Mirogabalin: could it be the next generation gabapentin or pregabalin?

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INTRODUCTION
Other than the use of carbamazepine in treating trigeminal neuralgia, gabapentinoids have become the standard drugs in treating neuropathic pain. There are 2 calcium channels in the human body: voltage-gated calcium channels (VGCCs) and ligand-gated (receptor-operated) calcium channels. The mechanism of relief for neuropathic pain is strongly related to the $\alpha_2\delta$ ligands which bind to the $\alpha_2\delta$ subunits of VGCCs non-specifically.

VGCCs are usually made up of the main pore-forming $\alpha_1$ subunit and auxiliary subunits, including the $\beta$ and $\alpha_2\delta$, or sometimes $\gamma$ subunits. Four $\alpha_2\delta$ ($\alpha_2\delta-1$, $\alpha_2\delta-2$, $\alpha_2\delta-3$, and $\alpha_2\delta-4$) subunit genes have been cloned. The $\alpha_2\delta-1$ subunit is widely distributed in the skeletal, smooth, and cardiac muscles, as well as the central and peripheral nervous systems, and endocrine tissues. Cardiac dysfunction or neuropathic pain is the representative pathologic condition with an $\alpha_2\delta-1$ subunit disorder. The $\alpha_2\delta-2$ subunit is principally located in the central nervous system, especially the...
cerebellum. Pathology in the $\alpha_2\delta$-2 subunit may exhibit itself as epilepsy or cerebellar ataxia [1].

Therefore, conventional gabapentinoids, gabapentin and pregabalin, bind to the $\alpha_2\delta$-1 and $\alpha_2\delta$-2 subunits non-selectively, and produce unwanted adverse drug reactions (ADRs) in the central nervous system, such as dizziness, ataxia, somnolence, and headache. A novel gabapentinoid anticonvulsant needs selectivity for the $\alpha_2\delta$ subunits for increasing its therapeutic effect for neuropathic pain via the $\alpha_2\delta$-1 subunits, and for decreasing central ADRs through the $\alpha_2\delta$-2 subunits.

Mirogabalin besylate (DS-5565, Tarlige®; Daiichi Sankyo Company Limited, Tokyo, Japan), which selectively binds to and modulates the $\alpha_2\delta$-1 subunits of VGCCs, was recently approved for manufacturing and marketing for treatment of peripheral neuropathic pain in Japan on January 8, 2019, after completing phase 3 clinical trials on patients with diabetic peripheral neuropathic pain (DPNP) and postherpetic neuralgia (PHN). While the drug has received approval for use in Japan, it is still awaiting approval in other countries. Tablets with various doses of mirogabalin besylate are available, including 2.5, 5, 10, and 15 mg. The initial recommended dose for adults starts from 5 mg, given orally twice a day. The dose is slowly increased by 5 mg, at an interval of at least a week, to 15 mg [2,3].

Following studies focusing on selectivity, celecoxib (Celebrex®; Pfizer, New York, NY), a selective cyclooxygenase 2 inhibitor non-steroidal anti-inflammatory drug (NSAID), or oliceridine (Olinvo®; Trevena Inc., King of Prussia, PA), a $\mu$-receptor G protein pathway selective modulator opioid, has been used or developed for increasing therapeutic effects, while decreasing ADRs [4].

This review examines expectations for mirogabalin, as a novel ligand of the $\alpha_2\delta$-1 subunits (compared to the $\alpha_2\delta$-2 subunits) containing VGCCs.

MAIN BODY

1. VGCCs

The current trends in development of novel drugs focus on target selectivity, rather than polypharmacy, for achieving increased therapeutic effects, but decreased ADRs [5]. A novel gabapentinoid, mirogabalin, has been introduced for treatment of neuropathic pain, including DPNP and PHN in 2019, highlighting its higher selective binding affinity/slow dissociation half-life to the $\alpha_2\delta$-1 rather than the $\alpha_2\delta$-2 subunit. However, while, like pregabalin, it showed greater selective binding affinity to the $\alpha_2\delta$-1 than to the $\alpha_2\delta$-2 subunit, it showed a markedly slower dissociation rate from $\alpha_2\delta$-1 compared to $\alpha_2\delta$-2, in a human and rat study [6].

Calcium channels can be divided into voltage- and ligand-gated channels. The VGCCs, which open when the membrane potential is changed, include 1) high threshold-activated channels: (1) L [long-lasting or dihydropyridine (DHP), Ca,1.1, and 1.2]-, (2) P/Q (Purkinje/question Ca,2.1)-, and (3) N (neural, Ca,2.2)-type, 2) intermediate threshold-activated channels: Ca,1.3, Ca,1.4, and R (residual, Ca,2.3)-type channels, and 3) low threshold-activated channels: T (transient, Ca,3.1, 3.2, and 3.3)-type channels [7,8]. However, the ligand-gated calcium channels, which are activated by ligands binding, include the inositol 1,4,5-triphosphate (Ins3P or IP3) receptors, ryanodine receptors, two-pore channels, cation channels of the sperm, and store-operated channels (Table 1) [9].

Among the Ca,1 family (L-type channels), Ca,1.1 ($\alpha_1S$ subunit) is located in the skeletal muscle, while Ca,1.2 ($\alpha_1C$ subunit) is found mainly in the cardiac muscle and neurons. Ca,1.3 ($\alpha_1D$ subunit) has a role in neurotransmission in auditory cells and pacemaker activity, and Ca,1.4 ($\alpha_1F$ subunit) acts on synaptic transmission in the retina [7,8].

The VGCCs contain 5 different subunits: $\alpha_1$ (170-240 kDa), $\alpha_2$ (150 kDa), $\beta$ (50-78 kDa), $\delta$ (17-25 kDa), and $\gamma$ (32 kDa) in stoichiometric amounts [7,8,10]. The main pore-forming $\alpha_1$ subunit is bonded non-covalently to the auxiliary $\alpha_2$, $\beta$, and $\delta$ subunits, as well as to calmodulin, which modulates the calcium ion trafficking and biophysical properties of the main $\alpha_1$ subunit [9,10].

