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# MODERN ASPECTS OF THE TREATMENT OF PAINFUL DIABETIC NEUROPATHY USING NEW GABAPENTINOID MIROGABALIN

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International Diabetes Federation (IDF) classifies diabetes mellitus (DM) as a rapidly progressing global pandemic of the 21st century. According to expert forecasts, by 2045 the prevalence of DM in the world population will reach 12.2%, which will correspond to 783.2 million people [1]. In 2020, the number of patients with type 2 diabetes mellitus (T2DM) worldwide was 445 million, while, according to the forecast data, in 2050 it will increase to 730 million if the prevalence remains unchanged, to 1.095 billion if the prevalence increases by 50%, to 657 million if the prevalence decreases by 10%, and to 1.153 billion if the prevalence corresponds to previous trends in most countries of the world during 1990–2019. In all scenarios, sub-Saharan Africa and low-income countries have the highest relative increase in the number of people with T2DM. In turn, T2DM is expected to "age" in the future, with the proportion of people with T2DM aged < 60 years declining from 5 of 10 in 2020 to 4 of 10 in 2050 under all scenarios [2]. It is also predicted that in the coming decades, the increase in the diagnosis of DM and prediabetes will correlate with an increase in the prevalence of its complications. This is particularly true of diabetic polyneuropathy (DPN), which has various forms, affects approximately one third of people with DM and can develop even in patients with prediabetes [3]. DPN is associated with significant morbidity, higher risk of physical and psychosocial impairment, increased risk of mortality and reduced quality of life, mainly due to neuropathic pain (NP) and foot ulcers. However, symptoms caused by DPN usually include, in addition to NP (often severe, affecting up to 30% of all individuals with DPN), paresthesias, dysesthesias and numbness of the distal lower extremities. On the other hand, an asymptomatic form of DPN can be observed in about 50% of patients with this disease. In such cases, the manifestation of DPN often occurs only at the stage of diagnosis of T2DM [4].

Unfortunately, DPN is still underdiagnosed and thus not treated properly in clinical prac-

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tice worldwide [5]. In general, the treatment of DPN should include three cornerstones:

1) treatment that acts on the cause, including lifestyle modification; intensive DM therapy aimed at near-normal glycemia; and multifactorial intervention to reduce cardiovascular risk;
2) pharmacotherapy focused on pathogenesis;
3) symptomatic treatment of NP [5–7].

The latter principle of DPN treatment deserves special attention from clinicians, as NP is quite difficult to treat, leading to an increased risk of comorbidities such as sleep disturbances, further reduced quality of life, polypharmacy, socioeconomic consequences (e.g. higher healthcare costs and reduced ability to work or perform daily activities), morbidity and mortality [8, 9]. The International Association for the Study of Pain (IASP) defines NP as pain caused by damage or disease of the somatosensory nervous system [10, 11]. Painful focal peripheral disorders are caused by pathological processes that involve one or more peripheral nerves or nerve roots [12]. Peripheral neuropathy alters the electrical properties of sensory nerves, which then leads to an imbalance between central excitatory and inhibitory signaling, leading to disruption of inhibitory interneurons and descending control systems. In turn, sensory signal transmission and disinhibition or facilitation mechanisms are altered at the level of dorsal horn neurons of the spinal cord. Previous preclinical studies have identified several anatomical, molecular, and electrophysiological changes from the periphery to the central nervous system (CNS) that result in enhanced function, providing a more detailed understanding of NP and its treatment principles. Increased excitation and loss of inhibition are evident in the periphery, spinal cord, and brain. These changes shift sensory pathways toward a state of hyperexcitability, and the sequence of changes over time from the periphery to the brain may contribute to the chronicity of NP. Ectopic activity in primary afferent fibers may play a key role in the pathophysiology of NP in the setting of peripheral nerve injury. Patients with painful DPN have demonstrated complete loss of ipsilateral spontaneous and evoked pain when treated with peripheral nerve block (with lidocaine, which blocks voltage-gated sodium channels) [12, 13]. Microneurographic studies have also revealed spontaneous activity — mainly in C fibers — associated with pain, suggesting a potential peripheral mechanism for NP [14, 15]. In general, the hyperexcitability underlying NP results from changes in ion channels, leading to increased excitability, signal transduction, and neurotransmitter release. Indeed, the crucial role of sodium channels is demonstrated by the loss or enhancement of pain in individuals with inherited channelopathies [16]. At the same time, there is an apparent loss of potassium channels, which normally modulate neural activity. If an afferent fiber is disconnected from the periphery due to trauma or damage, a loss of sensation will occur [17]. The remaining intact fibers are hyperexcitable, so-called excitable nociceptors [18]. As a result, the patient may experience constant pain and numbness. The altered impulses to the spinal cord, combined with increased calcium channel function (due to greater expression in nerve terminals), lead to increased neurotransmitter release and increased excitatory synaptic transmission in the nociceptive circuit. Thus, in recent years, the study of pharmacological effects on voltage-gated calcium channels (VGCCs) has been one of the main areas of intervention in patients with NP caused by DPN. Some VGCC ligands exhibit analgesic effects that are mediated by reducing calcium influx into CNS neurons. Such VGCC ligands include gabapentin and pregabalin, both of which are used worldwide as first-line drugs for the treatment of NP caused by DPN [19].

