Sankyo, is in the same class as gabapentin and pregabalin (Figure 1). First approved in Japan in January 2019 for the treatment of peripheral neuropathic pain, mirogabalin is a ligand of the $\alpha 2\delta$ -1 and $\alpha 2\delta$ -2 subunits of VGCCs. Oral formulations are available in 2.5, 5, 10, and 15 mg tablets with a recommended starting dose of 5 mg twice daily (BID) with weekly increases by 5 mg up to a maximum dose of 15 mg BID (1, 2). It hopes to join other first-line treatments for neuropathic pain like serotonin-noradrenaline reuptake inhibitors (duloxetine and venlafaxine), tricyclic antidepressants (amitriptyline, nortriptyline, desipramine, imipramine), and the other gabapentinoids (pregabalin, gabapentin) (3). Mirogabalin could also provide an alternative for patients in whom the other gabapentinoids do not work. A retrospective study that looked at patients who switched from pregabalin treatment to mirogabalin as a result of lack of efficacy or adverse events demonstrated significant decreases in pain scale ratings after only 1 week of treatment with

mirogabalin ($P < 0.0001$) (4). This review seeks to provide a basic introduction to the pharmacology and indications for mirogabalin.

2. Pharmacological Properties

Mirogabalin belongs to the class of drugs called gabapentinoids. Originally synthesized to treat refractory epilepsy, gabapentinoids are now considered first-line treatment for neuropathic pain (5-7). Mirogabalin is a potent, selective ligand of the $\alpha 2\delta$ -1 and $\alpha 2\delta$ -2 subunits of VGCCs. Like the other gabapentinoids, it provides analgesia by reducing dorsal horn sensitivity through VGCC blockade (1). By inhibiting neurotransmitter release at the presynaptic end of the neuron, mirogabalin attenuates neuronal hyperexcitability in the brain and spinal cord (8, 9).

Studies show that the analgesic effects may be related more to the $\alpha 2\delta$ -1 subunit, which is found in skeletal, smooth, and cardiac muscle, central and peripheral nervous systems, and endocrine tissues (2). One of the important advantages of mirogabalin over the other

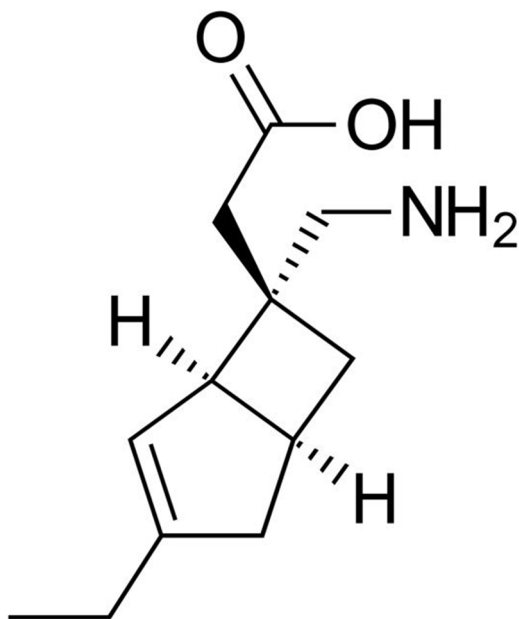


Figure 1. Chemical structure of mirogabalin.

gabapentinoids is that it dissociates from the $\alpha 2\delta$ -1 subunit more slowly than gabapentin and pregabalin, resulting in greater potency and sustained analgesia (5). In a pharmacology study, the dissociation constant (Kd) of the $\alpha 2\delta$ -1 subunit for mirogabalin was 13.5 nM (11.9 - 15.4) versus that of pregabalin was 62.5 nM (55.6 - 71.4) (9). The Kd of the $\alpha 2\delta$ -2 subunit for mirogabalin was 22.7 nM (20.8 - 24.4) versus that of pregabalin was 125.0 nM (76.9 - 333.3). This demonstrated that the binding affinity of mirogabalin for both $\alpha 2\delta$ -1 and $\alpha 2\delta$ -2 subunits is greater than that of pregabalin. Another advantage of mirogabalin is that it can achieve maximum plasma concentration in less than 1 hour, compared to the 1 hour it takes for pregabalin and 3 hours for gabapentin (2, 10).