1) Main pore-forming $\alpha_1$ subunits of VGCCs

The pore-forming $\alpha_1$ subunit has 24 transmembrane $\alpha$-helices, making 4 homogenous repeats (I-IV). The 4th transmembrane segment (S4) of each repeat has 5 positively charged amino acids with the 1st, 2nd, and 3rd segments (S1, S2, and S3) producing the voltage-sensing domain of the channel. There are pore loops present between the 5th and 6th segments (S5 and S6). There are also loops between I (S6) and II (S1), II (S6) and III (S1), and III (S6) and IV (S1) (Fig. 1) [9,11].

2) Auxiliary $\alpha_2$, $\beta$, and $\delta$ subunits for modulating $\alpha_1$ subunits of VGCCs

The $\alpha_2$, $\delta$, and $\beta$ subunits are located extracellularly, in the membrane, and intracellularly, respectively.

1) $\beta$ subunits

The intracellular (cytosolic) $\beta$ subunits are composed of an Src homology (SH++) domain and a guanylate kinase (GK) domain. The GK domain binds to the intracellular linker...
**Table 1.** Calcium channels in the human body

| Voltage-gated calcium channels | Type | Voltage activated | Main α subunit (gene name) | Auxiliary subunits | Location |
|-------------------------------|------|-------------------|-----------------------------|--------------------|----------|
| L [long-lasting or dihydropyridine (DHP)] type | High | Cα1.1 (CACNA1S) | Aβδ, β, and γ | Skeletal muscles |
| | Intermediate or low | Cα1.2 (CACNA1C) | | Cardiac muscles and neurons |
| | | Cα1.3 (CACNA1D) | | Auditory cells in the brain |
| | | Cα1.4 (CACNA1F) | | Retina |
| Non-L type | High | Cα2.1 (CACNA1A) | Aβδ, β, or γ | Purkinje cells of the cerebellum/neurons in the brain |
| P (Purkinje)/Q (question) type | High | Cα2.2 (CACNA1B) | Aβδ, β, β, β, or γ | Neural tissues |
| N (neural or non-L) type | Intermediate | Cα2.3 (CACNA1E) | Aβδ, β, or γ | Neuron in the brain |
| R (residual) type | Low | Cα3.1 (CACNA1G) | ? | Heart and central nervous system |
| T (transient) type | | Cα3.2 (CACNA1H) | | |
| | | Cα3.3 (CACNA1I) | | |

| Ligand-gated calcium channels | Type | Gated by | Gene | Location | Function |
|-----------------------------|------|----------|------|----------|----------|
| Inositol 1,4,5-triphosphate (IP3) receptor | IP3 | ITPR1-3 | Endoplasmic reticulum (ER) and sarcoplasmic reticulum (SR) | Calcium release from ER/SR in response to IP3 |
| Ryanodine receptor | DHP receptor in T-tubules and calcium induced calcium release (CICR) | RYR1-3 | ER/SR | CICR in the myocytes |
| Two-pore channel | Nicotinic acid adenine dinucleotide phosphate (NAADP) | TPCN1-2 | Endosomal/lysosomal membranes | NAADP-activated calcium transport across the endosomal/lysosomal membranes |
| Cation channel of sperm | CICR | | | Non-selective calcium-activated cation channel |
| Store-operated channels | Indirectly by ER/SR depletion of calcium | Polycystin-2 (PKD2) family | Sperm | Calcium signaling to the cytoplasm |

Adapted from Dolphin AC. Voltage-gated calcium channel αβδ subunits: an assessment of proposed novel roles. F1000Res 2018; 7: F1000 Faculty Rev 1830 [7]. Adapted from Dolphin AC. Calcium channel auxiliary αβδ and β subunits: trafficking and one step beyond. Nat Rev Neurosci 2012; 13: 542-55 [8] with original copyright holder’s permission. Adapted from Burnashev N. Calcium permeability of ligand-gated channels. Cell Calcium 1998; 24: 325-32 [9] with original copyright holder’s permission.
Gabapentinoids inhibit forward (anterograde) trafficking of voltage-gated calcium channels (VGCCs) (from the endosomal reticulum through the Golgi complex to the cell membrane) intracellularly. Inhibition of anterograde trafficking reduces VGCCs, calcium entry, and excitatory amino acids (glutamates). (2) They inhibit the Rab-11-dependent final recycling of endosomal VGCCs intracellularly, resulting in reduced excitatory neurotransmitter release in the synapse. The small guanosine triphosphatases (GTPases, Rab) are the main regulators of intracellular membrane trafficking, from formation of transport vesicles to their fusion into the membranes. Reduced recycling of endosomal VGCCs results in reduced transmembrane VGCCs, calcium entry into the cell, and glutamate in the synapse. (3) They inhibit astrocyte-derived thrombospondin (TSP, extracellular matrix protein)-mediated excitatory synapse formation extracellularly (reduction of excitatory synaptogenesis). (4) They stimulate glutamate uptake by excitatory amino acid transporters (EAATs) extracellularly. (5) Gabapentinoids may show inhibition of descending serotonergic facilitation, stimulation of descending inhibition, anti-inflammatory effect, and influence on the affective component of pain. A magnified illustration for the transmembrane VGCC is shown in the upper left (in the DRGs) and right (in the cerebellum) quadrants. Adapted from Chincholkar M. Analgesic mechanisms of gabapentinoids and effects in experimental pain models: a narrative review. Br J Anaesth 2018; 120: 1315-34 [14].

between domains I and II of the αδ subunit. The membrane-anchored αδ subunit consists of the extracellular αδ and membrane-associated δ subunits. They are connected with a disulfide bond (Fig. 1) [9,11].

(2) αδ subunits

The membrane (glycosylphosphatidylinositol, GPI)-anchored αδ subunit is tasked with modulation of the calcium channel current kinetics, and with increasing trafficking of the channel to the membrane. The αδ subunit determines VGCC abundance in the presynaptic terminals, and configures synaptic VGCCs to drive exocytosis through an extracellular metal ion-dependent adhesion site (MIDAS), a conserved set of amino acids with the predicted von Willebrand A (VMA) domain of the αδ subunit [12].

