—Review—

Pharmacotherapy for Neuropathic Pain in Japan

Ritsuko Masuda, Junko Ajimi and Tomohiko Murata

Department of Anesthesiology, Tokai University Hachioji Hospital, Tokyo, Japan

Neuropathic pain (NeP) results from injury to, or disease of, the peripheral or central components of the neural systems involved in pain. In contrast to inflammatory pain, NeP can persist after healing from the initial injury has resolved. Antipyretic agents, such as non-steroidal anti-inflammatory drugs, steroids, and acetaminophen are ineffective, while specific agents such as gabapentinoids, antidepressants, antiepileptics, and opioids are effective in treating NeP. In this review, we address the definition of NeP, pharmacotherapy for NeP in Japan, pain classification, setting goals for successful NeP medication, and the Japanese algorithm for the pharmacotherapy of NeP with specific prescription guidance.
(J Nippon Med Sch 2017; 84: 258–267)

Key words: neuropathic pain, analgesics, pharmacotherapy, algorithm

Introduction

Pharmacotherapy for alleviating neuropathic pain (NeP), which manifests as numbness and pain, is the most fundamental and important noninvasive support tool for the home-based care of patients and their families. When administered properly, pharmacotherapy alleviates suffering from NeP, which in turn facilitates rehabilitation for preserving physical function. Pain alleviation also gives patients time to make careful decisions about surgery.

Because NeP is a common physical condition, especially in an aging society such as Japan, treating NeP is not only challenging but also very important for both specialists and non-specialists. The development of a medical care algorithm for the management of NeP[1] has been led by the Japan Society of Pain Clinicians (JSPC). This paper presents an algorithm for the pharmacotherapy of NeP, discusses important treatment points, and focuses on treatments by Japanese non-specialists.

The most important clinical considerations in the pharmacotherapy for NeP are as follows:

・Screening and evaluation of the pain are essential prior to starting pharmacotherapy. Physicians must screen sensory function, reflexes, and motor function, as well as physical function. Annual screening and X-ray, CT, and MRI findings are needed to recognize neuropathy.

・NeP therapy is likely to be effective if the site of pain has a sensory abnormality, such as numbness, or shooting, lancinating, stabbing, or burning pain.

・Pharmacotherapy should be prescribed to avoid early central nervous adverse reactions such as sleepiness, dizziness and falls.

・The dose should be started at a very low level and titrated to the optimal level while adverse reactions are carefully monitored.

Definition of NeP

The International Association for the Study of Pain (IASP) defines neuropathic pain as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system."[2] In 2011 this was revised by the IASP's Neuropathic Pain Special Interest Group (NeuPSIG) for the assessment of patients with NeP[3]. **Figure 1** shows the flow chart of the grading system for NeP created based on the findings reported by Treede et al.[2] and Haanpää et al.[3].

A careful history and examination are essential for the diagnosis of NeP. In addition, there should also be an awareness of the need to consider the pain mechanism as follows:

1) Questions about altered sensation and motor weakness.

2) To evaluate altered or absent sensations, it is important to assess the response to a pin-prick, vibration, hot, cold, or simple touch, in addition to mapping the sen-

Correspondence to Ritsuko Masuda, MD, PhD, Professor and Director of Department of Anesthesiology and Pain Medicine, Tokai University Hachioji Hospital, 1838 Ishikawa-cho, Hachioji, Tokyo 192–0032, Japan
E-mail: rinet-m@ga2.so-net.ne.jp
Journal Website (http://www2.nms.ac.jp/jnms/)

