

**Guidelines for the Pharmacologic
Management of Neuropathic Pain
Second Edition**

Preface

In 2010, noncancer pain was added as a new indication for an opioid analgesic, Fentanyl patch, and furthermore, pregabalin and tramadol, which are indicated for treatments of neuropathic pain and cancer pain, respectively, appeared on the market in Japan. In the following year, buprenorphine transdermal patch and tramadol-acetaminophen combination started out being marketed. Since then, “pain” and “pain management” have attracted considerable attention in Japan as a matter of course. This made many professionals, not only the members of Japan Society of Pain Clinicians but also the members of other academic societies or medical professionals involved in the treatments of “pain”, aware of the necessity to issue a guideline of pharmacologic management for neuropathic pain which reflects current situation in Japan and also follows the international EBM. In response to this request, the Japan Society of Pain Clinicians published the first edition of “Guidelines for the Pharmacologic Management of Neuropathic Pain” in July 2011. This version was reprinted for several times during the next 5 years, and eventually became a best-seller as we all know.

During these 5 years, more analgesics and adjuvant analgesics such as duloxetine, tapentadol and methadone were further introduced, and indications of tricyclic antidepressants were finally expanded for treatments of pain. Thus, as new pain medications appear on the market one after another, interest in pain has grown even further in the entire medical society.

However, many troubles have been also reported associated with these drugs as the number of medications introduced in the market or prescribed by physicians not specialized in pain management increased in a short period of time. Hence, once again, the demand for publishing a revised version of the guideline which shows us how to use analgesics, especially, how to organize and utilize knowledge of each one of the analgesics and adjuvant analgesics for neuropathic pain, which is hard to treat, and enables us to appropriately understand the concomitant use, adverse reactions, indications and evidences on these drugs has increased in these years.

Therefore, the Japan Society of Pain Clinicians organized “the Committee for the Guidelines for the Pharmacologic Management of Neuropathic Pain of JSPC”. In preparation of this guideline, core members first created items and clinical questions (CQs), and then contributors started working on commentaries for each item and CQ, the level of evidence, and a summary of overall evidence. These descriptions were further cross-checked twice by the core members and discussed at meetings frequently held by the core members. The entire draft was eventually proofread by all committee members, and then the final version was published here after receiving public comments made by the members of the Japan Society of Pain Clinicians.

The structure of the second edition of this guideline has been created based on the

“Minds Handbook for Clinical Practice Guideline Development 2014”, the version revised in 2014, presenting a CQ, summary, evidence level, the level of recommendation, and commentary for each item. This structure is characterized as follows : the evidence level determines outcomes for the CQ : a systematic review is performed for each outcome, and a comprehensive evaluation is made on the outcomes as a whole ; the level of evidence is determined not only by evaluating a specific outcome but also by evaluating all the important outcomes including hazards ; the level of recommendation is determined according to the cumulative result of each outcome, and is a consensus taking the level of the evidence into consideration ; review all important articles, evaluate all main outcomes, and present the entire evidence including hazards before discussing whether the treatment is recommended or not. It is also a characteristic of this new guideline that the level of recommendation is determined considering that the treatment would be strongly recommended if the difference between the benefit and the hazard is large despite the low evidence level, and that it would be weakly recommended if the difference is small despite the high evidence level. In addition, it was basically created in the CQ style as much as possible, incorporating expert opinions in appropriate use of drugs such as opioids as well as commentaries on general remarks. Thus, integrity of “the Guidelines for the Pharmacologic Management of Neuropathic Pain, the second edition” is far higher than the original version as a guideline.

However, needless to say, this “the Guidelines for the Pharmacologic Management of Neuropathic Pain, the second edition” was created for the purpose of determining management methods or of making judgments for referrals to specialized facilities. Hence, I would clearly mention again that it should not be used in any other situations (e.g. compensation and lawsuit).

Finally, I would like to thank Dr. Naoki Nago, the director of the Musashi Kokubunji Park Clinic, and Dr. Naohito Yamamoto, the professor of Tokyo Women’s Medical University, for various valuable advice. Further, I would like to appreciate the members of the Japan Society of Pain Clinicians who gave us the public comments, as well as the members of “the Committee for the Guidelines for Pharmacologic Management of Neuropathic Pain” and its chairman Dr. Sei Fukui for their great contributions and efforts.

Toyoshi Hosokawa
President of Japan Society of Pain Clinicians
May 2016

Introduction

There are various types of pain associated with diseases. However, it is well known that neuropathic pain has been drawing attention of clinicians to its intractable nature. Taking this into consideration, the Japan Society of Pain Clinicians published “Guidelines for the Pharmacologic Management of Neuropathic Pain” in both Japanese and English versions in June 2011. We are now preparing a revised version of these guidelines which include new drugs/treatments as well as new findings associated with neuropathic pain. From now on, we are going to publish the latest version of these guidelines every three years.

The “Guidelines for the Pharmacologic Management of Neuropathic Pain, second edition” has been prepared following materials obtained from Japan Council for Quality Health Care, a handbook for guideline preparation manual published by Minds (Medical Information Network Distribution Service) (“Minds Handbook for Clinical Practice Guideline Development 2014”), or AGREE II. We present here the revised version of the guidelines based on ideas of EBM (evidence-based medicine).

We hope that these guidelines will be widely used so that QOL (quality of life) of the patients with neuropathic pain would be much more improved.

The purpose of preparing the “Guidelines for the Pharmacologic Management of Neuropathic Pain (Second Edition)”

These guidelines are prepared not only for physicians in pain clinics or many other medical professionals involved in pain management but also for primary care physicians to understand the basic prescriptions for neuropathic pain so that QOL of patients with neuropathic pain would be improved.

Basic principles of the “Guidelines for the Pharmacologic Management of Neuropathic Pain (Second Edition)”

These guidelines will present evidences of the latest neuropathic pain treatments to the public and help medical professionals to design treatment plans or promote mutual understanding between the clinicians and the patients.

This revised version is prepared based on the “Minds Handbook for Clinical Practice Guideline Development 2014” or AGREE II with expert opinions on CQs (clinical questions), commentary, the levels of evidence for items of CQs, establishment of the levels of recommendation, and appropriate use of opioids, etc. We intended to prepare the content of these guidelines in the CQ style as much as possible. With this style, it will be easier not only for pain specialists but also for local primary care physicians, including doctors of general medicine or general practitioners, to understand these guidelines.

According to the “Minds Handbook for Clinical Practice Guideline Development 2014” (<http://minds4.jcqhc.or.jp/minds/guideline/handbook2014.html>), we fundamentally attempted to follow the consistent style of presenting CQs along with the levels of recommendations and commentary in the order of definition of neuropathic pain, epidemiology, diagnosis, treatment, effects on improvement of

QOL, which is the goal of chronic pain treatment, and symptoms associated with pain (e.g. sleep disorder or depression). The most important element is evidence. We also included drugs which are not covered by insurance. For such products, we left commentaries so that not only the specialists but also the doctors in general medicine or general practitioners will be able to have a better understanding. Furthermore, in order to make this revised version more practical for clinical settings, we discussed and described in details the effectiveness of drugs on each disease.

We also included opinions of young contributors in middle positions apart from those of particular authorities so that the content would be created on neutral ground, reflecting our society.

Moreover, in order to maintain consistency with the first edition of “Guidelines for Prescribing Opioid Analgesics for Chronic Non-Cancer Pain” and the first edition of “Guidelines for the Pharmacologic Management of Neuropathic Pain”, we established a guideline committee in which approximately a half of the members are from the former guideline committee and the other half are from the latter to work in collaboration.

For classifications of opioids, we presented the drugs in categories of “weak opioids” and “strong opioids” to be consistent with the “Guidelines for Prescribing Opioid Analgesics for Chronic Non-Cancer Pain” and also of “weak (for weak pain)” (e.g. tramadol), “moderate (for moderate pain)” (e.g. buprenorphine) and “strong (for strong pain)” (e.g. fentanyl) following the WHO classification.

This second edition was prepared mainly by the core members of the “Committee of the Guidelines for Neuropathic Pain, a revised edition” of the Japan Society of Pain Clinicians with rest of the members and contributors. We completed our mission on the basis of frequent committee meetings, core-member meetings, mailing-list meetings and discussions.

We deeply appreciate Dr. Naoki Nago (the director of the Musashi Kokubunji Park Clinic) as an external expert for helping us with various valuable advices and opinions.

Finally, we also would like to appreciate the members and core-members of “the Committee for the Guidelines for the Pharmacologic Management of Neuropathic Pain, a revised edition” of the Japan Society of Pain Clinicians as well as advisors who gave us valuable supports and opinions, external experts, the members of the Japan Society of Pain Clinicians and all other people involved in the related society.

Sei Fukui

The chairman of the Committee for the Guidelines for the Pharmacologic Management
of Neuropathic Pain, Second Edition
Japan Society of Pain Clinicians

Preparative Method of Guideline

Basic structure of the guideline

The guideline consists of sections following the “Minds Handbook for Clinical Practice Guideline Development 2014” which basically includes CQ (clinical questions), summary, levels of evidence, levels of recommendation, and commentary. The introduction and summary, which provide basic knowledge of neuropathic pain, contains items only presenting the evidence levels. Each one of the items in summary and discussion was created by the core members of the guideline preparation committee.

Preparation of clinical questions (CQs)

A draft of clinical questions (CQs) was created by the core members of the Committee for the Guidelines and the authors for each one of the sections along with summary and commentary for CQs.

Levels of evidence

The levels of evidence for treatments were created following the “Minds Handbook for Clinical Practice Guideline Development 2014” ; for CQs, general evaluations (listed below) were added to the systematic review for each outcome in the “answers” of Q&A.

The gross summary of the entire evidence for CQs (strength of the entire evidence for the outcome in general) was determined as follows based on the summary of the entire evidence to create the levels of recommendation in the “Minds Handbook for Clinical Practice Guideline Development 2014”.

A (Strong) : The estimate of an effect is strongly reliable.

B (Moderate) : The estimate of an effect is moderately reliable.

C (Weak) : The estimate of an effect is somewhat reliable but limited.

D (Very weak) : The estimate of an effect is hardly reliable.

It is not always required to present the levels of evidence for each one of the reference articles according to the “Minds Handbook for Clinical Practice Guideline Development 2014”. However, these were added in references in this guideline, except for the commentary in summary, considering that it would be helpful for readers to have general evaluations made by “the Oxford Centre for Evidence-Based Medicine Levels of Evidence” (<http://www.cebm.net/index.aspx?o=1025>) on treatment/prevention, etiology/hazard, prognosis, diagnosis, and economical evaluation.

Levels of recommendation

A systematic review was performed on each outcome for CQ, following “Minds Handbook for Clinical Practice Guideline Development 2014”. Then, the levels of recommendation were determined as follows by integrating the evidence level for each outcome.

1 : Strongly recommended

2 : Weakly recommended (suggestion)

If the level of recommendation could not be determined, it was presented as “N/A”.

At the end of summary, examples for the above-mentioned recommendation levels 「1」 were added along with the levels of evidence (A, B, C, D).

- (1) It is strongly recommended to perform treatment I for patient-P (1A) ; (strong recommendation based on strong evidence)
- (2) It is suggested to perform treatment I rather than treatment C for patient P (2C) ; (weak recommendation based on weak evidence)
- (3) It is suggested not to perform neither treatment I nor treatment C for patient P (2D) ; (weak recommendation based on very weak evidence)
- (4) It is strongly recommended not to perform treatment I for patient P (1B) ; (strong recommendation based on moderate evidence)

These definitions were made considering that the recommendation can be strong if the difference between advantage and disadvantage is significant in terms of balance, even if the evidence level is low ; or the recommendation can be weak if the difference between advantage and disadvantage is not significant in terms of balance, even if the evidence level is high.

The levels of recommendation and the levels of evidence were evaluated comprehensively taking into account the following principles.

1. The levels of evidence and the levels of recommendation are not the same ; the evidence level is merely a factor to determine the recommendation level.
2. The levels of recommendation are consensus achieved taking the levels of evidence into consideration.
3. The levels of evidence can be obtained by systematic reviews on each one of the outcomes.
4. The levels of evidence are not determined by evaluating only particular outcomes but by evaluating all important outcomes including hazards.

The levels of recommendation were first suggested by the authors and cross checked twice by the core members, and then finally determined by the entire guideline committee. Evaluations were made on all crucial outcomes, including hazard, of all important articles. Then they discussed the entire evidence to decide whether or not it can be recommended.

Revision of documents

The document created by each author was reviewed and revised twice in a cross-checking manner and then finally reviewed and revised again by the entire team members. The final levels of recommendation for each one of the CQs were determined by the entire committee members.

Reference search and adoption

In some fields, only outdated articles such as for tricyclic antidepressant were available for references. Hence, the entire articles, including the latest ones, were reviewed regardless of the published year. The reference articles included those searched under PubMed, Japan Medical Abstract Society (excluding the minutes), and Cochrane Collaboration.

Oxford Center for Evidence-Based Medicine Levels for Evidence (<http://www.cebm.net/index.aspx?o=1025>)

Level	
1a	Systematic review (with homogeneity) of RCTs
1b	Individual RCT (with narrow confidence interval)
1c	All or none
2a	Systematic review (with homogeneity) of cohort studies
2b	Individual cohort study (including low quality of RCT; e.g., <80% follow-up)
2c	Outcomes" Research; Ecological studies
3a	Systematic review (with homogeneity) of case-control studies
3b	Individual Case-Control study
4	Case-series (and poor quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first" principles

Conflicts of interest

All individuals involved in preparation of this guideline declared the conflicts of interest. Only the names of committee members and companies were disclosed. The detailed information about the conflicts of interest for each individual are listed on the website of Japan Society of Pain Clinicians.

Indication for treatments

In overseas countries, the NEP Special Interest Group of International Association for the Study of Pain (IASP) proposed an excellent systematic review guideline in 2015. Meanwhile in Japan, we present this guideline on the basis of ideas of EBM for all medical professionals involved in the field of pain management, including primary care physicians.

If there is not enough evidence in a particular field, or if there is no evaluation criterion available for a specific treatment, those should be mentioned as well.

Needless to say, with regard to indications of pharmacotherapy for chronic pain, psychological and social backgrounds of individual patients should be considered carefully according to the history of each case.

It should be also noted that the drugs described in this guideline should be used with adequate explanations provided to the patients regardless if these are indicated or not.

We hope that clinicians do not only skim read the levels of evidences but rather do read the content, summary and commentary of this guideline when they consider implementation of pharmacotherapies.

This guideline was created to be used for designing treatment plans or making decisions on referrals to specialists. Hence, it should not be used for any other situations (e.g. compensations or lawsuits).

Sei Fukui,

The Chairman of the Committee for the Guidelines for the Pharmacologic Management of
Neuropathic Pain, Second Edition
Japan Society of Pain Clinicians

Guidelines for the Pharmacologic Management of Neuropathic Pain

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Definition of neuropathic pain : Pain caused by a lesion or disease of somatosensory nervous system

1. Difinition of neuropathic pain

CQ1 : How do we define and understand neuropathic pain in clinical medicine?

Neuropathic pain is defined as “pain caused by a lesion or disease of the somatosensory nervous system”. Neuropathic pain should not indicate a single disease but rather should be recognized as a pathological condition involved in many patients complaining of pain.

Summary of overall evidence : A

Comments :

Varied lesions or diseases can develop neuropathic pain ; experts in each field have made a diagnosis of this condition using the term “neuropathic pain” from their own perspectives. Hence, the single concept of neuropathic pain had never been shared among different clinical fields, resulting in confusion in the clinical settings. In order to resolve this confusion with this particular term, the IASP defined neuropathic pain as “pain initiated or caused by a primary lesion or dysfunction in the nervous system”¹⁾ in 1994. However, because there is no doubt that the “nervous system” is always involved in pain (it is meaningless to point out) and because the term “dysfunction” has not been clearly defined, the Neuropathic Pain Special Interest Group of the IASP redefined neuropathic pain as “pain arising as a direct consequence of a lesion or disease affecting the somatosensory nervous system”²⁾ in 2008. According to the definition introduced in 1994, migraine with aura, induced by abnormal excitability (that is, dysfunction) of neurons in the visual cortex of the occipital lobe, which is certainly one of the nervous system but not the neural basis of pain recognition, is included in the neuropathic pain category. However, with the new definition established in 2008, migraine is not included in neuropathic pain. Thus, neuropathic pain entities consequently became more specific by redefinition of the term in 2008, and the concept became further generalized among different clinical and basic research fields. However, there were also some concerns pointed out in clinical settings due to limitation of this concept³⁾. This definition reportedly had some disadvantages that some patients lose an opportunity to receive treatments for neuropathic pain as a consequence of false negative judgment due to low specificity of demonstrating anatomical damage in diagnosis of neuropathic pain. In addition to these problems, there was also a concern that neuropathic pain might still be misunderstood as a single disease due to the limitation of this concept after introducing the new definition in 2008. It

was more desirable to define neuropathic pain as a syndrome which consists of various symptoms and signs developed by a variety of pathological mechanisms. Consequently, in 2011, it was further revised as “pain caused by a lesion or disease of the somatosensory nervous system”⁴⁾. It was noteworthy that clinical criteria, which is based on overall findings of patients with neuropathic pain, will be necessary in diagnosis of neuropathic pain because it is often impossible to demonstrate consistent data from diagnostic tests for neuropathic pain.

In “Guidelines for Pharmacologic Treatment of Neuropathic Pain” published by Japan Society of Pain Clinicians in 2011, a term “damage” had been used to describe a “lesion”. As this term includes a condition which does not involve an irreversible anatomical change such as compression, it was changed to “lesion” according to the “Taxonomy for Pain Clinics” issued by Japan Society of Pain Clinicians (2016).

Guidelines for Pharmacologic Treatment of Neuropathic Pain

References

- 1) Mersky H, Bogduk N : Classification of chronic pain, 2nd ed. IASP Press, 1994
- 2) Loeser JD, Treede RD : The Kyoto protocol of IASP basic pain terminology. Pain 2008 ; 137 : 473-477
- 3) Eisenberg E : Reassessment of neuropathic pain in light of its revised definition : Possible implications and consequences. Pain 2011 ; 152 : 2-3
- 4) Jensen TS, Baron R, Haanpaa M, et al : A new definition of neuropathic pain. Pain 2011 ; 152 : 2204-2205

2. Pathology of neuropathic pain

CQ2 : How do we understand pathology of neuropathic pain?

Neuropathic pain, which is defined as “pain caused by a lesion or disease of the somatosensory nervous system”, emerges when there is a lesion or disease in any of the nociceptive pathways from peripheral nerves to the cerebrum. The pathological mechanisms include abnormal sensitivity of the somatosensory nervous system and functional impairment in the descending pain modulatory system.

Summary of overall of evidence : A

Comments :

Pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”¹⁾. Pain intrinsically functions as a warning system which notifies a body of nociceptive stimuli. Nociceptive pain is perceived when excitability of nociceptor is transmitted from peripheral nerve endings to the spinal cord and then to the cerebrum. Alternatively, if the pain pathway is damaged, spontaneous pain, hyperalgesia and/or allodynia sometimes emerge regardless of decrease or loss of somatosensory inputs to the supraspinal central nervous system. For such a pain without nociceptive inputs, two pathological conditions, namely, neuropathic pain which is induced by a lesion or disease of the somatosensory nervous system and psychogenic pain which emerges due to a psychiatric and psychological problems, have been currently assumed.

If there is a lesion or disease in any of the nociceptive pathways from peripheral nerves to the cerebrum, hypersensitivity hyperalgesia, allodynia and/or spontaneous pain of neurons can develop. Such abnormal excitability of neuronal firings is considered as neuropathic pain. For the onset of neuropathic pain, various molecular biological mechanisms such as a change in ion channels, increase in expression of NMDA receptors, sprouting of nerve fibers, and activation of glial cells have been suggested. It has been also demonstrated electrophysiologically that peripheral nerve damage can induce the “wind-up” phenomenon and long-term potentiation (LTP)²⁾. Moreover, in peripheral nerve damage, it has been shown that hypersensitivity of spinal dorsal horn neurons such as hyperalgesia and allodynia develop as a consequence of impairment of the “OFF” neuron functions which inhibit the descending pain modulatory system³⁾.

In addition to these biological factors, it should be mentioned that pain is

Definition of pain :

An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

Nociceptive pain

Allodynia

Hyperalgesia

NMDA : N-methyl-D-aspartate

Wind-up phenomenon

Long-term potentiation

usually affected by bio-psycho-social factors. Hence, we need clinical criteria, with which we do not only evaluate the pathological condition of the somato-sensory nervous system but also predict presence or absence of psychosocial factors. We should evaluate their impact on their QOL from findings in a patient as a whole, and then determine the management plan.

References

- 1) Mersky H, Bogduk N : Classification of chronic pain, 2nd ed. IASP Press, 1994
- 2) Kuner R : Central mechanisms of pathological pain. Nature Medicine 2010 ; 16 : 1258-1266
- 3) Leong ML, Gu M, Spelz-Paiz R, et al : Neuronal loss in the rostral ventromedial medulla in a rat model of neuropathic pain. J Neurosci 2011 ; 31 : 17028-17023

3. Diseases which present neuropathic pain

CQ3 : What diseases are associated with neuropathic pain?

Nutrition metabolism, traumatic, ischemic, toxic, genetic, infectious, compression/entrapment, immune, neoplastic or neurodegenerative disorders can cause neuropathic pain. Following diseases can be associated with neuropathic pain (Table 1). These are just examples, and there are more diseases which are not listed in this table.

Summary of overall evidence : A

Table 1 Pathological Classification of Pain in General Diseases (A list of diseases which may cause neuropathic pain) (Referred from the Reference 1)

<p>Nutrition metabolism :</p> <p>Alcoholic polyneuropathy</p> <p>Alcoholic neuropathy</p> <p>Neuropathy due to malnutrition (e.g. beriberi, pellagra)</p> <p>Hypothyroid neuropathy</p> <p>Painful diabetic neuropathy</p> <p>Uremic neuropathy</p> <p>Fabry disease</p> <p>Porphyric neuropathy, etc.</p> <p>Genetic :</p> <p>Hereditary polyneuropathy with liability to pressure palsy</p> <p>Hereditary sensory and autoimmune neuropathy, etc.</p>	<p>Traumatic :</p> <p>Iatrogenic neuropathy</p> <p>Postthoracotomy pain syndrome</p> <p>Posttraumatic sequelae / post-operative sequelae (e.g. persistent post-operative wound pain)</p> <p>Postischemic myelopathy</p> <p>Phantom pain</p> <p>Nerve root avulsion</p> <p>Neuropathic myelopathy</p> <p>Nerve injury sequelae</p> <p>Tethered cord syndrome</p> <p>Spinal cord Hemorrhage / infarction</p> <p>Spinal cord injury sequelae</p> <p>Multiple cranial neuropathy</p> <p>Stump neuralgia</p> <p>Postmastectomy</p> <p>Stroke sequelae (e.g. thalamic pain, CNS vascular malformation)</p> <p>Complex Regional Pain Syndrome</p> <p>Postherniorrhaphic pain</p> <p>Radiation-induced plexopathy</p> <p>Radiation-induced myelopathy / radiation-induced encephalopathy</p> <p>Radiation-induced encephalopathy / myelopathy</p> <p>Peripheral neurotmesis / injury</p> <p>Brachial plexus avulsion, etc.</p>	
<p>Ischemic :</p> <p>Allergic granulomatous vasculitis</p> <p>Reversible ischemic neuropathy</p> <p>Ischemic neuropathy</p> <p>Connective tissue disease (vasculitis)</p> <p>Polyarteritis nodosa</p> <p>Cryoglobulinemia</p> <p>Mononeuritis multiplex, etc.</p>	<p>Toxic :</p> <p>Chemotherapy-induced neuropathy</p> <p>Gold</p> <p>Mercurial poisoning</p> <p>Toxic neuromyopathy</p> <p>Thinner</p> <p>Lead</p> <p>Arsenic poisoning</p> <p>Drug-induced polyneuropathy</p> <p>SMON, etc.</p>	<p>Infectious :</p> <p>Diphtheric polyneuropathy</p> <p>Neurosyphilis</p> <p>Tabes dorsalis</p> <p>Postherpetic neuralgia</p> <p>Leprosy neuropathy</p> <p>Lyme disease</p> <p>HIV sensory neuropathy</p> <p>HIV myelopathy</p> <p>HIV neuropathy, etc.</p>

Table 1 Pathological Classification of Pain in General Diseases (A list of diseases which may cause neuropathic pain)-2

Compression / entrapment :		
Crural neuralgia Cervical spondylotic radiculopathy Cubital / anterachial / wrist / foot / thigh / shoulder entrapment neuropathy Entrapment neuropathy Sciatica Sciatic nerve entrapment Trigeminal neuralgia Cervical / thoracic / lumbosacral spinal cord radiculopathy Neuralgia	Carpal tunnel syndrome Cervical / lumbar spondylolisthesis Myeloradiculopathy Myelopathy Spinal canal stenosis Compressive myelopathy due to spinal canal stenosis Glossopharyngeal neuropathy Hypoglossal neuropathy Multiple sclerosis Polyneuropathy	Polyneuropathy Intervertebral disc displacement Chronic neuralgia Chronic cauda equine disorder Lumbar sciatic neuralgia Lumbar spondylosis Low back pain Intercostal neuralgia
Immune :	Neoplastic :	Degenerative, etc.
Carcinomatous neuropathy Guillain-Barre syndrome Sjogren's syndrome Autoimmune neuropathy Autoimmune neuropathy Plexitis Inflammatory demyelinating polyneuropathy Idiopathic neuropathy, etc.	Malignant tumor Nerve compression by tumor or neuralgia due to tumor invasion Spinal cord tumor Brain tumor Peripheral nerve tumor Neuroma Neurosarcoidosis Neurilemmoma, etc.	Amyloidotic autonomic neuropathy Charcot joint Autonomic neuropathy Syringomyelia / syringobulbia Parkinson's disease Adrenomyeloneuropathy, etc.

Reference

- 1) Hanaoka K, Ogawa S, Hotta N, et al: Progress and future prospects for neuropathic pain treatment in Japan: A proposal from the expert consensus conference. Pain Clinic (Jp) 2013; 34: 1227-1237

4. Neuropathic pain classification and mixed pain condition

CQ4 : Neuropathic and nociceptive pain classification and its clinical significance?

Pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”¹⁾. The types of pain developed by bodily-specific causes are classified into nociceptive pain and neuropathic pain. However, pathological conditions of nociceptive pain and neuropathic pain are often clinically overlapped, and such state is called as the mixed pain condition. To control the mixed pain condition, pharmacotherapies for each pathologic condition would be necessary for appropriate pain control.

Summary of overall evidence : A

Comments :

Nociceptive pain is defined as “pain that arises from actual or threatened damage to non-neural tissues and is due to the activation of nociceptors”. It will be helpful to classify and evaluate nociceptive pain and neuropathic pain when we plan to treat pain caused by for these causes. Thus, diseases accompanied by pain can be generally classified into either nociceptive pain and neuropathic pain. However, we should understand that these conditions can be present at the same time as the somatosensory nervous system might become hypersensitive according to severity or persistence of pain or as pain is developed by excitability of nociceptors associated with neuroinflammation.

References

- 1) Mersky H, Bogduk N : Classification of chronic pain, 2nd ed. IASP Press, 1994
- 2) Cohen SP, Mao J : Neuropathic pain : Mechanisms and their clinical implications. BMJ 2014 ; 348 : 656
- 3) Leung L, Cahill CM : TNF- α and neuropathic pain : A review. J Neuroinflamm 2010 ; 7 : 27

5. Pain associated with acute peripheral nerve inflammation

CQ5 : Is acute pain associated with peripheral nerve inflammation regarded as neuropathic pain?

There is a controversy regarding whether or not this should be included in the neuropathic pain category. In this guideline, acute pain associated with peripheral nerve inflammation is not included in the neuropathic pain category.

The level of recommendation and the summary of overall evidence : 2C

Comments :

The most representative diseases which develop acute pain in association with direct inflammation on the peripheral nerve include shingles in the acute phase and radiculopathy due to intervertebral disc displacement. It is considered that, in shingles, varicella-zoster virus which has caused latent infection in the dorsal root ganglia induces inflammatory reactions on nerves¹⁾, and in intervertebral disc displacement, herniation of the nucleus pulposus of the intervertebral disc induces inflammations on nerve roots and dorsal root ganglia, resulting in development of pain²⁾. Although it is agreed that chronic pain induced by shingles or intervertebral disc displacement is neuropathic pain, there is a controversy regarding whether or not this acute pain is considered as the neuropathic pain due to the following reasons.

1) It is the neuropathic pain

Inflammation on the peripheral nerve trunk induces various types of pain, such as pain caused by stimulation of sensory nerve terminal distributed in the connective tissues around the nerve trunk including the epineurium, pain caused by inflammation developed over the posterior root ganglion cells, and pain caused via CNS sensitization by inflammation developed over the nerve axons. These types of pain may be present at the same time according to the pathological condition³⁾. Although details are unknown, it is considered that acute pain associated with peripheral nerve inflammation may develop mainly due to stimulation of sensory nerve terminals or due to inflammation over dorsal root ganglia. Epineurium and dorsal root ganglia are also a part of nerve tissues. Therefore, considering that the definition of neuropathic pain suggested by IASP is “pain caused by a lesion or disease of somatosensory nervous system”, this acute pain should be included in the neuropathic pain category.

2) It is not the neuropathic pain

Neuropathic pain is chronic refractory pain caused via CNS sensitization ; it is pathological pain not alleviated by resolving the problems on the peripheral nerve terminals. The acute pain associated with shingles or intervertebral disc displacement may disappear if inflammatory response is controlled⁴⁻⁶⁾, or it disappears if nucleus pulposus is removed. Therefore, it is not appropriate to regard this pain as neuropathic pain which would not be improved even if the cause is removed, though it directly involves the somatosensory system.

Thus, there is a controversy regarding definition of neuropathic pain. Besides, although nociceptive pain and neuropathic pain may be present at the same time during a transition phase from acute to chronic pain in association with peripheral nerve inflammation, it is currently difficult to figure out how much of the acute pain induced by shingles or intervertebral disc displacement is neuropathic pain. Therefore, in this guideline, we would not include the acute pain associated with terminal nerve inflammation in the neuropathic pain category. It may respond well however to antiepileptic agent or antidepressant^{7,8)}. This will be discussed in details in each commentary.

References

- 1) Muraki R, Iwasaki T, Sata T : Pathology of shingles : From histopathological observation of rash. *Journal of Japan Society of Pain Clinicians*. 1998 ; 5 : 86-91
- 2) Mulleman D, Mammou S, Griffoul I, et al : Pathophysiology of disk-related sciatica. I. Evidence supporting a chemical component. *Joint Bone Spine* 2006 ; 73 : 151-158
- 3) Xu Q, Yaksh TL : A brief comparison of the pathophysiology of inflammatory versus neuropathic pain. *Curr Opin Anaesthesiol* 2011 ; 24 : 400-407
- 4) Chou R, Huffman LH : Medications for acute and chronic low back pain : A review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. *Ann Intern Med* 2007 ; 147 : 505-514 [1a]
- 5) Kennedy DJ, Plataras C, Casey E, et al : Comparative effectiveness of lumbar transforaminal epidural steroid injections with particulate versus nonparticulate corticosteroids for lumbar radicular pain due to intervertebral disk herniation : A prospective, randomized, double-blind trial. *Pain Med* 2014 ; 15 : 548-555 [1b]
- 6) Balakrishnan S, Bhushan K, Bhargava VK, et al : A randomized parallel trial of topical aspirin-moisturizer solution vs. oral aspirin for acute herpetic neuralgia. *Int J Dermatol* 2001 ; 40 : 535-538 [2b]
- 7) Berry JD, Petersen KL : A single dose of gabapentin reduces acute pain and allodynia in patients with herpes zoster. *Neurology* 2005 ; 65 : 444-447 [1b]
- 8) Liang L, Li X, Zhang G, et al : Pregabalin in the treatment of herpetic neuralgia : Results of a multicenter Chinese study. *Pain Med* 2015 ; 16 : 160-167 [1b]

6. Chronic pain syndrome and neuropathic pain

CQ6 : What is the chronic pain syndrome presented by neuropathic pain patients?

There is no definition for the chronic pain syndrome. However, pain diseases, such as neuropathic pain, might induce intensive pain which is far greater than that for the bodily-specific pathologic conditions (underlying mechanisms) or impairment in ADL and QOL. Such patients' state is considered as the chronic pain syndrome, and the chronic pain syndrome would emerge as a consequence of complex interactions of bio-psycho-social factors.

