EXTENDED EDITORIAL

A New Era of Pharmacotherapy for Neuropathic Pain with Mirogabalin

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What should we, as healthcare professionals, aim for in the treatment of chronic pain? The words written by Ambroise Paré—"to cure sometimes, to relieve often, to comfort always"[1]—show an important philosophy that remains relevant to modern pain management. In pain management, in addition to medical interventions such as nerve blocks and pharmacotherapy, it is essential to listen to the patient's complaints, show empathy, and strive to understand the full extent of the suffering they experience. Among these approaches, pharmacotherapy is a cornerstone of chronic pain management, and it is impossible to discuss pain management without it.

On the other hand, the goal of pharmacotherapy for chronic pain is not merely to reduce pain intensity. Pain includes not only sensory aspects but also multifaceted elements such as emotions, cognition, and behavior. Therefore, even if a medication improves scores on the numerical rating scale (NRS) or visual analog scale (VAS), treatment will not necessarily be satisfactory for the patient if daily life is impaired by side effects such as drowsiness, dizziness, or unsteadiness.

In this editorial, I outline pharmacotherapy for chronic pain—particularly neuropathic pain—focusing on Ca^{2+} channel $\alpha 2\delta$ ligands, their efficacy and safety, and approaches to enhance patient satisfaction in clinical practice.

Pathophysiology and pharmacotherapy of chronic pain

Pain does not arise solely from the transmission of noxious stimuli from the periphery to the central nervous system. While nociceptive stimuli are received and transmitted to the central nervous system via the ascending pain transmission system, this transmission is modulated by the descending pain inhibitory system. Furthermore, sensations, emotions, cognition, reactions, and behavior mutually influence one another to form the final experience of "pain." In chronic pain, it is necessary to consider the possibility that this complex pain information processing mechanism itself has undergone changes.

The pathophysiology of pain includes nociceptive pain defined as pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors; neuropathic pain defined as pain caused by a lesion or disease of the somatosensory nervous system; and pain in which psychosocial factors play a significant role and cannot be fully explained by physical abnormalities alone. Recently, nociplastic pain, defined as pain that

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arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain, has also emerged. In actual patients with chronic pain, these categories are not always clearly separable, and it is not uncommon for multiple pathophysiological mechanisms to coexist.

For this reason, when prescribing medication, it is necessary to select drugs after evaluating the underlying pathophysiology as thoroughly as possible. For example, non-steroidal anti-inflammatory drugs (NSAIDs) are used for nociceptive pain, while treatment options for neuropathic pain include Ca^{2+} α2δ channel ligands, tricyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors (SNRIs).

The ability to select medications based on the specific pathological condition represents a major advancement in pain management. However, precisely because the range of available medications has expanded, it is now crucial to consider not only "what to administer" but also "how to administer it, to what dosage, when to evaluate the response, and when to reassess the treatment."

Neuropathic pain and ca^{2+} channel α2δ ligands

Pharmacotherapy for neuropathic pain has advanced significantly over the past 20 years. As international treatment guidelines were revised in 2003[2], 2007[3], and 2015[4], Ca^{2+} channel α2δ ligands have consistently been positioned as first-line treatments. In the 2025 guidelines for pharmacotherapy and non-invasive neuromodulation for neuropathic pain[5], Ca^{2+} channel α2δ ligands are also identified as one of the primary pharmacological treatments. On the other hand, opioid analgesics are now viewed with greater caution than in the past and are categorized as options for use in specific patients.

Ca^{2+} channel α2δ ligands are thought to exert their analgesic effects by binding to the α2δ subunit of voltage-dependent Ca^{2+} channels and inhibiting the release of excitatory neurotransmitters from presynaptic terminals[6-8]. However, Ca^{2+} channel α2δ ligands also present significant challenges. Typical side effects include somnolence, dizziness, unsteadiness, falls, edema, and weight gain; these can have a significant impact on activities of daily living, particularly in the elderly. Since many patients with neuropathic pain are elderly and often have impaired renal function or are on polypharmacy, it is essential to select medications that consider not only efficacy but also tolerability.