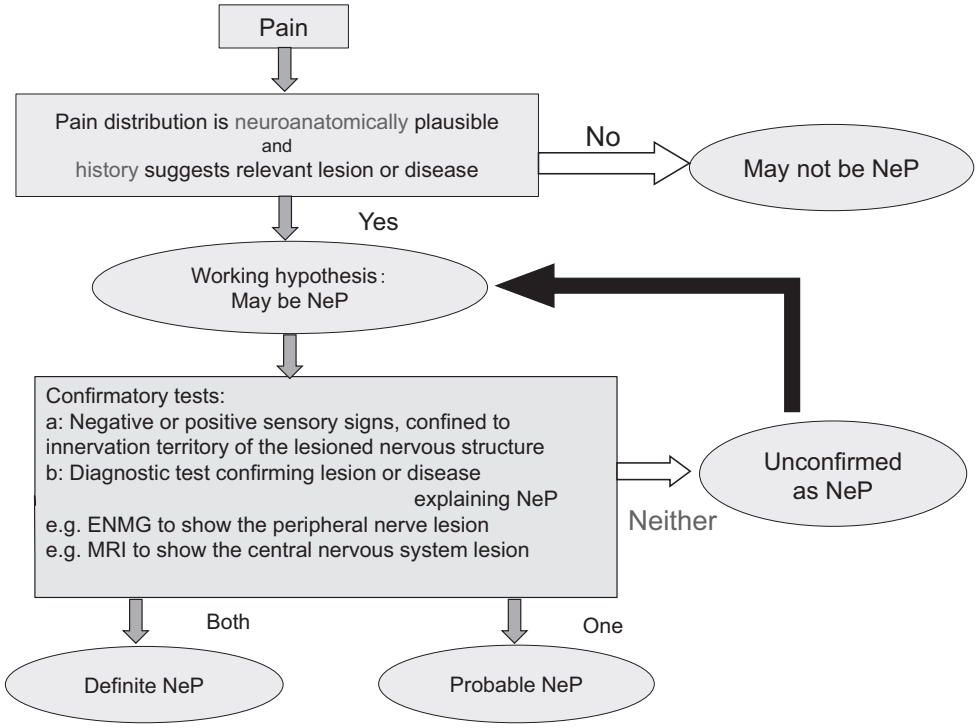


Fig. 1 Flow chart of the grading system for NeP[3]

sory abnormalities. The responses to these evaluations should be graded as normal, decreased, or increased. The stimulus-evoked (positive) pain types are classified as hyperalgesic or allodynic, and categorized in accordance with the dynamic or static character of the stimulus[2–4].

3) Additional examinations (laboratory tests, nerve-conduction examinations, X-rays, CT, MRI, and tissue-biopsy) might also be performed in order to help identify NeP.

Setting the Goals for Successful Pain Management

As stated in the beginning, analgesic therapy, which alleviates physical suffering in a home-based setting, is the most fundamental form of noninvasive relief that can be managed by the patient. However, patients prescribed analgesics must be advised that pharmacotherapy for NeP is not curative, and that analgesics should be used to ultimately preserve or improve physical function.

Patients also need to be informed that analgesics are intended to alleviate the symptoms of pain and that the overall focus of treatment must be on resolving the underlying causes and improving physical function. When treating a patient with noncancer NeP, physicians need to set goals to improve physical function, no matter how small at every visit. Examples include being able to sleep through the night, getting strong enough to be able to transfer to a wheelchair, being able to undertake certain tasks, walk around the neighborhood, or go shopping, etc. Being able to carry out certain tasks is a suitable goal, as many of these are easy to perform. Repeated small successes encourages patients by giving them a better idea of the importance of pharmacotherapy. However, if the pharmacotherapy proves to be ineffective, the patient's prescription should be tapered or discontinued. The following "4 A's" have been proposed for the use in assessing the efficacy of the pharmacotherapy:[5]

- Analgesia
- Activity
- Adverse effects
- Aberrant behavior*

*Checking for aberrant behavior is an important factor in patients receiving opioid therapy.

Pain Classification

Pain has been classified as follows:

A. *Physical pain* appears as (1) nociceptive pain, (2) neuropathic pain, and (3) mixed pain (**Table 1**). Physical pain of types (1) and (2) respond best to different analgesics. However, as the pain intensifies and becomes chronic, this can impair social activities (in the form of unemployment, dropping out of school, or family discord), cause the patient to lose self-respect, become anxious, lose hope, and become afraid. These conditions often can trigger psychogenic pain (B).

B. *Psychogenic pain* modifies and exacerbates physical pain. Within the classification of cancer pain, spiritual

Table 1 Type of physical pain

Nociceptive pain	Mixed pain	NeP
Injury Skin, muscle, internal organs	Injury Nerve+other organs	Nerve injury/nerve disease
Inflammation	Cancer pain	●Peripheral NeP
Post operative pain	Bone metastasis	Diabetic neuropathy
Arthropathy	Post operative pain	Post herpetic neuralgia
Myofascial pain	Acute herpetic pain	Trigeminal pain
Lumbago	Lumbago	Chemotherapy induced
without radiculopathy	with radiculopathy	peripheral neuropathy (CIPN)
Labor pain, menstrual pain		Polyneuropathy
Ureter calculi pain		Carpal tunnel syndrome
Other visceral pain		Radiculopathy
		●Central NeP
		Post stroke pain
		Spinal cord injury pain (SCIP)
		Multiple myeloma
		Spinal cord tumor
		Avulsion pain

pain is a typical form of psychogenic pain. Thus, psychogenic pain must be treated with a psychological or psychiatric approach. However, due to space limitations, this type of pain is not covered in this current review.

Nociceptive Pain and Neuropathic Pain

1) Nociceptive pain

Nociceptive pain is physical pain perceived by the upper central nervous system from pain-sensitive regions via the nervous system in response to invasive stimuli or tissue damage, inflammation, or ischemia. Nociceptive pain often responds well to acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and cyclooxygenase 2 inhibitors (COX-2 inhibitors). Nociceptive pain lacks an abnormal sensation at the affected site.