At least 4 αδ subunit genes are cloned: ① The αδ-1 subunit mRNA was cloned from skeletal muscle (Cα,1.1); however, it is found throughout the human body, including the cardiac and smooth muscles associated with Cα,1.2. It is also found in many neuronal cell types and the dorsal root ganglia (DRGs), especially in excitatory rather than inhibitory interneurons. ② The αδ-2 subunit mRNA is found mainly in the brain (such as the Purkinje cells in the cerebellum, medulla, hippocampus, and striatum) or in the lungs. ③ The αδ-3 subunit mRNA is found in the brain (cerebral cortex, caudate-putamen, and hippocampus), heart, and skeletal muscle. ④ The recently identified αδ-4 subunits are distributed in the non-neuronal tissues, such as the adrenal or pituitary glands. The human αδ-4 protein sequence shares 30%, 32%, and 61% of its identity with human αδ-1, αδ-2, and αδ-3, respectively. The αδ-4 subunits are located in the retina, therefore, they are deeply...
related to night blindness [1,13].

2. Action mechanisms of mirogabalin

1) Conventional gabapentinoids

Gabapentin and pregabalin bind to the $\alpha_2\beta_1$ and $\alpha_2\delta$-2 subunits, especially, to the 3rd arginine (R, rectus) in the RRR motif, which is located N-terminal to the VMA domain. The $\alpha_2\delta$-1 subunit plays a role in development of chronic neuropathic pain, and is the target for treatment. The $\alpha_2\delta$-2 subunit is concentrated in the Purkinje cells of the cerebellum, and this explains why the conventional gabapentinoid anticonvulsants present the representative ADRs, such as dizziness and ataxia (Fig. 1) [1].

In general, mechanisms of action for gabapentinoids include: (1) Gabapentinoids inhibit forward (anterograde) trafficking of $\alpha_2\delta$-1 (from the endoplasmic reticulum through the Golgi complex to the cell membrane) intracellularly. (2) They inhibit Rab-11-dependent final recycling of endosomal VGCCs intracellularly, resulting in reduced excitatory neurotransmitter release in the synapse. (3) They inhibit thrombospondin (TSP, extracellular matrix protein)-mediated processes extracellularly, resulting in reducing excitatory synaptogenesis. (4) They stimulate glutamate uptake by excitatory amino acid transporters extracellularly. (5) Minor mechanisms related to gabapentinoids may include inhibition of descending serotonergic facilitation, stimulation of descending inhibition, antiinflammatory effect, and influence on the affective component of pain [14] (Fig. 1).

The $\alpha_2\beta$-1 and $\beta$ subunits in the DRGs mediate forward trafficking of calcium channels (exocytosis) to the dorsal horn from the endoplasmic reticulum which is facilitated by protein kinase C (PKC) through the Golgi complex to the cell membrane [15].

Gabapentinoids act on the DRGs and A nerve fibers, especially medium-sized neurons associated with A$\delta$ nerve fibers and small isolecitin B4 (IB4)-negative DRGs, projecting to the excitatory neurons in the lamina I and II of the spinal dorsal horn (compared to large neurons associated with A$\beta$ nerve fibers and IB4-positive neurons, projecting to the inhibitory neurons) [14].

The $\alpha_2\delta$-1 and $\beta$ subunits of the VGCCs mediate forward trafficking of the calcium channels from the endoplasmic reticulum, facilitated by PKC. The reduced recycling of endosomal VGCCs leads to a reduced calcium channel expression and decreased transmitter release at the synaptic membrane. Gabapentinoids inhibit Rab-11 (master regulators of the surface expression of receptors and adhesion protein)-dependent recycling of endosomal VGCCs. In addition, TSP 4 (a family of 5 extracellular matrix oligomeric glycoproteins) mediates excitatory synaptogenesis with cellular migration, attachment, and cytoskeletal dynamics. It also mediates the binding to the $\alpha_2\delta$-1 subunits. However, gabapentin does not seem to target TSPs/$\alpha_2\delta$-1 directly [15,16].

On the other hand, 2 systems for intracellular calcium extrusion include the plasma membrane Ca$^{2+}$ ATPase (PMCA) and plasma membrane Na$^+$/Ca$^{2+}$ exchanger (NCX). The NCX has a low calcium affinity but a high capacity for calcium transport, whereas the PMCA has the opposite properties [17].

2) Comparison of binding and dissociation kinetics of gabapentin, pregabalin, and mirogabalin for the $\alpha_2\delta$-1 and $\alpha_2\delta$-2 subunits

Gabapentinoids, including gabapentin and pregabalin, have become the drugs of choice for the treatment of neuropathic pain with positive symptoms [4].

Binding affinity is measured by the equilibrium dissociation constant ($K_d$). The smaller the $K_d$ value, the greater the binding affinity of the ligand for its target. Gabapentin is known to bind to $\alpha_2\delta$ subunits with greater affinity for $\alpha_2\delta$-1 ($K_d = 59 \text{ nmol/L}$) compared to $\alpha_2\delta$-2 ($K_d = 153 \text{ nmol/L}$) [15].

Pregabalin also shows greater affinity to the $\alpha_2\delta$-1 ($K_d = 62.5 \text{ nmol/L}$) compared to the $\alpha_2\delta$-2 ($K_d = 125.0 \text{ nmol/L}$). Mirogabalin similarly exhibits greater affinity to the $\alpha_2\delta$-1 ($K_d = 13.5 \text{ nmol/L}$), compared to the $\alpha_2\delta$-2 ($K_d = 22.7 \text{ nmol/L}$). However, pregabalin show similar dissociation time from the $\alpha_2\delta$-1 ($K_{off} = 0.5051 \text{ per hour}$) and the $\alpha_2\delta$-2 ($K_{off} = 0.5103 \text{ per hour}$). Mirogabalin exhibits slow dissociation from the $\alpha_2\delta$-1 ($K_{off} = 0.0627 \text{ per hour}$) compared to the $\alpha_2\delta$-2 ($K_{off} = 0.2837 \text{ per hour}$). Its dissociation half-life is also longer from the $\alpha_2\delta$-1 (t$_{1/2} = 11.1 \text{ per hour}$) than the $\alpha_2\delta$-2 (t$_{1/2} = 2.4 \text{ per hour}$) [6].