Summary of overall evidence : B

Comments :

Neuropathic pain is accompanied by various comorbidities such as sleep disorder, hypodynamia, depression, anxiety, dry mouth and loss of appetite, other than pain¹⁾. Although it has not been clearly understood how these comorbidities

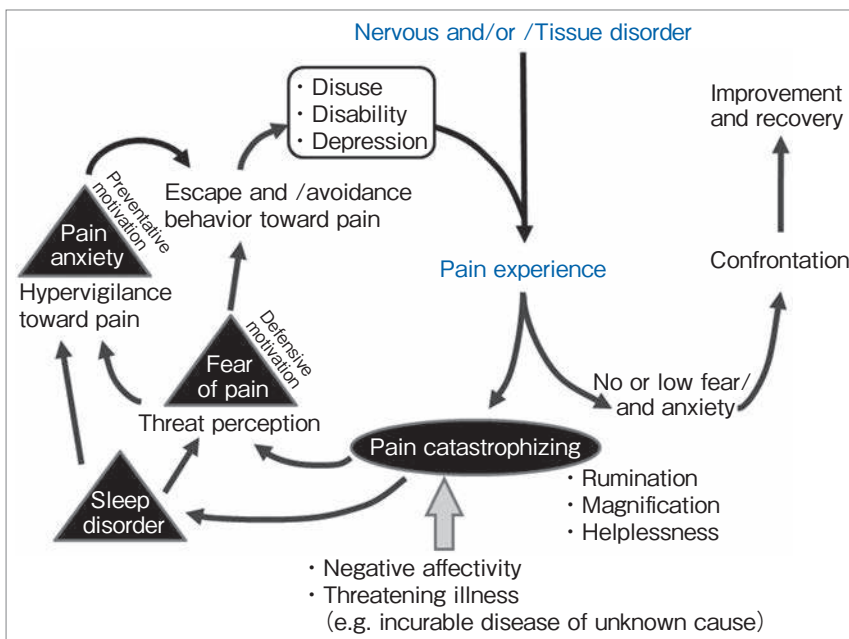


Figure 1 Fear Avoidance Model of Pain (Referred and partially modified from Reference 2)

Neuropathic pain becomes chronic and aggravated due to circulatory interactions with bio-psycho-social factors.

Fear-avoidance model

Pain catastrophizing

ties are associated with pain, the factors for these conditions are consistent with those of a vicious circle model known as a fear-avoidance model ([Figure 1](#))²⁾. In other words, “pain catastrophizing”, which is a thought pattern of a patient for pain, reinforces his/her pain obsession. As a consequence, the patient begins to avoid daily activities which may induce pain and remains rested, resulting in disuse syndrome, functional decrease in ADL, and a tendency to become depressed. These conditions do not only further reinforce pain obsession (a bias toward pain recognition) and pain presentation behavior but also form a negative spiral which aggravates ADL and QOL²⁾. In the treatment of neuropathic pain, which appears to be under such a state of chronic pain syndrome, a perspective to evaluate these negative bio-psycho-social factors is required.

References

- 1) Meyer-Rosberg K, Kvamström A, Kinnman E, et al : Peripheral neuropathic pain : A multidimensional burden for patients. *Eur J Pain* 2001 ; 5 : 379-389
- 2) Leeuw M, Goossens MEJB, Linton SJ, et al : The fear-avoidance model of musculoskeletal pain : Current state of scientific evidence. *J Behav Med* 2007 ; 30 : 77-94

7. Epidemiology of neuropathic pain

CQ7 : Are there any epidemiological surveys on prevalence of neuropathic pain?

There are a few reports from large-scale surveys on the prevalence of neuropathic pain. These surveys have been conducted in only a few countries, however, and are varied in their age and criteria for the intensity/frequency of pain. The judgments on whether or not the pain was of neuropathic origin were made only based on the scores obtained from questionnaire surveys for screening but not following the diagnostic procedure for neuropathic pain.

Summary of overall evidence : D

Comments :

In 2010, an online survey was conducted in Japan involving 20,000 people from the general population aged between 20 and 69. An individual with chronic pain was defined as a person who had had pain of 4 or above in the numeric rating scale (NRS) for at least twice per week for more than 3 months. Of these, the subjects who were likely to have neuropathic pain on the “Neuropathic Pain Screening Questionnaire (Japanese version)” were defined as individuals with neuropathic pain. According to the results from the survey, prevalence for chronic pain and neuropathic pain was 26.4% and 6.4% , respectively¹⁾. Applying these percentages to the entire adult population in Japan, it can be assumed that 6,000,000 people suffer from neuropathic pain in this country. Aside from the above online survey, a postal survey on musculoskeletal chronic pain was conducted also in Japan in 2010 involving 19,198 people. Of these, 660 persons who had had pain persisting for more than 6 months were examined for neuropathic pain using “painDetect” ;7% of subjects were likely to have neuropathic pain and 13% had some factors of neuropathic pain. Those with greater factors of neuropathic pain generally suffered from more intensive pain²⁾.

Outside Japan, an interview/postal/telephone survey conducted in France in 2004 in 23,712 persons aged 18 years or older revealed that 31.7% were suffering from chronic pain of 1 or above in visual analog scale (VAS) every day for more than 3 months and 6.9% from neuropathic pain as defined in “DN-4”³⁾. A telephone survey conducted in Germany in 2007 in 3,011 subjects aged 15 years or older revealed that 24.9% suffered from chronic pain for at least 3 times per week for more than 3 months and 6.5% from neuropathic pain as defined in “DN4” and “painDetect”⁴⁾. In another telephone survey conducted in

NRS : numeric rating scale
Pain is rated in integer values of 11 levels from 0 (no pain) to 10 (the maximum pain that the person can think of).

VAS : visual analogue scale
Pain is rated on a scale of 100 mm. According to the IASP definition, 0 indicates no pain, and 100 indicates the maximum pain that the person can think of.

DN4 : the Douleur Neuropathique en 4 questions (4-item questionnaire for neuropathic pain)

LANSS : Leeds assessment of neuropathic symptoms and signs : One of the diagnostic methods for neuropathic pain

Morocco in 5,328 subjects, the prevalence of chronic pain reported every day for more than 3 months was 21% , and that of neuropathic pain according to “DN4” was 10.6%⁵⁾.

In 2006, a postal questionnaire survey was conducted in 6,000 subjects in 3 cities in the U.K. Of 2,957 subjects who responded to this questionnaire, the prevalence of chronic pain persisting more than 3 months was 48% , and that of neuropathic pain according to “LANSS” was 8.2%⁶⁾. In a telephone survey conducted in Canada in 2009 in 1,207 subjects of 18 years or older, the prevalence of chronic pain for more than 3 months was 35% and that of neuropathic pain as defined in “DN4” was 17.9%⁷⁾. A questionnaire survey conducted in 1,597 subjects in Brazil in 2012 revealed that the prevalence of chronic pain persisting more than 6 months was 42% , and that of neuropathic pain using “DN-4” was 10%⁸⁾.

References

- 1) Ogawa S, Iseki M, Kikuchi S : A large-scale survey on chronic pain and neuropathic pain in Japan. The Journal of the Japanese Clinical Orthopaedic Association 2012 ; 47 : 565-574
- 2) Nakamura M, Nishiwaki Y, Sumitani M, et al : Investigation of chronic musculoskeletal pain (3rd report) : With special reference to the importance of neuropathic pain and psychogenic pain. J Orthop Sci 2014 ; 19 : 667-675
- 3) Bouhassira D, Lantéri-Minet M, Attal N, et al : Prevalence of chronic pain with neuropathic characteristics in the general population. Pain 2008 ; 136 : 380-387
- 4) Ohayon MM, Stingl JC : Prevalence and comorbidity of chronic pain in the German general population. J Psychires 2012 ; 46 : 444-450
- 5) Harifi G, Amine M, Ait Ouazar M, et al : Prevalence of chronic pain with neuropathic characteristics in the Moroccan general population : A national survey. Pain Med 2013 ; 14 : 287-292
- 6) Torrance N, Smith BH, Bennett MI, et al : The epidemiology of chronic pain of predominantly neuropathic origin : Results from a general population survey. J Pain 2006 ; 7 : 281-289
- 7) Toth C, Lander J, Wiebe S : The prevalence and impact of chronic pain with neuropathic pain symptoms in the general population. Pain Med 2009 ; 10 : 918-929
- 8) de Moraes Vieira EB, Garcia JB, da Silva AA, et al : Prevalence, characteristics, and factors associated with chronic pain with and without neuropathic characteristics in São Luís, Brazil. J Pain Symptom Manage 2012 ; 44 : 239-251

CQ8 : Are there any epidemiological surveys on prevalence of neuropathic pain in cancer patients?

There exist epidemiological surveys on neuropathic pain in cancer patients. As neuropathic pain in cancer patients include (1) pain directly associated with cancer (invasion / metastasis of the tumor to nerves or the spinal canal), (2) pain associated with cancer treatments (surgery, chemotherapy and radiotherapy) and (3) pain associated with diseases other than cancer (postherpetic neuralgia and others). However, those surveys vary in their scopes : some separate the types (1) through (3) while others mix them together. Definition of pain also varies among the surveys ranging from those with definitive diagnoses and those evaluated from the scores of questionnaires for neuropathic pain screening.

Summary of overall evidence : C

Comments

According to a systematic review of Bennet et al. that analyzed pathological conditions of pain in 11,063 patients with cancer pain, 59.4% were nociceptive pain, 19.0% pure neuropathic pain, 20.1% a mixture of nociceptive pain and neuropathic pain and 1.5% unknown or other types of pain¹⁾. European Association for Palliative Care (EAPC) conducted a survey using painDETECT in 670 patients with pain out of 1,051 cancer patients. According to its results, 534 patients had nociceptive pain, 113 neuropathic pain and 23 pain of unknown cause. Compared to the patients with nociceptive pain, those with neuropathic pain used stronger opioid analgesics and/or adjuvants and their performance state (PS) scores were worse²⁾. In another study conducted using DN4 in 8,615 cancer patient at 46 hospitals in Spain, 366 patients had neuropathic pain. Among the patients, 55% also had nociceptive pain, 78.8% had been under treatments for cancer and 56% had been treated with neurotoxic chemotherapy. A background factor analysis in the same patients revealed that 68% of the patients had pain directly associated with cancer, 42.9% had pain associated with cancer treatment, and 18.6% had pain not associated with cancer³⁾. In Japan, 18.6% of 220 patients with the mean survival time of 21.5 days (0–173 days) suffered from neuropathic pain directly associated with cancer⁴⁾.

Mixed pain condition

EAPC : European Association for Palliative Care

DN4 : the Douleur Neuropathique en 4 questions

References

- 1) Bennett MI, Rayment C, Hjermstad M, et al : Prevalence and a etiology of neuropathic pain in cancer patients : A systematic review. Pain 2012 ; 153 : 359–3652. [2b]
- 2) Rayment C, Hjermstad M, Aass N, et al : European Palliative Care Research Collaborative (EPCRC) : Neuropathic cancer pain : Prevalence,

severity, analgesics and impact from the European Palliative Care Research Collaborative-Computerised Symptom Assessment study. *Palliat Med* 2012 ; 27 : 714-721. [\[2b\]](#)

- 3) García de Paredes ML, Hjerstad M, Aass N, et al : First evidence of oncologic neuropathic pain prevalence after screening 8, 615 cancer patients : Results of the On study. *Ann Oncol* 2011 ; 22 : 924-930. [\[2b\]](#)
- 4) Harada S, Tamura F, Ota S : The prevalence of neuropathic pain in terminally ill patients with cancer admitted to a palliative care unit : A prospective observational study. *Am J Hosp Palliat Care* 2016 ; 33 : 594-598. [\[2b\]](#)

☐ I . Overview of neuropathic pain

☒ II . Diagnosis and treatment of neuropathic pain

- 8. Diagnosis of neuropathic pain CQ9, CQ10
- 9. Clinical characteristics of neuropathic pain CQ11
- 10. Neuropathic pain and QOL CQ12
- 11. Management plan for neuropathic pain: general remarks CQ13
- 12. Treatment goal for neuropathic pain CQ14

☐ III . Pharmacotherapies for neuropathic pain

☐ IV . Diseases which present neuropathic pain

8. Diagnosis of neuropathic pain

CQ9 : How do we screen potential patients with neuropathic pain?

This guideline recommends the use of the screening tools (questionnaires) which have been developed for the identification of neuropathic pain. The screening tools for neuropathic pain available in Japan are the neuropathic pain screening questionnaire (Japanese version only), and the Japanese version of the painDETECT.

The level of recommendation and the summary of overall evidence : 1D

Comments :

Multiple screening tools have been developed to easily evaluate the possibility that a patient has neuropathic pain. There is a tool known as the neuropathic pain screening questionnaire¹⁾ developed in Japan, and in overseas countries, there are LANSS²⁾, S-LANSS³⁾, NPQ⁴⁾, DN4⁵⁾, ID Pain⁶⁾, painDETECT⁷⁾, and StEP⁸⁾. Of these, StEP was developed to identify neuropathic low back pain.

The neuropathic pain screening questionnaire (Figure 2), has 7 questions in 5 levels. In a study conducted in 238 Japanese patients with chronic pain, pa-

LANSS : the Leeds Assessment of Neuropathic Symptoms and Signs

S-LANSS : Short versions of the LANSS

NPQ : Neuropathic Pain Questionnaire

DN4 : the Douleur Neuropathique en 4 questions

StEP : the Standardized Evaluation of Pain

How would you describe your pain in the area marked × ?

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 the skin or cold wind

☐ Never ☐ Slightly ☐ Moderately ☐ Strongly ☐ Very strongly

6) Hypoesthesia or hyperesthesia in the painful area

☐ Never ☐ Slightly ☐ Moderately ☐ Strongly ☐ Very strongly

7) Swelling or skin color change (red or purple) in the painful area

☐ Never ☐ Slightly ☐ Moderately ☐ Strongly ☐ Very strongly

Figure 2 Neuropathic Pain Screening Questionnaire (Reference 1)

Notice : This questionnaire has been developed and validated only in Japan, and this English version has not been validated.

tients with neuropathic pain could be identified at sensitivity and specificity of 70% and 76% respectively with a cutoff value of 9 points when evaluated on the total score (0–28 points : evaluated in 5 levels of 0–4), and when evaluated on weighted scores (0–9), sensitivity and specificity were 88% and 72% respectively with a cutoff value of 4 points¹⁾. Out of all screening tools developed in foreign languages, painDETECT was translated into Japanese (Figure 3 “painDETECT–Japanese version”. See p.35 as Japanese language), and its reliability and validity have been confirmed⁹⁾. The original study demonstrated that patients with neuropathic pain could be identified at sensitivity and specificity of 85% and 80% respectively at a cutoff value of 19 points when the patients were evaluated on the scores (0–38) for 9 questions⁷⁾.

There are also guidelines for assessment and diagnostic methods of neuropathic pain such as EFNS guidelines¹⁰⁾ and NeuPSIG guidelines of IASP¹¹⁾. Superiority or inferiority of a particular tool has not been evaluated in these guidelines. Although there is an advantage for each screening tool that it can be used by non-specialist physicians, 10–20% patients diagnosed with neuropathic pain cannot be identified with these tools. Therefore, these guidelines recommend that we should not diagnose neuropathic pain only using a result of the screening tool^{10,11)}, and validation study for epidemiological studies is necessary¹⁰⁾.

There is a systematic review conducted by Mathieson et al, which compared and evaluated quality (e.g. validity, reliability) of each screening tool¹²⁾. They concluded that, the quality level had been shown to be relatively high for the original version of DN4 and NPQ, although all screening tools had been supported at the low evidence level, and the screening tools should not replace a detailed clinical assessment.

Therefore, this guideline recommends that we should use the screening tools available in Japan for screening of potential patients with neuropathic pain in the clinical practice. However, we should not diagnose neuropathic pain only using the result of the screening questionnaires.

EFNS : European Federation
of Neurological Societies

IASP : International
Association for the Study of
Pain

References

- 1) Ogawa S: Development of the neuropathic pain screening questionnaire for Japanese patients with chronic pain. *Pain Clinic* 2010; 31: 1187–1194 [5]
- 2) Bennett M: LANSS pain scale: The Leeds Assessment of Neuropathic Symptoms and Signs. *Pain* 2001; 92: 147–157 [5]
- 3) Bennett M, Smith BH, Torrance N, et al: The S-LANSS score for identifying pain of predominantly neuropathic origin: Validation for use in clinical and postal research. *J Pain* 2005; 6: 149–158 [5]
- 4) Krause SJ, Backonja MM: Development of a Neuropathic Pain Questionnaire. *Clin J Pain* 2003; 19: 306–314 [5]
- 5) Bouhassira D, Attal N, Alchaar H, et al: Comparison of pain syndromes

- associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain* 2005 ; 114 : 29–36, [5]
- 6) Portenoy R : Development and testing of a neuropathic pain screening questionnaire : ID Pain. *Curr Med Res Opin* 2006 ; 22 : 1555–1565 [5]
 - 7) Freynhagen R, Baron R, Gockel U, et al : PainDETECT : A new screening questionnaire to identify neuropathic components in patients with back pain. *Curr Med Res Opin* 2006 ; 22 : 1911–1920 [5]
 - 8) Scholz J, Mannion RJ, Hord DE, et al : A novel tool for the assessment of pain : Validation in low back pain. *PLoS Med* 2009 ; 6 : e1000047 [5]
 - 9) Matsubayashi Y, Takeshita K, Sumitani M, et al : Validity and reliability of the Japanese version of the PainDETECT questionnaire : A multi-centre observational study. *PLoS One* 2013 ; 8 : e68013 [5]
 - 10) Cruccu G, Sommer C, Anand P, et al : EFNS guidelines on neuropathic pain assessment : Revised 2009. *Eur J Neurol* 2010 ; 17 : 1010–1018 [5]
 - 11) Haanpää M, Attal N, Backonja M, et al : NeuPSIG guidelines on neuropathic pain assessment. *Pain* 2011 ; 152 : 14–27 [5]
 - 12) Mathieson S, Maher CG, Terwee CB, et al : Neuropathic pain screening questionnaires have limited measurement properties : A systematic review. *J Clin Epidemiol* 2015 ; 68 : 957–966 [5]

CQ10 : How do we diagnose neuropathic pain?

We should firstly identify the present illness and the past medical history which suggest neuropathic pain, and then perform neurological examination to assess sensory disturbance and tests to diagnose a neurological lesion or disease. We recommend to confirm the diagnosis following an algorithm (grading system).

The level of recommendation and the summary of overall evidence : 1D

Comments :

There are guidelines for assessment and diagnostic methods of neuropathic pain developed by EFNS¹⁾ and IASP²⁾, with a recommended diagnostic algorithm (grading system)³⁾ formulated by Neuropathic Pain Special Interest Group (NeuPSIG) of IASP (Figure 4). They recommend to assess and diagnose neuropathic pain following the identical algorithm regardless of a lesion or disease which causes neuropathy. This algorithm (grading system) is widely used as a current international standard for the diagnosis of neuropathic pain. However, no high-quality study has been conducted yet to verify the effectiveness of the diagnostic method.

First, we closely ask a patient about the present illness and the past medical history suggestive of neuropathic pain. If we are able to confirm pain distribution which is neuroanatomically plausible and the past medical history suggestive of a lesion or disease ^{Note 1} affecting the somatosensory nervous system, we can judge the patient may have neuropathic pain. The pain distribution per-

EFNS : European Federation of Neurological Societies

IASP : International Association for the Study of Pain

NeuPSIG : Neuropathic Pain Special Interest Group

Note 1 : Refer to "3. Diseases which present neuropathic pain"

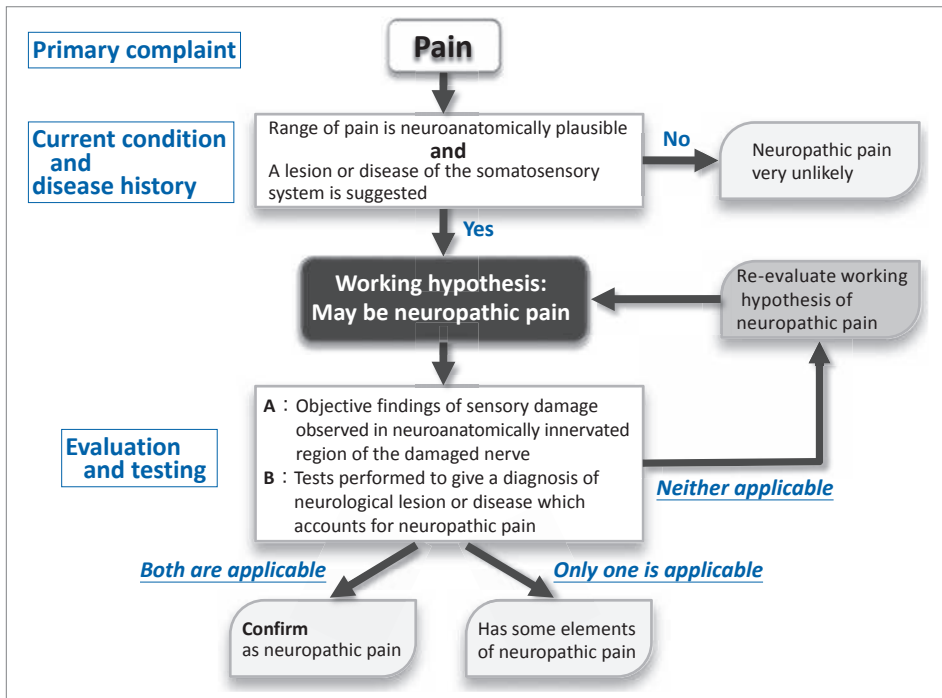


Figure 4 Algorithm for diagnosing neuropathic pain (Referred and modified from Reference 3)

ceived by the patient with neuropathic pain may not often completely coincide with the dermatome of the affected nerve ; while patients with nociceptive pain may perceive referred pain along particular dermatome (e.g. the patient with hip osteoarthritis may perceives radiating pain from the buttocks to the lower thigh). Therefore, it is often difficult for a physician not specialized in pain treatment to evaluate whether or not the pain distribution is neuroanatomically valid. We should take into consideration whether or not the pain distribution pattern is typical for the underlying disease, or if the nature of pain is characteristic to neuropathic pain ^{Note 2} when we assess neuropathic pain.

If we can judge the patient may have neuropathic pain, the following assessment should be made : (A) neurological examination to assess the presence or absence of sensory disturbance (e.g. hypoesthesia, hyperesthesia, allodynia) in the area corresponding to the anatomical innervation of the affected nerve, and (B) tests to diagnose a lesion or disease explaining neuropathic pain. It is confirmed that the patient has neuropathic pain if both A and B are applicable, or it is considered that the patient has some elements of neuropathic pain if either one is applicable. These patients should be treated as neuropathic pain except for when neither one is applicable.

Note 2 : Refer to "9. Clinical characteristics of neuropathic pain"

QST : Quantitative Sensory Testing

LEP : Laser-evoked potentials

CCM : corneal confocal microscopy

There is no method to clinically evaluate the sensory disturbance of deep tissues (e.g. muscles, tendons, joints) and viscera in the neurological examination except for vibratory sensation. Hence, the region for assessing the sensory disturbance is generally the skin. It is often evaluated for tactile sensation (by lightly touching the skin with a cotton wool) and pain sensation (by stimulating the skin with a tip of a pin) and dynamic allodynia. However, we should also assess heat sensation, cold sensation, vibration sensation, static allodynia and thermal allodynia in order to avoid a false-negative result. The quantitative sensory testing (QST) is effective tool for more detailed evaluations of sensory abnormality^{1,2,4,5)} though it is currently used only for research purposes. For any of these evaluation methods, we should be aware that sensory disturbance, also pain, is based on subjective assessment by patients, and that patients may perceive sensory abnormality even in the unaffected area (e.g. primary hyperalgesia due to inflammation, central sensitization, and a psychophysiological reactions such as conversion disorder).

The tests used for assessing the neurological lesion or disease explaining neuropathic pain include imaging tests (MRI, CT), neurophysiological tests (e.g. nerve conduction studies, trigeminal reflex, laser-evoked potentials [LEPs]), corneal confocal microscopy (CCM) and skin biopsy^{1,2,5)}. The imaging tests are performed to assess degeneration, compression and infiltration of the central and peripheral nerves. However, we should be aware that there are many neurological diseases which cannot be evaluated on the images and that the severity of neuropathic pain is not associated with the image findings. The nerve conduction studies cannot detect the damage of A δ and C fibers associated with pain sensation, though it can detect large fibers (A β fibers). Therefore, the necessity of that test is limited. It has been also reported that the trigeminal reflex can be useful for a differential diagnosis between trigeminal neuralgia and neuropathic pain in the facial area^{1,2,5,6)}, LEPs for the assessment of A δ fiber dysfunction^{1,2,5)}, CCM for the assessment of diabetic polyneuropathy^{5,7)}, and the evaluation of intraepidermal nerve fiber density using skin biopsy for the assessment of small fiber neuropathy^{1,2,5)}. However, these tests have currently been used only for research purposes in Japan. Thus, it is not clinically necessary to demonstrate the neurological lesion or disease explaining neuropathic pain by tests. It is crucial to perform careful interviews and neurological examinations in order to make a diagnosis of neuropathic pain.

References

- 1) Cruccu G, Sommer C, Anand P, et al: EFNS guidelines on neuropathic pain assessment: Revised 2009. *Eur J Neurol* 2010; 17: 1010–1018 [5]
- 2) Haanpää M, Attal N, Backonja M, et al: NeuPSIG guidelines on neuro-

- pathic pain assessment. *Pain* 2011 ; 152 : 14–27 [5]
- 3) Treede RD, Jensen TS, Campbell JN, et al : Neuropathic pain : Redefinition and a grading system for clinical and research purposes. *Neurology* 2008 ; 70 : 1630–1635 [5]
 - 4) Rolke R, Baron R, Maier C, et al : Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS) : Standardized protocol and reference values. *Pain* 2006 ; 123 : 231–243 [5]
 - 5) Mainka T, Maier C, Enax-Krumova EK : Neuropathic pain assessment : Update on laboratory diagnostic tools. *Curr Opin Anaesthesiol* 2015 ; 28 : 537–545 [5]
 - 6) Cruccu G, Biasiotta A, Galeotti F, et al : Diagnostic accuracy of trigeminal reflex testing in trigeminal neuralgia. *Neurology* 2006 ; 66 : 139–141 [5]
 - 7) Jiang MS, Yuan Y, Gu ZX, et al : Corneal confocal microscopy for assessment of diabetic peripheral neuropathy : A meta-analysis. *Br J Ophthalmol* 2016 ; 100 : 9–14 [5]

9. Clinical characteristics of neuropathic pain

CQ11 : What are clinical characteristics of neuropathic pain?

The patient has spontaneous pain or pain induced by stimulation at the site corresponding to the area supplied by the affected nerve, which is complicated by abnormal sensations of this site.

The level of recommendation and the summary of overall evidence : 2D

Comments :

Neuropathic pain presents distinctive pain which is different from nociceptive pain. It is characterized by spontaneous pain (continuous or intermittent) or pain induced by stimulation (allodynia, hypersensitivity) at the site corresponding to the area supplied by the affected nerve, which is complicated by various sensory abnormalities caused by disturbance of a nerve¹⁾. Neuropathic pain is suspected especially when the patient has allodynia and hypo/hyper-

Table 2 Comparisons among various screening tools (Prepared based on References 2, 4-8)

	ID Pain ⁴⁾	NPQ ⁵⁾	pain DETECT ⁶⁾	LANSS ⁷⁾	DN4 ⁸⁾	Neuropathic pain screening tool ²⁾
Stinging, prickling pain	+	+	+	+	+	+
Pain like electric shock or shooting pain	+	+	+	+	+	+
Hot or burning pain (irritation)	+	+	+	+	+	+
Tingling pain	+	+	+		+	+
Pain induced by light touch	+	+	+	+		+
Cold or freezing		+			+	
Pain induced by slight pressure			+			
Pain induced by heat or cold			+			
Pain induced by weather change		+				
Pain limited to joints	—					
Itchiness				+		
Pain pattern			+			
Pain radiating to the other areas (referred pain)			+			
Accompanied by change in the autonomic nerve	+					+
Hypo/hypersensitivity						+

Table 3 Differences in the features of pain characteristic to each disease
(Prepared based on References 2, 9–12)

Postherpetic neuralgia ⁹⁾	Painful diabetic neuropathy ¹⁰⁾	Pain after spinal cord injury ¹¹⁾	Neuropathic pain in general ^{2,12)}
Dull pain	Dull pain		
Burning pain	Burning pain	Burning pain	Burning pain
Shooting pain	Shooting pain		Shooting pain
			Irritating pain
	Prickling pain		
	Stabbing pain		
	Cramping pain		
		Tearing pain	
		Penetrating pain	
Itchiness	Itchiness		Itchiness
	Tingling pain	Tingling pain	Tingling pain
Allodynia	Allodynia	Allodynia	Allodynia
Hypersensitivity		Hypersensitivity	Hypersensitivity

Table 4 Differences in features between neuropathic pain and nociceptive (inflammatory) pain (referred and modified from Reference 13)

		Neuropathic pain	Nociceptive pain (inflammatory pain)
Positive symptoms/signs	Spontaneous pain at the affected site	Present	Present
	Hypersensitive to pain against nociceptive warmth stimulation	Rare	Frequent
	Allodynia against cold stimulation	Frequent	Rare
	Increased sensory threshold against pressure stimulation and hypersensitivity to pain	Often	Basically none
	Persistent feeling of stimulation after somatosensory stimulation	Often	Rare
	Characteristic subjective symptoms	Sudden pain, burning pain	Throbbing pain
	Pain spreading beyond the affected area	Basically none	Basically none
Negative symptoms/signs	Sensory disturbance in the area supplied by the affected nerve	Present	None
	Motor disturbance in the area supplied by the affected nerve	Often	None

sensitivity in addition to burning pain and numbness²⁾.

The characteristic features of neuropathic pain can be referred to the descriptions of the screening tools developed in the EU and US and in Japan (Table 2)²⁻⁸⁾.

However, a diagnosis of neuropathic pain should not be made based on these features. We should recognize that these are valid only for the screening level. It should be emphasized as mentioned in the previous section that physical examinations to evaluate whether or not the range of pain is neurologically valid or if there is a sensory disturbance at the corresponding site are necessary to make a diagnosis along with supportive past medical history and test findings including those on imaging tests¹⁾.

The differences in the features of pain characteristic to each disease are presented in Table 3^{1,9-12)}. Positive and negative findings in the somatosensory nervous system of neuropathic pain and nociceptive pain can be useful when making a diagnosis (Table 4)¹³⁾.

References

- 1) Haanpää M, Treede RD: Diagnosis and Classification of Neuropathic Pain. IASP Clinical Updates 2010; 18: Issue 7 [5]
- 2) Ogawa S: Development of the neuropathic pain screening questionnaire for Japanese patients with chronic pain. Pain clinic 2010; 31: 1187-1194 [5]
- 3) Cruccu G, Truini A: Tools for assessing neuropathic pain. PLoS Med 2009; 6: Issue 4 [5]
- 4) Portenoy R: Development and testing of a neuropathic pain screening questionnaire: ID Pain. Curr Med Res Opin 2006; 22: 1555-1565 [5]
- 5) Krause SJ, Backonja MM: Development of a neuropathic pain questionnaire. Clin J Pain 2003; 19: 306-314 [5]
- 6) Freynhagen R, Baron R, Gockel U, et al: PainDETECT: A new screening questionnaire to detect neuropathic components in patients with back pain. Curr Med Res Opin 2006; 22: 1911-1920 [5]
- 7) Bennett MI: The LANSS Pain Scale: The Leeds Assessment of Neuropathic Symptoms and Signs. Pain 2001; 92: 147-157 [5]
- 8) Bouhassira D, Attal N, Alchaar H, et al: Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain 2005; 114: 29-36 [5]
- 9) Johnson RW, Whittton TL: Management of herpes zoster (shingles) and postherpetic neuralgia. Expert Opin Pharmacother 2004; 5: 551-559 [5]
- 10) Tesfaye S, Kempler P: Painful diabetic neuropathy. Diabetologia 2005; 48: 805-807 [5]
- 11) Hulsebosch CE: From discovery to clinical trials: treatment strategies for central neuropathic pain after spinal cord injury. Curr Pharm Des 2005; 11: 1411-1420 [5]
- 12) Irving GA: Contemporary assessment and management of neuropathic pain. Neurology 2005; 64: S21-S27 [5]
- 13) Jensen TS: Pathophysiology of pain: From theory to clinical evidence. Eur J Pain 2008; 2: s13-7

10. Neuropathic pain and QOL

CQ12 : What is the effect of neuropathic pain on QOL?

Pain severity of neuropathic pain is relatively higher than that of other pain conditions, and neuropathic pain affects greatly patients' QOL. The higher the severity in pain, the lower the QOL remains.

The level of recommendation and the summary of evidence : 1B

Comments :

QOL indicates the quality of life and living style in a broad sense, and it is often described as health-related QOL (HRQL) especially in the medical field. In other words, compared to the non-health related QOL which include dignity and joys in one's life, values for depth of joys and sorrows, hope, goal, family structure, economical situation, and cultural activities, health-related QOL consists of not only the objective evaluations on patients' health conditions but also of their subjective understandings on health conditions and the degree of well-being as well as their values in their lives in general. In this section, we only discuss the health-related QOL.

The intimate relationship between HRQOL and neuropathic pain has been revealed in a large epidemiological surveillance^{1,2)} reported from France. The number of patients with chronic pain which had persisted for more than 3 months reached 31.7% of the population. Of these, about 20% of the patients had neuropathic pain (morbidity was approximately 7% per population [more than 5,000,000 when converted to Japanese population]). More than 70% (5% of the population) of patients with neuropathic pain assessed their level of pain at moderate or severe²⁾, which was higher in severity than that of patients who had other types of chronic pain, and they were likely to have prolonged disease duration and to pay more medical expenses³⁾. Consequently, we can understand that severity in neuropathic pain is particularly higher than that of other chronic diseases.