Gabapentin was first synthesized in 1977 in an attempt to obtain a structural analogue of gamma-aminobutyric acid (GABA) with a higher lipophilicity than the original neurotransmitter, increasing its ability to penetrate the CNS. However, it was found that this new compound does not act as a GABA mimetic and does not bind to GABA receptors. Years later, it was found that gabapentin binds with high affinity to the auxiliary α2-δ subunit of VGCC. It was used to treat refractory epilepsy in 1993. A more modern structural analogue of GABA, pregabalin, was synthesized in 1991 and approved for the treatment of NP and refractory epilepsy in 2004 and 2005, respectively [20, 21].

However, both of these pharmacological agents do not fully provide adequate therapeutic support for many patients with DPN. In addition, they exhibit a number of expected adverse reactions, such as dizziness, drowsiness, and weight gain, which significantly limits their widespread use in patients with DM complicated by DPN. It should be noted separately that many patients with DPN are not satisfied with the results of their treatment. This can be explained by a number of reasons, including insufficient pain relief, poor tolerability of therapeutic agents, and low analgesic response. Thus, the effectiveness of treatment decreases over time, and the need for additional therapy or dose increase becomes quite relevant. For the above reasons, patients with DPN need modern drugs that provide maximum efficacy with minimal adverse reactions that are well tolerated [19].

Mirogabalin is a novel oral selective ligand for the α2δ subunit of the CNS VGCC. This drug was specifically developed for the treatment of NP, including painful form of DPN [22]. Mirogabalin has a higher affinity for the α2δ-1 and α2δ-2 subunits than pregabalin, exhibits a lower dissociation rate from α2δ-1 than α2δ-2, and a lower dissociation rate from α2δ-1 compared to pregabalin. Since the α2δ-1 subunit of VGCC contributes to the analgesic effect, while the α2δ-2 subunit contributes to the CNS side effects, mirogabalin may have a longer analgesic effect and a greater safety margin with respect to CNS side effects [19, 20, 23].

Mirogabalin, the third known drug in the gabapentinoid family, was first approved in Japan in January 2019 for the treatment of peripheral neuropathy (PN) and received a general indication for the treatment of neuropathy, including chronic neuropathy (CN), in 2022. It was also approved in South Korea for the treatment of PN in 2020. In the same year, mirogabalin was also approved for the treatment of DPN and postherpetic neuralgia (PHN) in Taiwan, China. In 2022, mirogabalin was approved for the treatment of PN in Thailand. In June 2024, based on active observation in a phase 3 study involving Chinese patients with DPN, the Center for Drug Evaluation of the National Medical Products Administration (NMPA) approved mirogabalin for the indication of DPN in China. Currently, numerous studies of mirogabalin as a treatment for DPN, PHN, postoperative neuropathy, and chemotherapy-induced peripheral neuropathy are being conducted in Asian countries [24].