2) NeP (neuropathic pain)

NeP is "pain caused by a lesion or disease of the somatosensory nervous system"[2–4]. Characteristic features include pain induction without a nociceptor stimulus or a stimulus otherwise too weak to cause pain.

The diagnostic criteria for neuropathic pain[2,3] require the identification of sensory damage by checking for a past or present lesion or disease of the somatosensory system along with thorough neurological evaluations. The terms "stinging pain", "electric-like pain", "burning pain", and "numbness" are typical ways used to express neuropathic pain. **Table 2** shows the Japanese terms used during interviews to screen for the presence of neuropathic pain[6].

NeP does not respond to antipyretic analgesics (acetaminophen, NSAIDs, and COX-2 inhibitors). Pharmacotherapies that do work include neuroactive pregabalin, gabapentin, antiepileptics, tricyclic antidepressants (TCAs), and serotonin/noradrenaline reuptake inhibitors, among others. However, changes in the weather can often also cause flare-ups of NeP.

Although nociceptor injury heals relatively quickly, resulting in quick resolution of nociceptive pain, nerve damage is very slow to heal and may not heal at all in elderly subjects. NeP persists for months, years, or even until death. Therefore, patients need to be encouraged to relax during the long healing process, which could take years.

Pharmacotherapy for NeP in Japan

Analgesic therapy must not interfere with curative treatments. Basic requirements for the use of analgesics for NeP are:

・Take into account the balance between efficacy and adverse reactions.

・Free from organ damage with long-term use.

・Less drug-drug interactions.

・The treatment regimen should maximize physical function, activities of daily living (ADL), and quality of life (QOL).

Effective guidance on analgesic therapy was developed primarily in western countries around the time when gabapentinoids (gabapentin and pregabalin) first became available as NeP treatments. The IASP proposed recommendations for analgesic therapy in 2007[7]. Since this time, these have served as the basis for the pharmacotherapeutic algorithms developed for NeP throughout the

Table 2 Japanese NeP Screening Questionnaire[6]

How would you describe your pain in the affected part ? (in Japanese language)					
1) Stinging pain					
	☐ Never	☐ Slightly	☐ Moderately	☐ Strongly	☐ Very strongly
2) Electric like pain					
	☐ Never	☐ Slightly	☐ Moderately	☐ Strongly	☐ Very strongly
3) Burning pain					
	☐ Never	☐ Slightly	☐ Moderately	☐ Strongly	☐ Very strongly
4) Numbness					
	☐ Never	☐ Slightly	☐ Moderately	☐ Strongly	☐ Very strongly
5) Pain induced by mild stimulation such as clothing touching or cold wind					
	☐ Never	☐ Slightly	☐ Moderately	☐ Strongly	☐ Very strongly
6) Hypoesthesia or hyperesthesia in the painful region					
	☐ Never	☐ Slightly	☐ Moderately	☐ Strongly	☐ Very strongly
7) Swelling or skin color change (red or purple) in the painful region					
	☐ Never	☐ Slightly	☐ Moderately	☐ Strongly	☐ Very strongly

The Japanese NeP Screening Questionnaire contains 7 questions with 5 levels. In a study of 238 Japanese patients with chronic pain, patients with NeP were identified with a sensitivity and specificity of 70% and 76%, respectively, with a cutoff value of 9 points on the total score (0–28 points: evaluated with 5 levels of 0–4)[6].

world. These recommendations encourage physicians to strike a balance between the efficacy, or the number needed to treat (NNT), and the adverse reactions, or the number needed to harm (NNH).

1) Pharmacotherapeutic algorithm for nociceptive pain

Acetaminophen, which has an excellent safety and tolerability profile, is a first-line treatment when an anti-inflammatory effect is not required. An NSAID, or selective COX-2 inhibitor, should be used in patients with extensive inflammation but no cardiovascular or renal risk factors. However, these drugs should only be used after taking into consideration possible cardiovascular (hypertension, and ischemic heart disease), gastrointestinal, and renal disorders. Tramadol or another weak opioid should be considered for moderate or greater pain, while a strong opioid should be considered for more severe pain.

2) Pharmacotherapeutic algorithm for NeP

Table 3 presents JSPC's pharmacotherapeutic algorithm for NeP. This algorithm recommends medications on the basis of randomized controlled clinical trials (RCTs) while trying to achieve a balance between the NNT and NNH. Three classes of medications were recommended as first-line treatments: the gabapentanoids which include pregabalin and gabapentin, the TCA antidepressants, and the serotonin-norepinephrine reuptake inhibition (SNRIs) antidepressants. Tramadol and opioids were recommended as second-line or third-line treatments, except in certain clinical situations such as cancer pain. Though opioid analgesics are effective for severe NeP, they are not recommended for routine first-line use because of their risks of physical or psychological dependence with long-term use. Since all medications used to treat NeP can cause dose-related sleepiness, dizziness, and sedation, it is necessary for physicians to start with low doses and then cautiously titrate the dosage.

