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Mirogabalin – A Novel Drug In Treating Neuropathic Pain of Various Etiologies

Sadia Raoof[1], BSV Raju[2], Sufia Khan[1], S P Srinivas Nayak[3*]

[1]Department of Pharmacy Practice, Sultan-Ul-Uloom College of Pharmacy, Affiliated to JNTU-H, India
[2]MBBS, MS, MCH, DNB- Neurosurgeon, Aster Prime Hospital, Hyderabad, India
[3]Assistant Professor, Department of Pharmacy Practice, PIPR, Parul University, Vadodara, Gujarat
*Corresponding author: S P Srinivas Nayak

Abstract

Mirogabaline besylate is a novel gabapentinoid approved for use in the treatment of diabetic neuropathic pain and postoperative neuralgia Further studies had explored the role of mirogabalin in chemotherapy-induced neuropathy, trigeminal trophic syndrome, chronic psychological stress, psychiatric disorders like anxiety-related behaviours and tactile allodynia and neuropathic pain of various etiologies. This review article is aimed to comtemplate all the studies on mirogabalin, its role, superiority over other gabapentanoids as well as to validate its efficacy and safety profile.

Key Words: Mirogabalin, Pregabalin, Neuropathic pain, Analgesic, Neuralgia

Introduction

Neuropathic pain may be a difficult downside that features a negative impact on patient's physical health and psychological eudaimonia that ends up in poor quality of life. Neuropathic pain is very difficult to manage because of its heterogeneity of etiologies, symptoms, and underlying mechanisms. Use of conventional oral therapies have been limited due to negative factors such as systemic side effects, drug-drug interactions, slow onset of action, the need for titration, multiple daily dosing, as well as the potential risk of addiction, dependence, withdrawal symptoms and abuse. It's so expected that new medicine and covering area unit being sought-after that would improve the effectiveness of neuropathic pain [1].

In this armamentarium one of the new drug is Mirogabalin. In this review, focus will be specifically on new drug therapy for neuropathic pain Mirogabalin for which clinical data are already available.

Mirogabalin appears to be a selective and well-tolerated next-generation orally administered gabapentinoid developed by Daiichi Sankyo, Japan, which binds to and selectively regulates the α2δ1 subunits of VGCC and also has a unique binding profile and long duration of action for the treatment of peripheral neuropathic pain such as diabetic peripheral neuropathy, posterior neuralgia, lumbar spine disease, and cancer pain. Mirogabalin (Tarlige®; 2.5, 5, 10, and 15 mg) tablets were approved in Japan, in January 2019. [2]

Mechanism of Action

Mirogabalin belongs to the gabapentinoids, group of drugs that affect the α2δ subunits of voltage-gated calcium channels (VGCCs). Two subunits of VGCCs are α2δ1 present in skeletal, cardiac and smooth muscles these plays important role during neuropathic pain development that contributes to analgesic effect of gabapentanoids and α2δ2 present in cerebellum that contributes for CNS side effects. Mirogabalin has selective and potent binding affinity for α2δ1 and α2δ2 subunits of VGCCs, which reduces calcium (Ca^{2+}) influx and neurotransmission in dorsal root ganglia (DRG), inhibits neurotransmitter release (e.g., calcitonin gene-related peptide (CGRP), glutamate, substance P) in presynaptic neuron endings, thereby hyperexcitability of central nervous system (CNS) neurons decreases, which has a number of pharmacological effects like analgesic, anxiolytic, and anticonvulsant [25].

Compared to pregabalin, mirogabalin shows stronger binding affinity for α2δ1 and α2δ2 subunits of VGCCs and a slower dissociation rate for the α2δ1 subunit than α2δ2 subunit results in longer duration of action that contributes to its higher analgesic efficacy, wider safety margin, and relatively lower incidence of CNS adverse effects (AEs).

Pharmacokinetics

Mirogabalin was tested in healthy volunteers at doses ranging from 3 to 75 mg. It is rapidly absorbed on oral administration with mean time to maximum plasma concentration (Tmax) 0.5-1.5 hours of single or repeated doses. With daily administration, steady-state plasma concentrations are reached by day 3 (Brown et al., 2018) [3].