It should be emphasized that since the development of mirogabalin, the efficacy of this drug has been studied in many clinical trials. In a double-blind, multicenter, placebo-controlled phase 3 trial (NCT02318706), mirogabalin was found to have balanced efficacy and safety in Asian patients (Japan, Korea, Taiwan (China), and Malaysia) with dose-dependent pain relief outcomes. A total of 834 patients ≥ 20 years of age with type 1 diabetes mellitus (T1DM) or T2DM and concomitant DPN of at least 6 months duration were randomized to receive mirogabalin 15 mg/day (n = 164), 20 mg/day (10 mg twice daily; n = 165), and 30 mg/day (15 mg twice daily; n = 165), including 1–2 weeks of stepwise dose titration and placebo (n = 330). At week 14, the primary endpoint of average daily pain score (ADPS) from baseline was -1.34, -1.47, and -1.81 for mirogabalin 15, 20, and 30 mg/day, respectively, and -1.31 for placebo. The reduction in APDS began at week 1 in all mirogabalin treatment groups, including one that was significantly greater for 30 mg/day compared to placebo. Mirogabalin 30 mg/day showed a significantly higher response rate of ≥ 50% improvement in APDS compared to placebo (p = 0.0048). There was also a significantly better change from baseline to week 14 in the visual analogue scale (VAS) of the Short Form of the McGill Pain Questionnaire (SF-MPQ) and the average daily sleep interference score (ADSIS) as assessed by patients on mirogabalin 30 mg/day (p = 0.0018 and 0.0001). In the patient global impression of change (PGIC) > 30 mg/day, «minimal improvement or better» (score ≤ 3: 70.3% vs. 58.8%, p = 0.0129) or «significant improvement or better» (score ≤ 2: 40.0% vs. 26.1%, p = 0.0016) were recorded. The results suggest an improvement in quality of life with patient satisfaction [26].

In an open-label, phase 3 extension study (NCT02318706), 214 patients from Japan, Korea, and Taiwan (China) received mirogabalin for 52 weeks (4-week titration of 5 mg twice daily followed by 48 weeks of variable dosing of 10 or 15 mg twice daily). VAS scores (mean change: -9.8) and other SF-MPQ subscales (sensory

score: -1.2; affective score: -0.3; global score: -1.5; current pain intensity: -0.2) were reduced from baseline to week 52, demonstrating the long-term analgesic effects of mirogabalin in patients with DPN [24].

A multicenter, randomized, double-blind, phase 3 trial (NCT04094662) in Chinese patients ≥ 18 years of age with T1DM or T2DM also examined the efficacy of mirogabalin in DPN. A total of 393 patients were randomized to receive mirogabalin or placebo for a 2-week titration period of 5 or 10 mg twice daily and a 12-week fixed-dose period of 15 mg twice daily. The change from baseline in weekly ADPS scores at week 14 was the primary endpoint. Mirogabalin produced significant improvement compared with placebo ($p = 0.0301$). The response rates of ≥ 30% (54.1% vs. 46.2%) and ≥ 50% (29.1% vs. 26.4%) reduction in APDS from baseline to week 14 were numerically higher in the mirogabalin group compared with placebo, without significance, which may be due to the high placebo response rate and high baseline scores in the placebo group (6.09 vs. placebo and 5.60 in Asian patients) [26]. Patients receiving mirogabalin improved on the VAS SF-MPQ (-3.3 vs. placebo; $p = 0.0929$). Notably, the percentage of PGIC as «minimal improvement or better» (87.2% vs. 79.2%, $p = 0.0341$) and «much or very much improvement» (63.8% vs. 42.6%, $p < 0.0001$) was higher in those receiving mirogabalin than in those receiving placebo. Mirogabalin demonstrated significant changes from baseline to week 14 in the ADSIS (least squares mean (LSM) vs. placebo: −0.45, $p = 0.0073$), index score (0.0291, $p = 0.0107$), and VAS (2.8, $p = 0.0457$) of the EuroQol 5 Dimensions 5 Levels (EQ-5D-5L). Thus, mirogabalin was shown to be safe and effective in Chinese patients with DPN, as well as in Asian patients from other countries/regions.