The side effects are primarily somnolence and dizziness. These CNS side effects might be related more to the $\alpha 2\delta$ -2 subunit, which is found mainly in the central nervous system (2, 11). Mirogabalin has been shown to have longer dissociation half-lives against the $\alpha 2\delta$ -1 subunit when compared to the $\alpha 2\delta$ -2 subunit: 11.1 h (8.3 - 16.4) versus 2.4 h (2.1 - 2.8). Pregabalin, on the other hand, has the same dissociation half-life for both subunits: 1.4 h (1.3 - 1.4) versus 1.4 h (0.9 - 2.7). This can translate into long-lasting analgesic effects with a wider safety margin for side effects (9).

Mirogabalin is rapidly eliminated in the urine un-

changed (61% - 72%), meaning there is no significant accumulation with repeated dosing and high oral bioavailability of > 85% regardless if patients are eating or fasting (12). Pharmacokinetic modeling revealed total clearance of mirogabalin decreased by 25%, 54%, and 76% in patients with mild (CrCl = 50 - 80 mL/min/1.73 m²), moderate (CrCl = 30 - 50 mL/min/1.73 m²), and severe (CrCl < 30 mL/min/1.73 m²) renal impairment, respectively (13). Mirogabalin exposure ratios when compared to healthy controls were 1.3, 1.9, 3.6 for mild, moderate, and severe renal disease, respectively (14). Overall exposure would be similar if mirogabalin dose is reduced by 50% for moderate renal impairment and 75% for severe renal impairment (13). Given that many patients with diabetic peripheral neuropathic pain suffer from renal impairment, mirogabalin dosing could present a challenge. However, a phase III open-label study showed that adverse events in patients with renal impairment were comparable to the general patient population if mirogabalin was dose reduced to 7.5 mg BID for moderate (CrCl = 30 - 59 mL/min/1.73 m²) and 7.5 mg daily for severe (CrCl = 15 - 529 mL/min/1.73 m²) renal impairment (15). Of note, a small fraction (13% - 20%) of mirogabalin is metabolized by hepatic uridine 5'-diphospho-glucuronosyltransferase isoforms. No significant effect on mirogabalin exposure was noted in patients with mild-to-moderate hepatic impairment (16).

Drug interactions are also an important consideration for new treatments. A couple of studies have commented on coadministration of mirogabalin with other drugs. Given its use in diabetic peripheral neuropathic pain, the effect of coadministration of metformin with mirogabalin was examined and revealed no evidence of drug-drug interaction (17). Chronic pain is often treated multimodally with medications with varying mechanisms of action (18-25). Retrospectively, concomitant use of opioids was not found to increase the benefit of mirogabalin and actually increased incidence of CNS adverse events. Neurotrophin, a nonprotein extract from the inflamed skin of rabbits, was found to be associated with the ability of mirogabalin to relieve neuropathic pain (26). Mirogabalin is also known to be a substrate for organic anion transporters 1 and 3 (OAT1/3), organic cation transporter 2 (OCT2), and multidrug and toxin extrusion (MATE) transporter, prompting further study into its interaction with probenecid, a uridine 5'-diphospho-glucuronosyltransferase (UGT) inhibitor and OAT1/3 inhibitor, and cimetidine, a OCT2 and MATE inhibitor. A study by Tachibana et al. (27), found that mirogabalin exposure was increased more with coadministration of probenecid, which inhibits both metabolic and renal elimination, versus cimetidine, which only inhibits renal elimination. However, the increase in exposure was not clinically significant in either case and similar

to that of mild renal impairment (27).

Finally, an important question with all pain medications is the abuse potential (28, 29). Two studies done by Mendell et al. (30) compared mirogabalin to diazepam in one and to pregabalin in the other. They found that only mirogabalin doses four (60 mg) or seven (105 mg) times the therapeutic dose showed significant differences in Drug Liking visual analog scales when compared to placebo and were comparable to that of therapeutic pregabalin. Furthermore, the maximal effect of the supratherapeutic doses of mirogabalin took 8 hours to achieve compared to the 1.5 hours for diazepam and 4 hours for pregabalin.