There is an increase by dose-dependent in plasma maximum concentration (Cmax) and concentration–time curve (AUC). Mirogabalin has a low plasma protein binding of approximately 25%. It was shown, that after administration mirogabalin is quickly converted into its free form in which A200-700 is the main active circulating isoform.

The drug is cleared mainly unchanged (61–72%) via renal excretion by filtration and active secretion, however a slight fraction of drug (13–20%) is metabolized by hepatic uridine 50 -diphospho-glucuronosyltransferase isoforms. The mean elimination half-life of mirogabalin observed in clinical trials was 2-3 h, 3.5 h, and 3–4.9 h [4]. Mirogabalin 90% is excreted through the kidneys, with only 1% of the dose excreted in the feces. Mirogabalin is excreted renally by glomerular filtration and active secretion. The urinary metabolites of mirogabalin contain lactams and N-glucuronide conjugate.

Patients with hepatic impairment

The mean plasma protein binding of mirogabalin is reduced approximately to 22.1%. It does not necessary to alter the dosage of mirogabalin in patients with mild or moderate hepatic impairment [4]. Generally, a single dose of mirogabalin (15 mg) is well tolerated by patients with moderate and mild hepatic impairment.

Patients with renal impairment

It is necessary to modify the dosage of the drug a dose adjustment of 50% is needed in people with moderate renal impairment (creatinine clearance (CrCl) 30–50 mL/min/1.73 m2) and of 75% in people with severe renal impairment (CrCl < 30 mL/min/1.73 m2) [6].

Dosing and titration strategy

Tablets 2.5 mg, 5 mg, 10 mg, 15 mg (generic name: mirogabalin besilate) due to availability of various dose tablets and rapid absorption it has flexible dosing regimen. The dose of mirogabalin ranges from 10 to 30 mg/day. It should be initiated at a dose of 10 mg/day (preferably in divided doses, i.e. 5 mg twice/day and increased weekly by 10 mg/day per week until maximal is reached) up to 30 mg/day). Twice-daily dosing of mirogabalin was predicted to yield a lower incidence rate of dizziness than once-daily dosing; thus, titration of dosages should reduce adverse event rates. Doses up to 30 mg/day when divided into two divided doses daily are well tolerated with adequate analgesic activity.

Adverse drug events

Mirogabalin binds selectively and with greater affinity to the α2δ1 subunit by which takes longer to dissociate (dissociation half-life 11.1 hours) than from α2δ2 in vitro (dissociation half-life 2.4 hours) whereas pregabalin requires 1.4 hours to dissociate. Due to low affinity and rapid dissociation of α2δ2 subunits in the cerebellum it results in ataxia and other CNS side effects at lower rates [4].

The most common side effects of mirogabalin are dizziness (8-16%), somnolence (6-24%) and headache (6-14%). Problems such as constipation, nausea, diarrhea, vomiting, edema, fatigue, and weight gain are rarely seen.

Maladaptive changes

New data suggest that early preventive treatment with gabapentinoids may prevent unstable excitatory synapse formation and the development of pain states, which, if clinically validated, could be one way interesting approach to prevent the development of neuropathic pain. Voltage-regulated calcium channels (VGCCs) play important roles in physiological functions, including regulation of neurotransmitter release, neural network activities, and pathways, intracellular signaling and gene expression. Several medical conditions, including nerve damage, can lead to dysregulation of VGCC and their subunits. This can lead to dysfunction of the VGCC and its subunits as well as other plasticity changes, which may contribute to the development of disorders such as pain sensation. Blocking α2δ subunits with gabapentinoids can significantly reverse neuropathic pain with relatively mild side effects. Emerging data suggests that early preventive treatment with gabapentinoids can prevent unstable excitatory synapse formation and the development of chronic pain. [19]

Efficiency over other gabapentinoids

A systematic review and meta-analysis was performed to examine the efficacy and safety of mirogabalin in patients [24]. Four databases from inception to 1st July 2020, was included all randomised controlled trials (RCTs) which assessed the effectiveness and safety of mirogabalin. The quality of the included