Pharmacological characteristics of mirogabalin

Mirogabalin is a drug classified as a Ca^{2+} channel α2δ ligand. One of its characteristics is the difference in dissociation rates for the α2δ-1 and α2δ-2 subunits[9]. While α2δ-1 is involved in analgesic effects, α2δ-2 has been suggested to be associated with adverse effects on the central nervous system; mirogabalin exhibits different binding characteristics for these two subunits.

Mirogabalin is already listed as a first-line treatment—alongside other Ca^{2+} channel α2δ ligands such as pregabalin and gabapentin—in the international association for the study of pain (IASP)'s guidelines for pharmacotherapy and non-invasive neuromodulation of neuropathic pain[5].

This is clinically significant. In the treatment of chronic pain, the fact that a single drug is ineffective or cannot be continued due to side effects does not necessarily mean that the entire pharmacological class is ineffective. The existence of multiple options within the same class enables individualized treatment that takes into account efficacy and tolerability for each patient.

Clinical Data on mirogabalin

The efficacy and safety of mirogabalin for neuropathic pain have been demonstrated in numerous clinical trials[10,16]. Clinical trials of mirogabalin have included international Phase III trials conducted in Asia, targeting conditions such as diabetic peripheral neuropathic pain (DPNP)[10], postherpetic neuralgia (PHN)[11], and central neuropathic pain (CNP)[12,13].

In the phase III trial for DPNP[9], the change from baseline in the average daily pain score (ADPS) at week 14 was –1.31 in the placebo group, –1.47 in the mirogabalin 20 mg/day group, and –1.81 in the

30 mg/day group; a statistically significant improvement was observed in the 30 mg/day group compared to the placebo group. Furthermore, improvements were observed not only in pain but also in sleep disturbances. In the phase III trial for PHN[10], the change in ADPS at Week 14 was –1.20 in the placebo group, –1.68 in the mirogabalin 20 mg/day group, and –1.97 in the 30 mg/day group, confirming pain relief.

Additionally, efficacy has been demonstrated for CNP in a trial targeting post-spinal cord injury neuropathic pain[12]. Furthermore, in long-term administration trials, efficacy and safety were demonstrated in a diverse patient population, including not only post-spinal cord injury neuropathic pain but also post-stroke pain and CNP associated with Parkinson's disease[13]. These results suggest that mirogabalin may serve as a treatment option for a wide range of neuropathic pain, from peripheral to central.

From "effective medications" to "sustainable medications"

In the treatment of chronic pain, it is necessary to consider the balance between efficacy and safety, rather than evaluating them separately. In clinical trials of DPNP[10], typical side effects observed with mirogabalin administration include somnolence, vertigo, peripheral edema, and weight gain. Particularly in the elderly, even mild drowsiness or dizziness can lead to falls or fractures. Even if pain is alleviated, it is difficult to say that the patient's well-being has improved if drowsiness prevents them from going out. Conversely, even if pain does not completely disappear, if sleep improves, walking distance increases, and going out or working becomes possible, the treatment holds great value for the patient. This perspective is at the heart of "pharmacotherapy focused on patient satisfaction."

In real-world clinical practice, "whether the effective dose can be achieved" is crucial.

There is a significant gap between clinical trials and real-world clinical practice. Actual patients often have underlying conditions such as advanced age, impaired renal function, or polypharmacy, and it is not uncommon for doses to be limited out of concern for side effects, preventing the use of a sufficient dosage. The MIROP study[14], which examined the switch from pregabalin to mirogabalin, is particularly interesting in considering this issue. In the MIROP study, the mean age of enrolled patients was 66.1 years, the VAS score at enrollment was 67.4 mm, 87.5% were taking some form of concomitant medication, and 46.1% were also receiving non-pharmacological therapies. In other words, this was a patient population closely resembling real-world clinical practice.