3. Clinical Indications

The results of the trials described below (Table 1) has led to mirogabalin being approved in Japan for the treatment of peripheral neuropathic pain, specifically diabetic peripheral neuropathic pain and post-herpetic neuralgia. The drug is not currently approved in the US by the FDA.

3.1. Diabetic Peripheral Neuropathic Pain

The International Diabetes Federation estimates the global population of diabetes patients to reach 366 million by 2030. Of the complications, peripheral neuropathy is the most common and 20% - 30% of patients with it develop diabetic peripheral neuropathic pain (DPNP) (38, 39). Treatment can be challenging, and mirogabalin has been shown to provide benefit (40-43). An initial phase II randomized, double-blind trial of 435 patients with DPNP showed significant reductions in average daily pain score (ADPS) when compared to placebo after 5 weeks of treatment of mirogabalin at 15, 20, or 30 mg/day (31). This same study showed no significant improvement in ADPS with pregabalin at 300mg/day. However, a phase II randomized, double-blind trial of 450 Asian patients with DPNP found no significant differences from placebo in ADPS after 7 weeks of treatment of mirogabalin at 15, 20, or 30 mg/day (33). A phase III randomized, double-blind trial (NEUCOURSE) of 834 Asian patients DPNP was conducted over 14 weeks, and a statistically significant decrease of 1.81 in ADPS when compared to placebo ($P = 0.0027$) was observed for a mirogabalin dose of 30 mg/day (32). This study was extended into a 52-week open-label study to determine the long-term safety and efficacy (37). Patients were started on mirogabalin at 5 mg twice daily (BID) and then increased to the maintenance dose of 10 or 15 mg BID. Visual Analogue scale (VAS) scores improved from baseline throughout the entire 52-week study period, suggesting long-term efficacy of mirogabalin. Treatment was

also well-tolerated with no serious side effects with only 27.6% of treatment-emergent adverse events (TEAE) being linked to mirogabalin. The most common side effects were somnolence, dizziness, peripheral edema, and weight gain with an increase in incidence, but not severity, of TEAEs with dose (33). Overall, these studies show that mirogabalin is both an effective and tolerable new agent for DPNP.

3.2. Post-herpetic Neuralgia

Postherpetic neuralgia (PHN) develops in around 10% of patients with acute herpes zoster and has been difficult to manage with a clinically significant reduction of pain by 30% in only half of patients (44). Mirogabalin may help provide a new treatment option for these patients. A phase III randomized, double-blind trial (REDUCER) of 763 Asian patients with PHN randomized patients to placebo or mirogabalin doses of 15, 20, or 30 mg/day for 14 weeks and showed reduction in ADPS when compared to placebo of -0.41 ($P = 0.0170$), -0.47 ($P = 0.0058$), and -0.77 ($P < 0.0001$), respectively (34). Just like for DPNP, this study was extended into a 52-week open-label study to determine the long-term safety and efficacy (35). VAS scores improved from baseline throughout the entire 52-week study period, suggesting long-term efficacy of mirogabalin. Treatment was also well-tolerated with no serious side effects with only 39.7% of treatment-emergent adverse events (TEAE) being linked to mirogabalin. Overall, these studies show that mirogabalin is both an effective and tolerable new agent for PHN.

3.3. Fibromyalgia

Fibromyalgia plagues between 1 to 6% of the world and requires treatment with both pharmacologic and lifestyle modalities (45). Given the success of mirogabalin with DPNP and PHN, it was expected to produce similar results in fibromyalgia. Three phase III randomized, double-blind trials (ALDAY) of 1293, 1270, and 1301 patients with fibromyalgia randomized them to placebo, pregabalin 150 mg BID, or mirogabalin at 15 mg daily or 15 mg BID for 13 weeks (36, 46). Unfortunately, no significant reductions in ADPS were seen with mirogabalin when compared to placebo while pregabalin was found to significantly reduce ADPS in two of the three trials ($P = 0.0008$ and $P = 0.0001$). This negative result does not necessarily mean that mirogabalin has no place in the treatment of fibromyalgia. A key limitation was that all the phase III trials were based on phase II trial data in patients with DPNP. No phase II study was done in fibromyalgia patients to determine optimal dosing. Mirogabalin was noted to provide some benefit to other symptoms of fibromyalgia like fatigue and insomnia. Further studies will need to be con-