RCTs was evaluated using the Cochrane risk of bias assessment tool. We pooled dichotomous outcomes as risk ratios and continuous outcomes as mean differences with 95% confidence intervals, both under the random- or fixed-effects model. Three RCTs matched our inclusion criteria with a total of 1732 patients with DPNP: 1057, 534 and 141 patients received mirogabalin, placebo and pregabalin, respectively. The quality of included RCTs was marked as moderate-to-high. Mirogabalin treatment was considerably associated with a major reduction within the average daily pain score (ADPS) compared with placebo over 7 weeks. Compared with pregabalin, mirogabalin was associated with more decrease in ADPS only after 3, 4 and 5 weeks. The proportion of patients with ≥30% and ≥50% reduction in the ADPS was significantly higher in the mirogabalin vs placebo and pregabalin groups. Compared with placebo, mirogabalin was associated with more adverse events of dizziness, increased weight, peripheral edema and somnolence. The safety profile was comparable between mirogabalin and pregabalin. The result of systematic review and meta-analysis revealed that, mirogabalin treatment was superior to placebo and pregabalin in decreasing the pain over time with larger safety margin and associated with some adverse events that could be managed conservatively.

Methodology

This review was done by utilizing the databases PubMed, PMC as the source of information with keywords " Mirogabalin" and "Mirogabalin in PHN and DPNP". Some of the acclaimed studies are used in this review.

Discussion

(1) In healthy volunteers

Mirogabalin at dose up to 30 mg/day when divided into two divided doses daily for 7 days [7], showed safety, adequate analgesic activity and tolerability with ADRs.

(2) In inflammatory pain

Mirogabalin is a newly approved α2δ ligand in Japan for the treatment of peripheral neuropathic pain. In the study, the analgesic characteristics and site of action of mirogabalin, on inflammatory pain was investigated by using the rat formalin test [8]. Open-field trials have been performed to evaluate the effects of oral, intramuscular, and intramuscular administration of mirogabalin on locomotor ability and orientation performance.

Oral administration

It produces analgesic effect when the formalin test is done 4 hours, but not 1 or 2 hours, after oral administration. In the oral administration mirogabalin attenuates the moving distance after 1 or 2 hours, after its administration.

Intrathecal administration

It produces analgesic effect when mirogabalin is administered 10 minutes before formalin injection. In the intrathecal administration, mirogabalin produces analgesic effect but did not affect walking distance.

Intracerebroventricular administration

Mirogabalin attenuates the moving distances 10 min after intracerebroventricular administration. In the intracerebroventricular administration, mirogabalin don't produce analgesic effect but affects walking distance property.

(3) In postherpetic neuralgia (PHN)

Mirogabalin is effective and safe to use in treatment of various neuropathic pain syndromes. This study investigates the safety and efficacy of mirogabalin, a novel, potent, selective ligand of the α2δ subunit of VGCCs, for the treatment of postherpetic neuralgia (PHN). In this multicenter, double-blind, placebo-controlled phase 3 study, Asian patients ≥20 years with PHN were randomized 2:1:1:1 to placebo or mirogabalin 15, 20, or 30 mg/day for up to 14 weeks. The primary efficacy endpoint was the change from baseline in average daily pain score at week 14, defined as a weekly average of daily pain (0 = "no pain" to 10 = "worst possible pain," for the last 24 hours).

Of 765 patients randomized, 763 received ≥ 1 dose of the study drug and were included in the analysis; 303, 152, 153, and 155 received placebo, mirogabalin 15, 20, or 30 mg/day, respectively. A total of 671 (87.7%) patients completed the study. At week 14, the difference in average daily pain score least squares mean vs placebo was −0.41, −0.47, and −0.77, respectively; all mirogabalin groups showed statistical significance. Mirogabalin was superior to placebo in all groups for relieving PHN and appeared to be well tolerated [9].

