Management of neuropathic pain

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Abstract
Neuropathic pain is intractable pain caused by damage to the nervous system. Recent approval and expansion of the indications of a series of drugs are expected to improve the treatment strategies for neuropathic pain. Here, we present an outline of pain transmission pathways and relevant pharmacological effects, along with points to consider in the use of neuropathic pain medications according to the guidelines of Japan Society of Pain Clinicians. The content of this article is almost similar to my other Japanese article that was published in the Journal of the Japanese Society of Internal Medicine. Although complete recovery from pain may be difficult, pharmacotherapy can relieve pain, thereby improving the patients’ quality of life.

KEYWORDS
duloxetine, neuropathic pain, pregabalin, tramadol, tricyclic antidepressants

1 | INTRODUCTION

The International Association for the Study of Pain (IASP) defines “pain” as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” The IASP classifies pain into two main categories: nociceptive pain and neuropathic pain. Neuropathic pain, as outlined here, is defined as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system.

The morbidity rate of neuropathic pain is estimated to be approximately 1%-7% in developed countries, and several million people in Japan suffer from this form of pain. While neuropathic pain may occur due to various diseases and ailments, the most common causes are peripheral neuropathy of varying origins, spinal cord disorder, multiple sclerosis, and stroke. These underlying diseases are often intractable, and the accompanying neuropathic pain also requires prolonged treatment. Patients with neuropathic pain usually do not respond well to a wide range of therapies and often have concomitant psychiatric symptoms, such as depression, leading to a marked deterioration of the patients’ quality of life.

However, analgesic drugs have been steadily launched in the market or approved for additional indications since 2010, and therapeutic options for neuropathic pain are expanding. In Europe and the United States, the European Federation of Neurological Societies (EFNS) and other sources have proposed therapeutic guidelines, which are useful in clinical practice. In 2011, the Japan Society of Pain Clinicians has also issued practical pharmacotherapy guidelines, which will be useful in routine clinical practice.

2 | PAIN TRANSMISSION AND PHARMACOLOGY

Pain is transmitted by two types of afferent sensory fibers, that is, Aδ and C fibers, from cutaneous receptors to the second-order neurons at the dorsal horn of the spinal cord, via first-order neurons with cell bodies in the spinal cord dorsal root ganglion. Then, it ascends the lateral spinothalamic tract to the thalamus, where the third-order neurons are projected from the thalamus to the cerebral cortex (Figure 1). Two types of pain systems, that is, the lateral and medial systems, send projections to the cerebral cortex. In the lateral system, neurons are projected to the somatosensory cortex; in the medial system, they are projected to the anterior cingulate cortex and insular cortex. The lateral system is involved in recording pain intensity and the site of transmission; the medial system is involved in pain-associated anxiety and fear.
At nerve terminals in the spinal cord dorsal horn, N-type voltage-dependent calcium channels release neurotransmitters, such as glutamate and substance P, which act on postsynaptic receptors. This step is regulated by both local inhibitory interneurons and descending projection neurons from the brainstem to the spinal cord, which is a pharmacologically important target site. Major inhibitory neurotransmitters include opioid peptides, norepinephrine, glycine, and γ-aminobutyric acid (GABA) (Figure 2).

For instance, opioid receptors, which are 7-transmembrane-spanning G protein-coupled receptors, are categorized into three subtypes (μ, δ, and κ receptors). The μ opioid receptor plays an important role in the analgesic action of morphine. Opioids act not only on the central end of the primary sensory neuron, but also on the brain, brainstem, and spinal cord.

Norepinephrine is released from the projection neurons descending from the brainstem to the spinal cord and acts on α2-adrenergic receptors. Serotonin is also released from these descending projection neurons and is thought to act on several types of receptors, including 5-HT2a receptors.

### 3 | PATHOLOGY AND PATHOGENIC MECHANISM OF NEUROPATHIC PAIN

Allodynia, hyperalgesia, and spontaneous pain are characteristic symptoms of neuropathic pain. Allodynia is a condition in which mild touch, such as contact with clothing, causes pain. This condition seems to involve thick (Aβ) afferent fibers, which mediate tactile sensation, but not pain, under normal conditions. Hyperalgesia and spontaneous pain are considered to be associated with damaged peripheral sensory neurons with increased excitability, evoking continuous firing. Such persistent noxious input from the periphery leads to increased excitability of spinal cord dorsal horn neurons, a condition referred to as central nervous system sensitization, and the pain system then becomes hypersensitive. Although pain is essential for body protection, nociception must be appropriately controlled.

### 4 | PRACTICE OF NEUROPATHIC PAIN

When dealing with a patient presenting with pain and numbness, the physician should consider the following questions at the interview: the site, intensity, course, nature, occurrence pattern, known triggers, and factors worsening and relieving the pain, as well as the degree of impact that the pain has on the patient’s daily and social life. In the early phase of management, neurological findings are essential, but care should be exercised in examination of the site of numbness and pain, as this in itself may induce abnormal pain.