Therefore, mirogabalin, compared with pregabalin, has a similar degree of greater affinity to the $\alpha_2\delta$-1 compared to the $\alpha_2\delta$-2, however, its dissociation time from the $\alpha_2\delta$-1, compared to the $\alpha_2\delta$-2, is longer than with pregabalin. The secret is that mirogabalin, compared to pregabalin, shows a greater therapeutic analgesic effect for neuropathic pain and lesser ADRs due to the slow dissociation from the $\alpha_2\delta$-1 subunits, not due to the binding affinity to the $\alpha_2\delta$-1 subunits. Mirogabalin has a longer dissociation half-life from the $\alpha_2\delta$-1 subunits than the $\alpha_2\delta$-2 subunits, in contrast to pregabalin.

In conclusion, mirogabalin has a high affinity to and slow dissociation from the $\alpha_2\delta$-1 subunits in the DRGs, producing greater therapeutic effects; it also has a low affinity to and fast dissociation from the $\alpha_2\delta$-2 subunits in the cerebellum, producing lesser ADRs.
| Classification          | Author                        | Title                                                                 | Journal                                      |
|------------------------|-------------------------------|----------------------------------------------------------------------|----------------------------------------------|
| Review articles (8)    | Deeks                         | Mirogabalin: first global approval.                                    | Drugs 2019;79:463-8. [2]                    |
|                        | Javed et al.                  | Mirogabalin and emerging therapies for diabetic neuropathy.           | J Pain Res 2018;11:1599-66. [19]             |
|                        | Calandre et al.               | Alpha-delta ligands, gabapentin, pregabalin and mirogabalin: a review of their clinical pharmacology and therapeutic use. | Expert Rev Neurother 2018;18:1253-77. [21] |
|                        | Javed et al.                  | Mirogabalin and emerging therapies for diabetic neuropathy.           | J Pain Res 2018;11:1599-66. [19]             |
|                        | Calandre et al.               | Alpha-delta ligands, gabapentin, pregabalin and mirogabalin: a review of their clinical pharmacology and therapeutic use. | Expert Rev Neurother 2018;18:1253-77. [21] |
|                        | Domon et al.                  | Binding characteristics and analgesic effects of mirogabalin, a novel ligand for the alpha(2)delta subunit of voltage-gated calcium channels. | J Pharmacol Exp Ther 2018;365:573-82. [6] |
|                        | Burgess et al.                | Emerging therapies in clinical development and new contributions for neuropathic pain. | Drugs Today (Barc) 2020;56:135-49. [23]       |
|                        | Merante                      | The mirogabalin ALDYP program in pain associated with fibromyalgia: the lessons learned. | Curr Med Res Opin 2020;36:661-6. [22]        |
|                        | Alcántara Montero et al.      | Emerging therapies in clinical development and new contributions for neuropathic pain. | Rev Esp Anestesiol Reanim 2019;66:324-34. [18] |
|                        | Alyoubi et al.                | Efficacy and safety of mirogabalin treatment in patients with diabetic peripheral neuropathic pain: a systematic review and meta-analysis of randomized controlled trials. | Int J Clin Pract 2020;66:10.1111/ijs.15744. [20] |
|                        | Baba et al.                   | Efficacy and safety of mirogabalin treatment in patients with diabetic peripheral neuropathic pain: a systematic review and meta-analysis of randomized controlled trials. | J Pain Res 2020;13:1811-1814. [37]           |
|                        | Kato et al.                   | Long-term safety and efficacy of mirogabalin in Asian patients with diabetic peripheral neuropathy and PHN: a phase IV, open-label, multicenter, randomized, double-blind, placebo-controlled, 14-week study. | Medicine (Baltimore) 2020;99:2197-226. [26]  |
|                        | Akoum et al.                  | Mirogabalin treatment in patients with sensory marker-detectable pain associated with diabetic peripheral neuropathy: a randomized, double-blind, placebo-controlled trial. | J Pain Res 2020;13:1811-1814. [37]           |

| Classification          | Author                        | Title                                                                 | Journal                                      |
|------------------------|-------------------------------|----------------------------------------------------------------------|----------------------------------------------|
| Clinical Trials (22)   | Baba et al.                   | Efficacy and safety of mirogabalin treatment in patients with diabetic peripheral neuropathic pain: a systematic review and meta-analysis of randomized controlled trials. | Int J Clin Pract 2020;66:10.1111/ijs.15744. [20] |
|                        | Kato et al.                   | Long-term safety and efficacy of mirogabalin in Asian patients with diabetic peripheral neuropathy and PHN: a phase IV, open-label, multicenter, randomized, double-blind, placebo-controlled, 14-week study. | Medicine (Baltimore) 2020;99:2197-226. [26]  |

**Table 2. Summary of review articles, clinical trials, case reports, and animal research in English related to mirogabalin**