(4) In diabetic peripheral neuropathic pain (DPNP)

In patients with DPNP, mirogabalin 30 mg showed significant pain relief, in a phase 3 study (an Asian, phase 3, multicenter, randomized, doubleblind, placebocontrolled 14-week study of mirogabalin in patients with diabetic peripheral neuropathic pain, followed by a 52-week openlabel extension, REDUCER clinical trial) in Japan, Taiwan, South Korea, and Malaysia [10]. Of 834 randomized patients, 330, 164, 165 and 165 received placebo, mirogabalin 15, 20 or 30 mg/day, respectively, and were included in analyses, 755 (90.5%) completed the study.

In a phase 2 study, the average daily dose of mirogabalin of 5, 10, 15, 20, and 30 mg for 5 weeks, showed a decrease in average daily pain score and sleep interference score. In another phase 2 study, mirogabalin (5, 10, 15, 20, and 30 mg twice a day) decreased the average daily pain score, average daily sleep interference score, and ADRs.

In addition, mirogabalin 10 or 15 mg twice a day showed longterm (52 wk) safety and efficacy in patients with DPNP.

(5) In trigeminal trophic syndrome (TTS)

Trigeminal syndrome (TTS) is second to neurological conditions, including shingles a rare cause of facial ulcers, characterized by intense itching and scratching in the territory of the trigeminal nerve, which is treated using psychostimulants. TTS was successfully treated with mirogabalin. [11]

(6) In neuropathic pain from lumbar spine disease

Mirogabalin improves leg symptoms, low back pain, and sleep disturbances in patients with lumbar spine disease. [12]
Group 1 (25 patients who presented with leg symptoms that lasted for less than 3 months) and group 2 (35 patients with leg symptoms that lasted longer than 3 months). The leg symptoms in both groups significantly improved at 4 and 8 weeks of treatment, and sleep disturbance and quality of life were improved at 8 weeks as well. Mirogabalin treatment was stopped at less than eight weeks in eight patients. Compared to group 2, the pretreatment leg symptoms and QOL were significantly worse in group 1, and their improvement after 8 weeks of mirogabalin treatment was significantly better ($p<0.05$). Of the 60 original patients, 17 suffered adverse effects, which were mild in 16 patients and required treatment cessation due to excessive weight gain in one patient.

(7) In chronic psychological stress

Psychiatric disorders such as anxiety and depression are commonly observed in neuropathic pain patients and have a negative impact on their quality of life. Study was performed to investigate its anxiolytic effects in an experimental animal model of psychosis (chronic constrictive lesion (CCI) model mouse), mechanical hypersensitivity was determined by the von Frey test [13]. Anxiety- and depression-related behaviors were assessed using the overhead maze test and the forced swim test, respectively. The CCI model mice showed persistent tactile disturbance, followed by anxiety-related, not depressive-related behaviors. A single oral dose of mirogabalin (3 or 10 mg/kg) in a dose-dependent manner reduces the anxiety-related behaviors and the tactile disturbances mentioned above. Mirogabalin attenuates both anxiety-related behaviors and sensory disturbances in CCI model rats by providing effective anxiety relief as well as pain relief effect.

(8) In fibromyalgia

We investigated the effect of mirogabalin in two experimental models of fibromyalgia: the intermittent low-temperature stress model (ICS model) and the unilateral acidic saline intramuscular injection model (Sluka model). To induce chronic mechanical hypersensitivity, mice were placed under ICS conditions for 3 days and rats were injected with acidic saline (pH 4) twice into the gastrocnemius muscle at 4-day intervals. Pain susceptibility was assessed by the von Frey test. In both the ICS and Sluka models, a long-

term increase in pain response score or a decrease in pain threshold to von Frey stimulation was observed [14].

Mirogabalin (1, 3, or 10 mg / kg, orally) reduced mechanical hypersensitivity in a dose-dependent manner, with a significant duration of effect 6 or 8 hours after administration. The standard α2δ ligand, pregabalin (30 mg / kg, orally), also significantly reduced the mechanical hypersensitivity. In summary, mirogabalin showed analgesic effects in ICS model mice and Sluka model rats. Therefore, mirogabalin can provide effective analgesic effect for patients with fibromyalgia.