3) Clinical use of first-line drugs in Japan

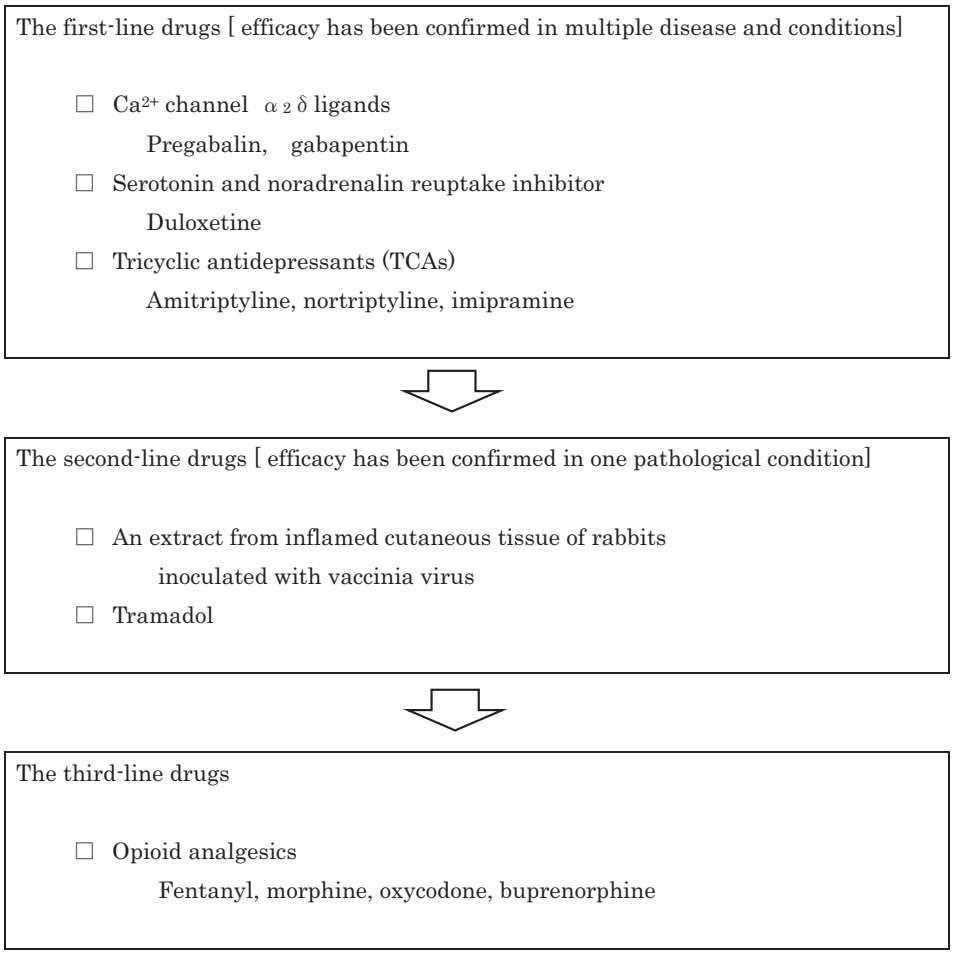
a) Pregabalin and gabapentin:

Pregabalin and gabapentin have been shown to induce significant analgesic effects for a variety of NeP conditions by binding the $\alpha_2\delta$ subunits of Ca^{2+} channels in the nervous system. Although pregabalin and gabapentin exhibit few drug interactions and serious side effects, patients with renal insufficiency require dosage reduction. In addition, while pregabalin has been approved for central and peripheral NeP (all kinds of NeP), and gabapentin has been approved for partial seizures, the use of gabapentin for NeP is still off-label in Japan.

b) Duloxetine

Duloxetine in one of the SNRIs that are viewed as being safer to use compared with TCAs. The advantage of duloxetine is that it also can be used to effectively treat depression, diabetic NeP, and other NeP conditions. Although nausea is the most common side effect, its occurrence appears to be reduced when patients are started at

Table 3 Pharmacotherapeutic algorithm for NeP in Japan[1]



the lowest dose. In addition, duloxetine also appears to be safe from a cardiovascular standpoint. Currently, duloxetine has been approved for depression, chronic lower back pain, and painful diabetic NeP. As of 2017, the use of duloxetine for other types of NeP, except diabetic NeP, is off-label in Japan.

c) TCAs

The equivalent analgesic benefits of TCAs in both depressed and non-depressed patients with NeP appear to be due to norepinephrine and serotonin reuptake inhibition. Advantages of using TCAs include their low cost, once-daily dosing, and their beneficial effects on depression, which is a common comorbidity with NeP patients. The disadvantage of TCAs includes the risk of anticholinergic side effects (such as dry mouth, constipation and urinary retention), orthostatic hypotension, and cardiac toxicity. Thus, these are often not recommended for elderly NeP patients. Amitriptyline has also been approved for depression and various NeP conditions in Japan.