Using EQ-5D, which is the standard QOL scale used in Europe, EQ-5D of average neuropathic patients is 0.4-0.6, and that of severe neuropathic patients is around 0.2. The EQ-5D answers numbers between 0-1, where "0" indicates death and "1" indicates a healthy state. The EQ-5D score of 0.4-0.5 is equivalent to the QOL of terminal cancer patients who have been living on their beds as they feel fatigue, etc. with or without pain, and the EQ-5D score of 0.2 is equivalent to the QOL of patients with myocardial infarction who have been strictly confined to bed. Thus, the QOL of patients with neuropathic pain is remarkably affected.

QOL : quality of life

HRQL : health-related QOL

EQ-5D : EuroQol 5 Dimension HRQL developed in the EU31.

References

- 1) Bouhassira D, Lanteri-Minet M, Attal N, et al: Prevalence of chronic pain with neuropathic pain characteristics in the general population. *Pain* 2008 ; 136 : 380-387 [4]
- 2) Attal N, Lanteri-Minet M, Laurent B, et al: The specific disease burden of neuropathic pain : Results of a French nationwide survey. *Pain* 2011 ; 152 : 2836-2843 [4]
- 3) O'Connor AB : Neuropathic pain : Quality-of-life impact, costs and cost effectiveness of therapy. *Pharmacoeconomics* 27 ; 95-112, 2009 [3b]

11. Management plan for neuropathic pain : general remarks

CQ13 : What is a summary of management plan for neuropathic pain?

The severity is relatively high in neuropathic pain compared to the other types of chronic pain, and the QOL of these patients has been remarkably decreased. Hence, the treatment goal should be planned on the basis of both the severity in pain and their impaired ADL and QOL. The basic treatment strategy is a pharmacotherapy which can relieve the pain. However, if the patients do not respond well to pharmacotherapy, which is prescribed in a step-wise manner, or when their adherence for pharmacotherapy is not adequate, neuromodulation treatments or several interventional treatments are considered.

ADL : activity of daily living

Further, in order to improve the patients' ADL and QOL, functional exercises such as rehabilitations are provided to the patients so that they will be able to recover their self-efficacy. Thus, it is really important to provide inter- or multi-disciplinary treatment for neuropathic pain by combining various treatment approaches according to the bio-psycho-social factors.

Summary of overall evidence : B

Comments :

Neuropathic pain is complicated by various conditions other than pain such as sleep disorder, impaired ADL, depression, anxiety, dry mouth, and loss of appetite¹⁾. These can be negative factors which form a vicious circle model of pain (fear-avoidance model) with negative spirals of ADL and QOL²⁾. In order to treat neuropathic pain which usually has fallen into such chronic pain syndrome, we need perspectives to evaluate these negative bio-psycho-social factors in respective patients ; hence, the treatment goal is planned on the basis of both severity in pain and their impaired ADL and QOL.

The basic treatment strategy for pain relief is pharmacotherapy. However, if patients do not respond to it, which is prescribed in a step-wise manner, or when their adherence for it is not adequate, neuromodulation treatments^{3,4)} or several interventional treatments are considered. Further, in order to improve patients' ADL and QOL, functional exercises such as rehabilitations are provided to patients so that they will be able to recover their self-efficacy. Thus, it is really important to provide inter- or multi-disciplinary treatments for neuropathic pain by combining various treatment approaches according to their bio-psycho-social factors. In addition, the treatment goal should be set not only to control pain but also to improve their meaningful daily lives and spend their

lifetimes as quietly as possible without any psychological distresses.

References

- 1) Meyer-Rosberg K, Kvamstrom A, Kinnman E, et al: Peripheral neuropathic pain: A multidimensional burden for patients. *Eur J Pain* 2001 ; 5 : 379–389
- 2) Leeuw M, Goossens MEJB, Linton SJ, et al: The fear-avoidance model of musculoskeletal pain: Current state of scientific evidence. *J Behav Med* 2007 ; 30 : 77–94
- 3) Deer TR, Krames E, Mekhail N, et al: The appropriate use of neurostimulation: New and evolving neurostimulation therapies and applicable treatment for chronic pain and selected disease states. *Neuromodulation* 2014 ; 17 : 599–615
- 4) NICE clinical guideline 2008 [spinal cord stimulation for chronic pain of neuropathic or ischaemic origin]

12. Treatment goal for neuropathic pain

CQ14 : How do we establish the treatment goal for neuropathic pain ?

The drugs used for neuropathic pain cannot completely cure the condition. Therefore, it is important not only to relieve the pain but also to establish a goal to achieve improvements in ADL and QOL.

The level of recommendation and the summary of overall evidence : 1D

Comments :

The onset mechanism of neuropathic pain has not been adequately revealed. Hence, there is no drug which can induce remission of the pathological condition at this point. When conducting a pharmacotherapy, we must consider safety, adherence and interactions with other drugs in addition to the analgesic effects. Moreover, potentials for dependency or abuse, as well as long-term effects on the patients' bodies should be also taken into consideration¹⁾.

In guidelines of EFNS and NeuPSIG of IASP, alleviation of pain intensity (e.g. VAS) has been prioritized over the multifaceted evaluations of pain (MPQ) : the ADL has been currently included in the secondary outcomes. According to IMMPACT, it is recommended to evaluate the following 6 items : intensity of pain, physical functions, mental functions, the level of patients' satisfaction, signs of adverse reactions, and adherence to the treatments, in a clinical study of chronic pain^{2,3)}. It is considered crucial to evaluate these factors comprehensively in the clinical practice.

It is also important in the care of neuropathic pain not only to improve the degree of pain, but also to proceed the treatments aiming to improve the patients' ADL and QOL such as the levels of their life-activities and social activities.

References

- 1) Dworkin RH, O'Connor AB, Backonja M, et al: Pharmacologic management of neuropathic pain : Evidence-based recommendations. *Pain* 2007 ; 132 : 237-251 [1a]
- 2) Turk DC, Dworkin RH, Allen RR, et al: Core outcome domains for chronic pain clinical trials : IMMPACT recommendations. *Pain* 2003 ; 106 : 337-345 [1a]
- 3) Dworkin RH, Turk DC, Wyrwich KW, et al: Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials : IMMPACT recommendations. *J Pain* 2008 ; 9 : 105-121 [1a]

EFNS : European Federation of Neurological Societies

IASP-NeuPSIG : Neuropathic Pain Special Interest Group

MPQ : McGill Pain Questionnaire

IMMPACT : Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials

☐ I . Overview of neuropathic pain

☐ II . Diagnosis and treatment of neuropathic pain

☒ III . Pharmacotherapies for neuropathic pain

13. Pharmacotherapies for neuropathic pain [CQ15](#), [CQ16](#)
14. Ca^{2+} channel $\alpha_2\delta$ ligand [CQ17](#)
15. Tricyclic antidepressant [CQ18](#), [CQ19](#)
16. Serotonin–noradrenalin reuptake inhibitor (SNRI) [CQ20](#)
17. Extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus [CQ21](#)
18. Opioid analgesics[weak] : Tramadol [CQ22](#)
19. Opioid analgesics[moderate] : Buprenorphine [CQ23](#), [CQ24](#), [CQ25](#), [CQ26](#)
20. Opioid analgesics[strong] : Fentanyl, etc. [CQ27](#)
21. Type and usage of selective drugs for neuropathic pain
22. Other antidepressants [CQ28](#)
23. Anti-epileptics [CQ29](#)
24. N-methyl-*D*-aspartate (NMDA) receptor agonists [CQ30](#)
25. Anti-arrhythmic drug [CQ31](#)
26. Chinese herbal medicine [CQ32](#)

☐ IV . Diseases which present neuropathic pain

13. Pharmacotherapies for neuropathic pain

CQ15 : What are indexes of treatment effects of pharmacotherapy for neuropathic pain and the level of recommendation for respective drugs ?

For treatment effects of pharmacotherapy for neuropathic pain, focus should be placed not only on the improvement of pain but also on patients' QOL.

Out of all analgesics approved in Japan, tricyclic antidepressant (amitripty-

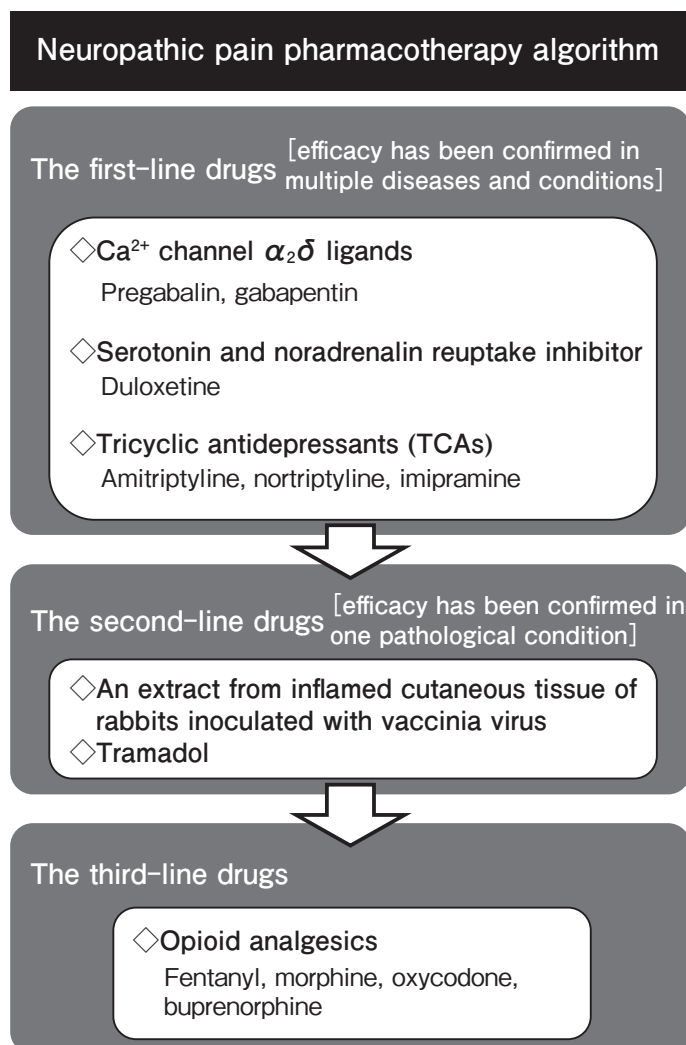


Figure 5 Neuropathic pain pharmacotherapy algorithm in Japan

line), pregabalin, and duloxetine ^{Note 1} are recommended as the first-line drugs, and tramadol and an extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus as the second-line drugs. The third-line drugs could be opioid analgesics except for tramadol. However, we should be careful in clinical use as the names of insurance-approved diseases are different for each drug. For a long-term use of opioid analgesics including tramadol and introduction of opioid analgesics, it is desirable to receive a collaborative consultation from a pain management specialist.

The level of recommendation and the summary of overall evidence : 1B

Comments :

Pathological conditions and diseases associated with neuropathic pain vary greatly ^{Note 2} ; it is extremely difficult to conduct a clinical study for each one of the conditions and diseases. Therefore, in this guideline, we aim to present recommendations for neuropathic pain and selected drugs, which would have a potential to demonstrate analgesic effects on multiple diseases associated with neuropathic pain and have been approved in Japan as analgesics, were selected as the first-line drugs. For recommendation of the second-line drugs, we selected analgesic drugs which are effective for only 1 type of diseases associated with neuropathic pain (Figure 5). Opioid analgesics are shown to be effective for multiple diseases associated with neuropathic pain. However, we consider them as the third-line drugs because there have safety concerns for a long-term use. Of all opioid analgesics, tramadol has been exceptionally classified as the second-line drug as its improvement effect on QOL is relatively high and its risk of developing addiction is low. It is desirable to receive a collaborative consultation from a pain management specialist when considering a long-term administration of opioid analgesics including tramadol.

Note 1 : Duloxetine : approved for depression, chronic low back pain, painful diabetic neuropathy. For precautions when using this drug for pain, appropriateness of administration of this drug should be judged carefully taking into consideration the risk of developing psychiatric symptoms such as suicidal ideation, suicidal attempt, hostility and aggression.

Note 2 : Refer to Table 1 "Diseases associated with neuropathic pain"

13–1. First-line drugs

Pregabalin/gabapentin

Pregabalin ^{Note 1} inhibits the release of excitatory neurotransmitters by combining with $\alpha_2\delta$ subunits of voltage-dependent Ca^{2+} channels in the central nervous system. It has been shown to induce significant analgesic effects on postherpetic neuralgia¹⁻⁵⁾, pain and numbness associated with diabetic neuropathy⁶⁻¹⁴⁾, and pain after spinal cord injury^{15,16)} compared to placebo and improves sleep disturbance, depression and anxiety associated with neuropathic pain ; These favorable effects can be clearly observed not only in pain but also in patients' QOL. Further, its analgesic effects have been also confirmed for radicu-

Note 1 : Pregabalin : approved for neuropathic pain

Note 2 : Gabapentin :
approved for partial seizure

Note 3 : Gabapentin enacarbil : approved for idiopathic restless legs syndrome

Note 4 : Amitriptyline has been approved for depression and neuropathic pain, and other TCAs for depression.

Note 5 : Duloxetine : approved for depression, chronic low back pain, painful diabetic neuropathy. For precautions when using this drug for pain, appropriateness of administration of this drug should be judged carefully taking into consideration the risk of developing psychiatric symptoms such as suicidal ideation, suicidal attempt, hostility and aggression.

SNRI : serotonin-noradrenaline re-uptake inhibitor

lopathy¹⁷⁾ and for the pain after spinal cord injury and post-stroke pain^{16,18)}. Although pregabalin may induce adverse effect such as sleepiness, lightheadedness, and dizziness, requiring careful and gradual increase in dose, tolerability is relatively high¹⁹⁾. The dose needs to be reduced however in patients with decreased renal function. The initial dose of pregabalin is supposed to be 150 mg/day, twice a day after breakfast and dinner to start with. While in elderly patients and in those who are at the risk of emerging adverse effects, it can be started at 25–75 mg/day once daily at bedtime.

Similar to pregabalin, gabapentin^{Note 2} and gabapentin enacarbil^{Note 3} are also the drugs which act as $\alpha_2\delta$ subunit ligands for Ca^{2+} channels. Neither one of these drugs has been approved as an analgesic agent in Japan. However, in overseas, analgesic effects and improvement effects of QOL have been revealed with gabapentin in multiple diseases associated with neuropathic pain ; hence, it is considered as the first-line drug in those countries²⁰⁾.

Tricyclic antidepressants (TCAs)

TCAs^{Note 4} are significantly effective for a variety of peripheral and central neuropathic pain compared to placebo. It has been revealed that analgesic properties of TCAs are different from those of antidepressant mechanism. Out of all TCAs, analgesic effects of amitriptyline for neuropathic pain were nearly consistent in various diseases and pathological conditions, regardless of their types, such as postherpetic neuralgia^{21–23)}, pain and numbness associated with diabetic neuropathy^{24,25)}, traumatic nerve injury²⁶⁾ and cerebral stroke²⁷⁾. It is known that there is no difference in analgesic effects between the tertiary amine TCAs (amitriptyline and imipramine) which show well-balanced serotonin-noradrenaline reuptake inhibition and the secondary amine TCA (nortriptyline) which shows relatively selective noradrenaline reuptake inhibition^{28,29)} ; hence, the secondary amine TCA (nortriptyline) is considered more favorable than the tertiary amine TCAs (amitriptyline and imipramine) for being superior in tolerability but equivalent in analgesic effects. It has been particularly reported for elderly patients that incidence of fall and cardiac sudden death increase at doses higher than 75 mg and 100 mg, respectively ; hence TCAs should be used carefully, starting from a low dose²⁰⁾. As majority of clinical studies using TCAs had been conducted before the year 2000, improvement effects on QOL are still unknown due to lack of appropriate evaluations made on QOL.

Serotonin-noradrenaline reuptake inhibitors (SNRI)

Duloxetine^{Note 5} is one of the serotonin-noradrenaline reuptake inhibitors (SNRI) which is safer to use compared to TCAs and is a good option for pa-

tients with cardiac diseases. The analgesic mechanism of SNRI is considered to be induced by activation of the descending pain inhibitory system. The analgesic effect of duloxetine has been demonstrated compared to placebo in a clinical study on pain and numbness associated with diabetic neuropathy³⁰⁻³⁴⁾, and its safety has been confirmed in a 52 week-study^{35,36)}. In addition, analgesic effects on cancer chemotherapy-induced neuropathy³⁷⁾ and low back pain associated with radiculopathy³⁸⁾ have been also observed. Of all adverse effects of duloxetine observed in clinical studies conducted in Japan, incidence of somnolence and nausea were 5% or above and were significantly higher than that of placebo though the severity was either weak or moderate³⁵⁾. In order to inhibit development of adverse reactions during the initial treatment stage, administration of this drug is started at a dose of 20 mg/day and increased up to the optimal dose (maintenance dose) at 40–60 mg/day in 1–2 weeks. The analgesic effect of duloxetine is obtained at this dose of 40–60 mg/day in 1 week after the start of treatment³⁵⁾. The analgesic effects of once daily administration at 60 mg/day and those of twice daily administration of 60 mg/day are reportedly equivalent, while incidence of adverse reactions are lower with the twice-daily administration of 60 mg/day³⁰⁾. It has been clearly shown that duloxetine improved not only pain but also QOL as well exclusively in patients with peripheral neuropathy. In addition to duloxetine, two other SNRIs, venlafaxine^{Note 6} and milnacipran^{Note 7} are available in Japan. It has been shown that venlafaxine has analgesic effects on multiple diseases associated with neuropathic pain, and the level of recommendation is equivalent to that of duloxetine in overseas²⁰⁾. While for milnacipran, its efficacy has not been revealed as there is no high-quality clinical study report available on its use for neuropathic pain³⁹⁾.

Note 6 : Venlafaxine :
approved for depression/
depressive state

Note 7 : Milnacipran :
approved for depression/
depressive state

13–2. Second-line drugs

Extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus^{Note 8}

In clinical studies conducted only in Japan, the extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus was shown to be effective particularly for postherpetic neuralgia, a type of peripheral neuropathic pain^{40,41)}. In addition to the analgesic effects, there are other features with this drug such as that it does not induce serious adverse reactions and the tolerability is very high. It has been used for more than 20 years in clinical practice in Japan and has been highly safe. Although sleep disorder associated with pain improved, efficacy for other aspects of QOL has not yet been evaluated. The patients with postherpetic neuralgia are treated with twice-daily adminis-

Note 8 : Extract from inflamed cutaneous tissue of rabbits inoculated with vaccine virus : approved for post-herpetic neuralgia, low back pain, cervicobrachial syndrome, scapulohumeral periarthritis, osteoarthritis

Note 9 : Opioid analgesic [weak] : opioid analgesics approved for weak pain

Note 10 : Tramadol : approved for chronic pain, cancer pain

Note 11 : Ethylmorphine hydrochloride : approved for intensive pain

Morphine hydrochloride oral liquid preparation / suppository / Morphine sulfate sustained release tablet : approved for moderate-severe cancer pain

Note 12 : Oxycodone hydrochloride sustained release tablet / powder : approved for moderate-severe cancer pain

Note 13 : Transdermal fentanyl preparation : 3-day patch type has been approved for moderate-severe chronic pain and cancer pain when switching from a narcotic analgesic. 1-day type has been approved for moderate-severe cancer pain when switching from other opioid analgesics.

Note 14 : Buprenorphine hydrochloride : approved for postoperative pain and cancer pain. Transdermal sustained release preparation has been approved for chronic pain associated with osteoarthritis / low back pain, which are difficult to be treated by non-opioid analgesics.

tration, in the morning and in evening, of 4 tables per day.

Opioid analgesic [weak]^{Note 9} : tramadol

Tramadol^{Note 10} acts as both a μ -opioid receptor agonist and SNRI. It is categorized as an opioid analgesic [weak], which is not designated as a restricted opioid for medical use. However, unlike pentazocine or buprenorphine, tramadol acts as a full agonist for μ -opioid receptors : there is no ceiling effect, and analgesic effects can be obtained dose-dependently (though the upper limit of its dose is at 400 mg/day in clinical practice as a risk of seizure has been reported at a high-dose). The analgesic effects of tramadol have been demonstrated for painful diabetic neuropathy^{42,43)}, postherpetic neuralgia⁴⁴⁾ and cancer-related neuropathic pain⁴⁵⁾, and improvement effects on QOL have been also confirmed. Although development of addiction is very unlikely⁴⁶⁾, cautions are required for a long-term use ; it is desirable to use this drug relatively for a short-term. Adverse effects (e.g. constipation, sleepiness, vomiting) induced by tramadol are generally milder than those of other opioid analgesics, and with both analgesic effects and QOL improvement effects, tramadol is given priority over other opioid analgesics. However, it is recommended not as the first-line but as the second-line drug due to safety concerns associated with a long-term use²⁰⁾.

For tramadol, oral forms and intravenous form are available in Japan. There are three forms of oral drugs : acetaminophen combination tablets (tablets), orally disintegrating (OD) tablets, and sustained-release tablets. The dosage form of orally-disintegrating tablets can be either 25 mg or 50 mg, and are rapidly released. Acetaminophen combination tablets are fast-releasing drugs containing 37.5 mg of tramadol and 325 mg of acetaminophen. The dosage of the sustained-release tablets is 100 mg. When using tramadol, it is desirable to administer in dose-escalation manner starting from a small amount so that higher tolerability will be achieved. After introducing/dose-escalating the rapid-release drug, it can be switched to a sustained-release drug. This is an idealistic way to maintain medication adherence.

13-3. Third-line drugs

Opioid analgesic

Opioid analgesics are effective for a variety of diseases associated with peripheral and central neuropathic pain, including painful diabetic neuropathy and postherpetic neuralgia. There is abundant evidence for morphine^{Note 11 47-49)} and oxycodone^{Note 12 50-52)}. Transdermal fentanyl preparation^{Note 13 53,54)} of 1-day patch type and 3-day patch type have been approved for moderate-severe

cancer pain when switching from other opioid. Buprenorphine hydrochloride [Note 14 54\)](#) is a partial agonist for μ -opioid receptors, showing equivalent efficacy. Incidence of adverse effects (e.g. nausea, constipation, sleepiness) induced by opioid analgesics is relatively high, and these could persist for a long time throughout the treatment period⁵⁵⁾. Moreover, there is no systematic investigation made on long-term safety of these opioid analgesics. Opioid analgesics might not be essentially safer than other drugs due to adverse effects such as development of hypogonadism or addiction though the incidence is low. Hence, it is desirable to receive a collaborative consultation from a pain management specialist when using opioid analgesics [moderate and strong]^{[Note 15](#)} listed in this chapter. Effective dosages of opioid analgesics vary greatly among patients ; either one of the following treatment-initiation methods is performed according to the individuals' clinical situations. Opioid analgesics described here should be considered after treatment with tramadol ; 10–15 mg of morphine hydrochloride, a short-acting opioid analgesic, is divided into 5–6 doses (every 4 hours) per day. Once the daily dose is determined, approximately, it is replaced by a long-acting opioid analgesic ^{[Note 16](#)}. Otherwise, a treatment can be started from the minimum dose of a long-acting opioid analgesic ^{[Note 17](#)}. It is desirable to administer opioid analgesics in a fixed schedule, and not in per-request medication. The maintenance dose of opioid analgesics is determined by gradually increasing/decreasing the dose, using the degree of severity of adverse effects, which emerge even with (a) analgesic effects and improvement effects on QOL, and (b) adequate measures (laxative for constipation), as a clinical index. We need to always continue evaluations on abuse or addiction when a patient is treated with an opioid analgesic. The recommended maintenance dose of an opioid analgesic is 15–120 mg/day when converted to morphine hydrochloride.

Note 15 : Opioid analgesics [moderate and strong] :
opioid analgesics approved for moderate and strong pain

Note 16 : No drug has been approved in Japan for such a use.

Note 17 : Only fentanyl patch has been approved in Japan for non-cancer neuropathic pain. Oxycodone is now being developed for moderate-severe chronic pain

References

- 1) Dworkin RH, Corbin AE, Young JP Jr., et al: Pregabalin for the treatment of postherpetic neuralgia: A randomized, placebo-controlled trial. *Neurology* 2003 ; 60 : 1274–1283 [\[1b\]](#)
- 2) Sabatowski R, Galvez R, Cherry DA, et al: Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic neuralgia: Results of a randomised, placebo-controlled clinical trial. *Pain* 2004 ; 109 : 26–35 [\[1b\]](#)
- 3) Stacey BR, Barrett JA, Whalen E, et al: Pregabalin for postherpetic neuralgia: Placebo-controlled trial of fixed and flexible dosing regimens on allodynia and time to onset of pain relief. *J Pain* 2008 ; 9 : 1006–1017 [\[1b\]](#)
- 4) van Seventer R, Feister HA, Young JP Jr., et al: Efficacy and tolerability of twice-daily pregabalin for treating pain and related sleep interference in postherpetic neuralgia: A 13-week, randomized trial. *Curr Med Res Opin* 2006 ; 22 : 375–384 [\[1b\]](#)

- 5) Ogawa S, Suzuki M, Arakawa A, et al: Efficacy and safety of pregabalin for post-herpetic neuralgia: A multicenter collaborative randomized placebo controlled double blind control study. *Journal of Japan Society of Pain Clinicians* 2010; 17: 141-152 [1b]
- 6) Arezzo JC, Rosenstock J, Lamoreaux L, et al: Efficacy and safety of pregabalin 600 mg/day for treating painful diabetic peripheral neuropathy: A double-blind placebo-controlled trial. *BMC Neurology* 2008; 8: 33 [1b]
- 7) Lesser H, Sharma U, Lamoreaux L, et al: Pregabalin relieves symptoms of painful diabetic neuropathy: A randomized controlled trial. *Neurology* 2004; 63: 2104-2110 [1b]
- 8) Richter RW, Portenoy R, Sharma U, et al: Relief of painful diabetic peripheral neuropathy with pregabalin: A randomized, placebo-controlled trial. *J Pain* 2005; 6: 253-260 [1b]
- 9) Rosenstock J, Tuchman M, Lamoreaux L, et al: Pregabalin for the treatment of painful diabetic peripheral neuropathy: A double-blind, placebo-controlled trial. *Pain* 2004; 110: 628-638 [1b]
- 10) Tolle T, Freynhagen R, Versavel M, et al: Pregabalin for relief of neuropathic pain associated with diabetic neuropathy: A randomized, double-blind study. *Eur J Pain* 2008; 12: 203-213 [1b]
- 11) Freynhagen R, Strojek K, Griesing T, et al: Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible-and fixed-dose regimens. *Pain* 2005; 115: 254-263 [1b]
- 12) Freeman R, Durso-DeCruz E, Emir B: Efficacy, safety, and tolerability of pregabalin treatment for painful diabetic peripheral neuropathy: Findings from seven randomized, controlled trials across a range of doses. *Diabet Care* 2008; 31: 1448-1454 [1a]
- 13) Satoh J, Yagihashi S, Baba M, et al: Efficacy and safety of pregabalin for treating neuropathic pain associated with diabetic peripheral neuropathy: A 14-week, randomized, double-blind, placebo-controlled trial. *Diabet Med* 2011; 28: 109-116 [1b]
- 14) Randomized, double-blind, multicenter, placebo-controlled study of pregabalin for pain associated with diabetic peripheral neuropathy. <http://www.clinicaltrials.gov/ct2/show/results/NCT00553475?term=A0081163&rank=2>
- 15) Cardenas DD, Nieshoff EC, Suda K, et al: A randomized trial of pregabalin in patients with neuropathic pain due to spinal cord injury. *Neurology* 2013; 80: 533-539 [1b]
- 16) Siddall PJ, Cousins MJ, Otte A, et al: Pregabalin in central neuropathic pain associated with spinal cord injury: A placebo-controlled trial. *Neurology* 2006; 67: 1792-1800 [1b]
- 17) Saldaña MT, Navarro A, Pérez C, et al: Patient-reported-outcomes in subjects with painful lumbar or cervical radiculopathy treated with pregabalin: Evidence from medical practice in primary care settings. *Rheumatol Int* 2010; 30: 1005-1015
- 18) Vranken JH, Dijkgraaf MG, Kruis MR, et al: Pregabalin in patients with central neuropathic pain: A randomized, double-blind, placebo-controlled trial of a flexible-dose regimen. *Pain* 2006; 136: 150-157 [1b]
- 19) Dworking RH, O'Connor AB, Backonja M, et al: Pharmacologic management of neuropathic pain: Evidence-based recommendations. *Pain* 2007; 132: 237-251

- 20) Finnerup NB, Attal N, Haroutounian S, et al: Pharmacotherapy for neuropathic pain in adults: A systematic review and meta-analysis. *Lancet Neurol* 2015; 14: 162-173
- 21) Graff-Radford SB, Shaw LR, Naliboff BN: Amitriptyline and fluphenazine in the treatment of postherpetic neuralgia. *Clin J Pain* 2000; 16: 188-192 [1b]
- 22) Max MB, Schafer SC, Culnane M, et al: Amitriptyline, but not lorazepam, relieves postherpetic neuralgia. *Neurology* 1988; 38: 1427-1432 [1b]
- 23) Rintala DH, Holmes SA, Courtade D, et al: Comparison of the effectiveness of amitriptyline and gabapentin on chronic neuropathic pain in persons with spinal cord injury. *Arch Phys Med Rehabil* 2007; 88: 1547-1560 [1b]
- 24) Vrethem M, Boivie J, Arnqvist H, et al: A comparison amitriptyline and maprotiline in the treatment of painful polyneuropathy in diabetics and nondiabetics. *Clin J Pain* 1997; 13: 313-323 [1b]
- 25) Max MB, Culnane M, Schafer SC, et al: Amitriptyline relieves diabetic neuropathy pain in patients with normal or depressed mood. *Neurology* 2003; 37: 589-596 [1b]
- 26) Kalso E, Tasmuth T, Neuvonen PJ: Amitriptyline effectively relieves neuropathic pain following treatment of breast cancer. *Pain* 1996; 64: 293-302 [1b]
- 27) Leijon G, Boivie J: Central post-stroke pain: A controlled trial of amitriptyline and carbamazepine. *Pain* 1989; 36: 27-36 [1b]
- 28) Gilron I, Watson CP, Cahill CM, et al: Neuropathic pain: A practical guide for the clinician. *CMAJ* 2006; 175: 265-275
- 29) Watson CPN, Vernich L, Chipman M, et al: Nortriptyline versus amitriptyline in postherpetic neuralgia: A randomized trial. *Neurology* 1998; 51: 1166-1171
- 30) Goldstein DJ, Lu Y, Detke MJ, et al: Duloxetine vs. placebo in patients with painful diabetic neuropathy. *Pain* 2005; 116: 109-118 [1b]
- 31) Raskin J, Pritchett Y, Chappell AS, et al: Duloxetine in the treatment of diabetic peripheral neuropathic pain: Results from three clinical trials. *European Federation of Neurological Societies* 2005; Sept 17-20; Athens, Greece [1b]
- 32) Wernicke JF, Pritchett YL, D'Souza DN, et al: A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. *Neurology* 2006; 67: 1411-1420 [1b]
- 33) Raskin J, Pritchett YL, Wang F, et al: A double-blind, randomized multicenter trial comparing duloxetine with placebo in the management of diabetic peripheral neuropathic pain. *Pain Med* 2005; 6: 346-356 [1b]
- 34) Wernicke JF, Wang F, Pritchett YL, et al: An open-label 52-week clinical extension comparing duloxetine with routine care in patients with diabetic peripheral neuropathic pain. *Pain Med* 2007; 8: 503-513 [2b]
- 35) Yasuda H, Hotta N, Nakao K, et al: Superiority of duloxetine to placebo in improving diabetic neuropathic pain: Results of a randomized controlled trial in Japan. *J Diabet Invest* (in press) [1b]
- 36) Raskin J, Smith TR, Wong K, et al: Duloxetine versus routine care in the long-term management of diabetic peripheral neuropathic pain. *J Palliat Med* 2006; 9: 29-40 [2b]
- 37) Smith EML, Pang H, Cirrincione C, et al: Effect of duloxetine on pain, function and quality of life among patients with chemotherapy-induced

- painful peripheral neuropathy. *JAMA* 2013; 309: 1359-1367 [2b]
- 38) Schukro RP, Oehmke MJ, Geroldinger A, et al: Efficacy of duloxetine in chronic low back pain with a neuropathic pain component. *Anesthesiology* 2016; 124: 150-158 [1b]
 - 39) Derry S, Phillips T, Moore RA, et al: Milnacipran for neuropathic pain in adults. *Cochrane Database Syst Rev* 2015 Jul 6; 7: CD011789. doi: 10.1002/14651858. CD011789 [3a]
 - 40) Yamamura H, Dan K, Wakasugi B, et al: Effects of neurotrophin tablets on post-herpetic neuralgia: A placebo-controlled multicenter double blind study. *Journal of Clinical and Experimental Medicine* 1988; 147: 651-664 [1b]
 - 41) Sofue I, Hanakago R, Matsumoto A, et al: SMON (subacute myelo-optico-neuropathy): Clinical evaluations on neurotrophin for sequelae: A multicenter double blind crossover study. *Journal of Clinical and Experimental Medicine* 1987; 143: 233-52 [2b]
 - 42) Harati Y, Gooch C, Swenson M, et al: Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. *Neurology* 1998; 50: 1842-1846 [1b]
 - 43) Sindrup SH, Andersen G, Madsen C, et al: Tramadol relieves pain and allodynia in polyneuropathy: A randomized, double-blind, controlled trial. *Pain* 1999; 83: 85-90 [1b]
 - 44) Boureau F, Legallier P, Kabir-Ahmadi M, et al: Tramadol in post-herpetic neuralgia: A randomized, double-blind, placebo-controlled trial. *Pain* 2003; 104: 323-331 [1b]
 - 45) Arbaiza D, Vidal O: Tramadol in the treatment of neuropathic cancer pain: A double-blind, placebo-controlled study. *Clin Drug Invest* 2007; 27: 75-83 [1b]
 - 46) Cicero TJ, et al: . Rates of abuse of tramadol remain unchanged with the introduction of new branded and generic products: Results of an abuse monitoring system, 1994-2004. *Pharmacoepidemiol drug safe* 2005; 14: 851-859 [1b]
 - 47) Huse E, Larbig W, Flor H, et al: The effect of opioids on phantom limb pain and cortical reorganization. *Pain* 2001; 90: 47-55 [1b]
 - 48) Wu CL, Agarwal S, Tella PK, et al: Morphine versus mexiletine for treatment of postamputation pain: A randomized, placebo-controlled, crossover trial. *Anesthesiology* 2008; 109: 289-296 [1b]
 - 49) Gilron I, Bailey JM, Tu D, et al: Morphine, gabapentin, or their combination for neuropathic pain. *N Engl J Med* 2005; 352: 1324-1334 [1b]
 - 50) Gimbel JS, Richards P, Portenoy RK: Controlled-release oxycodone for pain in diabetic neuropathy: A randomized controlled trial. *Neurology* 2003; 60: 927-934 [1b]
 - 51) Watson CPN, Babul N: Efficacy of oxycodone in neuropathic pain: A randomized trial in postherpetic neuralgia. *Neurology* 1998; 50: 1837-1841 [1b]
 - 52) Watson CPN, Moulin D, Watt-Watson J, et al: Controlled-release oxycodone relieves neuropathic pain: A randomized controlled trial in painful diabetic neuropathy. *Pain* 2003; 105: 71-78 [1b]
 - 53) Miyazaki H, Hanaoka K, Namiki A, et al: A clinical study I of Durotep® MT patch in chronic non-cancer pain patients: Four week and a long-term (52 week) application. *Journal of New Remedies & Clinics* 2010; 59: 157-180 [1b]
 - 54) Canneti A, Luzi M, Di Marco P, et al: Safety and efficacy of transdermal

buprenorphine and transdermal fentanyl in the treatment of neuropathic pain in AIDS patients. *Minerva Anesthesiol* 2013 ; 79 : 871-883 [2c]

- 55) Watson CPN, Watt-Watson JH, Chipman ML : Chronic non-cancer pain and the long term utility of opioids. *Pain Res Manage* 2004 ; 9 : 19-24 [5]

CQ16 : What is the level of recommendation of NSAIDs and acetaminophen for neuropathic pain ?