Table 1. Clinical Trial Data for Mirogabalin and Its Effect on Peripheral Neuropathic Pain

Clinical Condition	Authors	Study Design	Subjects Characteristics	Primary Endpoint	Active Comparator	Dose of Mirogabalin	Duration of Follow-up	Frequency of Adverse Events	Results
Diabetic peripheral neuropathic pain	Vinik et al. (31), 2014	Randomized, double-blind, placebo- and active comparator-controlled phase II trial	Adults with type 1 or 2 diabetes and DPNP; painful distal symmetric polyneuropathy for 6+ months; ADPS of 4+ on the 11-point scale; 40+ mm on the VAS of the SF-MPQ	Change from baseline in ADPS	Placebo; pregabalin	5 mg/d, 10 mg/d, 15 mg/d, 20 mg/d, 30 mg/d	5 weeks	CNS effects in 14.1% in mirogabalin groups versus 2.8% in placebo group versus 12.0% in pregabalin group	Mirogabalin significantly reduced the ADPS at 15, 20, and 30mg/day
	Baba et al. (32), 2019	Randomized double-blind, placebo-controlled phase III trial	Asian patients age 20+ years with type 1 or 2 diabetes and DPNP; painful distal symmetric polyneuropathy for 6+ months; ADPS of 4+ on the 11-point scale; 40+ mm on the VAS of the SF-MPQ	Change from baseline in ADPS	Placebo	15 mg/d, 20 mg/d, 30 mg/d	14 weeks	2.4% - 9.7% in mirogabalin groups versus 3.9% in placebo lead to treatment discontinuation	Mirogabalin significantly reduced the ADPS at a dose of 30 mg/day
	Baba et al. (15), 2020	Open-label extension study	Asian patients with DPNP who participated in the above phase III trial	Incidence of adverse events; change in pain on SF-MPQ	None	10 mg BID; 15 mg BID	52 weeks	91.1% of patients had a TEAE, but only 27.6% thought to be related to mirogabalin	Steady decrease in VAS throughout the study period
Postherpetic neuralgia	Baba et al. (33), 2020	Randomized, double-blind, placebo- and active comparator-controlled phase II trial	Asian patients age 20+ years with type 1 or 2 diabetes and DPNP; painful distal symmetric polyneuropathy for 6+ months; ADPS of 4+ on the 11-point scale; 40+ mm on the VAS of the SF-MPQ	Change from baseline in ADPS	Placebo; pregabalin	10 mg/d, 20 mg/d, 30 mg/d	7 weeks	48.9% - 73.3% in mirogabalin groups versus 3.9% in placebo group versus 53.4% in placebo group	No significant change from baseline ADPS
	Kato et al. (34), 2019	Randomized, double-blind, placebo-controlled phase III trial	Asian patients age 20+ years with PHN; ADPS of 4+ on the 11-point scale; 40+ mm on the VAS of the SF-MPQ	Change from baseline in ADPS	Placebo	15 mg/d, 10 mg BID, 15 mg BID	14 weeks	5.3% - 10.5% in mirogabalin groups versus 4.0% in placebo lead to treatment discontinuation	Mirogabalin significantly reduced the ADPS across all groups
	Kato et al. (35), 2020	Open-label extension study	Asian patients with PHN who participated in the above phase III trial	Incidence of adverse events; change in pain on SF-MPQ	None	10 mg BID; 15 mg BID	52 weeks	85.7% of patients had a TEAE, but only 39.7% thought to be related to mirogabalin	Steady decrease in VAS throughout the study period
Fibromyalgia	Arnold et al. (36), 2019	Randomized, double-blind, placebo- and active comparator-controlled phase III trial (3 separate studies)	Patients age 18+ with widespread pain for 3 months in 11+ of 18 point sites; ADPS of 4+ on the 11-point scale	Change from baseline in ADPS	Placebo; Pregabalin	15 mg/d, 15 mg BID	13 weeks	74.8% in mirogabalin groups versus 75.0% in pregabalin group versus 66.5% in placebo group	No significant change from baseline ADPS when compared to placebo
DPNP and PHN with renal impairment	Baba et al. (37), 2020	Open-label phase III trial	Asian patients age 20+ years with DPNP or PHN; CrCl 15 - 59 ml/min; ADPS of 4+ on the 11-point scale; 40+ mm on the VAS of the SF-MPQ	Safety and tolerability of mirogabalin	None	7.5 mg/d, 7.5 mg BID	14 weeks	Adverse events were comparable with patients without renal impairment	Mirogabalin significantly reduced the ADPS across both groups