Mirogabalin is suitable for the treatment of peripheral neuropathic pain, including DPNP and PHN. Mirogabalin is expected to become the fourth US FDA-approved therapy for DPNP, following pregabalin, duloxetine, and tapentadol. Mirogabalin shows a promising result for DPNP with ADRs, including fatigue, dizziness, sedation, somnolence, ataxia, weight gain, and edema. Mirogabalin has a potent pain-modulating effect with a uniquely high affinity and prolonged dissociation rate for the alpha(2)delta-1 subunit of voltage-gated calcium channels on the dorsal root ganglion. Mirogabalin shows potent and selective binding affinities for human and rat alpha(2)delta subunits, and slower dissociation rates for the alpha(2)delta-1 subunit than the alpha(2)delta-2 subunit. It shows potent and long-lasting analgesic effects in rat models of the central nervous system, due to its unique binding characteristics. Mirogabalin has a potential pain-modulating effect with a uniquely high affinity and prolonged dissociation rate for the alpha(2)delta-1 subunit of voltage-gated calcium channels on the dorsal root ganglion. Mirogabalin was well tolerated and significantly reduced pain scores over time. Besides, mirogabalin was largely safe and associated with some manageable adverse events. A flexible dose of 10 or 15 mg of mirogabalin twice a day was shown to be effective and well tolerated for treating PHN in an Asian multicenter, randomized, double-blind, placebo-controlled, 14-week study.
| Classification | Author | Title | Journal | Contents |
|---------------|--------|-------|---------|----------|
|               | Kim 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. | Mirogabalin (maximal dose: 30 mg/d) improved leg symptoms, low back pain, and sleep disturbance in patients with lumbar spine disease. |
|               | Dow et al. | 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. | Coadministration of mirogabalin 15 mg and metformin 850 mg is well tolerated in healthy subjects with no evidence of a drug-drug interaction. |
|               | Baba et al. | 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. | Mirogabalin 30 mg/d showed significant pain relief (vs. placebo) in Asian DPNP patients. All doses of mirogabalin tested were well tolerated. |
|               | Kato et al. | Mirogabalin for the management of postherpetic neuralgia: a randomized, double-blind, placebo-controlled phase 3 study in Asian patients. | Pain 2019; 160: 1175-85. | Mirogabalin was superior to a placebo in all groups (15, 20, and 30 mg/d) for relieving PHN. |
|               | Mendell et al. | Abuse potential of mirogabalin in recreational polydrug users. | Pain 2019; 160: 1905. | Therapeutic doses of mirogabalin (30 mg/d) demonstrated limited evidence of abuse potential, which was lower than for diazepam and pregabalin. |
|               | Arnold et al. | Efficacy and safety of mirogabalin for the treatment of fibromyalgia: results from three 13-week randomized, double-blind, placebo- and active-controlled, parallel-group studies and a 52-week open-label extension study. | Curr Med Res Opin 2019; 35: 1825-35. | Both mirogabalin 15 mg once daily and mirogabalin 15 mg twice daily did not improve in weekly average daily worst pain score at week 13 in patients with FM. |
|               | Vinik et al. | 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: 3253-61. | Mirogabalin 15, 20, and 30 mg/day had significant reductions the weekly change in average daily pain score in patients with DPNP. |
|               | Brown et al. | Tolerability, pharmacokinetics, and pharmacodynamics of mirogabalin in healthy subjects: results from phase 1 studies. | Pharmacol Res Perspect 2018; 6: e00418. | There was no difference of bioavailability between in fed and fasted states after single doses of mirogabalin 15 mg. Therefore, mirogabalin can be taken without food restrictions. |
|               | Merante et al. | 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: 2198-207. | Mirogabalin from 15 mg/d to 30 mg/d improved pain and sleep interference in DPNP. |
|               | Kato 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. | A mirogabalin dose adjustment will be needed in Japanese subjects with moderate to severe renal impairment and end-stage renal disease. The most common ADRs were dizziness, somnolence, and vomiting in patients with end-stage renal disease. |
| Classification | Author | Title | Journal | Contents |
|----------------|--------|-------|---------|----------|
| Tachibana 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. [42] | Coadministration of mirogabalin 15 mg and probenecid 500 mg inhibited both renal and metabolic clearance. Coadministration of mirogabalin 15 mg and cimetidine 400 mg inhibited renal clearance only. However, a priori dose adjustment is not recommended. |
| Jansen 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. [43] | Peak mirogabalin plasma concentration decreased by 28% following tramadol coadministration, and increased by 20% following ethanol 20% 240 mL for men and 200 mL for women coadministration. Coadministration of mirogabalin 10 mg twice a day with either lorazepam 2 mg or ethanol increased the pharmacodynamic effects. Mirogabalin/lorazepam and mirogabalin 10 mg/zolpidem 10 mg increased incidence of somnolence. Mirogabalin 10 mg/tramadol 100 mg and mirogabalin/ethanol increased incidence of nausea and headache, respectively. |
| Jansen 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. [24] | Mirogabalin was safe and tolerable in Asian and white subjects at doses up to 15 mg twice a day for 7 days. The most common ADRs were somnolence, headache, and dizziness. |
| Duchin et al. | 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. [40] | A single dose of mirogabalin 15 mg did not show effects on its pharmacokinetics in mild-to-moderate hepatic impairment. |
| Yin et al. | Population pharmacokinetic modeling and simulation for assessing renal impairment effect on the pharmacokinetics of mirogabalin. | J Clin Pharmacol 2016; 56: 203-12. [39] | A dose reduction by 50% or 75% in patients was needed in moderate or severe renal impairment, respectively. However, no dose adjustment seemed necessary for patients with mild renal impairment. |
| Baba et al. | Results of mirogabalin treatment for diabetic peripheral neuropathic pain in Asian subjects: a phase 2, double-blind, randomized, placebo-controlled, study. | Pain Ther 2020; 9: 261-78. [32] | In Asian patients with DPNP, mirogabalin (5, 10, and 15 mg twice a day) was well tolerated. There was a tendency toward improvement of pain with mirogabalin treatment. |
| Baba et al. | Long-term safety and efficacy of mirogabalin in Asian patients with diabetic peripheral neuropathic pain. | J Diabetes Investig 2020; 11: 693-8. [33] | It was safe and effective for the Asian patients with DPNP to a longterm flexible dosing regimen of mirogabalin 10 or 15 mg twice a day. |
| Hutmacher et al. | 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. [34] | Mirogabalin was known to be 17-fold more potent to pregabalin. It provided an equianalgesic effect to pregabalin 300 mg in patients with DPNP. ADRs were lower in the group of twice-daily regimen compared to in the group of once-daily regimen. |
### Table 2. Continued