There is no high-quality evidence on analgesic effects of NSAIDs used for neuropathic pain : NSAIDs are not recommended for neuropathic pain.

The level of recommendation and the summary of overall evidence : 1B

Comments :

There is no high-quality study which demonstrated efficacy of NSAIDs, including selective cyclooxygenase (COX)-2 inhibitor, for neuropathic pain. NSAIDs are not recommended in a systematic analysis either. However, a concomitant use of NSAIDs in addition to the treatments for neuropathic pain might be considered when a mixed pain condition, where neuropathic pain is complicated by nociceptive pain (especially inflammatory pain), is expected to occur ¹⁾.

Acetaminophen is not recommended as there is also no high-quality study which showed its efficacy for neuropathic pain. It is not recommended for the mixed pain condition either as there is hardly any anti-inflammatory effects with acetaminophen.

NSAIDs : nonsteroidal anti-inflammatory drugs

COX-2 : cyclooxygenase-2

Mixed pain condition

参考文献

- 1) Romano CL, Romano D, Bonora C, et al : Pregabalin, celecoxib, and their combination for treatment of chronic low-back pain. *J Orthopaed Traumatol* 2009 ; 10 : 185-191 [3b]
- 2) NICE clinical guideline 2013-Neuropathic pain in adults : Pharmacological management in non-specialist settings

14. Calcium (Ca^{2+}) channel $\alpha_2\delta$ ligand

CQ17 : What is the level of recommendation of pregabalin for neuropathic pain?

Analgesic effects of pregabalin for not only peripheral but also central neuropathic pain have been revealed in high-quality clinical studies ; it is the only drug which has been approved for indications of neuropathic pain in general (central and peripheral). The efficacy of pregabalin has been demonstrated not only for the analgesic effects on neuropathic pain but also for improvement effects on both ADL and QOL, such as depression, anxiety, and sleep disorder associated with neuropathic pain. Therefore, pregabalin is recommended as the first-line drug.

The level of recommendation and the summary of overall evidence : 1A

Comments :

Pregabalin ^{Note 1} inhibits the release of excitatory neurotransmitters by combining with $\alpha_2\delta$ subunits of voltage-dependent Ca^{2+} channel in the central nervous system and shows significant analgesic effects, compared to placebo, on postherpetic neuralgia^{1,2)}, pain and numbness associated with diabetic neuropathy³⁾, and pain after spinal cord injury⁴⁾. Neuropathic pain is complicated by various comorbidities other than pain, such as sleep disorder, decreased activity level, depression, anxiety, dry mouth, and loss of appetite⁵⁾, and the condition can be aggravated when a negative spiral of ADL and QOL is formed by these factors. Of these, approximately 60% of patients with neuropathic pain complain of moderate or severe sleep disorder, and their QOL has been severely affected. Pregabalin is not only shown to be effective for sleep disorder associated with neuropathic pain^{2,6)} but also on depression and anxiety associated with neuropathic pain, leading to remarkable improvement in ADL and QOL. Considering these clinical efficacy, pregabalin has been consistently recommended as the first-line drug in various management plans.

The Ca^{2+} channel $\alpha_2\delta$ ligands, other than pregabalin, include gabapentin ^{Note 2} and gabapentin enacarbil ^{Note 3}. Gabapentin is shown to be effective for multiple types of neuropathic pain and on improvement of QOL, and is considered as the first-line drug in overseas countries⁷⁾. Gabapentin enacarbil is a new drug in Japan with which only a few reports are available for neuropathic pain. However, the results of these studies have been suggesting potential efficacy of this drug on neuropathic pain, as well as efficacy in patients whose conditions have been resistant to gabapentin^{8,9)}. It requires attentions however as

Note 1 : Pregabalin :
approved for neuropathic pain and fibromyalgia

Note 2 : Gabapentin :
approved for partial seizure

Note 3 : Gabapentin enacarbil : approved for idiopathic rest-less legs syndrome

neither one of these drugs has been approved as analgesics.

References

- 1) Dworkin RH, Corbin AE, Young JP Jr., et al: Pregabalin for the treatment of postherpetic neuralgia: A randomized, placebo-controlled trial. *Neurology* 2003; 60: 1274–1283 [1b]
- 2) Ogawa S, Suzuki M, Arakawa A, et al: Efficacy and Safety of pregabalin for post-herpetic neuralgia: A multicenter collaborative randomized placebo control double blind comparative study. *Journal of Japan Society of Pain Clinicians* 2010; 17: 141–152 [1b]
- 3) Arezzo JC, Rosenstock J, Lamoreaux L, et al: Efficacy and safety of pregabalin 600 mg/day for treating painful diabetic peripheral neuropathy: A double-blind placebo-controlled trial. *BMC Neurology* 2008; 8: 33 [1b]
- 4) Cardenas DD, Nieshoff EC, Suda K, et al: A randomized trial of pregabalin in patients with neuropathic pain due to spinal cord injury. *Neurology* 2013; 80: 533–539 [1b]
- 5) Meyer-Rosberg K, Kvamstrom A, Kinnman E, et al: Peripheral neuropathic pain: A multidimensional burden for patients. *Eur J Pain* 2001; 5: 379–389
- 6) Satoh J, Yagihashi S, Baba M, et al: Efficacy and safety of pregabalin for treating neuropathic pain associated with diabetic peripheral neuropathy: A 14-week, randomized, double-blind, placebo-controlled trial. *Diabet Med* 2011; 28: 109–116 [1b]
- 7) Finnerup NB, Attal N, Haroutounian S, et al: Pharmacotherapy for neuropathic pain in adults: A systematic review and meta-analysis. *Lancet Neurol* 2015; 14: 162–173
- 8) Zhang L, Rainka M, Freeman R, et al: A randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of gabapentin enacarbil in subjects with neuropathic pain associated with postherpetic neuralgia (PXN110748). *J Pain* 2013; 14: 590–603 [1b]
- 9) Harden RN, Freeman R, Rainka M, et al: A phase 2a, randomized, crossover trial of gabapentin enacarbil for the treatment of postherpetic neuralgia in gabapentin inadequate responders. *Pain Med* 2013; 14: 1918–1932 [1b]

15. Tricyclic antidepressant

CQ18 : Are tricyclic antidepressants effective for neuropathic pain ?

NNT : number needed to treat

Number of patients that need to be treated in order for one to benefit.

SNRI : serotonin-noradrenaline reuptake inhibitor

TCA : tricyclic antidepressant

NNH : number needed to harm

NNT for neuropathic pain is the lowest with tricyclic antidepressants, and those of strong opioid and tramadol are almost equivalent. NNTs of SNRI, gabapentin and pregabalin are slightly higher than that of tricyclic antidepressants (TCA). TCA is one of the most effective drugs for neuropathic pain and is effective for the treatment.

The level of recommendation and the summary of overall evidence : 1B

Comments :

For the efficacy of analgesic drugs, NNT and NNH of TCAs for neuropathic pain in a systematic review published in 2015¹⁾ were reported to be 3.6 and 13.4, respectively.

NNT is quantified by a stochastic index "how many patients need to be treated in order for one patient to achieve reduction of pain by more than 50%". Thus, NNT is a useful index to take a general view of analgesic effects of various drugs. However, it should be noted that NNT is not an absolute index which can be used in the actual clinical practice as each designs of randomized controlled trials (RCTs) had been heterogeneous, the duration of the study period was too short in most of the RCTs, and the goal of the treatment for neuropathic pain is not only to relieve the pain but also to improve ADL and QOL ; moreover, although 50% pain intensity reduction is included as the efficacy criteria of NNT, even 30% pain intensity reduction could be meaningful in terms of QOL. This would apply to NNH, which is an index for adverse reactions.

It has been shown in RCTs that TCAs induce significant analgesic effects for a variety of peripheral and central neuropathic pain such as painful diabetic neuropathy²⁻⁴⁾, postherpetic neuralgia⁵⁻⁸⁾, pain after traumatic nerve injury⁹⁾, central post-stroke pain¹⁰⁾, and pain after spinal cord injury¹¹⁾. It has been also revealed that analgesic effects of TCAs are not related to the antidepressant effects, and that analgesic effects can be obtained at a lower dose in a shorter period of time compared to the antidepressant effects.

The major mechanism of analgesic effects is activation of the descending pain inhibitory system through the serotonin-noradrenaline reuptake inhibition. In addition, NMDA receptor antagonistic action and Na⁺ channel blocking action are involved^{12,13)}. Adverse reactions include anticholinergic effects such as dry mouth and constipation ; attention is needed for cardiotoxicity as

RCT : randomized controlled trial

well^{14,15}. With higher quality evidences and lower price, TCAs are considered more cost-effective than antidepressants or anti-epileptic agents^{1,16}.

CQ19 : What kind of drugs are included in the tricyclic antidepressants (TCAs) ? How can we differentiate them when we use?

Tricyclic antidepressants (TCAs) can be classified into tertiary amine TCAs (amitriptyline, imipramine, clomipramine) and secondary amine TCAs (nortriptyline, desipramine), which are active metabolites of the tertiary amine TCAs. The analgesic effects are slightly more prominent in the tertiary amine TCAs, while the tolerability for adverse reactions is greater in the secondary amine TCAs.

The level of recommendation and the summary of overall evidence : 1B

Comments :

For TCAs, there are tertiary amine TCAs (amitriptyline, imipramine, clomipramine) which induce well-balanced serotonin–noradrenaline reuptake inhibition, and secondary amine TCA (nortriptyline, desipramine) which inhibits relatively selective noradrenaline reuptake. Although the tertiary amine TCAs may be slightly superior in analgesic effects over the secondary amine TCAs (NNT for painful polyneuropathy : 2.1 vs 2.5, NTT for postherpetic neuralgia : 2.5 vs 3.1) the incidence of adverse reactions is higher ; the secondary amine TCAs are superior in terms of tolerability. It is worth trying to switch TCAs to obtain better analgesic effects or to reduce adverse reactions when either one of the TCAs was ineffective or when tolerability was too low for adverse reactions. The administration can be started at a low dose of 10–25 mg/day (10 mg/day in elderly patients) and gradually increase up to 25–150 mg/day^{13,17,18}.

Amitriptyline ^{Note 1}

There are some RCTs which show analgesic effects of amitriptyline^{5,10,11} and the quality of evidence is moderate¹. Most of the studies were conducted in small-scale and there was a risk of bias. However, the quality of the studies was satisfactory. Although amitriptyline is effective for neuropathic pain and is the first-line drug, not many patients can achieve adequate pain relief¹⁹.

Imipramine ^{Note 2}

Imipramine is a tertiary amine TCA, as amitriptyline, and effective for neuropathic pain. The analgesic effects of imipramine have been reported in some RCTs^{20–23}. However, the evidence level was low due to small sample size and

Note 1 : Amitriptyline : approved and marketed as an antidepressant and a treatment for enuresis. In August 2015, "peripheral neuropathic pain" was added as an indication.

Note 2 : Imipramine : approved and marketed as an anti-depressant and a treatment for enuresis; off-label use is allowed occasionally for depressive symptoms associated with chronic pain.

Note 3 : Clomipramine :
approved and marketed as an anti-depressant, a treatment for enuresis and cataplexy of narcolepsy ; off-label use is allowed occasionally for depressive symptoms associated with chronic pain.

Note 4 : Nortriptyline :
approved and marketed as an anti-depressant. off-label use is allowed occasionally for depressive symptoms associated with chronic pain.

short duration of the observation period²⁴⁾.

Clomipramine ^{Note 3}

Analgesic effects of clomipramine have been reported in RCT²⁵⁾. However, the evidence level was low due to small sample size and short duration of the observation period. Clomipramine is the only TCA drug which can be administered intravenously ; it can be used when a rapid effect is required or when an oral intake is ineffective^{26, 27)}.

Nortriptyline ^{Note 4}

Nortriptyline is a major metabolite of amitriptyline with less adverse reactions. Analgesic effects of nortriptyline have been studied in some RCT, though the efficacy varied among these studied²⁸⁻³²⁾. In any of the RCT, the evidence level was low due to small sample size and short duration of the observation period. Nortriptyline should not be used as the first-line drug for neuropathic pain ; it can be used when a patient did not respond to any other TCAs³³⁾ /

Desipramine

Efficacy for postherpetic neuralgia and painful diabetic neuropathy has been shown in RCT^{34, 35)}. As a secondary amine TCA, desipramine may also induce analgesic effects, which are similar to those of imipramine. However, it is no longer available in the market, and prescription is not currently allowed in Japan.

References

- 1) Finnerup NB, Attal N, Haroutounian S, et al : Pharmacotherapy for neuropathic pain in adults : A systematic review and meta-analysis. *Lancet Neurol* 2015 ; 14 : 162-173 [1a]
- 2) Max MB, Culnane M, Schafer SC, et al : Amitriptyline relieves diabetic neuropathy pain in patients with normal or depressed mood. *Neurology* 1987 ; 37 : 589-596 [1b]
- 3) Boyle J, Eriksson ME, Gribble L, et al : Randomized, placebo-controlled comparison of amitriptyline, duloxetine, and pregabalin in patients with chronic diabetic peripheral neuropathic pain : Impact on pain, polysomnographic sleep, daytime functioning, and quality of life. *Diabetes Care* 2012 ; 35 : 2451-2458 [1b]
- 4) Jose VM, Bhansali A, Hota D, et al : Randomized double-blind study comparing the efficacy and safety of lamotrigine and amitriptyline in painful diabetic neuropathy. *Diabet Med* 2007 ; 24 : 377-383 [1b]
- 5) Bowsher D : The effects of pre-emptive treatment of postherpetic neuralgia with amitriptyline : A randomized, double-blind, placebo-controlled trial. *J Pain Symptom Manage* 1997 ; 13 : 327-331 [1b]
- 6) Graff-Radford SB, Shaw LR, Naliboff BN : Amitriptyline and fluphenazine in the treatment of postherpetic neuralgia. *Clin J Pain*

- 2000; 16: 188–192 [1b]
- 7) Watson CP, Vernich L, Chipman M, et al: Nortriptyline versus amitriptyline in postherpetic neuralgia: A randomized trial. *Neurology* 1998; 51: 1166–1171 [1b]
 - 8) Watson CP, Chipman M, Reed K, et al: Amitriptyline versus maprotiline in postherpetic neuralgia: A randomized, double-blind, crossover trial. *Pain* 1992; 48: 29–36 [1b]
 - 9) Wilder-Smith CH, Hill LT, Laurent S: Postamputation pain and sensory changes in treatment-naïve patients: characteristics and responses to treatment with tramadol, amitriptyline, and placebo. *Anesthesiology* 2005; 103: 619–628 [1b]
 - 10) Leijon G, Boivie J: Central post-stroke pain—a controlled trial of amitriptyline and carbamazepine. *Pain* 1989; 36: 27–36 [1b]
 - 11) Rintala DH, Holmes SA, Courtade D, et al: Comparison of the effectiveness of amitriptyline and gabapentin on chronic neuropathic pain in persons with spinal cord injury. *Arch Phys Med Rehabil* 2007; 88: 1547–1560 [1b]
 - 12) Dick IE, Brochu RM, Purohit Y, et al: Sodium channel blockade may contribute to the analgesic efficacy of antidepressants. *J Pain* 2007; 8: 315–324 [2c]
 - 13) Gilron I, Watson CP, Cahill CM, et al: Neuropathic pain: A practical guide for the clinician. *CMAJ* 2006; 175: 265–275 [1a]
 - 14) Ray WA, Meredith S, Thapa PB, et al: Cyclic antidepressants and the risk of sudden cardiac death. *Clin Pharmacol Ther* 2004; 75: 234–241 [2b]
 - 15) Miura N, Saito T, Taira T, et al: Risk factors for QT prolongation associated with acute psychotropic drug overdose. *Am J Emerg Med* 2015; 33: 142–149 [2b]
 - 16) O'Connor AB, Noyes K, Holloway RG: A cost-effectiveness comparison of desipramine, gabapentin, and pregabalin for treating postherpetic neuralgia. *J Am Geriatr Soc* 2007; 55: 1176–1184 [2b]
 - 17) Finnerup NB, Otto M, McQuay HJ, et al: Algorithm for neuropathic pain treatment: An evidence based proposal. *Pain* 2005; 118: 289–305 [1a]
 - 18) Attal N, Bouhassira D: Pharmacotherapy of neuropathic pain: Which drugs, which treatment algorithms? *Pain* 2015; 156 (Suppl 1): S104–S114 [1a]
 - 19) Moore RA, Derry S, Aldington D, et al: Amitriptyline for neuropathic pain in adults. *Cochrane Databases Syst Rev.* 2015; 6: 7: CD008242. Doi: 10.1002/14651858.CD008242. Pub3. Review [1a]
 - 20) Kvinesdal B, Molin J, Froland A, et al: Imipramine treatment for painful diabetic neuropathy. *J Am Med Association* 1984; 251: 1727–1730 [1b]
 - 21) Sindrup SH, Gram LF, Brosen K, et al: The selective serotonin reuptake inhibitor paroxetine is effective in the treatment of diabetic neuropathy symptoms. *Pain* 1990; 42: 135–144 [1b]
 - 22) Sindrup SH, Tuxen C, Gram LF, et al: Lack of effect of mianserin on the symptoms of diabetic neuropathy. *Eur J Clin Pharmacol* 1992; 43: 251–255 [1b]
 - 23) Sindrup SH, Bach FW, Madsen C, et al: Venlafaxine versus imipramine in painful polyneuropathy: A randomized, controlled trial. *Neurology* 2003; 60: 1284–1289 [1b]
 - 24) Hearn L, Derry S, Phillips T, et al: Imipramine for neuropathic pain in

- adults. *Cochrane Databases Syst Rev* 2014 ; 19 ; 5 : CD010769. Doi : 10.1002/14651858. CD010769. Pub2. Review [1a]
- 25) Sindrup SH, Gram LF, Skjold TE, et al : Clomipramine vs desipramine vs placebo in the treatment of diabetic neuropathy symptoms : A double-blind cross-over study. *Br J Clin Pharmacol* 1990 ; 30 : 683-691 [1b]
 - 26) Yanaki M, Iwade M, Yamagata K, et al : Two cases of medicinal treatment of diabetic post treatment painful neuropathy. *Masui* 2013 ; 62 : 1400-1405 [4]
 - 27) Fallon BA, Liebowitz MR, Campeas R, et al : Intravenous clomipramine for obsessive-compulsive disorder refractory to oral clomipramine : A placebo-controlled study. *Arch Gen Psychiatry* 1998 ; 55 : 918-924 [1b]
 - 28) Hammack JE, Michalak JC, Loprinzi CL, et al : Phase III evaluation of nortriptyline for alleviation of symptoms of cis-platinum induced peripheral neuropathy. *Pain* 2002 ; 98 : 195-203 [1b]
 - 29) Khoromi S, Cui L, Nackers L, et al : Nortriptyline and their combination vs. placebo in patients with chronic lumbar root pain. *Pain* 2007 ; 130 : 66-75 [1b]
 - 30) Panerai AE, Monza G, Movilia P, et al : A randomized, within-patient, cross-over, placebo-controlled trial on the efficacy and tolerability of the tricyclic antidepressants chlorimipramine and nortriptyline in central pain. *Acta Neurologica Scandinavica* 1990 ; 82 : 34-38 [1b]
 - 31) Raja SN, Haythornthwaite JA, Pappagallo M, et al : Opioids versus antidepressants in postherpetic neuralgia : A randomized, placebo-controlled trial. *Neurology* 2002 ; 59 : 1015-1021 [1b]
 - 32) Gomez-Perez FJ, Rull JA, Dies H, et al : Nortriptyline and fluphenazine in the symptomatic treatment of diabetic neuropathy : A double-blind cross-over study. *Pain* 1985 ; 23 : 395-400 [1b]
 - 33) Derry S, Wiffen PJ, Aldington D, et al : Nortriptyline for neuropathic pain in adults. *Cochrane Databases Syst Rev*. 2015 ; 8 ; 1 : CD011209. Doi : 10.1002/14651868. CD11209. Pub2. Review [1a]
 - 34) Max MB, Kishore-Kumar R, Schafer SC, et al : Efficacy of desipramine in painful diabetic neuropathy : A placebo-controlled trial. *Pain* 1991 ; 45 : 3-9. [00]
 - 35) Kishore-Kumar R, Max MB, Schafer SC, et al : Desipramine relieves postherpetic neuralgia. *Neurology* 1990 ; 47 : 305-312. [1b]

16. Serotonin-noradrenaline reuptake inhibitor (SNRI)

CQ20 : Are SNRIs effective for neuropathic pain?

Duloxetine which is one of the serotonin-noradrenaline reuptake inhibitor is recommended as efficacy was observed for painful diabetic neuropathy with high level of evidence. Venlafaxine may be effective for peripheral neuropathic pain¹⁾.

The level of recommendation and the summary of overall evidence : 1A

Comments :

SNRIs act on serotonin system and noradrenalin system involved in the descending pain inhibitory system and inhibits serotonin-noradrenaline reuptake. It is considered that analgesic effects are induced when serotonin and noradrenaline levels increase between synapses, and serotonin and noradrenaline neurotransmissions are intensified. There are less adverse reactions induced by anticholinergic effects such as dry mouth or orthostatic hypotension, compared to TCAs. Attention is needed for nausea, however.

For one of the SNRIs, duloxetine ^{Note 1}, many RCTs were conducted for painful diabetic neuropathy, and high efficacy was observed²⁻⁶⁾. According to the Cochrane Database of Systematic Reviews, improvement of pain by 50% or more was observed with duloxetine at 40, 60 and 120 mg ^{Note 2}, compared to placebo, during the 12-week observation period ; however, there was no correlation between the dose and the degree of improvement. In addition, items for physical functions evaluated by SF-36 were significantly improved with duloxetine at 60 mg and 120 mg compared to placebo during the 12-week observation period⁷⁾.

It has been also reported in RCTs that duloxetine is effective for peripheral neuropathy associated with multiple sclerosis⁸⁾ and central post-stroke pain⁹⁾ ; further evaluations are needed.

Venlafaxine ^{Note 3}, which is highly recommended in major overseas guidelines, has been approved in Japan as an antidepressant. In RCT for painful diabetic neuropathy, decrease in pain intensity of 50% or more was observed in 56% of patients treated with oral venlafaxine (150-225 mg) and in 34% of patients who received placebo ; NNT of venlafaxine was 4.5¹⁰⁾. There was also a RCT comparing venlafaxine with imipramine¹²⁾, although the level of evaluation was low in Cochrane Database of Systematic Reviews¹⁾. It appears that efficacy evaluation would be difficult in Japan as it is not very commonly prescribed for neu-

Note 1 : Duloxetine : approved for depression, chronic low back pain, painful diabetic neuropathy. For precautions when using this drug for pain, appropriateness of administration of this drug should be judged carefully taking into consideration the risk of developing psychiatric symptoms such as suicidal ideation, suicidal attempt, hostility and aggression.

Note 2 : Duloxetine 120mg has not yet been approved in Japan

Note 3 : Venlafaxine : approved as an antidepressant; not approved as for neuropathic pain yet

ropathic pain.

As for milnacipran, there is no RCT reported for neuropathic pain.

References

- 1) Gallagher HC, Gallagher RM, Butler M, et al: Venlafaxine for neuropathic pain in adults. *Cochrane Database Syst Rev.* 2015 Aug 23;8:CD011091. doi: 10.1002/14651858.CD011091.pub2
- 2) Goldstein DJ, Lu Y, Detke MJ, et al: Duloxetine vs. placebo in patients with painful diabetic neuropathy. *Pain* 2005; 116: 109–118 [1b]
- 3) Raskin J, Pritchett YL, Wang F, et al: A double-blind, randomized multi-center trial comparing duloxetine with placebo in the management of diabetic peripheral neuropathic pain. *Pain Med* 2005; 6: 346–356 [1b]
- 4) Wernicke JF, Pritchett YL, D'Souza, et al: A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. *Neurology* 2006; 67: 1411–1420 [1b]
- 5) Gao Y, Ning G, Jia WP, et al: Duloxetine versus placebo in the treatment of patients with diabetic neuropathic pain in China. *Chin Med J (Engl)* 2010; 123: 3184–3192 [2b]
- 6) Yasuda H, Hotta N, Nakao K, et al: Superiority of duloxetine to placebo in improving diabetic neuropathic pain: Results of a randomized controlled trial in Japan. *J Diabetes Investig* 2011; 2: 132–139 [1b]
- 7) Lunn MP, Hughes RA, Wiffen RJ, et al: Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. *Cochrane Database Syst Rev.* 2014 Jan 3; 1: CD007115 [1a]
- 8) Vollmer TL, Robinson MJ, Risser RC, et al: A randomized, double-blind, placebo-controlled trial of duloxetine for the treatment of pain in patients with multiple sclerosis. *Pain Pract* 2014; 14: 732–744 [1b]
- 9) Brown TR, Slee A: A randomized placebo-controlled trial of duloxetine for central pain in multiple sclerosis. *Int J MS Care* 2015; 17: 83–89 [1b]
- 10) Rowbotham MC, Goli V, Kunz NR, et al: Venlafaxine extended release in the treatment of painful diabetic neuropathy: A double-blind, placebo-controlled study. *Pain* 2004; 110: 697–706 [1b]
- 11) Sindrup SH, Bach FW, Madsen C, et al: Venlafaxine versus imipramine in painful polyneuropathy: A randomized, controlled trial. *Neurology* 2003; 60: 1284–1289 [2b]

17. Extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus

CQ21 : What are the features of the extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus?

It requires a certain length of time until analgesic effects appear ; hence, it is desirable to continue the administration for more than 4 weeks in order to evaluate the effects. The incidence and severity of adverse reactions is low and mild, respectively.

The level of recommendation and the summary of overall evidence : 2B

Comments :

The extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus is a preparation containing non-proteinogenic physiologically active substance extracted from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus. There is no description of the generic name as no single active ingredient, which induces analgesic effects by itself, has been identified. Primary pharmacological actions include activation of the descending pain inhibitory system, anti-inflammatory effects, inhibition of a release of excitatory neuropeptides, inhibition of sympathetic nerves, improvement of blood flow, and neuroprotective effects¹⁾.

Clinical studies were conducted in Japan in patients with neuropathic pain such as postherpetic neuralgia and painful diabetic neuropathy, and the analgesic effects of this preparation were demonstrated^{2,3)}. In a RCT conducted in 228 patients with postherpetic neuralgia, significant improvement of pain was observed in a group which received 4 tablets per day (two tablets twice daily), for 4 weeks, compared to the group which received placebo²⁾. Also in a case-series study conducted in 36 patients with painful diabetic neuropathy, it was reported that spontaneous pain and numbness improved in more than 65% of the patients after 8 weeks of the administration³⁾.

This preparation is characterized, in addition to the analgesic effects, by very high tolerability with no serious adverse reaction. There is no precaution required for concomitant use of other drugs as it does not interact with any drugs. Four tablets per day, two tablets twice daily in the morning and one in the evening, are administered orally to adult patients for postherpetic neuralgia and pain which is likely to become chronic (e.g. low back pain, cervicobrachial syndrome, scapulohumeral periarthritis, and osteoarthritis). The administration should not be continued aimlessly if no effect was observed for 4 weeks⁴⁾.

Note 1 : Extract from inflamed cutaneous tissue of rabbits inoculated with vaccine virus : approved for post-herpetic neuralgia, low back pain, cervicobrachial syndrome, scapulohumeral periarthritis, osteoarthritis

References

- 1) Suzuki T : A novel development in action mechanism of Neurotropin[®]. Pain Clinic 2010 ; 31 : S441-S445 [5]
- 2) Yamamura H, Dan K, Wakasugi B, et al : Effects of neurotropin[®] tablets on post-herpetic neuralgia : A placebo-controlled multicenter double blind study. Journal of Clinical and Experimental Medicine 1988 ; 147 : 651-64 [1b]
- 3) Orimo H, Nakamura T, Ohsawa N, et al : Treatment effects of Neurotropin[®] tablets for diabetic neuropathy. Prog Med 1989 ; 9 : 1153-1160 [4]
- 4) Neurotropin[®] : Drug information [4]

18. Opioid analgesics [weak] : Tramadol

CQ22 : What is the recommendation of tramadol for neuropathic pain?

For tramadol, efficacy has been shown for postherpetic neuralgia and painful diabetic neuropathy with improvement effects on QOL. Compared to other opioid analgesics, tramadol induces far less addiction and appears to be relatively safe. For long-term use, it is desirable to receive a collaborative consultation from a pain management specialist. Tramadol should be recommended as a second-line drug for neuropathic pain.

The level of recommendation and the summary of overall evidence : 1A

Comments :

Tramadol ^{Note} acts as a μ -opioid receptor agonist and as a SNRI. The affinity (Ki) of tramadol opioid structure for μ -, δ - and κ -opioid receptors is far less than that of morphine, and the affinity of tramadol amine structure for a monoamine pump is far less than that of imipramine, which is a tricyclic antidepressant. Therefore, analgesic effects of tramadol can be considered as the product of synergistic effects induced by the actions of a μ -opioid receptor agonist and SNRI. Analgesic effects of tramadol cannot be completely inhibited, even if a μ -opioid receptor antagonist, naloxone, was administered. Although tramadol is regarded as an opioid analgesic [weak], it is different from other opioid analgesics [weak, moderate] such as pentazocine or buprenorphine. Tramadol and its metabolites act as full agonists for μ -opioid receptors ; there is no ceiling effect on analgesic effects for nociceptive pain, and the analgesic effects would be observed dose-dependently (however, as there is a risk of convulsion at a high dose, the upper limit of its dose has been set at 400 mg/day for clinical use). Out of all types of neuropathic pain, analgesic effects were observed for painful diabetic neuropathy^{1,2)} and postherpetic neuralgia³⁾ along with improvement effects on QOL. Although development of addiction is relatively rare for an opioid analgesic⁴⁾, attention is required for a long-term use. Hence, it is desirable to use it for relatively a short-term⁵⁾. Adverse effects (e.g. constipation, sleepiness, vomiting) induced by tramadol are weak, in general, than those of other opioid analgesics. Tramadol is superior to the other opioid analgesics due to its analgesic effects and improvement effects on QOL. However, as there is a safety concern for a long-term use, tramadol is recommended as a second-line drug rather than a first-line drug⁶⁾.

As with many other opioid analgesics and antidepressants, tramadol is me-

Note : Tramadol : approved for chronic pain, cancer pain, pain after tooth extraction

SNRI : serotonin-noradrenaline reuptake inhibitor

tabolized by cytochrome P450 (CYPs) : of these, the most important types are CYP2D6, CYP3A4, and CYP2B6. Therefore, adequate attention is required when tramadol is being used concomitantly with other drugs or food which may affect CYPs.