When prescribing medication, the physician should seek understanding of the patient’s general condition through a review of the past medical history and concomitantly used drugs. It is also useful to understand the patient’s lifestyle, including driving and operation of machinery, when deciding on a therapeutic strategy.

Because most drugs require some time to become effective, medication should be continued for at least several weeks before assessing its therapeutic efficacy. Pain assessment is performed using a visual analogue scale (VAS) or face-rating scale (Figure 3). A pain behavioral questionnaire table is used to rate the restriction of daily activities by pain.
In Table 1, an algorithm for the treatment of neuropathic pain is shown.

**TABLE 1** Algorithm for pharmacotherapy of neuropathic pain according to the guidelines of Japan Society of Pain Clinicians

| First-line therapy | Consider the following drugs only for postherpetic neuralgia and diabetic polyneuropathy |
|--------------------|------------------------------------------------------------------------------------------|
| Tricyclic antidepressants | | |
| Nortriptyline | Postherpetic neuralgia |
| Amitriptyline | Formulation containing extract from cutaneous tissue of rabbits inoculated with vaccinia virus |
| Imipramine | Diabetic polyneuropathy |
| Ca$^{2+}$ channel α2δ ligands | SNRI: duloxetine |
| Pregabalin | Antiarrhythmic: mexiletine |
| Gabapentin | Aldose reductase inhibitor: epalrestat |
| | | |
| Second-line therapy | Trigeminal neuralgia |
| Formulation containing an extract of cutaneous tissue of rabbit inoculated with vaccinia virus | First-line therapy |
| SNRI: duloxetine | Carbamazepine |
| Antiarrhythmic: mexiletine | Second-line therapy |
| | Lamotrigine |
| | Baclofen |
| | | |
| Third-line therapy | | |
| Narcotic analgesics | | |
| Fentanyl, morphine, oxycodone | | |
| Tramadol, buprenorphine | | |

5 PHARMACOTHERAPY

In Table 1, an algorithm for the treatment of neuropathic pain is shown.

5.1 Tricyclic antidepressants

Tricyclic antidepressants (TCAs) are thought to exert an antidepressant effect by inhibiting reuptake of noradrenaline and serotonin. The mechanism of analgesic action is speculated to activate the descending inhibitory system, although this has not yet been proven. TCAs exert an analgesic action at doses lower than that required for antidepressant action, independently of their antidepressant action. Much evidence has been accumulated in randomized placebo-controlled studies evaluating amitriptyline and nortriptyline in the treatment of neuropathic pain, including postherpetic neuralgia (PHN) and diabetic polyneuropathy (DPN). Because there are concerns about the adverse effects of these drugs, due to their anticholinergic effect, TCAs should be started at a low dose, for example, 10-25 mg, particularly in elderly patients, and should be up-titrated to 50-100 mg under careful monitoring of the patient’s condition TCA therapy is occasionally effective even at a low dose. TCAs have a long history of use with a low risk of serious adverse reactions, but precautions should be exercised in patients with concomitant diseases, such as heart disease, glaucoma, and prostatic hyperplasia in particular. Dry mouth and constipation are frequently reported, but are not of great clinical significance at the low doses used in the treatment of neuropathic pain.

5.2 Calcium channel α2δ ligands

Gabapentin and pregabalin are GABA analogs that have structural similarity to GABA. These do not bind to the GABA receptor, but rather bind to the voltage-dependent calcium channel auxiliary subunit α2δ, with a high affinity. These α2δ ligands are thought to exert an analgesic effect by suppressing the presynaptic calcium influx and inhibiting the release of excitatory neurotransmitters.

As compared with gabapentin, pregabalin shows a higher bioavailability, with a linear pharmacokinetics. However, gabapentin may be more effective in some patients. Both agents have been found to be effective for the treatment of the numbness and pain associated with PHN and DPN in many clinical studies in and outside of Japan.

In Japan, pregabalin was first approved for PHN with national health insurance coverage, in April 2010. Its indications have been sequentially expanded to “peripheral neuropathic pain” in October 2010, “fibromyalgia-associated pain” in June 2012, and “neuropathic
Pregabalin and gabapentin are mostly excreted in unmetabolized (unchanged) form by the kidney, demonstrating a simple pharmacokinetic profile. Therefore, their doses can be adjusted depending on the renal function of the individual, to reduce the risk of adverse reactions. Because elderly people and low-body-weight individuals have a lower muscle mass and a lower serum creatinine level, eGFR should be calculated in the assessment of renal function. In addition, eGFR varies depending on physical conditions, such as dehydration, and concomitantly used medications, including NSAIDs; thus, these factors should be taken into consideration.