| Classification | Author          | Title                                                                 | Journal                      | Contents                                                                                                                                 |
|----------------|-----------------|----------------------------------------------------------------------|------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
|                | Ye et al.       | Cost-effectiveness of mirogabalin for the treatment of post-herpetic neuralgia in Taiwan. | J Med Econ 2020; 23: 529-36. [28] | Mirogabalin 30 mg, a potent and selective α2δ ligand, is a cost-effective treatment option for PHN in Taiwan, with ICERs below the willingness-to-pay threshold. |
| Case reports (2) | Tetsunaga et al. | Short-term outcomes of mirogabalin in patients with peripheral neuropathic pain: a retrospective study. | J Orthop Surg Res 2020; 15: 191. [25] | Mirogabalin 5-15 mg twice a day is safe and effective for control peripheral neuropathic pain. They reported a case of development of neutropenia in a 77-year-old woman with squamous cell carcinoma of the lung, after taking mirogabalin at 10 mg/d for 6 weeks. |
|                | Takahashi et al. | A probable case of mirogabalin-induced neutropenia. | Cureus 2020; 12: e10182. [46] | They reported a case of successful treatment of trigeminal trophic syndrome secondary to herpes zoster in an 89-year-old female patient. |
|                | Matsuda et al.  | A case of trigeminal trophic syndrome responding to mirogabalin. | Eur J Dermatol 2020. doi: 10.1684/ijd.2020.3746. [47] | Mirogabalin inhibits N-type calcium channel currents in rat DRG culture neurons. Mirogabalin and pregabalin inhibited the calcium channel currents of rat DRG neurons at 50 μM and 200 μM, respectively. |
| Animal research (6) | Kitano et al. | Effects of mirogabalin, a novel ligand for the α2δ subunit of voltage-gated calcium channels, on N-type calcium channel currents of rat dorsal root ganglion culture neurons. | Pharmazie 2019; 74: 147-9. [49] | Mirogabalin showed potent and long-lasting analgesic effects in a rat model of spinal cord injury, suggesting its effective pain relief for patients with central neuropathic pain. |
|                | Domon et al.    | Analgesic effects of the novel α2δ ligand mirogabalin in a rat model of spinal cord injury. | Pharmazie 2018; 73: 659-61. [50] | Mirogabalin alleviated both anxiety-related behaviors and tactile allodynia in CCI model rats. It may provide both anxiety and pain relief in patients with neuropathic pain. |
|                | Murasawa et al. | Anxiolytic effects of the novel α2δ ligand mirogabalin in a rat model of chronic constriction injury, an experimental model of neuropathic pain | Psychopharmacology (Berl) 2020; 237: 189-97. [51] | Mirogabalin alleviated anxiety-related behaviors in an animal model, suggesting the potential to relieve anxiety in FM patients. |
|                | Murasawa et al. | Anxiolytic-like effects of mirogabalin, a novel ligand for α2δ ligand of voltage-gated calcium channels, in rats repeatedly injected with acidic saline intramuscularly, as an experimental model of fibromyalgia. | Pharmacol Rep 2020; 72: 571-9. [52] | Mirogabalin showed analgesic effects in intermittent cold stress model mice and in Sluka model rats, suggesting the potential to alleviate pain in patients with FM. |
|                | Saeki et al.    | Analgesic effects of mirogabalin, a novel ligand for α2δ subunit of voltage-gated calcium channels, in experimental animal models of fibromyalgia. | Naunyn Schmiedebergs Arch Pharmacol 2019; 392: 723-8. [53] | Mirogabalin prevents anxiety-like behavior and memory impairment induced by repeated restraint stress, related to hippocampal neurons. |
|                | Iwai et al.     | Mirogabalin prevents repeated restraint stress-induced dysfunction in mice. | Behav Brain Res 2020; 383: 112506. [54] | Mirogabalin alleviated anxiety-related behaviors and tactile allodynia in CCI model rats. It may provide both anxiety and pain relief in patients with neuropathic pain. |

Searched in PubMed on October 15, 2020.

ALDAY: a very large, multicenter program made by three, randomized, double-blind, placebo and active-controlled (pregabalin), 13-week studies, evaluating mirogabalin for the treatment of pain associated with fibromyalgia, aged ≥ 18 years or older, DPNP: diabetic peripheral neuropathic pain, PHN: postherpetic neuralgia, US FDA: United States Food and Drug Administration, ADRs: adverse reactions, FM: fibromyalgia, ICER: incremental cost-effectiveness ratio, DRG: dorsal root ganglion, CCI: chronic constriction injury.
3. Review articles, clinical trials, case reports, and animal studies

Thirty-eight studies related to mirogabalin had been published prior to October 15, 2020 when searching PubMed. The mirogabalin studies include 8 review articles, 22 clinical trials, 2 case reports, and 6 animal studies (Table 2).

1) Review articles

From the 8 review articles, mirogabalin was suitable for the treatment of peripheral neuropathic pain, especially DPNP and PHN [2,3,18]. It is expected to become the 4th United States Food and Drug Administration (U.S. FDA)-approved drug for DPNP, along with pregabalin, duloxetine, and tapentadol [19]. It showed a superior result to pregabalin in the average daily pain score, with manageable ADRs (fatigue, dizziness, sedation, somnolence, ataxia, weight gain, and edema) for DPNP [20,21].

However, it showed a negative result with fibromyalgia [from the pain in patients with fibromyalgia (a very large, multicenter program made by three, randomized, double-blind, placebo and active-controlled (pregabalin), 13-week studies, evaluating mirogabalin for the treatment of pain associated with fibromyalgia, aged 18 years or older, ALDAY) study] [22]. Relatively clear mechanisms of action for mirogabalin, related to binding affinity and dissociation rates to the \( \alpha_{2}\delta-1 \) and \( \alpha_{2}\delta-2 \) subunits of VGCCs, especially in the DRG and cerebellum have been introduced [6,23].

2) Clinical trials

(1) Healthy volunteers

For healthy volunteers, mirogabalin, at doses up to 15 mg twice a day for 7 days, showed safety and tolerability with ADRs [24].

(2) Patients with PHN

Mirogabalin was effective on various neuropathic pain syndromes [25]. In patients with PHN, 10 or 15 mg of mirogabalin twice a day for 52 weeks showed effective control of pain, with mild to moderate ADRs (An Asian, phase 3, multicenter, randomized double-blind, placebo-controlled 14-week study of DS-5565 in patients with postherpetic neuralgia followed by a 52-week open-label extension, NEUCOURSE clinical trial) [26]. All doses (15, 20, and 30 mg/d) for 14 weeks were superior to a placebo for relieving PHN [27]. Mirogabalin 30 mg, after a 1-month cessation of pregabalin, also showed effectiveness and safety for 187 patients with PHN in Taiwan [28].