Tramadol preparations are available in Japan for oral and intravenous administrations. There are three forms of oral drugs : acetaminophen combination tablets, orally disintegrating (OD) tablets, and sustained release tablets. There are 2 dose of orally-disintegrating tablets : 25 mg and 50 mg, and the pharmacokinetics of these forms are almost equivalent to each other ; namely, rapid-releasing. Acetaminophen combination tablets are fast-releasing drugs containing 37.5 mg of tramadol. The dosages of the sustained-release tablets are 100 mg. When using tramadol, it is desirable to administer in dose-escalation manner starting from a small amount so that higher tolerability will be achieved. After introducing/dose-escalating the rapid-release drug, it can be switched to a sustained-release drug. This is an idealistic way to maintain medication adherence.

Indications for its injection form are limited to postoperative pain and cancer pain, and for the method of administration, only intramuscular injection is performed.

References

- 1) Harati Y, Gooch C, Swenson M, et al : Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. *Neurology* 1998 ; 50 : 1842-1846. [1b]
- 2) Sindrup SH, Andersen G, Madsen C, et al : Tramadol relieves pain and allodynia in polyneuropathy : A randomized, double-blind, controlled trial. *Pain* 1999 ; 83 : 85-90. [1b]
- 3) Boureau F, Legallicier P, Kabir-Ahmadi M : Tramadol in post-herpetic neuralgia : A randomized, double-blind, placebo-controlled trial. *Pain* 2003 ; 104 : 323-331. [1b]
- 4) Cicero TJ, Inciardi JA, Adams EH, et al : Rates of abuse of tramadol remain unchanged with the introduction of new branded and generic products : Results of an abuse monitoring system, 1994-2004. *Pharmacoepidemiol drug safe* 2005 ; 14 : 851-859. [1b]
- 5) NICE clinical guideline 2013-Neuropathic pain in adults : Pharmacological management in non-specialist settings
- 6) Finnerup NB, Attal N, Haroutounian S, et al : Pharmacotherapy for neuropathic pain in adults : A systematic review and meta-analysis. *Lancet Neurol* 2015 ; 14 : 162-173. [1b]

19. Opioid analgesics [moderate] : Buprenorphine

CQ23 : What are the features of buprenorphine ?

Buprenorphine is clinically a full agonist for μ -opioid receptors, and there seems to be no problem using this drug concomitantly with other opioids. It does not induce respiratory depression, immunosuppressive action, or hypogonadism either : hence, it is an opioid relatively safe even for elderly people to use.

The level of recommendation and the summary of overall evidence : none

Comments :

Buprenorphine used to be considered as a partial agonist for μ -opioid receptors, which could not be used concomitantly with other opioids or there was a ceiling effect for its action. However, the results of a recent study conducted in humans using radioisotope labeling with buprenorphine revealed that, even though it is a partial agonist *in vitro*, clinically it can be a full agonist for analgesic actions, which can induce a full pain relief with less than 100% of μ -opioid receptor occupancy¹⁾. Also in a study of interactions with other μ -opioid receptor agonists using the tail flick test, additive or synergistic analgesic effects were observed with morphine, oxycodone and hydromorphone²⁾, suggesting that there would be no problem using this drug concomitantly with other opioids³⁻⁵⁾. It has been also suggested that, although there is no ceiling effect for pain relief with buprenorphine, there is for respiratory depression : in other words, even if respiratory depression occurred, it could be controlled by a high dose administration of naloxone. Hence, it may be an opioid which can be used safely in clinical practice.⁶⁻⁹⁾

In addition, it does not induce neither immunosuppressive effects, compared to morphine, oxycodone, and fentanyl¹⁰⁻¹¹⁾, nor hypogonadism¹²⁾. Constipation¹³⁻¹⁵⁾ and decreased cognitive function are rare for adverse reactions¹⁶⁻¹⁸⁾, and antihyperalgesia effects are observed instead of hyperalgesia which is induced by other opioids¹⁹⁾. It is an opioid which can be used safely even in high-risk chronic-pain patients such as those with renal dysfunction or elderly patients^{20,21)}.

Buprenorphine preparations available in Japan are injection (indications include postoperative pain, cancer pain, chest pain associated with myocardial infarction), suppository (indications include postoperative pain, cancer pain), and patches (chronic pain associated with osteoarthritis and low back pain) : indica-

tions described in the drug information must be complied for each product.

CQ24 : Is buprenorphine effective for neuropathic pain?

Buprenorphine can be effective for neuropathic pain in both animal studies and clinical studies. Its action mechanism seems to involve antihyperalgesia effects or inhibition of diffuse noxious inhibitory controls (DNIC).

The level of recommendation and the summary of overall evidence : 2C

Comments :

It has been reported in animal studies that subcutaneous injection of buprenorphine is effective for neuropathic pain. Significant improvement was observed in mechanical and cold allodynia or hyperalgesia in neuropathic rats after spinal cord injury²²⁾, and in diabetic peripheral neuropathy rats, significant improvement was observed in mechanical hyperalgesia²³⁾.

In clinical studies of buprenorphine, there are many reports which state that it was effective for chronic pain including nociceptive pain. In addition, there are 2 reports which exclusively demonstrated efficacy for neuropathic pain in clinical studies. In a double blind randomized study conducted in patients with pain after thoracotomy, intravenous (i.v.) administration of buprenorphine was effective for reduction of pain²⁴⁾. It was also effective in approximately 40% of patients with central neuropathic syndrome, who did not respond well to the other opioids.

It is considered that antihyperalgesia effects and inhibition of DNIC have been involved in the pain-relief mechanism of buprenorphine for neuropathic pain. Unlike any other opioids, buprenorphine inhibits hyperalgesia secondary to the CNS sensitization¹⁹⁾. In a study using rats²⁵⁾, administration of low-dose buprenorphine inhibited DNIC.

CQ25 : What is efficacy of buprenorphine patch for neuropathic pain?

Effectiveness of buprenorphine patch for neuropathic pain may be valid according to the results of open-label studies and case reports. However, further studies will be necessary in the future as there has been no RCT conducted so far on this potential.

The level of recommendation and the summary of overall evidence : 2C

Comments :

Effectiveness of buprenorphine patch for chronic non-cancer pain and chronic cancer pain has been demonstrated in two randomized control clinical stud-

DNIC : diffuse noxious
inhibitory controls

DNIC : diffuse noxious
inhibitory controls

ies²⁶⁻²⁷⁾. The subjects investigated in these studies had various chronic pain including neuropathic pain ; out of 294 patients included in these two studies, only 52 patients had received diagnoses of neuropathic pain. Therefore, evaluations should not be made only for neuropathic pain. Currently, there is no randomized controlled clinical study which were conducted only in patients with neuropathic pain who had been treated with buprenorphine patch.

Effectiveness of transdermal absorption buprenorphine preparation for neuropathic pain has been demonstrated in an open-label study and in a case report form^{28,29)}.

According to the reports of Rodriguez-Lopez²⁸⁾, in an open-label study of buprenorphine patch for neuropathic pain, a significant decrease of VAS (55%, $p < 0.001$) was observed after 8 weeks in 237 patients with neuropathic pain (patients with sciatic nerve pain 30%, persistent postoperative pain on shoulders 13%, postherpetic neuralgia 12%, etc.). The effectiveness of this treatment was also suggested in a case report form.

In an open-label clinical study conducted in 30 patients with chronic painful neuropathy³⁰⁾, decrease of VAS was observed in approximately 40% of these patients²⁹⁾. In prospective, noninterventional and postmarketing studies, 23 out of 37 patients who had shown in significant effects with conventional analgesic treatment and changed analgesics after a month were able to withdraw or reduce concomitant drugs by using buprenorphine patch.^{29,30)}

There are many case reports available for patients with neuropathic pain who had used the buprenorphine patch. These reports included both central and peripheral neuropathic pain such as thalamic pain^{32,33)}, postherpetic neuralgia³⁴⁾, trigeminal neuralgia³⁵⁾, tic douloureux associated with multiple sclerosis³³⁾, FBSS³⁵⁾, and lumbar radiculopathy after aortofemoral bypass³⁵⁾.

CQ26 : What about safety and tolerability of buprenorphine patch?

Buprenorphine induces fewer serious adverse reactions, such as respiratory depression, compared to other opioids, suggesting better tolerability.

The level of recommendation and the summary of oversll evidence : 1B

Comments :

For safety of buprenorphine patch in patients with chronic pain including nociceptive pain, there are reports of adverse reactions induced by opioids, and adverse reactions specifically induced by patches. In a RCT conducted in 315 patients with osteoarthritis, there was no significant difference observed in incidence of adverse events between the placebo group and the treatment group ; the events most commonly reported included nausea/vomiting, head-

ache, dizziness and somnolence, as well as pruritus and rash at the site where the patch had been applied⁶⁾. Similarly, in an open-label clinical study comparing buprenorphine patch with tramadol preparation in osteoarthritis patients, there was no significant difference in incidence of adverse events. Also, in clinical studies conducted in Japan, the significant difference was not observed either in incidence of adverse events between the treatment group and the placebo group^{37,38)}. In a long-term open-label clinical study conducted in Japan, adverse events such as nausea, pruritus at the site of treatment, constipation, vomiting, somnolence, erythema at the site of treatment, decreased body weight, dizziness, contact dermatitis, loss of appetite, and insomnia occurred at high incidence (more than 10%). However, none of these were serious, and only weak or moderate adverse events were observed in association with the opioid or with the patch, suggesting that the treatment was highly safe^{39,40)}.

Although it has been considered that opioids would decrease driving ability, there was no significant difference observed between the buprenorphine patch group and the healthy match group in a prospective noninferiority study using the Vienna test system (VTS). The VTS is a test used in Germany to measure driving ability, and the test items include the reaction time under pressure, attention, visual orientation, motor control, and the level of arousal⁴¹⁾.

Buprenorphine was not removed by hemodialysis as long as it was at the clinical level⁴²⁾. Hence, dose adjustment would not be needed up to 70 $\mu\text{g/hr}$ even in patients with renal dysfunction^{42,43)}.

With regard to respiratory depression, buprenorphine will be able to relieve pain without causing a remarkable decrease in respiratory rate with its ceiling effect⁶⁻⁹⁾, unless it is induced by concomitant treatments such as benzodiazepines, muscle relaxants, or alcohol. Therefore, attention is required in these conditions⁴²⁾.

For hypogonadism, a decrease in the plasma testosterone level was detected as with other opioids in an animal study using male rats, though there was no effect observed, unlike other opioids, in the intracranial (diencephalic) testosterone level. As clinical data, there is a report that no significant change was observed in the blood testosterone or cortisol level in both males and females of 60 patients who had been treated with the buprenorphine patch for 6 months⁴³⁾.

With regard to the safety of the buprenorphine patch in elderly patients, it has been reported in a study conducted in a total of 82 patients that no significant difference was observed in efficacy or safety between the group older than 65 years of age (the mean age 74.3 years, 30 patients) and the group younger than 65 (the mean age 51 years, 51 patients)⁴⁾. In addition, it has been also reported in another study that there was no increase observed in the

number of adverse reactions in elderly patients even when comparisons were made among groups : younger than 65 years old, between 65 and 75 years old, and over 75 years old ; therefore, no dose-adjustment was necessary^{14,21)}.

References

- 1) Greenwald MK, Johanson CE, Moody DE, et al : Effects of buprenorphine maintenance dose on μ -opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers. *Neuropsychopharmacology*. 2003 ; 28 : 2000-2009 [2c]
- 2) Kögel B, Christoph T, Straßburger W, et al : Interaction of μ -opioid receptor agonists and antagonists with the analgesic effect of buprenorphine in mice. *Eur J Pain* 2005 ; 9 : 599-611 [5]
- 3) Nemirovsky A, Chen L, Zelman V, et al : The antinociceptive effect of the combination of spinal morphine with systemic morphine or buprenorphine. *Anesth Analg* 2001 ; 93 : 197-203 [2c]
- 4) Mercadante S, Villari P, Ferrera P, et al : Safety and effectiveness of intravenous morphine for episodic breakthrough pain in patients receiving transdermal buprenorphine. *J Symptom Manage* 2006 ; 32 : 175-179 [2c]
- 5) Ofia S, White I, Sydoruk T, et al : Effects of intravenous patient-controlled analgesia with buprenorphine and morphine alone and in combination during the first 12 postoperative hours : A four arm randomized double blind trial in adults undergoing abdominal surgery. *Clin Ther* 2009 ; 31 : 527-541 [2c]
- 6) Budd K : High dose buprenorphine for postoperative analgesia. *Anaesthesia* 1981 ; 36 : 900-903 [2c]
- 7) Dahan A, Yassen A, Romberg R, et al : Buprenorphine induces ceiling in respiratory depression but not in analgesia. *Br J Anaesth* 2006 ; 96 : 627-632 [2c]
- 8) Dahan A, Yassen A, Bijl H, et al : Comparison of the respiratory effects of intravenous buprenorphine and fentanyl in humans and rats. *Br J Anaesth* 2005 ; 94 : 825-834 [2c]
- 9) Dahan A : Opioid-induced respiratory effects : new data on buprenorphine. *Palliat Med* 2006 ; 20 (suppl 1) : S3-S8 [5]
- 10) Van Loveren H, Gianotten N, Hendriksen CF, et al : Assessment of immunotoxicity of buprenorphine. *Lab Anim* 1994 ; 28 : 355-363 [2c]
- 11) Martucci C, Panerai AE, Sacerdote P : Chronic fentanyl or buprenorphine infusion in the mouse : Similar analgesic profile but difficult effects on immune response. *Pain* 2004 ; 110 : 385-392 [5]
- 12) Ceccarelli I, De Padova AM, Fiorenzani P, et al : Single opioid administration modifies gonadal steroids in both the CNS and plasma of male rats. *Neuroscience* 2006 ; 140 : 929-937 [5]
- 13) Evans HC, Easthope SE : Transdermal buprenorphine. *Drugs* 2003 ; 63 : 11-12
- 14) Likar R, Kayser H, Sittl R : Long-term management of chronic pain with transdermal buprenorphine : A multicenter, open-label, follow-up study in patients from three short-term clinical trials. *Clin Ther* 2006 ; 28 : 943-952 [2c]
- 15) Nasar MA, McLeavy MA, Knox J : An open study of sub-lingual buprenorphine in the treatment of chronic pain in the elderly. *Curr Med Res Opin* 1986 ; 10 : 251-255 [2b]

- 16) Glacomuzzi S, Haaser W, Pilsz L, et al: Driving impairment on buprenorphine and slow-release oral morphine in drug-dependent patients. *Forensic Sci Int* 2005; 152: 323-324 [2c]
- 17) Soyka M, Hock B, Kagerer S, et al: Less impairment on one portion of a driving-relevant psychomotor battery in buprenorphine-maintained than in methadone-maintained patients: Results of a randomized clinical trial. *J Clin Psychopharmacol* 2005; 25: 490-493 [1b]
- 18) Baewert A, Gombas W, Schindler SD, et al: Influence of peak and trough levels of opioid maintenance therapy on driving aptitude. *Eur Addict Res* 2007; 13: 127-135 [2b]
- 19) Koppert W, Ihmsen H, Körber N, et al: Different profiles of buprenorphine-induced analgesia and antihyperalgesia in a human pain model. *Pain* 2005; 118: 15-22 [2c]
- 20) Filitz J, Griessinger N, Sittl R, et al: Effects of intermittent hemodialysis on buprenorphine and norbuprenorphine plasma concentrations in chronic pain patients treated with transdermal buprenorphine. *EUR J Pain* 2006; 10: 743-748 [2b]
- 21) Hand CW, Sear JW, Uppington J, et al: Buprenorphine disposition in patients with renal impairment: Single and continuous dosing, with special reference to metabolites. *Br J Anaesth* 1990; 64: 276-282 [2b]
- 22) Poli Francois K, Jing-Xia H, Xiao-Jun X: Buprenorphine alleviates neuropathic pain-like behaviors in rats after spinal cord and peripheral nerve injury. *Eur J Pharmacol* 2002; 450: 49-53 [5]
- 23) Annalisa C, Alessia C, Cristina M, et al: Continuous buprenorphine delivery effect in streptozotocine-induced painful diabetic neuropathy in rats. *J Pain* 2009; 10: 961-968 [5]
- 24) Benedetti F, Vighetti S, Amanzio M, et al: Dose-response relationship of opioids in nociceptive and neuropathic postoperative pain. *Pain* 1998; 74: 205-211 [2c]
- 25) Guirimand F, Chauvin M, Willer JC, et al: Buprenorphine blocks diffuse noxious inhibitory controls in the rat. *Eur J Pharmacol* 1995; 294: 651-659 [5]
- 26) Sittl R, Griessinger N, Likar R: Analgesic efficacy and tolerability of transdermal buprenorphine in patients with inadequately controlled chronic pain related to cancer and other disorders: A multicenter, randomized, double-blind, placebo-controlled trial. *Clin Ther* 2003; 211: 150-168 [1b]
- 27) Sorge J, Sittl R: Transdermal buprenorphine in the treatment of chronic pain: Results of a phase III, multicenter, randomized, double-blind, placebo-controlled study. *Clin Ther* 2004; 26: 1808-1820 [1b]
- 28) Rodriguez-Lopez M: The opioid study Group of the Spanish Pain Society: Transdermal buprenorphine in the management of neuropathic pain. *Rev Soc Esp Dolor* 2004; 11 (Suppl V): 11-21
- 29) Griessinger N, Sittl R, Likar R: Transdermal buprenorphine in clinical practice: A post-marketing surveillance study of 13,179 patients. *Curr Med Res Opin* 2005; 21: 1147-1156 [3b]
- 30) Paola P, Angela C, Alfred M, et al: Short- and intermediate-term efficacy of buprenorphine TDS in chronic painful neuropathies. *J Peripheral Nervous System* 2008; 13: 283-288 [4]
- 31) Marek H: Transdermal buprenorphine in clinical practice: A multicenter, post-marketing study in the Czech Republic, with a focus on

- neuropathic pain components. *Pain Manage* 2012; 2: 169–175 [2b]
- 32) Michelle W, Constantine S, Eva G: Transdermal buprenorphine controls central neuropathic pain. *J Opioid Manag* 2012; 8: 414–415 [4]
- 33) Cristiana G, Chiara A, Franco Mi, et al: Transdermal buprenorphine for central neuropathic pain: Clinical reports. *Pain Pract* 2011; 11: 446–452 [4]
- 34) Induru RR, Davis MP: Buprenorphine for neuropathic pain-targeting hyperalgesia. *Am J Hospice Palliat Med* 2009; 26: 470–473 [4]
- 35) Rudolf Likar, Reinhard Sittl: Transdermal buprenorphine for treating nociceptive and neuropathic pain: Four case studies. *Anesth Analg* 2005; 100: 781–785 [4]
- 36) Catherine M, Margaret D, Nelson E, et al: A randomized, placebo-controlled, double-blinded, parallel-group, 5-week study of buprenorphine transdermal system in adults with osteoarthritis. *J Opioid Manag* 2010; 6: 193–202 [1b]
- 37) Nishida K, Ogawa S, Hattori S: Efficacy and safety of transdermal buprenorphine for osteoarthritis. *J New Rem Clin* 2015; 64: 243–259 [1b]
- 38) Ogawa S, Kikuchi S, Yabuki S, et al: Low-dose transdermal buprenorphine for low back pain: An enriched enrollement randomized withdrawal placebo-controlled study. *J New Rem Clin* 2014; 63: 1276–1291 [1b]
- 39) Ogawa S, Nishida K, Hattori S: Safety and efficacy of long-term administration of transdermal buprenorphine in patients with osteoarthritis. *J New Rem Clin* 2014; 63: 551–567 [1b]
- 40) Kikuchi S, Yabuki S, Ogawa S: Safety and efficacy of long-term administration of transdermal buprenorphine in patients with chronic low back pain. *J New Rem Clin* 2014; 63: 1420–1435 [1b]
- 41) Aloisi AM, Pari G, Ceccarelli I, et al: Gender-related effects of chronic non-malignant pain and opioid therapy on plasma levels of macrophage migration inhibitory factor (MIF). *Pain* 2005; 115: 142–151 [2b]
- 42) Calderon R, Copenhaver D: Buprenorphine for chronic pain. *J Pain Palliat Care Pharmacother* 2013; 27: 402–405 [5]
- 43) Aurilio C, Ceccarelli I, Pota V, et al: Endocrine and behavioural effects of transdermal buprenorphine in pain-suffering women of different reproductive ages. 2011; 58: 1071–1078
- 44) Likar R, Vadlau EM, Breschan C, et al: Comparable analgesic efficacy of transdermal buprenorphine in patients over and under 65 years of age. *Clin J Pain* 2008; 24: 536–543 [2b]

20. Opioid analgesics [strong] : Fentanyl, etc.

CQ27 : Are strong opioid analgesics effective for neuropathic pain?

Although efficacy of short-term administration of strong opioid analgesics has been observed for neuropathic pain, its tolerability for adverse reactions is not satisfactory. For long-term administration of strong opioid analgesics, there are concerns regarding addiction, etc. Therefore, the treatment should be provided to strictly selected patients by a pain management specialist, who has adequate knowledge of opioids, when considering this treatment.

The level of recommendation and the summary of overall evidence : 2C

Comments :

Before considering the efficacy of strong opioid analgesics in neuropathic pain, we should realize the fact¹⁾ that the analgesic effects of strong opioids are equivalent to those of other drugs.

The efficacy of strong opioid analgesics for neuropathic pain has been confirmed in many studies. There are also many guidelines which recommend strong opioid analgesics for neuropathic pain. Although these drugs will be selected when other treatments are ineffective in neuropathic pain, it is risky to consider them as the last option. Instead, it should rather be regarded as one of the possibilities which need to be carefully evaluated before being selected. When considering the use of strong opioid analgesics for patients with neuropathic pain, it is desirable that this treatment be prescribed by a pain management specialist who has adequate knowledge of opioid treatments to strictly selected patients, for the following reasons.

- i) There are limited numbers of efficacy reports available for strong opioid analgesics.
- ii) The incidence of adverse reactions is high in strong opioid analgesics.
- iii) Prolongation and dose escalation of strong opioid analgesics induce a variety of problems which decrease the patients' QOL.
- iv) It has been reported that strong opioid analgesics would never improve physical functions.
- v) There has been no systematized study conducted for long-term administration.
- vi) There is no report available which states that strong opioid analgesics are more effective than the other drugs.
- vii) The abuse of and psychological dependence on strong opioid analgesics

have been social issues in some countries.

According to the report of a systematic review on efficacy of strong opioid analgesics in neuropathic pain²⁾, efficacy of these drugs has been confirmed only for the short-term use, compared to placebo. However, its tolerability for adverse effects is considered poor.

The strong opioid analgesics suggested by WHO, which are currently available for clinical use in Japan, include morphine, the most commonly used opioid, and alternative drugs such as oxycodone, fentanyl, methadone, pethidine and tapentadol. However, the use of these drugs are limited in Japan by indications written on the drug information for each product : not all the strong opioid analgesics available for clinical use can be used for the treatment of neuropathic pain.

In order to adhere to the statement “maintain the prescription, use and the order of opioid analgesics in Japan”, which is one of the three objectives presented in the “Guidelines for Prescribing Opioid Analgesics for Chronic Non-cancer Pain” issued by Japan Society of Pain Clinicians, the strong opioid analgesics to be used for neuropathic pain must be restricted to a certain types of morphine and fentanyl, which can be effective for non-cancer chronic pain, based on indications written on the drug information.

The morphine preparations available for non-cancer neuropathic pain in Japan include morphine hydrochloride powder and tablets, and fentanyl patch (for 1-day and 3-days), the only fentanyl preparation that can be used. No other drugs have been approved for this treatment. Upon selection of the fentanyl patch, the following condition needs to be complied : “it should be used only to control cancer pain and chronic pain which require continuous administration of opioid analgesics in a patient whose tolerability has been confirmed by administration of other opioid analgesics for a certain period of time” as described in the drug information.

The detailed information for the prescription of strong opioid analgesics can be obtained in the “Guidelines for Prescribing Opioid Analgesics for Chronic Non-cancer Pain” issued by Japan Society of Pain Clinicians.

References

- 1) Eisenberg E, McNichol ED, Carr DB : Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin : Systematic review and meta-analysis of randomized control trials. JAMA 2005 ; 293 : 3043-3052. [1a]
- 2) Sommer C, Welsch P, Klose P, et al : Opioids in chronic neuropathic pain : A systematic review and meta-analysis of efficacy, tolerability and safety in randomized placebo-controlled studies of at least 4 weeks duration. Schmerz 2015 ; 29 : 35-46. [1b]

21. Type and usage of selective drugs

Table 5 First-line, second-line and third-line drugs for neuropathic pain

Drug name	Dosage form	Type	Specific usage
First-line drug			
Amitriptyline	Per-oral drug	TCA, tertiary amine	Initial dose 10 mg/day, maximum 150 mg Once daily, before bedtime Increase 10–25 mg every 3–7 days
Nortriptyline	Per-oral drug	TCA, tertiary amine	
Imipramine	Per-oral drug	TCA, secondary amine	
Gabapentin	Per-oral drug	Ca ²⁺ channel $\alpha_2\delta$ ligand	Initial dose 100–300 mg/day, maximum 3,600 mg 1–3 times/day Increase 100–300 mg every 1–7 days
Pregabalin	Per-oral drug	Ca ²⁺ channel $\alpha_2\delta$ ligand	Initial dose 25–150 mg/day, maximum 600 mg 1–3 times/day Increase 25–150 mg every 3–7 days
Duloxetine	Per-oral drug	SNRI (seritonine-noradrerline reuptake inhibitor)	Initial dose 20 mg/day, maximum 60 mg Once daily, after breakfast
Second-line drug			
An extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus	Per-oral drug (injection)	Non-proteinogenic physiologically active substance	4 tablets (16 unites)/day Twice daily
tramadol/acetaminophen combination	Per-oral drug	Opioid + acetaminophen	Initial dose 1–4 tablets/day, maximum 8 tablets 1–4 times/day
Tramadol	Per-oral drug (injection)	Opioid	Initial dose 25–100mg/day, maximum 400 mg 1 ~ 4 times/day
Third-line drug			
Buprenorphine	Patch (suppository, injection)	Opioid	Initial dose 5 mg/day, maximum 20 mg Once in 7 days
Fentanyl	1-day patch (injection)	Opioid	Establish the initial dose by calculating from the opioid dose used before switching the treatment. The maximum dose is 120 mg/day converted from morphine hydrochloride.
Fentanyl	3-day patch (injection)	Opioid	Establish the initial dose by calculating from the opioid dose used before switching the treatment. The maximum dose is 120 mg/day converted from morphine hydrochloride.
Morphine	Per-oral, suppository, injection	Opioid	Initial dose 10mg/day, maximum 120mg/day

for neuropathic pain

Judgment period for treatment effect	Indications	Adverse effects
First-line drug		
6–8 weeks; the maximum tolerable dose for at least 2 weeks	Depression, peripheral neuropathic pain	Anti-cholinergic effect, QT prolongation, suicide risk Contraindications : glaucoma, prostate hypertrophy, cardiac diseases Less adverse events with secondary amine Attention required when used concomitantly with tramadol
	Depression	
	Depression, enuresis	
In addition to 3–8 weeks of dose-escalation period, 2 more weeks at the maximum dose	Refractory epilepsy	Sleepiness, dizziness, peripheral edema, increased body weight A small dose should be used in patients with renal dysfunction.
4 weeks	Neuropathic pain, pain associated with fibromyalgia	
4 weeks	Depression, diabetic neuropathy, fibromyalgia, chronic low back pain	Nausea TCA, attention required when used concomitantly with tramadol
Second-line drug		
4 weeks	Post-herpetic neuralgia, low back pain, cervicobrachial syndrome, scapulohumeral periarthritis, knee osteoarthritis	Nausea, sleepiness : incidence is below 0.1%, high tolerability
4 weeks	Chronic pain, pain after tooth extraction	Nausea/vomiting, constipation, somnolence Attention required when used concomitantly with SSRI, SNRI, TCA and acetaminophen
4 weeks	Cancer pain, chronic pain	Nausea/vomiting, constipation, somnolence Attention required when used concomitantly with SSRI, SNRI and TCA.
Third-line drug		
4 weeks	Chronic pain difficult to treat with non-opioid analgesic (osteoarthritis, low back pain)	Nausea/vomiting, constipation, somnolence, respiratory control
4 weeks	Chronic pain and cancer pain difficult to treat with nonopioid analgesic Can be used just by switching from other opioids	Nausea/vomiting, constipation, somnolence, respiratory depression
4 weeks		
4 weeks	Cancer pain, chronic pain	Nausea/vomiting, constipation, somnolence, respiratory depression

22. Other antidepressants

CQ28 : Are antidepressants other than tricyclic antidepressants and SNRIs effective for neuropathic pain?

RCT : randomized controlled trial

SSRI : selective serotonin reuptake inhibitor

Compared to the antidepressants other than tricyclic antidepressants and SNRIs, there are less high-quality randomized controlled trials (RCTs) available ; hence, the level of recommendation for efficacy for neuropathic pain is low. These can be used as alternative options for patients who did not respond well to the standard treatment. However, attention is required when using a large amount of or multiple kinds of selective serotonin reuptake inhibitors (SSRIs) or when using a tramadol preparation concomitantly, as a risk of developing serotonin syndrome may increase.

The level of recommendation and the summary of overall evidence : 2C

Comments :

SSRIs induces analgesic effects by activating the descending pain inhibitory system with serotonin reuptake inhibition.

Note 1 : Paroxetine hydrochloride : approved and marketed for depression, depressive state, panic disorder, social anxiety disorder, obsessive-compulsive disorder, and posttraumatic stress disorder

Note 2 : Citalopram : approved and marketed for depression and depressive state

Note 3 : Fluvoxamine maleate : approved and marketed for depression, depressive state, obsessive-compulsive disorder, and social anxiety disorder

Note 4 : Sertraline hydrochloride : approved and marketed for depression, depressive state, panic disorder, and posttraumatic stress disorder

Note 5 : Mirtazapine : approved and marketed for depression, depressive state

Proxetine hydrochloride ^{Note 1}

In a RCT¹⁾ conducted in 19 patients with painful diabetic neuropathy, administration of paroxetine 40 mg significantly relieved neuropathic symptoms, although it was not as effective as imipramine (blood concentration 400–600 μ M).

Escitalopram ^{Note 2}

In a RCT²⁾ conducted in 41 patients with painful polyneuropathy, significant analgesic effects were observed with administration of escitalopram 20 mg compared to placebo. However, it should not be recommended as the standard treatment for neuropathic pain as the number of patients who clinically responded to the treatment was limited.

Fluvoxamine maleate ^{Note 3} and sertraline hydrochloride ^{Note 4}

No clinical study has ever been conducted to present analgesic effects of these products for neuropathic pain inside and outside the country. Hence, there is no rationale for recommending these drugs for neuropathic pain.

Noradrenergic and specific serotonergic antidepressant (Mirtazapine) ^{Note 5}

No clinical study has ever been conducted to present analgesic effects of mirtazapine for neuropathic pain inside and outside the country. Hence, there

is no rationale for recommending this drug for neuropathic pain.

SSRIs and mirtazapine can be used as alternative options for patients who did not respond well to the first, second and the third-line drugs. However, attention is required when using a large amount of or multiple kinds of SSRIs or when using a tramadol preparation concomitantly, as a risk of developing serotonin syndrome may increase.

References

- 1) Sindrup SH, Gram LF, Brosen K, et al: The selective serotonin reuptake inhibitor, paroxetine is effective in the treatment of diabetic neuropathy symptoms. *Pain* 1990 ; 42 : 135-144 [\[1b\]](#)
- 2) Otto M, Bach FW, Jensen TS, et al: Escitalopram in painful polyneuropathy : A randomized, placebo-controlled, cross-over trial. *Pain* 2008 ; 139 : 275-283 [\[1b\]](#)

23. Anti-epileptics

CQ29 : Are anti-epileptics other than pregabalin/gabapentin effective for neuropathic pain compared to placebo?

There are less high-quality randomized placebo controlled studies (RCTs) with high quality of evidence conducted for anti-epileptics other than pregabalin/gabapentin (carbamazepine, lamotrigine, topiramate, sodium valproate, clonazepam) compared to pregabalin/gabapentin, and for efficacy of these products for neuropathic pain, the results were not consistent among these studies. Although these products can be used as alternative options for patients who did not respond well to pregabalin/gabapentin, adequate attention is required when using these products as serious adverse reactions may develop.

The level of recommendation and the summary of overall evidence : 2C

Comments :

Carbamazepine ^{Note 1}

It blocks Na⁺ channels and enhances Na⁺-channel inactivation.. Although its efficacy has been established for the trigeminal neuralgia¹⁾, there are not many reports on efficacy for neuropathic pain other than trigeminal neuralgia. Hence, the level of recommendation is low in the systematic review²⁾. In an RCT³⁾ conducted for central post-stroke pain, there was no significant difference in analgesic effects between carbamazepine 800 mg/day and placebo. In one of the three RCT⁴⁻⁶⁾ conducted for painful diabetic neuropathy, a significant difference was observed in analgesic effects between oxcarbazepine ^{Note 2} 1,800 mg/day and placebo, while in other two RCTs, no significant effect was observed with oxcarbazepine 600–1,800 mg/day in analgesic effects compared to placebo. The NNH of carbamazepine/oxcarbazepine as a whole was 5.5 ; the safety level was low. Adverse effects of carbamazepine include dizziness, lightheadedness, aplastic anemia, agranulocytosis, toxic epidermal necrosis (TEN), and Stevens-Jonson syndrome.