In a randomized, double-blind, placebo-controlled phase 2 trial (NCT01496365), 913 US patients ≥ 18 years of age with T1DM or T2DM (HbA1c ≤ 10%) and DPN for ≥ 6 months were randomized to receive mirogabalin 5 mg/day (5 mg once daily), 10 mg/day (10 mg once daily), 15 mg/day (15 mg once daily), 20 mg/day (10 mg twice daily), and 30 mg/day (15 mg twice daily) in the treatment group; pregabalin 300 mg/day treatment group; or placebo group. At week 5, the mean changes from baseline in ADPS were -2.0, -2.3, -2.7, -2.6, and -2.8 for the escalating dose of mirogabalin, -1.8 for pregabalin, and -1.9 for placebo. The differences in LSM were statistically significant compared to placebo for mirogabalin 15, 20, and 30 mg/day (-0.94, -0.88, and -1.01, $p < 0.05$) and compared to pregabalin for mirogabalin 15 and 30 mg/day (-0.89 and -0.96, $p < 0.05$). Mirogabalin 15 and 20 mg/day demonstrated significantly higher percentages of ≥ 30% reduction in ADPS (66.7% and 60.7%) from baseline to week 5 compared with pregabalin (38.0%, $p < 0.05$) and placebo (41.7%, $p < 0.05$); a greater percentage of patients receiving 15, 20, and 30 mg/day of mirogabalin had a significant ≥ 50% reduction (39.2%, 42.9%, and 43.9%) compared with placebo (24.1%) [26, 27].

In addition, significant reductions in ADSIS were observed in the mirogabalin 15, 20, and 30 mg/day groups (-2.97, -2.52, and -2.69) compared with placebo (-1.98, $p < 0.05$), and in the mirogabalin 15 mg/day group compared with pregabalin (-1.94, $p < 0.05$). In the modified Brief Pain Inventory (BPI), the subscales of impact on daily functioning (-2.58 vs. -1.58), worst pain intensity (-2.96 vs. -1.93), least pain intensity (-1.95 vs. -1.19), and average pain intensity (-2.32 vs. -1.55) were improved more significantly with mirogabalin 30 mg/day than with placebo. Significant improvement in PGIC as «minimal improvement or better» was observed in the 5, 10, and 30 mg/day groups and «significant or very significant improvement» in all mirogabalin dose groups compared to placebo ($p < 0.05$). Available evidence supports the use of high-dose mirogabalin compared to pregabalin up to a certain point for the treatment of patients with DPN [28].

A double-blind, randomized, placebo-controlled phase 2 trial (NCT01504412) conducted in Japan, South Korea, and Taiwan (China) evaluated the effect of mirogabalin compared with pregabalin in the treatment of painful DPN caused by previously ineffective treatments available at the time of the study. In this trial, patients ($N = 450$) ≥ 20 years of age with T1DM or T2DM and existing DPN were randomized to receive mirogabalin 10, 20, or 30 mg/day; pregabalin 300 mg/day twice daily; or placebo for 7 weeks (dose escalation every

1 week). Although the placebo-adjusted LSM difference in change from baseline in ADPS at week 7 was –0.4 [–1.0, 0.2] in the 5 mg twice daily group, –0.4 [–0.9, 0.2] in the 10 mg twice daily group, –0.3 [–0.9, 0.3] in the 15 mg twice daily group, and 0.0 [–0.5, 0.5] in the pregabalin group. For secondary endpoints, mirogabalin at a dose of 30 mg/day significantly improved VAS scores [LSM: -7.4 (-13.0, -1.8), p = 0.0093] and SF-MPQ total score [LSM: -1.9 (-1.3, -0.4), p = 0.0002] and ADSIS [LSM: -0.9 (-1.3, -0.4), p = 0.0002] [19, 24].