Pregabalin and gabapentin are unlikely to cause drug-drug interactions and are generally well tolerated. Common adverse reactions include dizziness, lightheadedness, sleepiness, and edema, and there are reports of automobile accidents in individuals taking these medications, although infrequently.  These adverse reactions can be managed by starting the treatment at a low dose. The package insert states that pregabalin should be administered at a daily dose of 150 mg in two divided doses, with subsequent up-titration to 300 mg daily. However, the author routinely uses a starting daily dose of 50-75 mg (taken in divided doses, with subsequent up-titration to 300 mg daily. However, the author routinely uses a starting daily dose of 50-75 mg (taken in divided doses, with subsequent up-titration to 300 mg daily). It should be noted that tramadol monotherapy has been approved for cancer pain in 2010. In addition, it was also approved for chronic pain in 2013. Moreover, we can prescribe a sustained-release tramadol in 2015.

5.3 | Serotonin-noradrenalin reuptake inhibitor (SNRI)

Duloxetine is an antidepressant that has analgesic effects in DPN. This is attributed to activation of the descending pain inhibitory system by serotonin and noradrenalin.

Duloxetine is approved not only for depression, but also for DPN in Japan. The regimen is started at 20 mg once daily and is up-titrated every 1 or 2 weeks, to a daily dose of 40-60 mg. Common adverse reactions are somnolence, nausea, and constipation, but duloxetine is generally well tolerated and some physicians feel that it is easier to use than TCAs.

5.4 | Tramadol-acetaminophen combination formulation

Narcotic analgesics, such as weak opioids, are indicated for the control of cancer pain and postoperative pain and are used mainly in the treatment of nociceptive pain. Opioids are also very effective for the treatment of neuropathic pain, but are deemed as third-line therapy in Japan due to the higher incidence of adverse reactions and uncertain long-term safety of these drugs, and the insufficient experience of general clinicians with these agents.

Under these circumstances, a tramadol-acetaminophen combination tablet formulation had been approved for noncancer pain in 2011. This formulation contains 37.5 mg of tramadol and 325 mg of acetaminophen in each tablet and exerts an analgesic effect with both quick action (by acetaminophen) and sustained action (by tramadol). Analgesic effect of tramadol is attributed to interaction of the active ingredients with the μ opioid receptor as well as activation of the descending inhibitory system via inhibition of monoamine reuptake. Adverse reactions, such as nausea and vomiting, may occur after treatment initiation, but these can be controlled by concomitant use of an antiemetic agent. Other adverse events include dizziness, somnolence, and constipation, while dependency and abuse are infrequent. The formulation is easy to use because it is listed as an ordinary prescription drug, rather than a narcotic, for medical use.

5.5 | Other drugs

5.5.1 | Antiepileptic agents

The sodium channel-blocking antiepileptic agents carbamazepine, phenytoin, and lamotrigine are used for controlling neuropathic pain. In all cases, the treatment regimen should be started at a low dose and should be up-titrated with precautions against dizziness and somnolence.

Carbamazepine is positioned as a first-line therapy for the treatment of trigeminal neuralgia. It is also effective for the painful tonic seizures of multiple sclerosis. Cautions should be paid to serious skin eruptions, which may appear 2-4 weeks after treatment initiation. Phenytoin therapy requires monitoring of blood concentrations, as necessary, because its therapeutic range is close to its toxic range. For treatment with lamotrigine, sleepiness is less likely, but caution should be exercised against skin eruption in the early phase of treatment.

5.5.2 | Formulation containing extract of the inflamed cutaneous tissue of rabbits inoculated with vaccinia virus

A Japanese clinical study results support the use of a formulation based on an extract of the inflamed cutaneous tissue of rabbits inoculated with the vaccinia virus as effective for PHN. This formulation is relatively safe and is widely used in Japan.

5.5.3 | Topical capsaicin

Capsaicin is an irritating chemical found in chili peppers that causes burning pain upon contact with skin. Immediately after topical application, it induces the release of substance P, which causes vasodilation and local irritation. Upon chronic application, the nociceptive threshold is increased by depletion of substance P. Topical application of a less-irritating low concentration of capsaicin may be used for control of numbness and pain.

5.5.4 | Chinese herbal medicines

Gosha-jinki-gan is a mixture of hachimi-jio-gan, Achyranthes root, and Plantago seed, and may be effective for the treatment of chill in the lower body as well as for the relief of symptoms in diabetic peripheral neuropathy. Toki-shiyaku-ka-goshuyu-shoky-to may be useful for...
chill in the upper and lower extremities, as well as numbness associated with peripheral circulation failure.

6 | SUMMARY

We have here presented an overview of pharmacotherapy for neuropathic pain. Neuropathic pain is generally intractable and does not quickly respond to evidence-supported medications in many cases. However, therapeutic options have expanded in the past few years, due to approval and expansion of the indications for various drugs. In addition, recently approved drugs generally have a wider therapeutic dose range than in the past, given the increasing opportunities for global studies. These situations enable adequate therapy, depending on the extent of the symptoms and interindividual differences, but also require careful observation for determining the optimal dose while considering therapeutic efficacy and safety in individual patients. Furthermore, because pain perception varies with culture and ethnicity, practice-based research will be required for establishing evidence specific to Japanese patients.

It may not be easy to meet the needs of patients suffering from neuropathic pain fully, but physicians will do well with full knowledge and ingenious use of the available therapeutic drugs.

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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