Abbreviations: ADPS, average daily pain scale; BID, twice daily; CrCl, creatinine clearance; DPNP, diabetic peripheral neuropathic pain; PHN, postherpetic neuralgia; SF-MPQ, Short-form McGill Pain questionnaire; TEAE, treatment-emergent adverse event; VAS, visual analog scale.

ducted to determine if mirogabalin has any usefulness in the treatment of fibromyalgia.

4. Risks, Complications, Side Effects

Mirogabalin is primarily associated with CNS side effects, with the most common being somnolence, dizziness, and headache. These effects seem to increase in incidence, but not severity, with higher doses of mirogabalin. Other side effects include constipation, nausea, diarrhea, edema, weight gain, and fatigue (1, 3). Looking specifically at the effects of 15 mg BID of mirogabalin across the three main trials, serious treatment-emergent adverse event (TEAEs) were reported in 1.9% - 6.7% of treated patients versus 1.6% - 3.3% of patients in the placebo groups (32, 34, 36). These

TEAEs led to discontinuation of treatment in 7.7% - 13.9% of patients treated with mirogabalin versus 3.9% - 11.0% of patients treated with placebo. Mirogabalin continued to show tolerability in the 52-week open-label extensions with TEAEs related to the study drug occurring in only 27.6% - 39.7% of patients. Serious adverse events were only present in 0.4% - 1.4% of patients and most TEAEs resolved without any intervention (35, 37). Overall, mirogabalin appears to be well-tolerated with mainly mild to moderate TEAEs that resolve spontaneously.

5. Conclusion and Future Directions

Neuropathic pain is a problem that plagues many patients (7). Mirogabalin appears to offer a new effective and

safe alternative for treatment in patients with DPNP and PHN and is currently approved in Japan. However, there is a lack of trials comparing mirogabalin to other drugs treating the same disease to definitely say it is better than the alternatives. In addition, the current longest study with a control arm is only 14 weeks. While there were open-label studies that extend to 52 weeks, the long-term side effects of the drug are yet to be determined. Although one pharmacokinetic study showed similar parameters between Asian and white patients, most of the studies were also conducted with only Asian patients, prompting the question if the results are generalizable to the general population (10).

Although this drug is not yet FDA approved, it is still in its infancy and has shown promising results for peripheral neuropathic pain. However, mirogabalin might not be limited to that domain. One study in mice showed that mirogabalin can inhibit defecation by preventing the hyperactivation of hippocampal neurons—a possible treatment for irritable bowel syndrome (47). Another retrospective study found improvement in leg symptoms, low back pain, and sleep disturbance in those with lumbar disease after both 4 and 8 weeks of treatment (48). Mirogabalin could also be applied to central neuropathic pain as it has been shown to have significant analgesic effects lasting 6–8 hours in a rat model of spinal cord injury (49). Anxiety is often comorbid with chronic pain syndromes, and a single dose of mirogabalin 10mg/kg was comparable to a dose of diazepam 3mg/kg in rat models of anxiety (1, 45). Not only did mirogabalin improve the tactile allodynia for more than 8 hours in the rats, but also relieved anxiety-related behaviors for 4 hours (48, 50). Much is still to be learned as to the applicability of mirogabalin to other diseases besides peripheral neuropathic pain.

Footnotes

Authors' Contribution: Study concept and design: EYC, SSB, ADK, AES, and NRR. Analysis and interpretation of data: EYC, SSB, ADK, ANE, AES, NRR, EMC, and WJS. Drafting of the manuscript: EYC, SSB, ADK, ANE, SHK, AES, NRR, and EMC. Critical revision of the manuscript for important intellectual content: ADK, ANE, SHK, AES, and WJS. Statistical analysis: EYC, SSB, ADK, ANE, and AES.

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