(3) Patients with DPNP

In patients with DPNP, mirogabalin 30 mg showed significant pain relief, compared to a placebo, in a phase 3 study (an Asian, phase 3, multicenter, randomized, double-blind, placebo-controlled 14-week study of mirogabalin in patients with diabetic peripheral neuropathic pain, followed by a 52-week open-label extension, REDUCER clinical trial) in Japan, Taiwan, South Korea, and Malaysia [29]. In a phase 2 study, the average daily pain score was reduced at a daily dose of mirogabalin of 5, 10, 15, 20, and 30 mg for 5 weeks, compared to a placebo [30]. A similarly-designed phase 2 study showed a decreased average daily pain score and sleep interference score [31]. 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 [32]. In addition, mirogabalin 10 or 15 mg twice a day showed long-term (52 wk) safety and efficacy in patients with DPNP [33].

Mirogabalin (17.7 mg) was estimated to be 17-fold more potent than pregabalin (300 mg) in patients with DPNP. Twice-daily dosing of mirogabalin decreased dizziness more than once-daily dosing [34].

(4) Patients with fibromyalgia

Unfortunately, mirogabalin showed a negative result. Both mirogabalin 15 mg once and twice daily did not improve the worst weekly average daily pain score at week 13 [35]. In addition, the ALDAY phase 3 study did not decrease pain in patients with fibromyalgia [22].

(5) Patients with neuropathic pain from lumbar spine disease

Mirogabalin improved leg symptoms, low back pain, and sleep disturbance in patients with lumbar spine disease [36].

(6) Patients with neuropathic pain in renal or hepatic dysfunction

In patients with renal failure, a fixed dose of 7.5 mg once and twice a day reduced DPNP and PHN with a tolerable level of ADRs [37]. In moderate or severe renal dysfunction, a dose reduction was needed by 50% or 70%. However, a dose adjustment was not needed in mild renal dysfunction [38,39]. In patients with mild or moderate hepatic impairment, a single 15 mg dose of mirogabalin did not produce signifi-
cantly to the acceptable intake limit on October 5, 2020. Even though the use of metformin is currently reduced, it is difficult to avoid coadministration. Coadministration of metformin and mirogabalin was well-tolerated in healthy volunteers [41].

Probenecid, treating gout and hyperuricemia, has known interactions with some commonly-used drugs, such as non-steroidal anti-inflammatory drugs (indomethacin, ketoprofen, ketorolac, and naproxen), antibiotics (cephalosporins, quinolones, and penicillins), methotrexate, acyclovir, and lorazepam, and reduces excretion of these drugs [42].

Probenecid inhibits both renal and metabolic clearance; cimetidine reduces renal clearance. Even though renal excretion of a single oral dose of mirogabalin 15 mg in healthy volunteers was slightly decreased with coadministration of both probenecid 500 mg and cimetidine 400 mg, adjustment of the dose of mirogabalin was not recommended clinically in a phase 1 study [42].

Peak plasma mirogabalin concentration decreased by 28% following tramadol coadministration, but increased by 20% following ethanol coadministration. Coadministration of both probenecid 500 mg and cimetidine 400 mg, adjustment of the dose of mirogabalin was not recommended clinically in a phase 1 study [42].

There have been 2 case reports. Neutropenia induced by mirogabalin 10 mg for 6 weeks was noted in patients with squamous cell carcinoma of the lung, even after cessation of coadministration of acetaminophen and mexiletine [46].

There was a case of trigeminal trophic syndrome (TTS) responding to mirogabalin [47]. TTS is a rare facial ulceration which may appear after damage to the trigeminal nerve or its central sensory connections (herpes zoster or Hansen’s disease). A triad of TTS consists of anesthesia, paresthesia, and facial ulceration [48]. It is not uncommon to use mirogabalin for the treatment of herpes zoster in the territory of the trigeminal nerve.

4) Animal research

Six animal studies can be found in PubMed. Focused on the unique binding ability of mirogabalin and pregabalin to the αδ-1 subunit of VGCCs, on N-type calcium channel currents of rat DRG culture neurons, they inhibit N-type calcium currents at 50 μM and 200 μM, respectively. The authors concluded that the potent and prolonged analgesic effects of mirogabalin are associated with its potent and selective binding to the αδ-1 subunits, resulting in functional inhibition of calcium channel currents [49]. However, it is better to understand the mechanisms of action for mirogabalin as resulting from slow dissociation from the αδ-1 subunits in the DRGs and rapid dissociation from the αδ-2 subunits in the cerebellum (rather than its more potent and selective binding affinity to the αδ-1 subunits in comparison to the αδ-2 subunits) from their previous article [6].

In a spinal cord injury model, established by acute compression of the spinal cord at the T6-T7 level in rats, mirogabalin showed potent and long-lasting central analgesic effects [50].

In a chronic constriction injury (CCI) model in rats, mirogabalin showed dose-dependent anxiety-related behavior, as well as tactile allodynia [51]. A similar study on the anxiolytic effect of mirogabalin, by the same study group, was performed in the Sluka model (2 intramuscular injections of acid saline into the gastrocnemius muscle). A mirogabalin study showed an analgesic effect in an intermittent cold stress model in mice and Sluka model rats, suggesting effectiveness in patients with fibromyalgia [52]. Mirogabalin alleviated anxiolytic behavior in Sluka model rats, suggesting potential to relieve anxiety in fibromyalgia [53]. On the other hand, there was no analgesic effect in patients with fibromyalgia in the ALDAY phase 3 program and a 13-week study using mirogabalin 15 mg once or twice a day [22]. Another anxiety-related study showed...
that mirogabalin protected multiple brain functions from repeated restraint stress (2 hr/day), mediated by inhibition of hippocampal neuron hyperactivation [54].

4. Clinical application of mirogabalin

1) Pharmacokinetics

Available mirogabalin besylate tablets include 2.5, 5, 10, and 15 mg. The initial dose for adults without renal dysfunction is recommended starting from 5 mg, given orally twice a day. The dose is gradually increased by 5 mg, at an interval of at least a week, to 15 mg at the 3rd week [2,3,25-33].