Sodium valproate ^{Note 3}

It has been believed to enhance pre- and post-synaptic GABAergic effect. Efficacy of sodium valproate 1,000–2,400 mg/day for analgesic effects varied among studies. In an RCA⁷⁾ conducted for pain after spinal cord injury, no efficacy was observed for sodium valproate at 2,400 mg/day. In two out of three RCT⁸⁻¹⁰⁾ for painful diabetic neuropathy, higher analgesic effects were observed with sodium valproate 1,000–1,200 mg/day compared to placebo. Also in a RCT¹¹⁾

Note 1 : Carbamazepine :
Approved and marketed for epilepsy, manic psychosis, and trigeminal neuralgia

Note 2 : Oxcarbazepine :
not approved in Japan.

NNH : Number needed to harm (Number of patients that need to be treated in order for one to develop an adverse event).

TEN : toxic epidermal necrolysis

Note 3 : Sodium valproate : approved and marketed for epilepsy and manic psychosis

conducted for postherpetic neuralgia, higher analgesic effects were observed as well for sodium valproate 1,000 mg/day compared to placebo. However, the efficacy of sodium valproate observed in these RCTs^{8,9,11)} were from the same group : the results might have been biased due to the nature of the single center study. The level of recommendation is low as serious adverse effects such as hepatic dysfunction, drug-induced pancreatitis (aggravated by concomitant use of topiramate), and teratogenicity may develop.

Lamotrigine Note 4

It induces anti-epileptic effects by inhibiting voltage-dependent Na^+ channels. In many of RCTs¹²⁻¹⁷⁾ conducted abroad, efficacy was not observed for neuropathic pain. In a RCT¹⁸⁾ conducted for post-stroke pain, significant analgesic effects were observed with lamotrigine 200 mg/day compared to placebo, while in RCTs for pain after spinal cord injury¹⁹⁾ or central pain associated with multiple sclerosis²⁰⁾, no significant difference was observed between the treatment group and the placebo group. For painful diabetic neuropathy and other neuropathic pain, there are not many reports suggesting efficacy of lamotrigine. Hence, the level of recommendation is low. Meanwhile, lamotrigine can be somewhat effective for trigeminal neuralgia. In a randomized double blind crossover study where 14 patients with refractory trigeminal neuralgia who had been treated with carbamazepine or phenytoin received additional lamotrigine 400 mg or placebo, significant analgesic effects were observed with lamotrigine compared to placebo. The NNT was reported to be 2.1^{21,22)}, and adverse effects include serious skin disorders such as toxic epidermal necrosis (TEN) and Stevens-Jonson syndrome.

Note 4 : Lamotrigine :
approved and marketed for
refractory epilepsy

Topiramate Note 5

It induces anti-epileptic effects by inhibiting voltage-dependent Na^+ channels. In two RCTs^{23,24)} conducted for painful diabetic neuropathy, efficacy of topiramate 400 mg/day was observed in one study, but not in the other. In a RCT²⁵⁾ conducted for radiculopathy, no significant difference was observed in analgesic effects between topiramate 400 mg/day and placebo. The adverse effects include somnolence, weight loss, and closure-angle glaucoma. NNH was 6.3. The safety level is not very high.

Note5 : Topiramate :
approved and marketed for
refractory epilepsy

Clonazepam Note 6

It acts on post-synaptic GABA_A receptors and induces somnolence and anti-anxiety/epileptic effects. There is no RCT which meets the certain standard for diseases associated with neuropathic pain, and the level of recommendation for neuropathic pain is low. There is also a report²⁶⁾ which showed efficacy for

Note 6 : Clonazepam :
approved and marketed for
refractory

BMS : burning mouth
syndrome

burning mouth syndrome (BMS).

References

- 1) Sindrup SH, Jensen TS: Pharmacotherapy of trigeminal neuralgia. *Clin J Pain* 2002; 18: 22-27 [1a]
- 2) Finnerup NB, Attal N, Haroutounian S, et al: Pharmacotherapy for neuropathic pain in adults: A systematic review and meta-analysis. *Lancet Neurol* 2015; 14: 162-173 [1a]
- 3) Leijon G, Boivie J: Central post-stroke pain: A controlled trial of amitriptyline and carbamazepine. *Pain* 1989; 36: 27-36 [2b]
- 4) Dogra S, Beydoun S, Mazzola J, et al: Oxcarbazepine in painful diabetic neuropathy: A randomized, placebo-controlled study. *Eur J Pain* 2005; 9: 543-554. Epub 2004 [1b]
- 5) Grosskopf J, Mazzola J, Wan Y, et al: A randomized, placebo-controlled study of oxcarbazepine in painful diabetic neuropathy. *Acta Neurol Scand* 2006; 114: 177-180 [1b]
- 6) Beydoun A, Shaibani A, Hopwood M, et al: Oxcarbazepine in painful diabetic neuropathy: Results of a dose-ranging study. *Acta Neurol Scand* 2006; 113: 395-404 [1b]
- 7) Drewes AM, Andreassen A, Poulsen LH: Valproate for treatment of chronic central pain after spinal cord injury: A double-blind cross-over study. *Paraplegia* 1994; 32: 565-569 [2b]
- 8) Kochar DK, Jain N, Agarwal RP, et al: Sodium valproate in the management of painful neuropathy in type 2 diabetes: A randomized placebo controlled study. *Acta Neurol Scand* 2002; 106: 248-252 [2b]
- 9) Kochar DK, Rawat N, Agrawal RP, et al: Sodium valproate for painful diabetic neuropathy: A randomized double-blind placebo-controlled study. *QJM*. 2004; 97: 33-38 [2b]
- 10) Agrawal RP, Goswami J, Jain S, et al: Management of diabetic neuropathy by sodium valproate and glyceryl trinitrate spray: A prospective double-blind randomized placebo-controlled study. *Diabetes Res Clin Pract* 2009; 83: 371-378 [2b]
- 11) Kochar DK, Garg P, Bumb RA, et al: Divalproex sodium in the management of post-herpetic neuralgia: A randomized. *QJM* 2005; 98: 29-34 [2b]
- 12) Eisenberg E, Lurie Y, Braker C, et al: Lamotrigine reduces painful diabetic neuropathy: A randomized, controlled study. *Neurology* 2001; 57: 505-509 [1b]
- 13) Vinik AI, Tuchman M, Safirstein B, et al: Lamotrigine for treatment of pain associated with diabetic neuropathy: Results of two randomized, double-blind, placebo-controlled studies. *Pain* 2007; 128: 169-179 [1b]
- 14) Simpson DM, Olney R, McArthur JC, et al: A placebo-controlled trial of lamotrigine for painful HIV-associated neuropathy. *Neurology* 2000; 54: 2115-2119 [2b]
- 15) Simpson DM, McArthur JC, Olney R, et al: Lamotrigine HIV Neuropathy Study Team: Lamotrigine for HIV-associated painful sensory neuropathies: A placebo-controlled trial. *Neurology* 2003; 60: 1508-1514 [1b]
- 16) McCleane G: 200 mg daily of lamotrigine has no analgesic effect in neuropathic pain: A randomised, double-blind, placebo controlled trial. *Pain* 1999; 83: 105-107 [1b]

- 17) Silver M, Blum D, Grainger J, et al : Double-blind, placebo-controlled trial of lamotrigine in combination with other medications for neuropathic pain. *J Pain Symptom Manage* 2007 ; 34 : 446-454 [2b]
- 18) Vestergaard K, Andersen G, Gottrup H, et al : Lamotrigine for central poststroke pain : A randomized controlled trial. *Neurology* 2001 ; 56 : 184-190 [1b]
- 19) Finnerup NB, Sindrup SH, Bach FW, et al : Lamotrigine in spinal cord injury pain : A randomized controlled trial. *Pain* 2002 ; 96 : 375-383 [1b]
- 20) Breuer B, Pappagallo M, Knotkova H, et al : A randomized, double-blind, placebo-controlled, two-period, crossover, pilot trial of lamotrigine in patients with central pain due to multiple sclerosis. *Clin Ther* 2007 ; 29 : 2022-2030 [2b]
- 21) Zakrzewska JM, Chaudhry Z, Nurmikko TJ, et al : Lamotrigine (lamictal) in refractory trigeminal neuralgia : Results from a double-blind placebo controlled crossover trial. *Pain* 1997 ; 73 : 223-230 [2b]
- 22) Finnerup NB, Sindrup SH, Jensen TS : The evidence for pharmacological treatment of neuropathic pain. *Pain* 2010 ; 150 : 573-581 [1a]
- 23) Raskin P, Donofrio PD, Rosenthal NR, et al : CAPSS-141 Study Group : Topiramate vs placebo in painful diabetic neuropathy : Analgesic and metabolic effects. *Neurology* 2004 ; 63 : 865-873 [1b]
- 24) Thienel U, Neto W, Schwabe SK, et al : Topiramate Diabetic Neuropathic Pain Study Group : Topiramate in painful diabetic polyneuropathy : Findings from three double-blind placebo-controlled trials. *Acta Neurol Scand* 2004 ; 110 : 221-231 [1b]
- 25) Khoromi S, Patsalides A, Parada S, et al : Topiramate in chronic lumbar radicular pain. *J Pain* 2005 ; 6 : 829-836 [2b]
- 26) Heckmann SM, Kirchner E, Grushka M, et al : A double-blind study on clonazepam in patients with burning mouth syndrome. *Laryngoscope* 2012 ; 122 : 813-816 [2b]

24. NMDA (N-methyl-*D*-aspartate) receptor antagonists

CQ30 : Are NMDA receptor antagonists effective for neuropathic pain?

There are not many high-quality randomized controlled trial (RCT) conducted with NMDA receptor antagonists ; the level of recommendation in terms of efficacy for neuropathic pain is low. It can be used as an alternative option for patients who did not respond to the standard treatment.

The level of recommendation and the summary of overall evidence : 2C

Comments :

NMDA receptor antagonists induce analgesic effects by blocking nociceptive transmission and central sensitization.

Note 1 : Dextromethorphan hydrobromide : Approved and marketed for acute bronchitis

Dextromethorphan hydrobromide ^{Note 1}

In a RCT ¹⁾ conducted in 379 patients with painful diabetic neuropathy, analgesic effects were observed dose-dependently with dextromethorphan hydrobromide 30 mg and 45 mg when used concomitantly with quinidine 30 mg.

Note 2 : Memantine hydrochloride : Approved and marketed for Alzheimer's disease

Memantine hydrochloride ^{Note 2}

There are a few RCT ^{2,3)} conducted on memantine hydrochloride. However, none of these demonstrated its efficacy for neuropathic pain.

Note 3 : Ketamine hydrochloride : Approved and marketed for general anesthesia induction

Ketamine hydrochloride ^{Note 3}

In a RCT ⁴⁾ conducted in 92 patients with painful diabetic neuropathy, postherpetic neuralgia and postoperative/posttraumatic neuropathy, topical administration of 1% [w/v] ketamine did not relieve neuropathic pain compared to placebo. Moreover, there has been no clinical study conducted so far inside / outside the country for systemic administration of ketamine hydrochloride which could show its analgesic effects. Hence, there is no rationale for recommendation of ketamine hydrochloride for neuropathic pain. This drug induces both harmful central actions and addiction, and it has been scheduled as a narcotic drug in Japan since 2007 due to issues of illegal abuse. Hence, careful administration should be required when using this product.

References

- 1) Aziz IS, Laura EP, Ronald T, et al : Efficacy and safety of dextromethorphan/quinidine at two dosage level for diabetic neuropathic pain : a

- double-blind, placebo-controlled, multicenter study. *Pain Med* 2012; 13: 243-254 [\[1b\]](#)
- 2) Eisenberg E, Kleiser A, Dortort A, et al: The NMDA (N-methyl-D-aspartate) receptor antagonist memantine in the treatment of postherpetic neuralgia: A double-blind, placebo-controlled study. *Eur J Pain* 1998; 2: 321-327 [\[1b\]](#)
 - 3) Sang CN, Booher S, Gilron I, et al: Dextromethorphan and memantine in painful diabetic neuropathy and postherpetic neuralgia: Efficacy and dose-response trials. *Anesthesiology* 2002; 96: 1053-1061 [\[1b\]](#)
 - 4) Lynch ME, Clark AJ, Sawynok J, et al: Topical 2% amitriptyline and 1% ketamine in neuropathic pain syndromes: A randomized, double-blind, placebo-controlled trial. *Anesthesiology* 2005; 103: 140-146 [\[1b\]](#)

25. Anti-arrhythmic drug

CQ31 : Is an anti-arrhythmic drug (mexiletine hydrochloride) effective for neuropathic pain?

RCT : randomized controlled trial

Mexiletine hydrochloride has been approved in Japan for painful diabetic neuropathy. However, there is no randomized controlled trial (RCT) conducted abroad which showed efficacy of mexiletine. Hence, the level of recommendation of this drug for neuropathic pain, including diabetic neuropathic pain, is low.

The level of recommendation and the summary of overall evidence : 2B

Comments :

Note 1 : Mexiletine hydrochloride : Approved and marketed for painful diabetic neuropathic pain

Mexiletine hydrochloride ^{Note 1}

It is an anti-arrhythmic drug of class 1b which acts as a Na⁺ channel blocker. In a multicenter RCT¹⁾ conducted in Japan, significant analgesic effects were observed with mexiletine hydrochloride 300 mg/day, compared to placebo, for painful diabetic neuropathy. Although administration of mexiletine hydrochloride 300 mg/day (divided into 3 doses) has been approved in Japan for painful diabetic neuropathy, discontinuation of the treatment should be considered if there was no effect for 2 weeks. Adequate attention is required for development of arrhythmia ; it is recommended to perform electrocardiography regularly²⁾. However, in multiple RCTs³⁻⁷⁾ conducted abroad, efficacy was not observed with mexiletine hydrochloride 225-1,200 mg/day for painful diabetic neuropathy, pain after spinal cord injury, and phantom limb pain. For adverse effects, it often induces nausea and other symptoms such as sedation, trismus, insomnia, headache, nightmare and tremor. Due to low efficacy and high incidence of adverse effects⁸⁾, mexiletine is not recommended for neuropathic pain.

Administration of mexiletine hydrochloride 300 mg/day (divided into 3 doses) has been approved in Japan for painful diabetic neuropathy. However, the treatment should be discontinued if there was no effect for 2 weeks. Serious cardiac failure or the second and third-degree atrioventricular block are contraindications for mexiletine

References

- 1) Matsuoka K, Hirata Y, Kanazawa Y, et al : A double blind comparative study of mexiletine hydrochloride (MX-DPN) for diabetic neuropathy. Japanese Journal of Medicine and Pharmaceutical Science 1997 ; 38 : 759-776 [2b]
- 2) The Japan Diabetes Society : Treatment of diabetic neuropathy (edited

- by The Japan Diabetes Society : Evidence-based Practice Guideline for the Treatment for Diabetes in Japan, revised version 2). Tokyo, Nankodo 2013 ; 93-104
- 3) Chiou-Tan FY, Tuel SM, Johnson JC, et al : Effect of mexiletine on spinal cord injury dysesthetic pain. *Am J Phys Med Rehabil* 1996 ; 75 : 84-87 [2b]
 - 4) Stracke H, Meyer UE, Schumacher HE, et al : Mexiletine in the treatment of diabetic neuropathy. *Diabetes Care* 1992 ; 15 : 1550-1555 [2b]
 - 5) Oskarsson P, Ljunggren JG, Lins PE : Efficacy and safety of mexiletine in the treatment of painful diabetic neuropathy : The Mexiletine Study Group. *Diabetes Care* 1997 ; 20 : 1594-1597 [2b]
 - 6) Wright JM, Oki JC, Graves L 3rd. : Mexiletine in the symptomatic treatment of diabetic peripheral neuropathy. *Ann Pharmacother* 1997 ; 31 : 29-34 [2b]
 - 7) Wu CL, Agarwal S, Tella PK, et al : Morphine versus mexiletine for treatment of postamputation pain : A randomized, placebo-controlled, crossover trial. *Anesthesiology* 2008 ; 109 : 289-296 [2b]
 - 8) Wallace MS, Magnuson S, Ridgeway B : Efficacy of oral mexiletine for neuropathic pain with allodynia : A double-blind, placebo-controlled, crossover study. *Reg Anesth Pain Med* 2000 ; 25 : 459-467 [1a]

26. Chinese herbal medicine

CQ32 : Is Chinese herbal medicine effective for neuropathic pain?

Chinese herbal medicine has been used in an empirical manner based on traditional medicine. However, none of them has ever shown efficacy for neuropathic pain.

The level of recommendation and the summary of overall evidence : 2D

Comments

It was shown that Goshajinkigan could inhibit peripheral neuropathy compared to placebo in a study conducted in 89 patients who had been treated with anti-cancer therapy using oxaliplatin¹⁾. It was however denied in a subsequent RCT²⁾.

Although treatment effects on neuropathic pain have been reported for keishikajutsubuto, powdered processed aconite root and yokukansan, these reports are limited to the case series studies.

In a prescription system of Chinese herbal medicine, treatment selections for an identical disease may be different from the perspective of Eastern medicine. This is considered as one of the reasons why evaluations have not been conducted in RCT.

References

- 1) Kono T, Hata T, Morita S, et al : Goshajinkigan oxaliplatin neurotoxicity evaluation (GONE) : A phase 2, multicenter, randomized, double-blind, placebo-controlled trial of goshajinkigan to prevent oxaliplatin-induced neuropathy. *Cancer Chemother Pharmacol* 2013 ; 72 : 1283-1290 [2b]
- 2) Oki E, Emi Y, Kojima H, et al : Preventive effect of Goshajinkigan on peripheral neurotoxicity of FOLFOX therapy (GENIUS trial) : A placebo-controlled, double-blind, randomized phase III study. *Int J Clin Oncol* 2015 ; 20 : 767-775 [2b]

☐ I . Overview of neuropathic pain

☐ II . Diagnosis and treatment of neuropathic pain

☐ III . Pharmacotherapies for neuropathic pain

☒ IV . Diseases which present neuropathic pain

- 27. Postherpetic neuralgia (chronic phase) [CQ33](#), [CQ34](#), [CQ35](#)
- 28. Posttraumatic peripheral neuropathy [CQ36](#), [CQ37](#), [CQ38](#)
- 29. Diabetic neuropathy [CQ39](#)
- 30. Trigeminal neuralgia [CQ40](#), [CQ41](#)
- 31. Central neuropathic pain [CQ42](#), [CQ43](#)
- 32. Pain after spinal cord injury [CQ44](#), [CQ45](#), [CQ46](#)
- 33. Chemotherapy-induced peripheral neuropathy [CQ47](#), [CQ48](#)
- 34. Neuropathic pain directly caused by cancer [CQ49](#), [CQ50](#)
- 35. Postoperative neuropathic pain [CQ51](#), [CQ52](#), [CQ53](#), [CQ54](#)
- 36. Cervical and lumbar radiculopathy [CQ55](#), [CQ56](#), [CQ57](#), [CQ58](#)

27. Postherpetic neuralgia (chronic phase)

CQ33 : What is the first drug to be considered for postherpetic neuralgia?

Tricyclic antidepressants and Ca^{2+} channel $\alpha_2\delta$ ligands are recommended owing to high-quality evidence of efficacy for postherpetic neuralgia.

The level of recommendation and the summary of overall evidence : 1A

Comments :

Tricyclic antidepressants (TCAs) such as amitriptyline (tertiary amine) and nortriptyline (secondary amine) are shown to be effective for postherpetic neuralgia (PHN).

In a placebo controlled trial conducted in PHN patients, a significant pain relief was observed with amitriptyline compared to placebo^{1,2)}. Further, in an 8-week RCT conducted in 76 PHN patients, a significant decrease of NRS was observed with nortriptyline and desipramine^{Note 1} compared to placebo (1.4 vs 0.2)³⁾. In a study comparing the effects of amitriptyline and nortriptyline, there was no difference between these two drugs in terms of efficacy for pain relief. However, nortriptyline has been reported to be superior in tolerability with lower incidence of adverse effects such as dry mouth and somnolence⁴⁾.

High efficacy has been demonstrated in many RCTs for Ca^{2+} channel $\alpha_2\delta$ ligands such as pregabalin⁵⁻⁸⁾ and gabapentin^{9,10)}. In a RCT conducted in 76 PHN patients comparing the effects of gabapentin and nortriptyline, similar improvements were observed in VAS and SF-MPQ scores, although gabapentin induced less adverse effects such as dry mouth and orthostatic hypotension¹¹⁾.

Adverse effects must be taken into consideration when selecting a drug. Attention is required for cardiotoxicity and anticholinergic effects with TCAs, and for CNS depressant actions with Ca^{2+} channel $\alpha_2\delta$ ligands. No RCT has been reported for PHN with duloxetine, a selective serotonin and noradrenaline reuptake inhibitor (SNRI), which is highly recommended for painful diabetic neuropathy.

References

- 1) Max MB, Schafer SC, Culnane M, et al: Amitriptyline, but not lorazepam, relieves postherpetic neuralgia. *Neurology*. 1988 ; 38 : 1427-1432 [2b]
- 2) Graff-Radford SB, Shaw LR, Naliboff BN: Amitriptyline and fluphenazine in the treatment of postherpetic neuralgia. *Clin J Pain* 2000 ; 16 : 188-192 [1b]
- 3) Raja SN, Haythornthwaite JA, Pappagallo M, et al: Opioids versus anti-

PHN : postherpetic neuralgia

TCA : tricyclic antidepressant

Note 1 : Desipramine :
Marketing has been suspended in Japan.

SNRI : selective serotonin and norepinephrine reuptake inhibitors

- depressants in postherpetic neuralgia : A randomized, placebo-controlled trial. *Neurology* 2002 ; 59 : 1015-1021 [1b]
- 4) Watson CP, Vernich L, Chipman M, et al : Nortriptyline versus amitriptyline in postherpetic neuralgia : A randomized trial. *Neurology* 1998 ; 51 : 1166-1171 [2b]
 - 5) Dworkin RH, Corbin AE, Young JP Jr, et al : Pregabalin for the treatment of postherpetic neuralgia : A randomized, placebo-controlled trial. *Neurology* 2003 ; 60 : 1274-1283 [1b]
 - 6) Sabatowski R, Gálvez R, Cherry DA, et al : Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic neuralgia : Results of a randomised, placebo-controlled clinical trial. *Pain* 2004 ; 109 : 26-35 [1b]
 - 7) van Seventer R, Feister HA, Young JP Jr, et al : Efficacy and tolerability of twice-daily pregabalin for treating pain and related sleep interference in postherpetic neuralgia : A 13-week, randomized trial. *Curr Med Res Opin* 2006 ; 22 : 375-384 [1b]
 - 8) Stacey BR, Dworkin RH, Murphy K, et al : Pregabalin in the treatment of refractory neuropathic pain : results of a 15-month open-label trial. *Pain Med* 2008 ; 9 : 1202-1208 [1b]
 - 9) Rowbotham M, Harden N, Stacey B, et al : Gabapentin for the treatment of postherpetic neuralgia : A randomized controlled trial. *JAMA* 1998 ; 280 : 1837-1842 [1b]
 - 10) Rice AS, Maton S : Postherpetic Neuralgia Study Group : Gabapentin in postherpetic neuralgia : A randomised, double blind, placebo controlled study. *Pain* 2001 ; 94 : 215-224 [1b]
 - 11) Chandra K, Shafiq N, Pandhi P, et al : Gabapentin versus nortriptyline in post-herpetic neuralgia patients : A randomized, double-blind clinical trial : the GONIP Trial. *Int J Clin Pharmacol Ther* 2006 ; 44 : 358-363 [1b]

CQ34 : Are opioids effective for postherpetic neuralgia ?

Opioids are effective for postherpetic neuralgia ; however, these are less effective than tricyclic antidepressants or Ca^{2+} channel $\alpha_2\delta$ ligands.

The level of recommendation and the summary of overall evidence : 2B

Comments :

In a RCT conducted in 127 PHN patients using tramadol for 6 weeks, it was reported that in the tramadol group, the percentage of patients who achieved pain relief was higher and the rate of rescue analgesic use was lower than those of the placebo group, and that there was no difference between the groups in terms of adverse events¹⁾.

There are also RCTs conducted for morphine and oxycodone as well^{2,3)}. In a RCT conducted in 76 PHN patients using morphine hydrochloride for 8 weeks, a significant decrease of NRS was observed in the treatment group compared to the placebo group (1.4 vs 0.2). However, it has been also reported that 48 out of 66 patients of the morphine hydrochloride group (10 out of 56 patients of

the placebo group) developed adverse events, and that 34 patients (10 patients of the placebo group) could not continue the study.

The pharmacotherapy for neuropathic pain can often continue for a long time, and risk-benefit aspects of opioid use have not been clearly revealed⁴⁾. When an opioid is used for PHN, there is a risk of addiction or abuse. As the safety of a long-term opioid use has not yet been established, it is necessary to obtain advice and strict observations of experts when it is administrated⁵⁾. Hence, it is considered less effective compared to tricyclic antidepressants or Ca^{2+} channel $\alpha_2\delta$ ligands.

References

- 1) Boureau F, Legallicier P, Kabir-Ahmadi M: Tramadol in post-herpetic neuralgia: A randomized, double-blind, placebo-controlled trial. *Pain* 2003; 104: 323-331 [1b]
- 2) Raja SN, Haythornthwaite JA, Pappagallo M, et al: Opioids versus antidepressants in postherpetic neuralgia: A randomized, placebo-controlled trial. *Neurology* 2002; 59: 1015-1021 [1b]
- 3) Watson CP, Babul N: Efficacy of oxycodone in neuropathic pain: A randomized trial in postherpetic neuralgia. *Neurology* 1998; 50: 1837-1841 [1b]
- 4) McNicol ED, Midbari A, Eisenberg E: Opioids for neuropathic pain. *Cochrane Database Syst Rev*. 2013 Aug 29; 8: CD006146 [1a]
- 5) Johnson RW, Rice AS: Clinical practice: Postherpetic neuralgia. *N Engl J Med* 2014; 371: 1526-1533 [5]

CQ35 : Is there any other drug which should be considered for post-herpetic neuralgia ?

The extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus has been shown to be effective for postherpetic neuralgia.

The level of recommendation and the summary of overall evidence : 1B

Comments :

In a RCT conducted in 228 PHN patients in Japan, the extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus was administered at 4 tablets/day, divided into two doses, for 4 weeks. According to the result, a significant improvement was reported in pain intensity in the treatment group compared to the placebo group¹⁾. Although there is no description of the extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus in major overseas guidelines as no RCT has been reported in any other countries, it may be a drug which is not likely to induce serious adverse effects and is high in tolerability.

Topical therapies with lidocaine^{2,3)} and capsaicin⁴⁻⁶⁾ have been reported effec-

tive in RCTs and are recommended in overseas guidelines, while these are not approved in Japan. Lidocaine gel and capsaicin cream however are used in some facilities as hospital preparations.

It is clinically effective to concomitantly use small doses of multiple drugs in order to reduce adverse effects induced by increased dose of a single drug⁷⁾. However, evidence cannot be evaluated due to limitations of RCTs⁸⁻¹⁰⁾ conducted on PHN.

References

- 1) Yamamura H, Dan K, Wakasugi B et al : Effects of neurotrophin (r) tablets on post-herpetic neuralgia : A multi-center double blind placebo controlled study. *Journal of Clinical and Experimental Medicine* 1988 ; 147 : 651-664 [1b]
- 2) Baron R, Mayoral V, Leijon G, et al : 5% lidocaine medicated plaster versus pregabalin in post-herpetic neuralgia and diabetic polyneuropathy : An open-label, non-inferiority two-stage RCT study. *Curr Med Res Opin* 2009 ; 25 : 1663-1676 [1b]
- 3) Rehm S, Binder A, Baron R : Post-herpetic neuralgia : 5% lidocaine medicated plaster, pregabalin, or a combination of both? : A randomized, open, clinical effectiveness study. *Curr Med Res Opin* 2010 ; 26 : 1607-1619 [1b]
- 4) Backonja M, Wallace MS, Blonsky ER, et al : NGX-4010 C116 Study Group : NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia : A randomised, double-blind study. *Lancet Neurol* 2008 ; 7 : 1106-1112 [1b]
- 5) Backonja MM, Malan TP, Vanhove GF, et al : C102/106 Study Group : NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia : A randomized, double-blind, controlled study with an open-label extension. *Pain Med* 2010 ; 11 : 600-608 [1b]
- 6) Irving GA, Backonja MM, Duntzman E, et al : NGX-4010 C117 Study Group : A multicenter, randomized, double-blind, controlled study of NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia. *Pain Med* 2011 ; 12 : 99-109 [1b]
- 7) Chaparro LE, Wiffen PJ, Moore RA, et al : Combination pharmacotherapy for the treatment of neuropathic pain in adults. *Cochrane Database Syst Rev*. 2012 Jul 11 ; 7 : CD008943 [1a]
- 8) Gilron I, Bailey JM, Tu D, et al : Morphine, gabapentin, or their combination for neuropathic pain. *N Engl J Med* 2005 ; 352 : 1324-34 [1b]
- 9) Gilron I, Bailey JM, Tu D, et al : Nortriptyline and gabapentin, alone and in combination for neuropathic pain : A double-blind, randomised controlled crossover trial. *Lancet* 2009 ; 374 (9697) : 1252-1261 [1b]
- 10) Baron R, Mayoral V, Leijon G, et al : Efficacy and safety of combination therapy with 5% lidocaine medicated plaster and pregabalin in post-herpetic neuralgia and diabetic polyneuropathy. *Curr Med Res Opin* 2009 ; 25 : 1677-1687 [1b]

28. Posttraumatic peripheral neuropathic pain

CQ36 : Are Ca^{2+} channel $\alpha_2\delta$ ligands effective for posttraumatic peripheral neuropathic pain ?

Pregabalin and gabapentin, which are Ca^{2+} channel $\alpha_2\delta$ ligands, induce moderate analgesic effects on posttraumatic peripheral neuropathic pain.

The level of recommendation and the summary of overall evidence : 2B

Comments :

In a randomized controlled trial (RCT) conducted in 254 patients with post-traumatic peripheral neuropathic pain, including 85 postoperative peripheral neuropathic pain patients, NNT of pregabalin 326 mg/day (median, range 150–600 mg/day) was 10.6¹⁾. A significant improvement of pain was observed with the treatment compared to placebo though its analgesic effect was not high. However, the percentage of patients who discontinued the trial due to ineffectiveness of the treatment was 1.6% , and that of patients who discontinued due to adverse effects was 7.1% ; there was no significant difference observed between the treatment and the placebo in either case. There are not many drugs which show high effectiveness other than pregabalin. Further, pregabalin hardly induce serious adverse effects. Hence, it is worth trying this treatment as long as we pay attention to the doses.

For gabapentin, a randomized controlled trial (RCT) was conducted in 24 patients with chronic phantom limb pain and residual limb pain²⁾. With the maximum dose of 3,600 mg/day, no significant difference was observed in the degree of pain compared to placebo. However, for more than a half of the patient treated with gabapentin, the pain was alleviated during the treatment period. There was also another randomized controlled trial (RCT) conducted in 19 patients with chronic phantom limb pain³⁾. In this study, the degree of pain decreased significantly in both the gabapentin group, which had received 300–2,400 mg/day, and the placebo group compared to the baseline, yet the change in the degree of pain was significantly greater with gabapentin than with placebo. However, as gabapentin is not indicated for peripheral neuropathy in Japan, priority should be given to pregabalin in the treatment.

References

- 1) Seventer R, Bach F, Toth C, et al: Pregabalin in the treatment of post-traumatic peripheral neuropathic pain : A randomized double-blind trial.

NNT : number needed to treat

Eur J Neurol 2010 ; 17 : 1082-1089 [1b]

- 2) Smith D, Ehde D, Hanley M, et. al: Efficacy of gabapentin in treating chronic phantom limb and residual limb pain. J Rehabil Res Dev 2005 ; 42 : 645-654 [1b]
- 3) Bone M, Critchley P, Buggy D: Gabapentin in postamputation phantom limb pain : A randomized, double-blind, placebo-controlled, cross-over study. Reg Anesth Pain Med 2002 ; 27 : 481-486 [1b]

CQ37 : Are opioids effective for posttraumatic peripheral neuropathic pain ?

Efficacy of morphine has been demonstrated for postamputation pain. However, it is not very effective due to problems associated with adverse effects.

The level of recommendation and the summary of overall evidence : 2C

Comments :

In a randomized controlled trial conducted in 60 patients with post-amputation pain¹⁾, NNT of morphine hydrochloride at 112 mg/day (median) was 5.6. However, due to adverse effects such as constipation (34%) and sleepiness (18%), the level of activities or disability in daily living did not improve. In a randomized comparative trial conducted in 12 patients with phantom limb pain²⁾, NNT of morphine sulfate at 70-300 mg/day was 2.4. A significant decrease in pain was observed compared to placebo. However, incidence of constipation, as an adverse effect, was significantly higher than placebo. In a RCT³⁾ conducted in 94 patients with postamputation phantom limb pain, tramadol 448 mg/day (median) was administered to the patients. According to the result, VAS value decreased by more than 10 mm in 48 patients (defined as responders). However, there was no significant difference observed in the level of decrease in pain among responders of 3 groups which received either tramadol, amitriptyline or placebo. For adverse effects, fatigue (60%), headache (44%), dizziness (40%), constipation (35%), and nausea (33%) were reported.