A meta-analysis of studies of the efficacy of mirogabalin treatment included three randomized controlled trials in 1732 patients with DPN [19]. Mirogabalin demonstrated significantly greater efficacy in reducing ADPS at 3, 4, and 5 weeks, and a significant increase in the proportion of patients with ≥ 30% and ≥ 50% reduction in ADPS was also found with mirogabalin compared with pregabalin and placebo [24].

## CONCLUSIONS

Therefore, since the question of effective therapeutic approaches for the treatment of NP, especially caused by DPN, is only partially resolved, a new gabapentinoid, mirogabalin, has been developed that selectively binds to α2δ subunits through a unique mechanism of slower dissociation from α2δ-1 than α2δ-2 and is a potential alternative for the treatment of NP. Although the global experience with mirogabalin is still in its infancy, this model has proven its efficacy and the current and future results of its use in patients with NP are certainly promising. As already reported, several phase 3 studies have demonstrated the efficacy of mirogabalin in patients with DPN and PHN, which has ensured clinical use in many countries/regions in Asia. It is possible that the results of subsequent clinical studies in other countries of the world, such as in Europe, will be able to further demonstrate the safety and efficacy of mirogabalin. These observations should also focus on exploring flexible doses within the effective range of 15-30 mg/day for mirogabalin that are consistent with clinical practice, with the hope of achieving better outcomes. In addition, comparative studies between mirogabalin and pregabalin, gabapentin, duloxetine, milnacipran, and amitriptyline will prove valuable in establishing the place of mirogabalin among other analgesics for the treatment of NP in many clinical situations and will help to focus physicians' attention on additional possibilities for personalizing therapy for these patients.

In preparing this review, a literature search was conducted in MEDLINE (via PubMed), EMBASE, the Cochrane Central Database, and the Web of Science database from their inception to February 2025.

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Diabetes mellitus (DM) is a rapidly growing global health challenge, with its prevalence projected to increase significantly by 2045. Type 2 diabetes mellitus (T2DM) accounts for the majority of cases and is expected to continue increasing, particularly in low-income countries. As DM and prediabetes become more widespread, the prevalence of their complications, including diabetic polyneuropathy (DPN), is also expected to rise. DPN affects approximately one-third of people with DM and is a leading cause of neuropathic pain (NP), foot ulcers, and reduced quality of life. Despite its significant burden, DPN remains underdiagnosed and undertreated worldwide. Current DPN management strategies focus on three key principles: addressing the underlying cause through glycemic control and lifestyle modification, pharmacotherapy targeting pathogenesis, and symptomatic treatment of NP. NP in DPN is notoriously difficult to manage, often requiring multiple therapeutic approaches. Gabapentinoids such as gabapentin and pregabalin are commonly used first-line treatments, but their effectiveness is often insufficient, and they can cause adverse effects, including dizziness, drowsiness, and weight gain, limiting their use in many patients. Mirogabalin, a novel gabapentinoid, selectively binds to the α2-δ subunit of voltage-gated calcium channels (VGCCs) with a unique pharmacokinetic profile, leading to prolonged analgesic effects and potentially fewer central nervous system side effects compared to pregabalin. Mirogabalin has been approved for the treatment of NP, including DPN, in several Asian countries. Clinical trials, including multiple phase 3 studies, have demonstrated its efficacy and safety in patients with DPN, showing significant reductions in pain scores and improvements in patient-reported outcomes. Additionally, mirogabalin has shown promise in improving sleep disturbances and quality of life, which are often affected in patients with DPN. While global experience with mirogabalin is still limited, its potential as an alternative treatment for NP in DPN is promising. Ongoing and future clinical trials, particularly in non-Asian populations, are expected to further clarify its role in neuropathic pain management and expand its availability worldwide. In preparing this review, a literature search was conducted in MEDLINE (via PubMed), EMBASE, the Cochrane Central Database, and the Web of Science database from their inception to February 2025.