Identifying Regimens that Treat NeP without Adverse Reactions

1) Characterizing the lifestyle of the patient

The analgesics listed in **Figure 2** are available for pain of different intensities. However, since analgesics for NeP and weak opioids (tramadol, tapentadol, buprenorphine, and codeine), as well as strong opioids (morphine, fentanyl, and oxycodone), can cause adverse CNS reactions (sleepiness, dizziness, sedation, and nausea), care needs to be taken in order to prevent falls and aspiration. Finding a prescription that provides efficacy without adverse reactions requires that the physicians evaluate the environment, physical function, and lifestyle habits of the patient. Patients need to be started on a very low dose of a first-line analgesic, with treatment gradually titrated while the efficacy is monitored. Gabapentinoids (pregabalin and gabapentin) for elderly patients should be started on the minimal dose at bedtime to avoid sleepiness and falls.

Table 4 lists the evaluations that should be performed prior to prescribing an analgesic to elderly patients. If it

is necessary to prescribe a drug for NeP, including an opioid, these patients need to be kept from driving. In addition, physicians must periodically check for package insert revisions.

2) Awareness of the adverse reaction profiles of analgesic drugs

Although elderly patients tolerate acetaminophen and low-dose pregabalin well, higher doses of pregabalin can cause dizziness and sleepiness, TCAs may cause constipation, urinary disorders, and increased intraocular pressure, and opioids may cause constipation, nausea, and other reactions, which overall can result in a lower tolerance. **Table 5** lists the advantages and disadvantages that need to be considered when selecting a drug for NeP. The considerations required for opioids are discussed later.

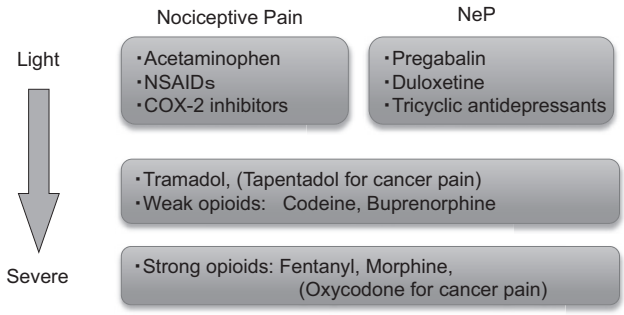


Fig. 2 Pain intensity and analgesics available in Japan

3) Specific prescription guidance (pharmacotherapy for NeP)

Start treatment at the lowest dose.

Tell the patient to take the drug after supper if there is concern that they might wake to go to the bathroom at night, which is often the cause of a fall while on the medication.

Start elderly patients at one 25 mg capsule of pregabalin at bedtime once daily.

Note: The 150 mg/day starting dose listed in the package insert may be excessive for some elderly Japanese patients. This dosage can cause light-headedness and falls.

Tell the patient in advance that the dose will be gradually increased over several days or weeks.

The prescription guidelines for neuropathic pain issued by the IASP in 2007[7] are the basis for guidelines that have been subsequently released in countries throughout the world. These initial guidelines proposed starting doses, titration intervals, maximum doses, and other specifics that were adapted for the 2016 guidelines of the JSPC[1]. **Table 6** lists the recommended initial dose, maximum dose, and the stepwise titration of NeP analgesics that are based on the JSPC 2016[1], IASP 2007[7], and the IASP's NeuPSIG 2015[8].

Table 4 Evaluations that should be performed prior to prescribing an analgesic in elderly patients

Physical function	Psychiatric performance	Environment
Walking ability	Cognitive function	Patient alone or with family?
Balance	Delirium	Living space
Swallowing ability	Patient capable of compliance	Steps or stairs
Renal function (especially relevant for pregabalin)	Self-care of pain	Nighttime bathroom use
Visual acuity		Car driving or not