Although opioids are effective for patients with postamputation phantom limb pain, special attention will be required for adverse effects compared to the other drugs. These can be accepted only when a patient does not respond to other treatments and when it is used for a short period of time : opioids are not effective for this treatment.

References

- 1) Wu C, Agarwal S, Tella PK, et al: Morphine versus mexiletine for treatment of postamputation pain : A randomized, placebo-controlled, cross-over trial. Anesthesiology 2008 ; 109 : 289-296 [1b]

- 2) Huse E, Larbig W, Flor H, et al : The effect of opioids on phantom limb pain and cortical reorganization. *Pain* 2001 ; 90 : 47-55 [1b]
- 3) Wilder-Smith C, Hill L, Laurent S : Postamputation pain and sensory changes in treatment-naïve patients : Characteristics and responses to treatment with tramadol, amitriptyline, and placebo. *Anesthesiology* 2005 ; 103 : 619-628 [1b]

CQ38 : Are there any other pharmacotherapies which are effective?

The number of randomized comparative trials which investigated effectiveness of drugs for posttraumatic peripheral neuropathic pain is very limited. Topical lidocaine could be effective. However, its use is limited as there is no product other than lidocaine spray available in Japan.

The level of recommendation and the summary of overall evidence : 2D

Comments :

There is no evidence other than randomized controlled trials which support efficacy for posttraumatic peripheral neuropathic pain on the following drugs : Antidepressants such as tricyclic antidepressants, serotonin-noradrenalin reuptake inhibitors and selective serotonin reuptake inhibitors, anti-arrhythmic drugs such as mexiletine, and anti-epileptic drugs such as lamotrigine, topiramate, carbamazepine, sodium valproate, and clonazepam. Therefore, efficacy of these drugs has not been well verified.

For topical drugs, a RCT was conducted in 31 patients with postoperative or posttraumatic peripheral neuropathic pain¹⁾. In this study, topical lidocaine spray was effective at 96 mg/day without inducing any systemic adverse effects, and a significant reduction in pain was observed compared to placebo.

References

- 1) Kanai A, Segawa Y, Okamoto T, et al : The analgesic effect of a metered-dose 8% lidocaine pump spray in posttraumatic peripheral neuropathy : A pilot study. *Anesth Analg* 2009 ; 108 : 987-991 [1b]

29. Painful diabetic neuropathy

CQ39 : What are the basic management plan and the level of recommendation of drugs for painful diabetic neuropathy?

In treatments of painful diabetic neuropathy, pregabalin, tricyclic antidepressants, duloxetine, the aldose reductase inhibitor, mexiletine and tramadol are recommended to use along with the treatment for the primary disease (diabetes mellitus). For a patient who is resistant to these drugs, use of tramadol and other opioid analgesics are considered. However, it is desirable to receive a consultation from a pain management specialist as well.

The level of recommendation and the summary of overall evidence : 1B

Comments :

The highest priority should be given to treatments for the primary disease (diabetes mellitus) which induce painful diabetic neuropathy, according to the “Evidence-based Practice Guidelines for the Treatment of Diabetes in Japan (2013)” edited by The Japan Diabetes Society¹⁾.

The analgesics recommended for treatment of neuropathic pain caused by diabetic neuropathy include pregabalin²⁻¹⁰⁾, tricyclic antidepressant (especially the secondary amines), duloxetine¹¹⁻¹⁸⁾, the aldose reductase inhibitor¹⁹⁻²⁴⁾, mexiletine²⁵⁻²⁸⁾ and tramadol^{29,30)}. Mexiletine has been approved to be indicated for painful diabetic neuropathy in Japan. However, there is also a systematic review which does not recommend mexiletine for the treatment of painful diabetic neuropathy taking into consideration that it had not always been demonstrated effective in meta-analysis conducted abroad and the results of relative comparisons made on adverse effects³¹⁾. Hence, descriptions of mexiletine were not included in the outline of the treatments for neuropathic pain in this guideline but only in this section of diabetic neuropathy. When using mexiletine, it is desirable to regularly examine electrocardiography and always evaluate adverse effects accordingly.

Opioid analgesics other than tramadol³³⁻³⁸⁾ are not the priority due to concerns associated with tolerability and long-term safety though these have been demonstrated effective for painful diabetic neuropathy. In addition, it is desirable to receive a consultation from a pain management specialist when performing a long-term tramadol administration or when using other opioid analgesics.

Note 1 : Epalrestat :
approved for subjective
symptoms (numbness and
pain) associated with
diabetic neuropathy.

Aldose reductase inhibitor

Epalrestat^{Note 1} controls intraneural sorbital accumulation and improves painful diabetic neuropathy by specifically inhibiting aldose reductase which acts in the process of sorbitol production from glucose. It has been reported that epalrestat may improve pain, numbness and autonomic nervous functions in painful diabetic neuropathy¹⁾. However, there is also a clinical study conducted in Japan concluding that no efficacy was observed for neuropathic pain^{19-21, 24, 39)}. Epalrestat is administered at 150 mg/day divided into 3 doses (before meals). Analgesic effects are likely to be observed in patients with (i) weak or moderate neuropathic pain and (ii) disease history of less than 3 years¹⁾.

References

- 1) The Japan Diabetes Society: Treatments for diabetic neuropathy (Evidence-based Practice Guidelines for the Treatment of Diabetes in Japan [2013] edited by The Japan Diabetes Society) 2013; 115-128
- 2) Arezzo JC, Rosenstock J, Lamoreaux L, et al: Efficacy and safety of pregabalin 600 mg/day for treating painful diabetic peripheral neuropathy: A double-blind placebo-controlled trial. BMC Neurology 2008; 8: 33 [1b]
- 3) Lesser H, Sharma U, Lamoreaux L, et al: Pregabalin relieves symptoms of painful diabetic neuropathy: A randomized controlled trial. Neurology 2004; 63: 2104-2110 [1b]
- 4) Richter RW, Portenoy R, Sharma U, et al: Relief of painful diabetic peripheral neuropathy with pregabalin: A randomized, placebo-controlled trial. J Pain 2005; 6: 253-260 [1b]
- 5) Rosenstock J, Tuchman M, Lamoreaux L, et al: Pregabalin for the treatment of painful diabetic peripheral neuropathy: A double-blind, placebo-controlled trial. Pain 2004; 110: 628-638 [1b]
- 6) Tolle T, Freynhagen R, Versavel M, et al: Pregabalin for relief of neuropathic pain associated with diabetic neuropathy: A randomized, double-blind study. Eur J Pain 2008; 12: 203-213 [1b]
- 7) Freynhagen R, Strojek K, Griesing T, et al: Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible-and fixed-dose regimens. Pain 2005; 115: 254-263 [1b]
- 8) Freeman R, Durso-DeCruz E, Emir B: Efficacy, safety, and tolerability of pregabalin treatment for painful diabetic peripheral neuropathy: findings from seven randomized, controlled trials across a range of doses. Diabet Care 2008; 31: 1448-1454 [1a]
- 9) Satoh J, Yagihashi S, Baba M, et al: Efficacy and safety of pregabalin for treating neuropathic pain associated with diabetic peripheral neuropathy: A 14-week, randomized, double-blind, placebo-controlled trial. Diabet Med 2011; 28: 109-116 [1b]
- 10) Randomized, double-blind, multicenter, placebo-controlled study of pregabalin for pain associated with diabetic peripheral neuropathy. <http://www.clinicaltrials.gov/ct2/show/results/NCT00553475?term=A0081163&rank=2>
- 11) Goldstein DJ, Lu Y, Detke MJ, et al: Duloxetine vs. placebo in patients

- with painful diabetic neuropathy. *Pain* 2005; 116: 109–118 [1b]
- 12) Raskin J, Pritchett Y, Chappell AS, et al: Duloxetine in the treatment of diabetic peripheral neuropathic pain: Results from three clinical trials. European Federation of Neurological Societies 2005; Sept 17–20; Athens, Greece. [1b]
 - 13) Wernicke JF, Pritchett YL, D'Souza DN, et al: A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. *Neurology* 2006; 67: 1411–1420 [1b]
 - 14) Raskin J, Pritchett YL, Wang F, et al: A double-blind, randomized multicenter trial comparing duloxetine with placebo in the management of diabetic peripheral neuropathic pain. *Pain Med* 2005; 6: 346–356 [1b]
 - 15) Yasuda H, Hotta N, Nakao K, et al: Superiority of duloxetine to placebo in improving diabetic neuropathic pain: Results of a randomized controlled trial in Japan. *J Diabet Invest* 2011; 2: 132–139 [1b]
 - 16) A Study for the treatment of diabetic peripheral neuropathic pain. <http://clinicaltrials.gov/ct2/show/results/NCT00552175?term=ly248686+japan&rank=1>
 - 17) Wernicke JF, Wang F, Pritchett YL, et al: An open-label 52-week clinical extension comparing duloxetine with routine care in patients with diabetic peripheral neuropathic pain. *Pain Med* 2007; 8: 503–513 [2b]
 - 18) Raskin J, Smith TR, Wong K, et al: Duloxetine versus routine care in the long-term management of diabetic peripheral neuropathic pain. *J Palliat Med* 2006; 9: 29–40 [2b]
 - 19) Goto Y, Shigeta Y, Sakamoto N, et al: A clinical study on epalrestat (ONO-2235) for diabetic neuropathy?: A double-blind group comparison study using a placebo control (containing a small amount of study drug). *Journal of Clinical and Experimental Medicine* 1990; 152: 405–416 [1b]
 - 20) Goto Y, Shigeta Y, Sakamoto N, et al: A clinical evaluation of aldose reductase inhibitor ONO-2235 for diabetic neuropathy: A double-blind comparative clinical study. *Gendai iryo* 1986; 18: 449–66 [1b]
 - 21) Aida K, Tsuchiya K, Tanaka H, et al: Clinical effects of long-term administration of aldose reductase inhibitor epalrestat for diabetic neuropathy for 3 years in Yamanashi region?: Including clinical course after discontinuation of the treatment. *Diabet Frontier* 2008; 19: 522–527 [2b]
 - 22) Hotta N, Akanuma Y, Kawamori R, et al: Long-term clinical effects of epalrestat, an aldose reductase inhibitor, on diabetic peripheral neuropathy: The 3-year, multicenter, comparative aldose reductase inhibitor–diabetes complications trial. *Diabet Care* 2006; 29: 1538–1544 [2b]
 - 23) Sako Y, Ashida K, Aoki T, et al: An investigation of actual situation of diabetic neuropathy and clinical effects of aldose reductase inhibitors for neuropathic subjective symptoms and autonomic neuropathy (CVR-R abnormality) in our clinic. *The Japanese Journal of Clinical and Experimental Medicine* 2005; 82: 723–732 [2b]
 - 24) Matsuoka T, Aoyama M, Himei H: Effects of aldose reductase inhibitor for subjective and objective findings of diabetic peripheral neuropathy. *Diabetic Complications* 2000; 15: 48–54 [2b]
 - 25) Matsuoka K, Hirata Y, Kanazawa Y, et al: Optimal clinical dose of mexiletine hydrochloride (MX-DPN) for diabetic neuropathy patients. *Japanese Journal of Medicine and Pharmaceutical Science* 1997; 38: 729–757 [1b]

- 26) Matsuoka K, Hirata Y, Kanazawa Y, et al : A double-blind comparative study on mexiletine hydrochloride (MX-DPN) for diabetic neuropathy. *Japanese Journal of Medicine and Pharmaceutical Science* 1997 ; 38 : 759–776 [2b]
- 27) Suzuki Y, Matsuoka K : Effects of mexiletine for diabetic neuropathic pain (a double-blind study). *Journal of New remedies & Clinics* 1992 ; 41 : 2347–2351 [2b]
- 28) Nishizawa Y, Yoshioka F, Nosaka S, et al : Improving and protecting effect and safety of mexiletine hydrochloride or mianserin hydrochloride on painful diabetic neuropathy in patients with type 2 diabetes mellitus for 2 years in prospective randomized well-controlled comparative study. *The Journal of the Japanese Society for the Study of Chronic Pain* 2005 ; 24 : 137–148 [2b]
- 29) Sindrup SH, Andersen G, Madsen C, et al : Tramadol relieves pain and allodynia in polyneuropathy : A randomised, double-blind, controlled trial. *Pain* 1999 ; 83 : 85–90 [1b]
- 30) Harati Y, Gooch C, Swenson M, et al : Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. *Neurology* 1998 ; 50 : 1842–1846 [1b]
- 31) Finnerup NB, Attal N, Haroutounian S, et al : Pharmacotherapy for neuropathic pain in adults : A systematic review and meta-analysis. *Lancet Neurol* 2015 ; 14 : 162–173
- 32) Gimbel JS, Richards P, Portenoy RK : Controlled-release oxycodone for pain in diabetic neuropathy : A randomized controlled trial. *Neurology* 2003 ; 60 : 927–934 [1b]
- 33) Gilron I, Bailey JM, Tu D, et al : Morphine, gabapentin, or their combination for neuropathic pain. *N Engl J Med* 2005 ; 352 : 1324–1334 [1b]
- 34) Watson CPN, Moulin D, Watt-Watson J, et al : Controlled-release oxycodone relieves neuropathic pain : A randomized controlled trial in painful diabetic neuropathy. *Pain* 2003 ; 105 : 71–78 [1b]
- 35) Gilron I, Bailey JM, Tu D, et al : Morphine, gabapentin, or their combination for neuropathic pain. *N Engl J Med* 2005 ; 352 : 1324–1334 [1b]
- 36) Boureau F, Legallicier P, Kabir-Ahmadi M : Tramadol in post-herpetic neuralgia : A randomized, double-blind, placebo-controlled trial. *Pain* 2003 ; 104 : 323–331 [1b]
- 37) Sindrup SH, Andersen G, Madsen C, et al : Tramadol relieves pain and allodynia in polyneuropathy : A randomised, double-blind, controlled trial. *Pain* 1999 ; 83 : 85–90 [1b]
- 38) Rowbotham MC, Twilling L, Davies PS, et al : Oral opioid therapy for chronic peripheral and central neuropathic pain. *N Engl J Med* 2003 ; 348 : 1223–1232 [1b]
- 39) Suzuki K, Kimura M : Effects of a concomitant use of Methycobal® and Kinedak®. *Japanese Journal of Medicine and Pharmaceutical Science* 1999 ; 41 : 281–295 [2b]

30. Trigeminal neuralgia

CQ40 : Is carbamazepine effective for trigeminal neuralgia compared to placebo?

Carbamazepine is effective for trigeminal neuralgia compared to placebo and recommended as the first-line drug for the treatment of trigeminal neuralgia.

Summary of the level of recommendation and overall evidence : 1B

Comments :

There are 4 randomized, double-blind, placebo controlled studies¹⁻⁴⁾, 1 meta-analysis⁵⁾, and 2 systematic reviews (guidelines, written by the same group)^{6,7)} on the effects of carbamazepine for trigeminal neuralgia compared to placebo. In a meta-analysis including randomized controlled studies conducted by Wiffen et al⁵⁾, NNT for carbamazepine in trigeminal neuralgia was 1.7 [95% CI 1.3 to 2.2] (risk ratio 6.0 [95% CI 2.8 to 13]). In a systematic review conducted by Cruccu et al⁶⁾, they concluded that the evidence of the effectiveness of carbamazepine for trigeminal neuralgia was robust.

Existing guidelines related to this clinical question have been issued by AAN and EFNS^{6,8)}. In EFNS guidelines on the pharmacological treatment of neuropathic pain conducted by Attal et al.⁸⁾, carbamazepine was recommended as the first-line drug in pharmacological treatment of trigeminal neuralgia, while it was also indicated that the effectiveness of carbamazepine could be affected by low tolerability and drug interactions (as CYP3A4 inducer). In a clinical practice guideline for trigeminal neuralgia conducted by Cruccu et al.⁶⁾, NNH of carbamazepine is 3.4 ^{Note 1}.

Thus, this guideline recommended carbamazepine as the first-line drug for trigeminal neuralgia. However, we should use carbamazepine with careful attention to adverse events and drug interactions.

References

- 1) Campbell FG, Graham JG, Zilkha KJ : Clinical trial of carbamazepine (tegretol) in trigeminal neuralgia. *J Neurol Neurosurg Psychiatry* 1966 ; 29 : 265-267 [1b]
- 2) Killian JM, Fromm GH : Carbamazepine in the treatment of neuralgia. *Arch Neurol* 1968 ; 19 : 129-136 [2b]
- 3) Nicol CF : A four year double blind study of tegretol in facial pain. *Headache* 1969 ; 9 : 54-57 [2b]
- 4) Rockcliff BW, Davis EH : Controlled sequential trials of carbamazepine in trigeminal neuralgia. *Arch Neurol* 1996 ; 15 : 129-136 [2b]
- 5) Wiffen PJ, Derry S, Moore RA, et al : Carbamazepine for chronic neuro-

NNT : number needed to treat

AAN : The American Academy of Neurology

EFNS : The European Federation of Neurological Societies

NNH : number needed to harm

Note 1 : See the section of "anti-epileptics" for major adverse events.

pathic pain and fibromyalgia in adults Cochrane Database Syst Rev, Issue 4, Art. No. : CD005451. DOI : 10. 1002/14651858. CD005451. pub3, 2014 [1a]

- 6) Cruccu G, Gronseth G, Alksne J, et al : AAN-EFNS guidelines on trigeminal neuralgia management. Eur J Neurol 2008 ; 15 : 1013-1028 [1a]
- 7) Gronseth G, Cruccu G, Alksne J, et al : Practice parameter : The diagnostic evaluation and treatment of trigeminal neuralgia (an evidence-based review) : Report of the Quality Standards Subcommittee of the American Academy of Neurology and the European Federation of Neurological Societies. Neurology 2008 ; 71 : 1183-1190 [1a]
- 8) Attal N, Cruccu G, Baron R, et al : EFNS guidelines on the pharmacological treatment of neuropathic pain : 2010 revision. Eur J Neurol 2010 ; 17 : 1113-23 [1a]

CQ41 : Are there any drugs other than carbamazepine that are effective for trigeminal neuralgia?

Baclofen, lamotrigine and botulinum toxin type A may be effective for trigeminal neuralgia. Oxcarbazepine may have comparable effectiveness with carbamazepine, although it is not approved in Japan.

The level of recommendation and the summary of overall evidence : 2C

Comments :

The drugs currently available in Japan other than carbamazepine that have been shown to be effective for trigeminal neuralgia in randomized, placebo controlled studies are baclofen¹⁾, lamotrigine²⁾, lidocaine^{3,4)}, sumatriptan⁵⁾ and botulinum toxin type A (BTX-A)⁶⁻⁸⁾. In addition, oxcarbazepine⁹⁾, pimozone¹⁰⁾ and topiramate¹¹⁾ have been shown to be equally or more effective than carbamazepine in randomized active-controlled studies. In a randomized, double-blind, crossover study of 10 patients with trigeminal neuralgia conducted by Fromm et al¹⁾, baclofen 50-80 mg/day significantly reduced the number of attacks compared to placebo (7 out of 10 patients in the baclofen group, 1 out of 10 patients in the placebo group). In a randomized double-blind crossover study of 14 refractory trigeminal neuralgia patients prescribed carbamazepine or phenytoin conducted by Zakrzewska et al²⁾, additional use lamotrigine 400 mg significantly improved composite index of efficacy compared to placebo, and NNT for lamotrigine was 2.1 [95% CI 1.3-6.1]¹²⁾. In randomized, double-blind, crossover studies using 8% [w/v] lidocaine spray (8% [w/v] lidocaine hydrochloride) or placebo intranasally (Kanai et al.³⁾) and intraorally (Niki et al.⁴⁾), significant pain reduction was observed 15 minutes after the treatment with lidocaine spray compared to the placebo. However, it was effective only for a short period of time, and pain recurred in most of the patients within 24 hours. In a randomized, double blind, crossover study of subcutaneous injection of sumatriptan

Oxcarbazepine : Not marketed in Japan

BTX-A : botulinum toxin type A

tan 3 mg or placebo in 24 trigeminal neuralgia patients conducted by Kanai et al.⁵⁾, sumatriptan significantly reduced the VAS score of attacks 15 minutes after compared to placebo. However, the duration of the effect was 7.9 [1–20] hours (median [range]). There are two randomized, double blind, placebo-controlled studies which investigated effects of BTX-A (subcutaneous or oral mucosal injection to the trigger points). Wu et al.⁶⁾ demonstrated that 75 U of BTX-A significantly reduced the pain intensity and the number of attacks until week 12 compared to placebo. In a study comparing 3 groups (BTX-A 75 U, 25 U and placebo) conducted by Zhang et al.⁷⁾, pain intensity was significantly lower, and the response rates and the patient satisfaction score were significantly higher until week 8 in the BTX-A group compared to the placebo group. There was no difference in terms of effectiveness between the BTX-A 75 U group and the 25 U group. The adverse events observed in these studies were all transient and classified as either weak or moderate^{6,7)}. The BTX-A products used in these studies were different from that available in Japan. However, a systematic review including open-label trials⁸⁾, showed the effectiveness of Botox® injection which is also available in Japan. In a randomized, double blind, controlled study comparing effects of oxcarbazepine and carbamazepine conducted by Liebel et al.⁹⁾, the number of attacks was reduced with oxcarbazepine as much as with carbamazepine. Also in a randomized, double blind, crossover study conducted by Lechin et al.¹⁰⁾ on effects of pimozone 4–12 mg/day and carbamazepine 300–1,200 mg/day in 48 patients with trigeminal neuralgia, the improvement rate was higher with pimozone than with carbamazepine (48 of 48 patients vs. 28 of 48 patients), although the incidence of adverse events was 83% for pimozone. In a meta-analysis conducted by Wang et al.¹¹⁾ on RCTs comparing effects of topiramate and carbamazepine, there was no difference in the effectiveness of each drug in one month after the start of treatment, while the effectiveness of topiramate was superior to carbamazepine after two months. However, the authors described that their studies were some limitations that all studies had been performed in only one country and was very low in terms of the quality of study.

There is a systematic review related to this clinical question, conducted by Zhang et al.¹³⁾ on non-antiepileptic drugs for trigeminal neuralgia. This study described about the studies on tizanidine, tocainide and 0.5% [w/v] propa-caine hydrochloride, in addition to pimozone described above, as drugs compared to carbamazepine in randomized controlled studies. However, there were no drugs comparable to carbamazepine.

Existing guidelines related to this clinical question have been issued by AAN and EFNS^{14,15)}. In EFNS guidelines on the pharmacological treatment of neuropathic pain conducted by Attal et al.¹⁵⁾, oxcarbazepine was recommended

VAS : visual analogue scale
(defined by IASP : 0 as no
pain and 100 [mm] as the
worst pain you could ever
imagine)

along with carbamazepine as the first-line drug in pharmacological treatment for trigeminal neuralgia.

Hence, this guideline concludes that baclofen, lamotrigine, and botulinum toxin type A may be effective for trigeminal neuralgia, although the use of these drugs for trigeminal neuralgia is not covered by insurance in Japan. Oxcarbazepine is recommended as the first-line drug in guidelines available in the US and Europe, however we do not refer to oxcarbazepine in this conclusion as it is not marketed and approved in Japan.

References

- 1) Fromm GH, Terrence CF, Chattha AS: Baclofen in the treatment of trigeminal neuralgia: Double-blind study and long-term follow-up. *Ann Neurol* 1984; 15: 240-244 [2b]
- 2) Zakrzewska JM, Chaudhry Z, Nurmikko TJ, et al: Lamotrigine (lamictal) in refractory trigeminal neuralgia: Results from a double-blind placebo controlled crossover trial. *Pain* 1997; 73: 223-230 [2b]
- 3) Kanai A, Suzuki A, Kobayashi M, Hoka S: Intranasal lidocaine 8% spray for second-division trigeminal neuralgia. *Br J Anaesth* 2006; 97: 559-563 [1b]
- 4) Niki Y, Kanai A, Hoshi K, et al: Immediate analgesic effect of 8% lidocaine applied to the oral mucosa in patients with trigeminal neuralgia. *Pain Med* 2014; 15: 826-831 [1b]
- 5) Kanai A, Saito M, Hoka S: Subcutaneous sumatriptan for refractory trigeminal neuralgia. *Headache* 2006; 46: 577-582 [1b]
- 6) Wu CJ, Lian YJ, Zheng YK, et al: Botulinum toxin type A for the treatment of trigeminal neuralgia: Results from a randomized, double-blind, placebo-controlled trial. *Cephalalgia* 2013; 32: 443-450 [2b]
- 7) Zhang H, Lian Y, Ma Y, et al: Two doses of botulinum toxin type A for the treatment of trigeminal neuralgia: Observation of therapeutic effect from a randomized, double-blind, placebo-controlled trial. *J Headache Pain* 2014; 15: 65 [2b]
- 8) Hu Y, Guan X, Fan L, et al: Therapeutic efficacy and safety of botulinum toxin type A in trigeminal neuralgia: A systematic review. *J Headache Pain* 2013; 14: 72 [2b]
- 9) Liebel JT, Menger N, Langohr H: Oxcarbazepine in der behandlung der trigeminusneuralgie. *Nervenheilkunde* 2001; 20: 461-465 [2b]
- 10) Lechin F, van der Dijs B, Lechin ME, et al: Pimozide therapy for trigeminal neuralgia. *Arch Neurol* 1989; 46: 960-963 [2b]
- 11) Wang QP, Bai M: Topiramate versus carbamazepine for the treatment of classical trigeminal neuralgia: A meta-analysis. *CNS Drugs* 2011; 25: 847-857 [1a]
- 12) Finnerup NB, Sindrup SH, Jensen TS: The evidence for pharmacological treatment of neuropathic pain. *Pain* 2010; 150: 573-581 [1a]
- 13) Zhang J, Yang M, Zhou M, et al: Non-antiepileptic drugs for trigeminal neuralgia. *Cochrane Database Syst Rev*. 2013 Dec 3; 12: CD004029. [4]
- 14) Cruccu G, Gronseth G, Alksne J, et al: AAN-EFNS guidelines on trigeminal neuralgia management. *Eur J Neurol* 2008; 15: 1013-1028 [1a]
- 15) Attal N, Cruccu G, Baron R, et al: EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol* 2010; 17: 1113-23 [1a]

31. Central neuropathic pain

CQ42 : What pharmacotherapies are effective for central post-stroke pain ?

Amitriptyline and lamotrigine are effective at a certain level for central post-stroke pain.

The level of recommendation and the summary of overall evidence : 2B

Comments :

RCTs have been conducted on pharmacotherapies for central post-stroke pain (CPSP) using amitriptyline, carbamazepine, pregabalin, lamotrigine, levetiracetam, morphine and lidocaine. In a study conducted in 15 CPSP patients, adverse effects such as weak to moderate malaise and dry mouth developed with amitriptyline 75 mg/day, while pain was significantly reduced by amitriptyline compared to placebo. On the other hand, it has been reported that no significant analgesic effect was observed with carbamazepine compared to placebo¹⁾. In a study conducted on efficacy of pregabalin in CPSP patients (219 subjects), significant improvement was observed in sleep and anxiety with pregabalin 300–600 mg/day compared to placebo, while no significant decrease was reported for pain²⁾. In a study investigating analgesic effects of lamotrigine in 35 CPSP patients, high tolerability was observed with lamotrigine 200 mg/day along with significantly higher analgesic effects compared to placebo³⁾. In a study conducted on efficacy of levetiracetam in 42 CPSP patients, no significant difference was observed in analgesic effects between levetiracetam 3,000 mg/day and placebo, and no improvement was reported either for QOL. Moreover, adverse effects such as malaise or dizziness developed in 21 patients in this study⁴⁾. In a RCT conducted using morphine in 15 patients (including 9 patients with pain after spinal cord injury), allodynia was significantly reduced by intravenous administration of morphine hydrochloride at 9–30 mg compared to placebo, although it was not effective for persistent pain⁵⁾. In a RCT conducted using lidocaine in 16 patients (including 10 patients with pain after spinal cord injury), significant decreases were observed with 30 minutes of intravenous lidocaine administration at 5 mg/kg compared to placebo in persistent pain until 45 minutes after injection and in the degree of allodynia⁶⁾.

It has been also mentioned in systematic reviews that further accumulation of studies will be necessary as there are not many studies with high evidence level available for amitriptyline and lamotrigine, which are recommended as analgesic drugs for CPSP^{7,8)}.

RCT : randomized controlled trial

CPSP : central post-stroke pain

RCT : randomized controlled trial

References

- 1) Leijon G, Boivie J : Central post-stroke pain : A controlled trial of amitriptyline and carbamazepine. *Pain* 1989 ; 36 : 27-36 [1b]
- 2) Kim JS, Bashford G, Murphy TK, et al : Safety and efficacy of pregabalin in patients with central post-stroke pain. *Pain* 2011 ; 152 : 1018-1023 [1b]
- 3) Vestergaard K, Andersen G, Gottrup H, et al : Lamotrigine for central poststroke pain : A randomized controlled trial. *Neurology* 2001 ; 56 : 184-190 [1b]
- 4) Jungehulsing GJ, Israel H, Safar N, et al : Levetiracetam in patients with central neuropathic post-stroke pain : A randomized, double-blind, placebo-controlled trial. *Eur J Neurol* 2013 ; 20 : 331-337 [1b]
- 5) Attal N, Guirimand F, Brasseur L, et al : Effects of IV morphine in central pain : A randomized placebo-controlled study. *Neurology* 2002 ; 58 : 554-563 [1b]
- 6) Attal N, Gaudé V, Brasseur L, et al : Intravenous lidocaine in central pain. *Neurology* 2000 ; 54 : 564-574 [1b]
- 7) Kim JS : Pharmacological management of central post-stroke pain : A practical guide. *CNS Drugs* 2014 ; 28 : 787-797 [1a]
- 8) Mulla SM, Wang L, Khokhar R, et al : Management of central poststroke pain : Systematic review of randomized controlled trials. *Stroke* 2015 ; 46 : 2853-2860 [1a]

CQ43 : What pharmacotherapies are effective for neuropathic pain associated with multiple sclerosis ?

Levetiracetam is effective at a certain level for neuropathic pain associated with multiple sclerosis.

The level of recommendation and the summary of overall evidence : 2C

Comments :

RCTs have been conducted on pharmacotherapies for central neuropathic pain associated with multiple sclerosis using levetiracetam and lamotrigine. There are 2 RCTs for levetiracetam. In a RCT conducted in 20 patients with central neuropathic pain associated with multiple sclerosis, significant alleviation of pain was observed with levetiracetam administration at 3,000 mg/day compared to placebo. In 3 out of 12 patients in the levetiracetam group however developed somnolence, 1 developed dizziness, and 1 developed nausea¹⁾. In another RCT conducted in 30 patients, no significant difference was observed in pain reduction between levetiracetam 3,000 mg/day and placebo. However, significant reduction in pain was observed compared to placebo when limited to patients presenting shooting pain or patients without allodynia. Adverse effects such as malaise or dizziness developed in 4 patients²⁾.

In a RCT investigating efficacy of lamotrigine 400 mg/day, no significant difference was observed in improvement effects on pain and quality of life compared to placebo³⁾.

References

- 1) Rossi S, Mataluni G, Codeca C, et al: Effects of levetiracetam on chronic pain in multiple sclerosis: Results of a pilot, randomized, placebo-controlled study. *Eur J Neurol* 2009; 16: 360-366 [1b]
- 2) Falah M, Madsen C, Holbech JV, et al: A randomized, placebo-controlled trial of levetiracetam in central pain in multiple sclerosis. *Eur J Pain* 2012; 16: 860-869 [1b]
- 3) Breuer B, Pappagallo M, Knotkova H, et al: A randomized, double-blind, placebo-controlled, two-period, crossover, pilot trial of lamotrigine in patients with central pain due to multiple sclerosis. *Clin Ther* 2007; 29: 2022-2030 [1b]

32. Pain after spinal cord injury

CQ44 : Are tricyclic antidepressants and Ca^{2+} channel $\alpha_2\delta$ ligands effective for pain after spinal cord injury?

Evidence of efficacy for amitriptyline and Ca^{2+} channel $\alpha_2\delta$ ligands is relatively high for pain after spinal cord injury.

The level of recommendation and summary of overall evidence : 1A

Comments :

It has been reported in a systematic review¹⁾ that NNT for pain after spinal cord injury was 4.4 for amitriptyline²⁾, 7 for pregabalin^{3,4)}, and ∞ for gabapentin²⁾. Meanwhile, in a RCT investigated on analgesic effects of gabapentin in 20 patients with pain after spinal cord injury, the reduction of the frequency and the degree of pain and the improvement of QOL were reported at doses of 900–3,600 mg/day compared to placebo⁵⁾.

In another systematic review, amitriptyline, pregabalin and gabapentin have been recommended as first-line drugs for pain after spinal cord injury. However, attention is required for adverse effects such as somnolence, dry mouth and malaise as high doses are needed to achieve adequate analgesic effects⁶⁾.