In this study, by adjusting the dose according to renal function, many patients were able to take mirogabalin at an effective dose or the maximum dose. After switching to mirogabalin, side effects specific to Ca^{2+} channel $\alpha2\delta$ ligands—such as somnolence, dizziness, and peripheral edema—were largely absent; even when they did occur, they were mild. In addition, a further significant reduction in VAS score was observed following the switch to mirogabalin.

It is important to note that these results do not support the conclusion that "mirogabalin is more potent than pregabalin." Many patients enrolled in the MIROP study were receiving relatively low doses of pregabalin and had not achieved adequate pain relief. Rather, what is important is the possibility that changing medications allowed for the administration of a Ca^{2+} channel $\alpha2\delta$ ligand at an effective dose, which consequently led to pain relief.

Application to neuropathic pain associated with musculoskeletal disorders

In clinical practice, neuropathic pain does not always occur in isolation. Particularly in conditions such as lumbar spinal stenosis, nociceptive pain and neuropathic pain may coexist, and medications with a single mechanism of action may not be sufficiently effective on their own.

The MiroTAS study[15], compared a group receiving NSAIDs alone with a group receiving additional mirogabalin in patients with lumbar spinal stenosis who continued to experience lower limb pain despite NSAID therapy. The study participants were relatively elderly, had a long duration of pain, and represented a population reflective of real-world clinical practice. After 12 weeks, the change in lower limb pain VAS score was significantly improved with

the addition of mirogabalin, and the between-group difference compared to NSAIDs monotherapy was 10.2 mm.

These results demonstrate the importance of not classifying patients with chronic pain according to a single pain mechanism and treating them with a single agent, but rather of evaluating the multiple pain mechanisms present in each patient and combining treatments tailored to each one.

What is drug therapy that enhances patient satisfaction?

In the management of chronic pain, it is not realistic to make "eliminating pain entirely" the sole treatment goal. What patients truly desire is not merely an improvement in their pain score, but an improvement in their quality of life itself—including sleep, walking, work, housework, hobbies, and social participation.

Therefore, when initiating drug therapy, it is important to discuss with the patient not only "how much to reduce the pain," but also "what the patient considers a successful outcome in terms of what they will be able to do as a result of the medication."

To achieve this, treatment should begin with a low dose and be gradually increased appropriately while monitoring efficacy and side effects. Renal function, age, and concomitant medications must be taken into account. Assess not only pain intensity but also sleep, activity level, activities of daily living (ADL), and quality of life (QOL). Furthermore, if the patient does not derive meaningful benefit from treatment even after an adequate duration and dosage, do not continue treatment indefinitely; instead, reevaluate the treatment plan.

In other words, in pharmacotherapy for chronic pain, it is important not only to "start" treatment but also to consider from the outset how to evaluate the medication, under what conditions to continue it, and when to reduce the dose, switch medications, or discontinue treatment.

Ca^{2+} channel α2δ ligands play an important role in the treatment of neuropathic pain; while some patients derive significant benefit from them, others are unable to continue treatment due to side effects or insufficient efficacy. Mirogabalin, as a new α2δ ligand with distinct pharmacological properties, is likely to broaden the treatment options for neuropathic pain. It has been emphasized that mirogabalin strikes a balance between efficacy and safety and has the potential to serve as an alternative treatment option for neuropathic pain.

However, the ultimate goal of chronic pain treatment is not simply to administer medication. What is important is to continuously assess whether the patient is deriving meaningful benefits. It is necessary to consider not only "which medication to choose" but also "to what extent to increase the dosage," "what criteria to use to assess efficacy," "when to reassess treatment," and "when to discontinue medication."

Even for patients whose pain cannot be eliminated, it is possible to alleviate their pain, improve sleep and physical function, and help them move closer to the lifestyle they desire. Medication is one means to that end, and future chronic pain treatment must prioritize the patient's well-being as the outcome.

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