(9) In chemotherapy-induced peripheral neuropathy

The treatment of cancer has been improved by chemotherapy regimens (combination of 5-fluorouracil, oxaliplatin, irinotecan, and leucovorin (FOLFIRINOX) or gemcitabine plus nab-paclitaxel (GnP)). Unfortunately, chemotherapy-induced peripheral neuropathy (CIPN) is a common adverse event of these two regimens. Thus, in this study, we aimed to clarify which drug (mirogabalin or pregabalin) was more valuable for improving CIPN [15]. A total of 163 Pancreatic Cancer patients who underwent FOLFIRINOX or GnP between May 2014 and January 2021 were enrolled. Among them, thirty-four patients were diagnosed with CIPN. Thirteen patients were treated with mirogabalin, and twenty-one patients were treated with pregabalin. Treatment efficacy was compared between these two groups. The grade of patients with CIPN at 2, 4, and 6 weeks after the initiation of treatment significant improvement was compared to the pre-treatment grade in both the mirogabalin group and pregabalin group. The rate of CIPN improvement was higher in the mirogabalin group than in the pregabalin group (2 weeks: 84.6% (11/13) vs 33.3% (7/21), *P* value = 0.005; 4 weeks, 6 weeks: 92.3% (12/13) vs 33.3% (7/21), *P* value = 0.001). Although both mirogabalin and pregabalin were effective in improving CIPN, mirogabalin might be a suitable first choice for CIPN in Pancreatic Cancer patients.

(10) In neuropathic pain in hepatic impairment

In patients with mild or moderate hepatic impairment [5], a single dose of 15 mg mirogabalin produced no significant adverse events.

(11) In neuropathic pain in renal impairment

PNP is common in the elderly, with the incidence of DPNP and PHN increasing with age. As renal function is also often impaired in elderly patients, mirogabalin can be used extensively in PNP patients with CKD. In patients with renal impairment, a fixed dose of 7.5 mg once or twice daily reduced DPNP and PHN with tolerable levels of adverse events. In case of moderate or severe renal impairment, the dose should be reduced by 50% or 70% [6]. However, dose adjustment is not necessary in patients with mild renal impairment.

(12) Bioavailability to food intake

Bioavailability of single dose of mirogabalin (15 mg) was not affected when taken after a high-fat meal or fasting state in healthy volunteers. No food restriction was needed when taking mirogabalin in a phase 1 study [3]. Three phase 1 pharmacokinetic (PK)/pharmacodynamics (PD) studies were conducted in healthy volunteers to characterize PK/PD, tolerability, and the safety of mirogabalin administration with or without food and to guide the dose selection and regimen for phase 2 and 3 clinical development. The 3 studies includes 2 randomized, double-blind, placebo-controlled, single- and multiple-ascending-dose studies, and 1 open-label, crossover study to evaluate the PK of mirogabalin administered under fasting and fed (high-fat meal) conditions.

Forty-eight and 47 healthy volunteers completed the single- and multiple-dose studies, respectively. Thirty subjects were enrolled and completed the food effect study. Mirogabalin was well tolerated in the fed and fasted states. After oral administration, mirogabalin was rapidly absorbed (time to maximum concentration, 1 hour) and eliminated through urine unchanged (61%-72% urinary excretion). Subjects receiving the highest mirogabalin doses (50 and 75 mg single dose) showed greater dizziness and sedation and higher rates of TEAEs than subjects receiving 3-30 mg. No result of Toxicity was seen as no significant accumulation occurred with multiple doses over 14 days. After single doses of mirogabalin (15 mg), the bioavailability was considered equivalent in the fed and fasted states, indicating that mirogabalin can be taken without food restrictions.

(13) Co-administration with other drugs

Metformin

Metformin a biguanide anti-hyperglycemic agent for type 2 diabetes, is an essential drug for blood sugar control. However, the US FDA has recalled some types of metformin because it may contain N-nitrosodimethylamine (NMDA), an organic compound that is hepatotoxic and carcinogenic, above the permissible limit as of October 5, 2020 [16]. Even if metformin use is now decreasing, it's going to be difficult to avoid co-administration. Co-administration of metformin (850mg) and mirogabalin (15mg) was well tolerated in healthy volunteers.