Table 5 Advantages and disadvantages of analgesics

Drug	Advantages	Adverse reactions and disadvantages
Pregabalin	Effective in neuropathic pain Drug-drug interactions are not a concern	Light-headedness, dizziness, and sleepiness at start of treatment Peripheral edema and weight gain
Duloxetine Tricyclic antidepressants	Elevate mood and provide antidepressant effect	Duloxetine: Caution needed when co-administered with tramadol Tricyclic antidepressants: Thirst, constipation, urinary retention, increased intraocular pressure, sleepiness, dizziness, QT interval prolongation, suicidal risk Serotonin syndrome
Opioids	Strong analgesic effect No drug-drug interactions No organ damage	Constipation, nausea, vomiting, sleepiness, sedation, Development of tolerance, Physical and psychiatric dependence, Drug abuse/illicit use, withdrawal symptoms

Table 6 Initial and maximum doses of agents used to treat NeP based on the recommendations by the JSPC 2016[1] and IASP 2007[6]

Drug	Type	Initial dose	Titration dose	Maximum dose	Judgement period
First line drug					
Pregabalin Per-oral drug	Ca^{2+} channel $\alpha_2\delta$ ligand	25–150 mg/day 1–3 times/day or before bedtime	Increase 25–150 mg every 3–7 days	600 mg/day 2–3 times/day	4 weeks
Gabapentin Per-oral drug	Ca^{2+} channel $\alpha_2\delta$ ligand	100–300 mg/day 1–3 times/day or before bedtime	Increase 100–300 mg every 1–7 days	3,600 mg/day 1–3 times/day	>3–8 weeks
Duloxetine Per-oral drug	SNRI	20 mg/day once daily, after breakfast	Increase 20 mg every 7 days	60 mg/day 2–3 times/day	>2 weeks
Amitriptyline	TCA	10 mg/day once daily, after bedtime	Increase 10–25 mg every 3–7 days	150 mg/day	>6–8 weeks
Nortriptyline	TCA (off label use for NeP)				
Imipramine	TCA (off label use for NeP)				
Second line drug					
An extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus	Non-proteinogenic physiologically active substance	4 tablets (16 units)/day Twice daily			4 weeks
Tramadol/acetaminophen combination	Opioid+acetaminophen	1–4 tablets/day 1–4 times/day	every 3–7 days	8 tablets/day 1–4 times/day	4 weeks
Tramadol	Opioid (weak)	25–100 mg/day 1–4 times/day	every 3–7 days	400 mg/day 1–4 times/day	4 weeks
Thrid line drug					
Buprenorphine patch	Opioid (weak)	5 mg/day	every 7 days	20 mg/day Once in 7 days	4 weeks
Fentanyl 1day patch (injection)	Opioid (strong)	Establish the initial dose by calculating from the opioid dose used before switching	every day	120 mg/day converted with from morphine	4 weeks
Fentanyl 3day patch (injection)	Opioid (strong)	Establish the initial dose by calculating from the opioid dose used before switching	every 3–7 days	120 mg/day converted with from morphine	4 weeks
Morphine Per-oral (injection)	Opioid (strong)	10 mg/day	every 7–14 days	120 mg/day for non cancer NeP	4 weeks
Oxycodone Per-oral (injection)	Opioid (weak/strong) Off-label use for non-cancer NeP	Establish the initial dose by calculating from the opioid dose used before switching		Off-label use for non-cancer NeP	

SNRI: serotonin-noradrenalin reuptake inhibitor

TCA: tricyclic antidepressant

Our Approach to Pharmacotherapy for NeP

1) The intensity of NeP depends on the location and extent of damage, with the required dosage dependent on the extent of the damaged nerve bundles

・A low dose is suitable for mild peripheral neuropathic pain, as in case 1.

・A high dose is required in intractable NeP cases when nerve damage is central/proximal and extensive, as in case 2.

Case 1: Very mild NeP (pregabalin, pharmaceutical alternatives, and topical agents)

A 78-year-old woman who had been treated with an antiviral drug presented with herpes zoster on her right hand (peripheral region of C6/C7). Although the skin rash was minimal, numbness and pain of the right palm prevented her from doing calligraphy, her favorite pastime. She was started on a 25 mg dose of pregabalin at bedtime. She responded but asked for a dose reduction because of daytime sleepiness. As a result, she was then started on a very low dose (0.2 mg) of clonazepam fine granules. While she failed to respond on the initial day of treatment, she gained pain relief on day 3. She experi-

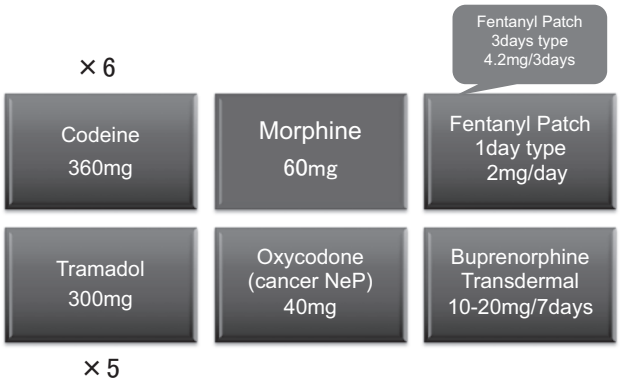


Fig. 3 Equipotent opioid analgesic doses with morphine

enced no light-headedness or sleepiness. Topical lidocaine (discussed later) was subsequently added. After 3 months, she was able to resume her normal lifestyle with the use of the topical treatment alone.