Keywords: diabetes mellitus, diabetic polyneuropathy, neuropathic pain, mirogabalin, review.

# СУЧАСНІ АСПЕКТИ ЛІКУВАННЯ БОЛЬОВОЇ ДІАБЕТИЧНОЇ НЕЙРОПАТІЇ З ВИКОРИСТАННЯМ НОВОГО ГАБАПЕНТИНОЇДУ МІРОГАБАЛІНУ

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Цукровий діабет (ЦД) є глобальною проблемою охорони здоров'я, яка швидко зростає, і, за прогнозами, його поширеність значно зросте до 2045 року. Цукровий діабет 2 типу (ЦД 2) є причиною більшості випадків ЦД, і очікується, що він продовжуватиме зростати, особливо в країнах з низьким рівнем доходу. Оскільки ЦД і прediабет стають більш розповсюдженими, очікується, що поширеність їх ускладнень, включаючи діабетичну полінейропатію (ДПН), також зросте. ДПН вражає приблизно одну третину осіб із ЦД і є основною причиною нейропатичного болю (НБ), виразок стопи та зниження якості життя. Незважаючи на значний тягар, ДПН залишається недостатньо діагностованою та не в повній мірі лікується у всьому світі. Сучасні стратегії лікування ДПН зосереджені на трьох ключових принципах: усунення основної причини шляхом контролю глікемії та модифікації способу життя, фармакотерапія, спрямована на патогенез, і симптоматичне лікування НБ. Відомо, що НБ при ДПН важко лікується, часто потребуючи кількох терапевтичних підходів. Габапентиноїди, такі як габапентин і прегабалін, зазвичай використовуються в лікуванні першої лінії НБ, але їх ефективність часто недостатня, і вони можуть спричинити побічні ефекти, включаючи запаморочення, сонливість і збільшення ваги, що обмежує їх використання у багатьох пацієнтів. Мірогабалін, новий габапентиноїд, вибірково зв'язується з α2-δ субодиницею потенціалзалежних кальцієвих каналів (VGCC) з унікальним фармакокінетичним профілем, що призводить до тривалого знеболюючого ефекту та потенційно меншої кількості побічних ефектів з боку центральної нервової системи порівняно з прегабаліном. Мірогабалін був схвалений для лікування НБ, у тому числі, ДПН, у кількох країнах Азії. Клінічні випробування, включаючи численні дослідження фази 3, продемонстрували його ефективність і безпеку у пацієнтів з ДПН, продемонструвавши значне зниження показників болю та покращення результатів, про які повідомляють пацієнти. Крім того, мірогабалін демонструє позитивні результати в плані покращення порушень сну та якості життя, які часто спостерігаються у пацієнтів із ДПН. Хоча світовий досвід застосування мірогабаліну все ще обмежений, його потенціал як альтернативного лікування НБ при ДПН є багатообіцяючим. Очікується, що поточні та майбутні клінічні випробування, особливо в неазіатських популяціях, додатково прояснять його роль у лікуванні НБ та розширять його доступність у всьому світі. Під час підготовки цього огляду було проведено пошук літератури в MEDLINE (через PubMed), EMBASE, Центральній базі даних Кокрана та базі даних Web of Science від їх створення до лютого 2025 року.

Ключові слова: цукровий діабет, діабетична полінейропатія, нейропатичний біль, мірогабалін, огляд.