Probenecid / Cimetidine

Significant changes in mirogabalin (15mg) exposure were observed when administered in combination with a drug that inhibits both renal and metabolic clearance (probenecid 500mg) rather than a drug that only affects renal clearance (cimetidine 400mg) [17]. However, prior dose adjustment is not recommended, as the increased exposure is not clinically significant.

Lorazepam / Zolpidem / Tramadol / Ethanol

While mirogabalin alone had little or no effect on PD parameters, co-administration of mirogabalin with either lorazepam or ethanol enhanced the PD effect in body sway and numeric symbol replacement test assays. Mirogabalin / lorazepam and mirogabalin / zolpidem increased the incidence of somnolence. An

increased incidence of nausea and headache was observed with mirogabalin / tramadol or mirogabalin / ethanol. The maximum plasma concentration of mirogabalin decreased by 28% after co-administration with tramadol, but increased by 20% after co-administration with ethanol [18]. Co-administration with either lorazepam or ethanol increased pharmacodynamic parameters. In addition, mirogabalin / lorazepam and mirogabalin / zolpidem increased drowsiness. Mirogabalin / tramadol and mirogabalin / ethanol increased the incidence of nausea and headache, respectively.

(10) Mirogabalin induced neutropenia

Mirogabalin is used to treat neuropathic pain similarly to pregabalin. Although the frequency of pregabalin-induced neutropenia has been reported to be 0.3% to 1%, mirogabalin-induced leukopenia has not been previously documented in the literature. Here we report what we believe to be the first case of mirogabalin-induced neutropenia. A 77-year-old woman with squamous cell carcinoma of the lung had been taking mirogabalin 10 mg/day for six weeks prior to our admission and also received two cycles of chemotherapy with carboplatin and nanoparticle-bound albumin (nab) paclitaxel for her lung cancer four months prior to admission, followed by two cycles of nivolumab up to one month prior to admission. The patient was hospitalized for a urinary tract infection (UTI), which was treated with oral amoxicillin/clavulanic acid 500/125 mg, 3 times a day for 5 days (until day 5 of admission), neutropenia (1278/μL) was noted, The neutrophil count was 755/μL on day 18 of admission. Mirogabalin was discontinued on day 19 of admission. The neutrophil count decreased to 320/μL and 118/μL in inpatient days 20 and 21, respectively, and recovered to 1064/μL on inpatient day 24, on 31st day neutropenia has not recurred since [20]. Neutropenia in the above case is most likely caused by mirogabalin. Although rare, mirogabalin-induced neutropenia is an adverse reaction the healthcare professionals should be aware of when prescribing this drug.

(11) Mirogabalin induced abuse potential

Mirogabalin is a selective calcium channel α2δ subunit ligand being developed for the treatment of neuropathic pain. According to U.S. Food and Drug Administration (FDA) guidelines, the potential for abuse in humans of mirogabalin (15-105 mg) has been examined, compared with placebo, diazepam (15 or 30 mg) and pregabalin (200 or 450 mg), in two single-dose, randomized, double-blind, placebo-controlled cross-sectional studies with multiple recreational users able to distinguish between an active comparison and a placebo [21]. Overall, the results of these studies demonstrates that mirogabalin has limited abuse potential at the 15 mg therapeutic dose and is well tolerated in patients with a history of polydrug user. At supertherapeutic doses (e.g., 60 and 105 mg), mirogabalin had more abuse potential than placebo, but was similar to that of pregabalin in a highly sensitive subgroup of polydrug users. At supertherapeutic doses (greater than 4 times the therapeutic dose), mirogabalin showed a higher potential for abuse than placebo, but a lower potential for abuse compared with diazepam and pregabalin.

Conclusion

There are currently no approved disease-modifying therapies for neuropathic pains, and there are only 3 US Food and Drug Administration-approved therapies (i.e., pregabalin, duloxetine, and tapentadol). They have moderate efficacy with limited adverse effects and optimal dose titration. There is a considerable need for new therapies for the management of painful neuropathy. It is therefore unsurprising that new drugs and treatments are being sought that could improve the effectiveness of neuropathic pain relief. One of the new drugs in this armamentarium is mirogabalin. Mirogabalin is expected to become the 4th US FDA-approved therapy [23]. Mirogabalin was known to be 17-fold more potent to pregabalin. It provided an equianalgesic effect to pregabalin 300 mg in patients with DPNP [22].