Case 2: Severe NeP

A 79-year-old woman presented with cervical ossification of the posterior longitudinal ligament (OPLL). She exhibited limb weakness, numbness, and pain due to cervical central cord injury previously caused by a fall. Due to these issues, she had been confined to her home, was wheelchair bound for 2 years, and has had long-term care level 4. In addition, she required extensive assistance from her family. Although she was started on a 50 mg/day dose of pregabalin, she experienced no improvement and continued to have pain-induced insomnia. Titration to 300 mg/day over 8 weeks finally allowed her to sleep through the night. After increasing the dose to 450 mg/day, she developed the will to undertake in-home rehabilitation. Subsequently she also gained the ability to stand while holding on to something and required less assistance.

2) The regimen should be changed if adverse reactions occur with continued use

If required, drugs used for NeP can be switched to alternative drugs. For example, if a drug produces adverse reactions, it can be replaced by a similar one in another class. The gabapentinoids (pregabalin and gabapentin) and antiepileptics (clonazepam, carbamazepine, and sodium valproate) have similar pharmacological actions. However, antiepileptics other than clonazepam and gabapentin cannot be recommended, as they can cause serious adverse reactions such as drug eruptions, and they are poorly tolerated. With regard to antidepressants, both duloxetine and TCAs have many similar prescription precautions. Nortriptyline has been successfully used off-label for NeP, as it is both inexpensive and well tolerated. Antidepressants have similar profiles and prescribing precautions (e.g., dizziness, constipation, intraocular pressure effects, and serotonin syndrome)[7]. **Table 5** presents the advantages and disadvantages of the same-class analgesics.

・When inappropriate, pregabalin may be replaced with gabapentin or clonazepam, although it is also possible to use them off-label for NeP in Japan.

・Low-dose clonazepam causes few serious adverse drug reactions and is well tolerated, but it has a long half-life of 1 to 2 days. Thus, initial dose regimens should be prescribed with caution, for example, one dose every few days.

・The TCA nortriptyline (starting at 10 mg/day, off-label use) is better tolerated than the on-label drug amitriptyline.

・Duloxetine is effective but expensive.

3) Topical lidocaine effectively treats NeP located in a small region

As stated in the IASP guidelines[7,8], topical lidocaine is highly effective when the neuropathic pain is limited to a small region. Even though topical lidocaine has a weak therapeutic effect, it facilitates lower oral medication doses because of its excellent safety profile without adverse reactions (e.g., sleepiness, light-headedness, falls, and other organ symptoms). The latest neuropathic pain guidelines currently recommend it be used as a second-line therapy[8]. The authors worked with the pharmacists at their hospital in order to create a topical lidocaine formulation. This product can be easily prepared from routine hospital agents and is readily available to those wishing to use it. This formulation has proven to be very effective and popular.

Ingredients in 10 g of 7% lidocaine ointment:

・Lidocaine powder, 0.7 g

・Magcorol ointment, 8.8 g

・Propylene glycol, 0.7 mL

4) How to treat mixed pain

Some patients dealing with pain from compensatory movements associated with trauma, other acute tissue injury, or nerve damage may require treatments that encompass both pain types if the level of pain requires it. For example, acetaminophen and tramadol can be independently administered, instead of as a two-drug combination product such as TRAMCET® combination tablets. Administration as separate agents facilitates any dose adjustments required during the course of the treatment.

Considerations for Starting Opioid Treatment

The opioid products shown in **Figure 3** are available

for moderate to severe non-cancer pain, in addition to their use in cancer pain. Characteristics common to all opioids are listed below. Opioids provide a highly reproducible pharmacological action but, when used chronically, can lead to improper or illicit use. This is why they should be considered only if the patient fails to respond to non-opioid treatment and why they are positioned after the second-line treatments[3,8].

Advantages and disadvantages of long-term opioid therapy[9–11]

・Advantages:

(1) Consistent, reproducible efficacy.

(2) Long-term use does not normally cause organ damage (but can affect the immune system and reproductive function if used for years).

・Disadvantages:

(1) Adverse reactions include constipation, nausea, sleepiness, and sedation.

(2) Physical and psychiatric dependence may occur as the patient develops tolerance.

Opioids other than tramadol, and in particular the strong opioids, pose concerns for improper and illicit use. Carefully consider the following criteria before prescribing them.