After taking oral mirogabalin, maximum plasma concentration was achieved at 1 hour [19,39]. Its plasma protein binding was relatively low, at less than 25% [39]. It was mostly excreted by the kidney, and underwent minimal metabolism [19].

According to renal function (creatinine clearance, Clcr), the administration dose of mirogabalin should be adjusted in at least 3 stages: (1) a mild degree (90 > Clcr ≥ 60 mL/m), (2) a moderate degree (60 > Clcr ≥ 30 mL/m), and (3) a severe degree (30 > Clcr mL/m) of renal dysfunction. In mild renal dysfunction, the initial dose starts from 5 mg twice a day, slowly increased by 5 mg at an interval of 1 week, to 15 mg. In moderate renal dysfunction, the initial dose starts from 2.5 mg twice a day, slowly increased by 2.5 mg at an interval of 1 week, to 7.5 mg twice a day. In severe renal dysfunction, the initial dose starts from 2.5 mg once a day, slowly increased by 2.5 mg at an interval of 1 week, to 7.5 mg once a day (Table 3) [55].

A dose reduction of mirogabalin is suggested by 50% and 75% in patients with moderate and severe renal dysfunction, respectively [19,38]. A single dose of mirogabalin 5 mg was tolerable in patients with various degree of renal failure, however, a dose adjustment should be considered in patients with severe degree and end-stage renal failure [38].

In a mild or moderate hepatic dysfunction, a single dose of mirogabalin 15 mg was also tolerable [40].

2) Pharmacodynamics

Mirogabalin binds to and dissociates from the αδ subunits. Its binding ability is stronger for αδ-1 than for αδ-2 subunits. It also dissociates from the αδ-1 subunits more slowly than the αδ-2 subunits [6]. Therefore, it showed a potent and long-lasting binding to the αδ-1 subunits, which exhibited a therapeutic analgesic effect through the DRGs, and a low incidence of ADRs through the cerebellum due to weak and short-lasting binding to the αδ-2 subunits, with a wide safety index (a broad therapeutic window).

In a streptozotocin-induced diabetic model in rats, an effective analgesic dose (ED50) of mirogabalin was 4 times lower than that of pregabalin. The effective dose for central nervous system ADRs (ED50) occurs at about double the analgesic dose (ED50) in the Rotarod performance test, and at 10 times the analgesic dose (ED50) in a locomotor activity test. The safety index (effective ADR dose/effective analgesic dose) of mirogabalin is 2.1 and 10.0, compared to 0.4 and 4.2 for pregabalin, in the Rotarod performance and the locomotor activity test, respectively [6].

The most common ADRs in the 277 patients with DPNP developed in the nervous system (28.0%), such as dizziness (9.4%), somnolence (6.1%), headache (6.1%), and balance disorder (0.5%). Gastrointestinal ADRs (13.7%) included constipation (4.3%), nausea (4.0%), diarrhea (2.9%), and vomiting (2.9%). Generalized ADRs (13%) included peripheral edema (4.7%), fatigue (3.6%), weight gain (1.8%), urinary tract infection (2.9%), hyperglycemia (2.2%), and fall (1.4%) [30].

Table 3. Initial administration, dose titration, and final maintenance dose for mirogabalin in renal failure

| Stage of renal dysfunction | Renal dysfunction |
|---------------------------|------------------|
|                           | Mild degree      | Moderate degree | Severe degree   |
|                           | (90 > Clcr ≥ 60 mL/m) | (60 > Clcr ≥ 30 mL/m) | (30 > Clcr mL/m) |
| Initial dosage            | 5 mg twice a day | 2.5 mg twice a day | 2.5 mg once a day |
| Daily dose                | 10-30 mg         | 5-15 mg          | 2.5-7.5 mg      |
| Effective dose            | Minimal dose     | 10 mg twice a day | 5 mg once a day  |
|                           | Recommended dose | 15 mg twice a day | 7.5 mg once a day |

Available mirogabalin besylate tablets include 2.5, 5, 10, and 15 mg. The initial dose for adults without renal dysfunction is recommended starting from 5 mg, given orally twice a day. The dose is gradually increased by 5 mg, at an interval of at least a week, to 15 mg twice a day at the 3rd week [2,3,25-33].

Adapted from Kitano et al. [Pharmacological, pharmacodynamics, and clinical profile of mirogabalin besylate (Tarlige® tablets 2.5 mg ∙ 5 mg ∙ 10 mg ∙ 15 mg)]. Nihon Yakurigaku Zasshi 2019; 154: 352-61. Japanese [55].
3) Equianalgesic dose

Mirogabalin 30 mg showed similar pain relief, number needed to treat (NNT), and a slightly lower incidence of withdrawal ADRs, compared with pregabalin 600 mg, gabapentin over 1,200 mg, and duloxetine 60 mg [19].

CONCLUSIONS

Maladaptation and dysregulation of the α2δ-1 subunits of VGCCs may cause neuropathic pain [56]. Mirogabalin has a strong binding affinity to and slow dissociation property from α2δ-1 in the DRGs of the spinal cord, exhibiting a potent and prolonged analgesic therapeutic effect. It also has an weak binding affinity to and fast dissociation property from α2δ-2 in the Purkinje fibers of the cerebellum, exhibiting weak and short-lasting ADRs.

The starting dose is 5 mg twice a day in the 1st week, escalating to 10 mg in the 2nd week, and finally achieving a dose of 15 mg in the 3rd week. Dose adjustment is needed in patients with renal dysfunction. An equianalgesic daily dose for gabapentin over 1,200 mg or pregabalin 600 mg is mirogabalin 30 mg. Food restriction is not needed. Tramadol decreases a peak concentration of mirogabalin, while ethanol increases it. Lorazepam or ethanol increases the pharmacodynamic effects of mirogabalin. Coadministration of lorazepam or zolpidem increases somnolence. Tramadol increases nausea and ethanol increases headache in patients taking mirogabalin.

A progression from gabapentin to pregabalin originated from its rapid peak in blood concentration (3 hr to 1 hr) resulting from an increased absorption area expanding from the small intestine into the ascending colon, resulting in linear absorption [57]. Even though it is indicated for PHN and DPNP currently, it is also available for all types of central and peripheral neuropathic pain.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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