Mirogabalin 30 mg showed similar pain relief and lower incidence of withdrawal ADRs, compared with pregabalin 600 mg, gabapentin 1,200 mg, and duloxetine 60 mg.

Mirogabalin is an oral next-generation gabapentinoid, which appears to be effective in the treatment of chronic diabetic neuropathic pain, posterior neuralgia, lumbar spine disease, and to some extent, cancer when combined with other drugs. It binds selectively and with greater affinity to the α2δ1 and α2δ2 subunits of human VGCC and thus has fewer central nervous system side effects, making it more tolerable with wide safety margin, and the relatively lower incidence of adverse effects compared to those of pregabalin and gabapentin.

It is effective in treatment of neuropathic pain of different etiologies with long-term analgesic efficacy, safety and compatibility with other treatment protocols.

Conflict of Interest

No conflict of interest.

References

1. Alcántara Montero A, Sánchez Carnerero CI, Goicoechea García C. Emerging therapies in clinical development and new contributions for neuropathic pain. Rev Esp Anestesiol Reanim. 2019;66:324–34. doi: 10.1016/j.redar.2019.02.003.

2. Kim, Jae-Yeon et al. “Mirogabalin: could it be the next generation gabapentin or pregabalin?.” The Korean journal of pain vol. 34,1 (2021): 4-18. doi:10.3344/kjp.2021.34.1.4

3. Brown K, Mendell J, Ohwada S, Hsu C, He L, Warren V, et al. Tolerability, pharmacokinetics, and pharmacodynamics of mirogabalin in healthy subjects: results from phase 1 studies. Pharmacol Res Perspect. 2018;6:e00418. doi: 10.1002/prp2.418.

4. 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;7:661–9. doi: 10.1002/cpdd.448.

5. Duchin K, Senaldi G, Warren V, Marbury T, Lasseter K, Zahir H. Open-label single-dose study to assess the effect of mild and moderate hepatic impairment on the pharmacokinetics of mirogabalin. Clin Drug Investig. 2018;38:1001–9. doi: 10.1007/s40261-018-0692-7.

6. Kato M, Tajima N, Shimizu T, Sugihara M, Furihata K, Harada K, et al. Pharmacokinetics and safety of a single oral dose of mirogabalin in Japanese subjects with varying degrees of renal impairment. J Clin Pharmacol. 2018;58:57–63. doi: 10.1002/jcph.974.

7. Burgess J, Javed S, Frank B, Malik RA, Alam U. Mirogabalin besylate in the treatment of neuropathic pain. Drugs Today (Barc). 2020 Feb;56(2):135-149. doi: 10.1358/dot.2020.56.2.3100504. PMID: 32163529.

8. Shuji Komatsu, Shingo Nakamura, Takahiro Nonaka, Toshihiko Yamada, Tatsuo Yamamoto. Analgesic characteristics of a newly developed $\alpha_2\delta$ ligand, mirogabalin, on inflammatory pain https://doi.org/10.1177/17448069211052167

9. Kato J, Matsui N, Kakehi Y, Murayama E, Ohwada S. Long-term safety and efficacy of mirogabalin in Asian patients with postherpetic neuralgia: results from an open-label extension of a multicenter randomized, double-blind, placebo-controlled trial. Medicine (Baltimore) 2020;99:e21976. doi: 10.1097/MD.0000000000021976.

10. 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;10:1299–306. doi: 10.1111/jdi.13013.

11. Kumar P, Thomas J. Trigeminal trophic syndrome. Indian J Dermatol. 2014;59:75–6. doi: 10.4103/0019-5154.123506.

12. Kim K, Isu T, Kokubo R, Iwamoto N, Morimoto D, Kawauchi M, et al. Therapeutic effect of mirogabalin on peripheral neuropathic pain due to lumbar spine disease. Asian Spine J. 2020:doi: 10.31616/asj.2020.0136. doi: 10.31616/asj.2020.0136.