Criteria for prescribing opioids for non-cancer NeP:

1. The organic cause of the persisting pain is clear, and the pain has minimal psychogenic involvement.

2. All non-opioid pain relief options are ineffective.

3. The patient is aware of the goals and adverse effects of opioid treatment.

4. The patient is able to comply with the treatment regimen and maintain good compliance with the medication.

5. The patient has no history of dependence (e.g., drugs, alcohol, smoking, compulsive substance abuse, or abnormal consumer behavior).

6. The patient is eager to return to work or school.

Generally, patients requiring an equivalent of 120 mg/day or greater of morphine should be referred to a higher order pain institution or pain specialist[1]. It must be remembered that weak opioids, at high doses, can also cause problems similar to those observed for the strong opioids (dependence, improper use, adverse drug reactions, and immune/reproductive effects). **Figure 3** presents the dose equivalents of the opioids available in Japan for treating NeP (equipotent opioid analgesic doses with morphine).

Physicians who prescribe opioids must remain vigilant in order to ensure that their patients benefit from the opioid prescription and that there is an absence of social (abuse, illicit use, or driving) and physical (dependence, abuse, poor concentration, or sedation) problems[9–11]. As previously noted, physicians always need to keep in mind the four "A's" (analgesia, activity, adverse effects, aberrant behavior) when treating patients. Furthermore, when opioid treatments result in little benefit, physicians should consider referring the patient to a medical institution with a pain specialist.

Conclusion

NeP is commonly encountered in the primary care setting. Even though NeP can be effectively treated with the algorithmic approach, physicians need to pay special attention to diagnosed and undiagnosed systemic diseases, pathological changes, decreases in physical function, and compliance with medication. It is important that both the patient and the physician recognize that the goal of pharmacotherapy for NeP should be to maintain or increase physical function, ADL, and QOL. Physicians should always keep in mind the four "A's" (analgesia, activity, adverse effects, and aberrant behavior). The prescription of opioids requires extreme caution, and a thorough consideration of both the advantages and disadvantages. A patient's prescription should be tapered or discontinued if the pharmacotherapy proves to be ineffective.

Conflict of Interest: The authors declare no conflict of interest.

References

1. The committee for the Guidelines for the Pharmacologic Management of Neuropathic Pain (Second Edition) of JSPC: Guidelines for the Pahrmacologic Management of Neuropathic Pain. Second Edition. 2016; Shinko Trading.
2. Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, Hansson P, Hughes R, Nurmikko T, Serra J: Redefinition of neuropathic pain and a grading system for clinical use: consensus statement on clinical and research diagnostic criteria. Neurology 2008; 70: 1630–1635.
3. Haanpää M, Attal N, Backonja M: NeuPSIG guidelines on neuropathic pain assessment. Pain 2011; 152: 14–27.
4. Jensen TS, Baron R, Haanpää M, Kalso E, Loeser JD, Rice AS, Treede RD: A new definition of neuropathic pain. Pain 2011; 152: 2204–2205.
5. Trescot AM, Boswell MV, Atluri SL, Hansen HC, Deer TR, Abdi S, Jasper JF, Singh V, Jordan AE, Johnson BW, Cicala RS, Dunbar EE, Helm S 2nd, Varley KG, Suchdev PK, Swicegood JR, Calodney AK, Ogoke BA, Minore WS, Manchikanti L: Opioid guidelines in the management of chronic non-cancer pain. Pain Physician 2006; 9: 1–39.
6. Ogawa S: Development of the neuropathic pain screening questionnaire for Japanese patients with chronic pain. Pain Clinic 2010; 31: 1187–1194.

7. Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, Kalso EA, Loeser JD, Miaskowski C, Nurmikko TJ, Portenoy RK, Rice AS, Stacey BR, Treede RD, Turk DC, Wallace MS: Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain 2007; 132: 237–251.
8. Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, Gilron I, Haanpää M, Hansson P, Jensen TS, Kamerman PR, Lund K, Moore A, Raja SN, Rice AS, Rowbotham M, Sena E, Siddall P, Smith BH, Wallace M: Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol 2015; 14: 162–173.
9. National Institute for Health and Clinical Excellence (NICE): Neuropathic Pain—Pharmacological Management. Clinical Guideline 96, 2010; NICE, London.
10. Edlund MJ, Martin BC, Fan MY, Devries A, Braden JB, Sullivan MD: Risks for opioid abuse and dependence among recipients of chronic opioid therapy: results from the TROUP study. Drug Alcohol Depend 2010; 112: 90–98.
11. Stannard CF: Opioids for chronic pain: promise and pitfalls. Curr Opin Support Palliat Care 2011; 5: 150–157.

(Received, June 4, 2017)
(Accepted, August 16, 2017)