13. Murasawa, H., Kobayashi, H., Saeki, K. et al. Anxiolytic effects of the novel $\alpha_2\delta$ ligand mirogabalin in a rat model of chronic constriction injury, an experimental model of neuropathic pain. Psychopharmacology 237, 189–197 (2020). https://doi.org/10.1007/s00213-019-05356-3

14. Saeki, K., Yasuda, Si., Kato, M. et al. Analgesic effects of mirogabalin, a novel ligand for $\alpha_2\delta$ subunit of voltage-gated calcium channels, in experimental animal models of fibromyalgia. Naunyn-Schmiedeberg's Arch Pharmacol 392, 723–728 (2019). https://doi.org/10.1007/s00210-019-01628-z

15. Sugimoto, M., Takagi, T., Suzuki, R. et al. Mirogabalin vs pregabalin for chemotherapy-induced peripheral neuropathy in pancreatic cancer patients. BMC Cancer **21,** 1319 (2021). https://doi.org/10.1186/s12885-021-09069-9

16. Dow J, Currie A, He L, Zaidi F, Zahir H. Effect of coadministration of metformin with mirogabalin: results from a phase 1, randomized, open-label, drug-drug interaction study. Int J Clin Pharmacol Ther. 2018;56:451–8. doi: 10.5414/CP203185.

17. Tachibana M, Yamamura N, Atiee GJ, Hsu C, Warren V, He L, et al. Coadministration of probenecid and cimetidine with mirogabalin in healthy subjects: a phase 1, randomized, open-label, drug-drug interaction study. Br J Clin Pharmacol. 2018;84:2317–24. doi: 10.1111/bcp.13674.

18. Jansen M, Mendell J, Currie A, Dow J, He L, Merante D, et al. Pharmacokinetics, pharmacodynamics, safety, and tolerability of mirogabalin when coadministered with lorazepam, zolpidem, tramadol, or ethanol: results from drug-drug interaction studies in healthy subjects. Clin Pharmacol Drug Dev. 2018;7:597–612. doi: 10.1002/cpdd.582.

19. Gong N, Park J, Luo ZD. Injury-induced maladaptation and dysregulation of calcium channel α_2 δ subunit proteins and its contribution to neuropathic pain development. Br J Pharmacol. 2018 Jun;175(12):2231-2243. doi: 10.1111/bph.13930. Epub 2017 Aug 1. PMID: 28646556; PMCID: PMC5980513.

20. Takahashi S, Ogata A, Nakamura M. A probable case of mirogabalin-induced neutropenia. Cureus. 2020;12:e10182. doi: 10.7759/cureus.10182.

21. Mendell J, Levy-Cooperman N, Sellers E, Vince B, Kelsh D, Lee J, et al. Abuse potential of mirogabalin in recreational polydrug users. Ther Adv Drug Saf. 2019;10:2042098619836032. doi: 10.1177/2042098619836032.

22. Hutmacher MM, Frame B, Miller R, Truitt K, Merante D. Exposure-response modeling of average daily pain score, and dizziness and somnolence, for mirogabalin (DS-5565) in patients with diabetic peripheral neuropathic pain. J Clin Pharmacol. 2016;56:67–77. doi: 10.1002/jcph.567.

23. Javed S, Alam U, Malik RA. Mirogabalin and emerging therapies for diabetic neuropathy. J Pain Res. 2018;11:1559–66. doi: 10.2147/JPR.S145999.

24. Alyoubi RA, Alshareef AA, Aldughaither SM, Aljaroudi AM, Alabdulwahed A, Alduraibi FM, et al. 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. 2020:doi: 10.1111/ijcp.13744. doi: 10.1111/ijcp.13744.

25. Zajączkowska, Renata et al. “Mirogabalin-A Novel Selective Ligand for the α2δ Calcium Channel Subunit.” Pharmaceuticals (Basel, Switzerland) vol. 14,2 112. 31 Jan. 2021, doi:10.3390/ph14020112.