References

- 1) Finnerup NB, Attal N, Haroutounian S, et al : Pharmacotherapy for neuropathic pain in adults : A systematic review and meta-analysis. *Lancet Neurol* 2015 ; 14 : 162–173 [1a]
- 2) Rintala DH, Holmes SA, Courtade D, et al : Comparison of the effectiveness of amitriptyline and gabapentin on chronic neuropathic pain in persons with spinal cord injury. *Arch Phys Med Rehabil* 2007 ; 88 : 1547–1560 [1b]
- 3) Siddall PJ, Cousins MJ, Otte A, et al : Pregabalin in central neuropathic pain associated with spinal cord injury : A placebo-controlled trial. *Neurology* 2006 ; 67 : 1792–1800 [1b]
- 4) Cardenas DD, Nieshoff EC, Suda K, et al : A randomized trial of pregabalin in patients with neuropathic pain due to spinal cord injury. *Neurology* 2013 ; 80 : 533–539 [1b]
- 5) Levendoglu F, Ogun CO, Ozerbil O, et al : Gabapentin is a first line drug for the treatment of neuropathic pain in spinal cord injury. *Spine* 2004 ; 29 : 743–751 [1b]
- 6) Hagen EM, Rekan T : Management of neuropathic pain associated with spinal cord injury. *Pain Ther* 2015 ; 4 : 51–65 [1a]

CQ45 : Are opioids effective for pain after spinal cord injury?

Opioids are moderately effective for pain after spinal cord injury, but are less effective compared to tricyclic antidepressants or Ca^{2+} channel $\alpha_2\delta$ ligands.

The level of recommendation and the summary of overall evidence : 2B**Comments :**

For opioids, analgesic effects of tramadol and morphine for pain after spinal cord injury have been investigated in RCTs. In a RCT conducted on analgesic effects of tramadol in 35 patients with pain after spinal cord injury, the pain score decreased significantly with administration at 150–400 mg/day compared to placebo. On the other hand, adverse effects such as malaise, dry mouth and dizziness have been reported in 91% of patients¹⁾. In a RCT conducted using morphine in 15 patients (including 6 patients with central post-stroke pain), a significant reduction of allodynia was observed with intravenous administration at 9–30 mg compared to placebo. It was not effective, however, for persistent pain²⁾.

Opioids are moderately effective for pain after spinal cord injury. However, a long-term use is not recommended considering the balance between the effects and adverse effects, as they often induce adverse effects including addiction. Thus, opioids are less effective compared to tricyclic antidepressants and Ca^{2+} channel $\alpha_2\delta$ ligands^{2,3)}.

References

- 1) Norrbrink C, Lundeberg T : Tramadol in neuropathic pain after spinal cord injury : A randomized, double-blind, placebo-controlled trial. Clin J Pain 2009 ; 25 : 177–184 [1b]
- 2) Attal N, Guirimand F, Brasseur L, et al : Effects of IV morphine in central pain : A randomized placebo-controlled study. Neurology 2002 ; 58 : 554–563 [1b]
- 3) Hagen EM, Rekan T : Management of neuropathic pain associated with spinal cord injury. Pain Ther 2015 ; 4 : 51–65 [1a]

CQ46 : Are there any drugs effective for pain after spinal cord injury other than tricyclic antidepressants, Ca^{2+} channel $\alpha_2\delta$ ligands, and opioids?

The number of RCT which investigated effectiveness of drugs for pain after spinal cord injury is very limited. It is currently unknown if there are any drugs which can be more effective than tricyclic antidepressants, Ca^{2+} channel $\alpha_2\delta$ ligands, and opioids.

The level of recommendation and the summary of overall evidence : 2C

Comments :

Analgesic effects of anti-epileptics including lamotrigine, carbamazepine, and levetiracetam and of anti-arrhythmic drug such as mexiletine for pain after spinal cord injury have been investigated in RCTs. Lamotrigine showed significant analgesic effects in patients presenting allodynia and patients with incomplete spinal cord injury, though no analgesic effect was observed in any other patients. NNT for the entire population was 12¹⁾. A short-time pain relief can be achieved with carbamazepine when administered in the early stage of spinal cord injury. It is not effective however in a long-term treatment²⁾. No significant analgesic effect was observed with levetiracetam³⁾ and mexiletine⁴⁾ compared to placebo.

References

- 1) Finnerup NB, Sindrup SH, Bach FW, et al: Lamotrigine in spinal cord injury pain: A randomized controlled trial. *Pain* 2002; 96: 375-383 [1b]
- 2) Salinas FA, Lugo LH, García HI: Efficacy of early treatment with carbamazepine in prevention of neuropathic pain in patients with spinal cord injury. *Am J Phys Med Rehabil* 2012; 91: 1020-1027 [1b]
- 3) Finnerup NB, Grydehøj J, Bing J, et al: Levetiracetam in spinal cord injury pain: A randomized controlled trial. *Spinal Cord* 2009; 47: 861-867 [1b]
- 4) Chiou-Tan FY, Tuel SM, Johnson JC, et al: Effect of mexiletine on spinal cord injury dysesthetic pain. *Am J Phys Med Rehabil* 1996; 75: 84-87 [1b]

33. Chemotherapy-induced peripheral neuropathy

CQ47 : Is duloxetine effective for chemotherapy-induced peripheral neuropathy ?

The level of evidence on efficacy of duloxetine for chemotherapy-induced peripheral neuropathy (CIPN) is moderate.

The level of recommendation and the summary of overall evidence : 1C

Comments :

Efficacy of duloxetine has been confirmed in a systematic review on treatments for CIPN, and the level of recommendation for this drug is moderate¹⁾. In a RCT conducted on analgesic effects of duloxetine in 231 CIPN patients compared to placebo, it was reported that numbness and prickling sensation, in addition to pain, had also been relieved. Moreover, it was suggested that duloxetine was more effective for CIPN induced by oxaliplatin than for CIPN induced by paclitaxel²⁾. In a small-scale RCT conducted in 34 Japanese patients, improvements were also reported in pain and numbness associated with chemotherapy-induced neuropathy³⁾.

References

- 1) Hershman DL, Lacchetti C, Dworkin RH, et al : Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers : American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 2014 ; 32 : 1941-1967 [1a]
- 2) Smith EM, Pang H, Cirrincione C, et al : Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy : A randomized clinical trial. JAMA 2013 ; 309 : 1359-1367 [1b]
- 3) Hirayama Y, Ishitani K, Sato Y, et al : Effect of duloxetine in Japanese patients with chemotherapy-induced peripheral neuropathy : A pilot randomized trial. Int J Clin Oncol 2015 ; 20 : 866-871 [1b]

CQ48 : Are there any drugs other than duloxetine effective for chemotherapy-induced peripheral neuropathy?

Currently, there is no drug other than duloxetine confirmed to be effective for chemotherapy-induced peripheral neuropathy.

The level of recommendation and the summary of overall evidence : 2D

Comments :

Duloxetine is currently the only drug so far which has shown efficacy for CIPN. RCTs have been also conducted on effects of tricyclic antidepressants and Ca^{2+} channel $\alpha_2\delta$ ligands for CIPN.

For tricyclic antidepressants, small-scale RCTs were conducted on amitriptyline and nortriptyline. In a RCT investigating analgesic effects of amitriptyline in 44 patients, no efficacy was observed with the treatment ; it was considered that a small sample size and low amitriptyline doses would probably account for the result¹⁾. In a RCT conducted on nortriptyline in 51 patients, a slight improvement was observed though the evidence was not strong²⁾.

For Ca^{2+} channel $\alpha_2\delta$ ligands, in a RCT investigating analgesic effects of gabapentin in 115 patients, no efficacy was observed with the treatment³⁾ ; it was considered that a significant difference was not observed as the patients participated in this study might not have had strong pain. For pregabalin, no RCT has been conducted. However, efficacy has been reported in a case-control study⁴⁾.

In a systematic review⁵⁾ made on these findings for the treatments of CIPN, it was suggested that for these drugs there was no evidence which clearly supported efficacy for pain associated with CIPN. However, it was considered appropriate to use them as treatment options for chemotherapy-induced neuropathy, as not many evidences had been available in the first place, and the effects for other types of neuropathic pain had been already revealed.

Though the evidence level is low, there are also other reports made for opioids, showing efficacy of tramadol/acetaminophen combination tablets⁶⁾ and oxycodone⁷⁾ or that of α -lipoic acid^{8,9)}.

References

- 1) Kautio AL, Haanpää M, Saarto T, et al : Amitriptyline in the treatment of chemotherapy-induced neuropathic symptoms. *J Pain Symptom Manage* 2008 ; 35 : 31-39 [1b]
- 2) Hammack JE, Michalak JC, Loprinzi CL, et al : Phase III evaluation of nortriptyline for alleviation of symptoms of cis-platinum-induced peripheral neuropathy. *Pain* 2002 ; 98 : 195-203 [1b]
- 3) Rao RD, Michalak JC, Sloan JA, et al : Efficacy of gabapentin in the management of chemotherapy-induced peripheral neuropathy : A phase 3 randomized, double-blind, placebo-controlled, crossover trial (N00C3). *Cancer* 2007 ; 110 : 2110-2118 [1b]
- 4) Saif MW, Syrigos K, Kaley K, et al : Role of pregabalin in treatment of oxaliplatin-induced sensory neuropathy. *Anticancer Res* 2010 ; 30 : 2927-2933 [3b]
- 5) Hershman DL, Lacchetti C, Dworkin RH, et al : Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers : American Society of Clinical Oncology clinical practice

- guideline. *J Clin Oncol* 2014; 32: 1941-1967 [1a]
- 6) Liu YC, Wang WS: Human μ -opioid receptor gene A118G polymorphism predicts the efficacy of tramadol/acetaminophen combination tablets (ultracet) in oxaliplatin-induced painful neuropathy. *Cancer* 2012; 118: 1718-1725 [3b]
 - 7) Cartoni C, Brunetti GA, Federico V, et al: Controlled-release oxycodone for the treatment of bortezomib-induced neuropathic pain in patients with multiple myeloma. *Support Care Cancer* 2012; 20: 2621-2626 [3b]
 - 8) Gedlicka C, Kornek GV, Schmid K, et al: Amelioration of docetaxel/cisplatin induced polyneuropathy by alpha-lipoic acid. *Ann Oncol* 2003; 14: 339-340 [3b]
 - 9) Gedlicka C, Scheithauer W, Schull B, et al: Effective treatment of oxaliplatin-induced cumulative polyneuropathy with alpha-lipoic acid. *J Clin Oncol* 2002; 20: 3359-3361 [3b]

34. Neuropathic pain directly caused by cancer

CQ49 : Are strong opioids effective for neuropathic pain directly caused by cancer?

For neuropathic pain directly caused by cancer, opioid analgesics should not be discontinued even if it was opioid resistant pain, but should be used concomitantly with therapeutic drugs for neuropathic pain. If patients are not tolerated with adverse effects due to high-dose opioid analgesics or if adverse effects developed due to concomitant use of other drugs, the doses of opioid analgesics should be reconsidered and reduced accordingly.

The level of recommendation and the summary of overall evidence : 1A

Comments :

The pathological condition of pain can be different for each case in neuropathic pain directly caused by cancer. It will remain difficult in the future to investigate efficacy of each drug for reasons such as that the doses of opioid analgesics being used may vary according to each condition. For details of pharmacotherapies for neuropathic pain directly caused by cancer, see “Clinical Guidelines for Cancer Pain Management, Second Edition (2014)” issued by Japanese Society for Palliative Medicine.

During cancer treatments, patients may develop subjective symptoms of neuropathic pain in various situations : (1) neuropathic pain directly caused by cancer, (2) neuropathic pain associated with adverse effects of cancer treatment, and (3) neuropathic pain not associated with cancer or cancer treatment. In this section, we discuss neuropathic pain directly caused by cancer.

Pathological conditions of neuropathic pain directly caused by cancer include cancer of neural origin, neural invasion by cancer, and neural compression by cancer, which can be also manifested by compression syndrome of the spinal cord, brachial plexus infiltration syndrome, malignant psoas syndrome, and symptomatic trigeminal neuralgia, etc. There may be various cases of cancer pain which involve neuropathic factors. The morbidity rate of neuropathic pain directly caused by cancer is reported to be 18.6% in terminal cancer patients in Japan¹⁾.

In case where neuropathic pain directly caused by cancer is suspected, a definitive diagnosis should be obtained by imaging tests²⁾, and cancer treatments other than pharmacotherapies, such as chemotherapy, surgical removal, and radiotherapy should be also considered positively³⁾.

It is important to understand that neuropathic pain directly caused by cancer is cancer pain. Hence, administration of opioid analgesics should be encouraged unlike the cases of non-cancer pain. Although there are some differences in terms of the levels, efficacy of opioid analgesics has been observed in neuropathic pain directly caused by cancer. For neuropathic pain caused by cancer which has been difficult to treat with opioid analgesics, drugs for non-cancer pain should be considered.

Moreover, for neuropathic pain directly caused by cancer, opioid analgesics should not be discontinued even if it was opioid resistant pain, but should be used concomitantly with therapeutic drugs for neuropathic pain. If patients are not tolerated with adverse effects due to high-dose opioid analgesics or if adverse effects developed due to concomitant use of other drugs, the doses of opioid analgesics should be reconsidered and reduced accordingly.

References

- 1) Harada S, Tamura F, Ota S: The prevalence of neuropathic pain in terminally ill patients with cancer admitted to a palliative care unit: A prospective observational study. *Am J Hosp Palliat Care* 2016; 33: 594–598 [4]
- 2) Cleeland CS, Farrar JT, Hausheerth FH: Assessment of cancer-related neuropathy and neuropathic pain. *The Oncologist* 2010; 15: S13–S18. [5]
- 3) Piano V, Schalkwijk A, Burgers J, et al: Guidelines for neuropathic pain management in patients with cancer: A European survey and comparison. *Pain Pract* 2013; 13: 349–357. [4]

CQ50 : Are neuropathic pain medications effective for neuropathic pain directly caused by cancer ?

In “Clinical Guidelines for Cancer Pain Management, Second Edition (2014)” issued by Japanese Society for Palliative Medicine, drugs such as anti-epileptics, anti-depressants, anti-arrhythmic drugs, NMDA receptor antagonists and steroids are weakly recommended to be used when opioids are not effective enough ; the most appropriate drug should be selected for each patient considering adverse effects of drugs and the patient’s condition. Meanwhile, efficacy of pregabalin and gabapentin has been examined and verified.

The level of recommendation and the summary of overall evidence : 2C

Comments :

The drugs other than opioid analgesics recommended for neuropathic pain directly caused by cancer, include Ca^{2+} channel $\alpha_2\delta$ receptor ligands and anti-depressants as in a case of non-cancer pain.

For Ca^{2+} channel $\alpha_2\delta$ receptor ligands, efficacy of pregabalin and gabapentin

has been examined and verified. However, gabapentin is not indicated for alleviation of pain in Japan. The doses of Ca^{2+} channel $\alpha_2\delta$ receptor ligands should be adjusted while observing tolerability of adverse effects in CNS.

For anti-epileptic drugs other than Ca^{2+} channel $\alpha_2\delta$ receptor ligands, administrations of sodium valproate, phenytoin, clonazepam can be considered. However, efficacy of these drugs for neuropathic pain directly caused by cancer has not been adequately studied. Indication of these drugs should be considered carefully, taking into consideration the aggravation of adverse effects associated with concomitant use of opioid analgesics.

For antidepressants, administrations of tricyclic antidepressants such as amitriptyline or nortriptyline, and serotonin/noradrenaline reuptake inhibitor duloxetine are recommended. However, there are not many studies reporting.

Efficacy of antidepressants for neuropathic pain directly caused by cancer, and no absolute efficacy has been verified.

For Ca^{2+} channel $\alpha_2\delta$ receptor ligands and antidepressants, drugs might be changed or used concomitantly with other drugs if no effect has been observed despite increasing doses for any drugs. Such changes or concomitant use of other drugs have been reported effective^{1,2)}. However, these procedures should be considered carefully while paying attention to adverse effects as there is no absolute evidence on efficacy. Considering adverse effects in CNS, it is recommended to consider administration of the second drug after dose reduction or discontinuation of the first drug.

For neuropathic pain directly caused by cancer, use of anti-arrhythmic drugs or NMDA receptor antagonists is likely to be considered unlike noncancer pain. Anti-arrhythmic drugs, such as lidocaine or mexiletine, and NMDA receptor antagonists such as ketamine, amantadine, dextromethorphan and ifenprodil appear to be considered in many cases. However, no absolute efficacy has been demonstrated. Hence, anti-arrhythmic drugs or NMDA receptor antagonists should not be positively recommended but rather should be considered as potential options.

Steroids can be considered for compression syndrome of the spinal cord, neural invasion, and neuropathic pain induced by nerve compression. There is no high-quality clinical study conducted on these treatments. Hence, steroids should not be positively recommended but rather should be considered as potential options.

The pathological condition of pain can be different for each case, and doses of opioid analgesics which are used concomitantly may vary in neuropathic pain directly caused by cancer. For these reasons, it will remain difficult in the future to investigate efficacy of each drug³⁾.

References

- 1) Matsuoka H, Makimura C, Koyama A, et al: Pilot study of duloxetine for cancer patients with neuropathic pain non-responsive to pregabalin. *Anticancer Res* 2012; 32: 1805–1809. [4]
- 2) Arai YC, Matsubara T, Shimo K, et al: Low-dose gabapentin as useful adjuvant to opioids for neuropathic cancer pain when combined with low-dose imipramine. *J Anesth* 2010; 24: 407–410. [1b]
- 3) Piano V, Verhagen S, Schalkwijk A, et al: Treatment for neuropathic pain in patients with cancer: Comparative analysis of recommendations in national clinical practice guidelines from European countries. *Pain Pract* 2014; 14: 1–7. [2a]

35. Postoperative neuropathic pain (e.g. painful scar) and iatrogenic neuropathy (e.g. postthoracotomy neuropathic pain, postmastectomy pain)

CQ51 : Does perioperative drug administration reduce postoperative neuropathic pain?

Although the number of RCTs which showed efficacy for postoperative pain (chronic phase) is limited, pregabalin was effective for a certain level.

The level of recommendation and the summary of overall evidence : 1B

Comments :

In a systematic review of pharmacotherapies for postoperative pain¹⁾, no significant improvement was observed with ketamine in 3 months postoperatively compared to placebo (odds ratio 0.82, 95% confidence interval 0.4–1.7), while in 6 months, pain significantly improved (odds ratio 0.50, 95% confidence interval 0.33–0.76). The pain did not improve significantly with gabapentin in 3 months postoperatively compared to placebo (odds ratio 0.97, 95% confidence interval 0.59–1.59). A significant improvement was observed in pain with pregabalin in 3 months postoperatively compared to placebo (odds ratio 0.60, 95% confidence interval 0.39–0.93).

In a systematic review of pregabalin for other post-operative pain²⁾, pregabalin significantly reduced the pain at rest/on physical movement and the amount of postoperative analgesics being used during the acute phase 24 hours postoperatively. The number of RCTs has been limited for the chronic phase after 3 months. However, in a RCT investigating the efficacy of pregabalin for total knee arthroplasty (TKA)³⁾, pain was reported to be significantly improved by pregabalin in 6 months, suggesting that this treatment might be effective.

TKA : total knee arthroplasty

References

- 1) Chaparro LE, Smith SA, Moore RA, et al : Pharmacotherapy for the prevention of chronic pain after surgery in adults. Cochrane Database Syst Rev 2013 ; 7 : CD008307 [1a]
- 2) Mishriky BM, Waldron NH, Habib AS, et al : Impact of pregabalin on acute and persistent postoperative pain : A systematic review and meta-analysis. Br J Anaesth 2015 ; 114 : 10–31 [1a]
- 3) Buvanendran A, Kroin JS, Della Valle CJ, et al : Perioperative oral pregabalin reduces chronic pain after total knee arthroplasty : A prospective, randomized, controlled trial. Anesth Analg 2010 ; 110 : 199–207 [1b]

CQ52 : Are there any drugs effective for complete chronic postthoracotomy pain?

Although Ca^{2+} channel $\alpha_2\delta$ ligands are effective for postthoracotomy pain, no conclusion has been obtained for doses and the timing of the treatment.

The level of recommendation and the summary of overall evidence : 1A

Comments :

Analgesic effects of Ca^{2+} channel $\alpha_2\delta$ ligands for postthoracotomy pain have been examined in a RCT. In a RCT investigating analgesic effects of gabapentin in 40 patients with postthoracotomy pain of VAS ≥ 5 (0–10) and LANSS ≥ 12 , who received operations more than 3 months ago, significant improvement was observed at 300–2,400 mg/day administered in a dose escalation manner, in VAS and LANSS after 45 days and 60 days from treatment intervention compared to naproxen (1,000 mg/day)¹⁾. Also in a RCT conducted on analgesic effects of pregabalin in 68 patients who received thoracotomy, significant improvements were observed at 150 mg/day in 1, 2 and 3 months postoperatively in the degree of pain, LANSS and sleep disorder compared to loxoprofen (180 mg/day). For adverse effects, incidence of mild sleepiness was significantly higher with pregabalin, and that of stomachache was significantly higher with naproxan²⁾.

In a prospective cohort study investigating analgesic effects of gabapentin in 45 patients with persistent pain for more than 1 month after thoracotomy or chest trauma, improvement was observed in pain intensity, abnormal sensation and patients' satisfaction level at 300–900 mg/day after 21 weeks on average compared to the baseline³⁾.

References

- 1) Solak O, Metin M, Esme H, et al: Effectiveness of gabapentin in the treatment of chronic post-thoracotomy pain. *Eur J Cardiothorac Surg* 2007; 32: 9–12 [1b]
- 2) Matsutani N, Dejima H, Takahashi Y, et al: Pregabalin reduces post-surgical pain after thoracotomy: A prospective, randomized, controlled trial. *Surg Today* 2015; 45: 1411–1416 [1b]
- 3) Sihoe AD, Lee TW, Wan IY, et al: The use of gabapentin for post-operative and post-traumatic pain in thoracic surgery patients. *Eur J Cardiothorac Surg* 2006; 29: 795–799 [1b]

VAS : visual analogue scale

LANSS : Leeds Assessment of Neuropathic Symptoms and Signs

Venlafaxine

CQ53 : Are there any drugs effective for complete chronic postmastectomy pain ?

Antidepressants (e.g. venlafaxine), Ca^{2+} channel $\alpha_2\delta$ ligands, and lidocaine are effective for a certain level for postmastectomy pain.

The level of recommendation and the summary of overall evidence : 1B

Comments :

In a RCT investigating efficacy of venlafaxine and gabapentin in 150 patients who received mastectomy, a significant and equivalent decrease was observed in the amount of analgesics being used between Day 2 and Day 10 postoperatively for both venlafaxine at 37.5 mg/day and gabapentin at 300 mg/day compared to placebo. In addition, venlafaxine significantly reduced the incidence and intensity of pain as well as the amount of analgesics being used in 6 months postoperatively compared to gabapentin or placebo¹⁾.

In a RCT which showed that multi-model analgesia using gabapentin and local anesthetics is effective, significant decreases in incidence of pain and the rate of analgesic use were observed in 3 months and 6 months postoperatively in the group which received gabapentin 2,400 mg/day and topical EMLA cream 20 g (2.5% [w/w] lidocaine + 2.5% [w/w] procaine) with infiltration anesthesia of 0.75% [w/v] ropivacaine 10 ml/ compared to the placebo group, although the significant difference in pain intensity varied until Day 8 according to the timing of observation. It was unknown however which drug had been effective as comparisons had been made between the combination of multiple analgesics and placebo²⁾.

According to a report made by the same research group on efficacy of lidocaine, in a RCT investigating the EMLA cream in 45 patients, no significant difference was observed with the treatment from perioperative period until Day 4 postoperatively in the degree of pain by Day 6 postoperatively compared to placebo. However, significant improvement was observed in intensity and incidence of pain in 3 months postoperatively³⁾.

In a RCT conducted on lidocaine in 36 patients (additional operations were performed in 13 patients), significant reductions in intensity and incidence of pain, pain at physical movement, and the range of pain sensitivity were observed with the continuous intravenous administration at 1.5 mg/kg/hr following bolus administration at 1.5 mg/kg during operations, in 3 months postoperatively compared to placebo⁴⁾.

References

- 1) Amr YM, Yousef AA : Evaluation of efficacy of the perioperative admin-

- istration of venlafaxine or gabapentin on acute and chronic postmastectomy pain. Clin J Pain 2010 ; 26 : 381–385 [2b]
- 2) Fassoulaki A, Triga A, Melemenis A, et al : Multimodal analgesia with gabapentin and local anesthetics prevents acute and chronic pain after breast surgery for cancer. Anesth Analg 2005 ; 101 : 1427–1432 [2b]
 - 3) Fassoulaki A, Sarantopoulos C, Melemenis A, et al : EMLA reduces acute and chronic pain after breast surgery for cancer. Reg Anesth Pain Med 2000 ; 25 : 350–355 [2b]
 - 4) Grigoras A, Lee P, Sattar F, et al : Perioperative intravenous lidocaine decreases the incidence of persistent pain after breast surgery. Clin J Pain 2012 ; 28 : 567–572 [2c]

CQ54 : What drug is effective for pain after inguinal hernia repair ?

Gabapentin may be effective for pain after inguinal hernia repair.

Summary of the level of recommendation and overall evidence : 2B

Comments :

Efficacy of gabapentin has been demonstrated in a RCT¹⁾ compared to placebo.

In a RCT conducted in 59 patients with inguinal hernia, the degree of pain was significantly reduced not only within 24 hours after the operation but also in 1, 3 and 6 months postoperatively with a single gabapentin administration at 1,200 mg performed one hour before the operation, compared to placebo¹⁾. There were also 2 other RCTs investigating 5% [w/w] lidocaine patch²⁾ and 8% [w/w] capsaicin patch³⁾. No significant difference was observed in pain compared to placebo in either RCT.

References

- 1) Sen H, Sizlan A, Yanarates O, et al : The effects of gabapentin on acute and chronic pain after inguinal herniorrhaphy. Eur J Anaesthesiol 2009 ; 26 : 772–776 [1b]
- 2) Bischoff JM, Petersen M, Uçeyler N, et al : Lidocaine patch (5%) in treatment of persistent inguinal postherniorrhaphy pain : A randomized, double-blind, placebo-controlled, crossover trial. Anesthesiology 2013 ; 119 : 1444–1452 [1b]
- 3) Bischoff JM, Ringsted TK, Petersen M, et al : A capsaicin (8%) patch in the treatment of severe persistent inguinal postherniorrhaphy pain : A randomized, double-blind, placebo-controlled trial. PLoS One 2014 ; 9 : e109144 [1b]

36. Cervical and lumbar radiculopathy

CQ55 : Are antidepressants effective for cervical and lumbar radiculopathy ?

Antidepressants such as tricyclic antidepressants and SSRIs may be effective for cervical and lumbar radiculopathy.

The level of recommendation and the summary of overall evidence : 2B

Comments :

Efficacy of milnacipran (100–200 mg/day) was shown in a RCT for lumbar radiculopathy associated with intervertebral disc lesions. It was also effective for nociceptive pain associated with the intervertebral disc lesions¹⁾. In addition, in a RCT for low back pain associated with lumbar radiculopathy, improvements were observed with duloxetine ^{Note 1} (120 mg/day) in general pain and radicular symptoms²⁾.

Meanwhile, in a systematic review on antidepressants including tricyclic antidepressants and SSRIs, no efficacy was observed with antidepressants for lumbar radiculopathy, although antidepressant is one of the first-line drugs for neuropathic pain³⁾.

In fact, in a randomized comparative study for chronic radiculopathy, pain was alleviated by 7–14% by nortriptyline hydrochloride (25–100 mg/day), morphine hydrochloride (15–90 mg/day), and a combination of these drugs. However, no significant reduction of lower limb pain or low back pain was observed with these drugs compared to benztropine (0.25–1 mg/day) which was used as placebo⁴⁾.

RCT : randomized controlled trial

Note 1 : Duloxetine : approved for depression, chronic low back pain, painful diabetic neuropathy. For precautions when using this drug for pain, appropriateness of administration of this drug should be judged carefully taking into consideration the risk of developing psychiatric symptoms such as suicidal ideation, suicidal attempt, hostility and aggression.

References

- 1) Marks DM, Pae CU, Patkar AA : A double-blind, placebo-controlled, parallel-group pilot study of milnacipran for chronic radicular pain (sciatica) associated with lumbosacral disc disease. *Prim Care Companion CNS Disord.* 2014 ; 16 (4) [1b]
- 2) Schukro RP, Oehmke MJ, Geroldinger A, et al : Efficacy of duloxetine in chronic low back pain with a neuropathic component : A randomized, double-blind, placebo-controlled crossover trial. *Anesthesiology* 2016 ; 124 : 150–158 [1b]
- 3) Dworkin RH, O'Connor AB, Backonja M, et al : Pharmacologic management of neuropathic pain : Evidence-based recommendations. *Pain* 2007 ; 132 : 237–251 [1a]
- 4) Khoromi S, Cui L, Nackers L, et al : Morphine, nortriptyline and their combination vs. placebo in patients with chronic lumbar root pain. *Pain* 2007 ; 130 : 66–75 [1b]

CQ56 : Are Ca^{2+} channel $\alpha_2\delta$ ligands effective for cervical and lumbar radiculopathy ?

Ca^{2+} channel $\alpha_2\delta$ ligands are effective for cervical and lumbar radiculopathy.

The level of recommendation and the summary of overall evidence : 1C

Comments :

There are few reports available for cervical and lumbar radiculopathy. In the review made on efficacy of gabapentin for lumbar radiculopathy, gabapentin administration at 1,200–3,600 mg/day was effective for low back and lower limb pain associated with radiculopathy¹⁾.

Its efficacy has been also verified in a non-randomized comparative study investigating effectiveness of pregabalin for cervical or lumbar radiculopathy. In addition, improvement was observed not only in pain but also in associated symptoms such as anxiety, depression and sleep disorder²⁾.

In an analytical epidemiological study, pregabalin alleviated pain when used by itself or when used concomitantly with other drugs. This resulted in reduction of medical cost and shortening of sick leave^{3,4)}. However, there is also a report stating that no efficacy was observed for cervical and lumbosacral radiculopathy compared to placebo in pain, activity and the patients' satisfaction level in a small-sized RCT⁵⁾.

References

- 1) Chou R, Huffman LH : American Pain Society : American College of Physicians : Medications for acute and chronic low back pain : A review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. *Ann Intern Med* 2007 ; 147 : 505–514 [1b]
- 2) Saldaña MT, Navarro A, Pérez C, et al : Patient-reported-outcomes in subjects with painful lumbar or cervical radiculopathy treated with pregabalin : Evidence from medical practice in primary care settings. *Rheumatol Int* 2010 ; 30 : 1005–1015 [4]
- 3) Sicras-Mainar A, Rejas-Gutiérrez J, Navarro-Artieda R, et al : Cost comparison of adding pregabalin or gabapentin for the first time to the therapy of patients with painful axial radiculopathy treated in Spain. *Clin Exp Rheumatol* 2013 ; 31 : 372–381 [3a]
- 4) Saldaña MT, Navarro A, Pérez C, et al : A cost-consequences analysis of the effect of pregabalin in the treatment of painful radiculopathy under medical practice conditions in primary care settings. *Pain Pract* 2010 ; 10 : 31–41 [2b]
- 5) Malik KM, Nelson AM, Avram MJ, et al : Efficacy of pregabalin in the treatment of radicular pain : Results of a controlled trial. *Anesth Pain Med* 2015 ; 5 : e28110 [1b]

CQ57 : Are opioids effective for cervical and lumbar radiculopathy ?

The number of RCTs investigating efficacy for cervical and lumbar radiculopathy is very limited. It is unknown if opioids are as effective as antidepressants or Ca^{2+} channel $\alpha_2\delta$ ligands for such conditions.

The level of recommendation and the summary of overall evidence : 2D**Comments :**

It has been reported that opioids are as effective as antidepressants such as tricyclic antidepressants or SSRIs and Ca^{2+} channel $\alpha_2\delta$ ligands which are classified as the first-line drugs for postherpetic neuralgia or neuropathic pain associated with diabetic neuropathy¹⁾. However, opioids are classified as the second-line drugs for the following reasons : incidence of adverse effects is higher with opioids compared with the other drugs, safety in immune functions and gonadal functions has not been established for long-term use of opioids, and opioids may induce hyperalgesia²⁾.

Meanwhile, only a few reports have been made on efficacy of opioids for radiculopathy. In a RCT for chronic radiculopathy, pain was alleviated by 7–14% by nortriptyline hydrochloride (25–100 mg/day), morphine hydrochloride (15–90 mg/day), and a combination of these drugs. However, no significant reduction of lower limb pain or low back pain was observed with these drugs compared to benzotropine (0.25–1 mg/day) which had been used as placebo³⁾.

References

- 1) Eisenberg E, McNicol ED, Carr DB : Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin : Systematic review and meta-analysis of randomized controlled trials. JAMA 2005 ; 293 : 3043–3052 [1a]
- 2) Dworkin RH, O'Connor AB, Backonja M, et al : Pharmacologic management of neuropathic pain : Evidence-based recommendations. Pain. 2007 ; 132 : 237–251 [1a]
- 3) Khoromi S, Cui L, Nackers L, et al : Morphine, Nortriptyline and their combination vs. placebo in patients with chronic lumbar root pain. Pain 2007 ; 130 : 66–75 [1b]

CQ58 : Are there any drugs other than antidepressants, Ca^{2+} channel $\alpha_2\delta$ ligands and opioids effective for cervical and lumbar radiculopathy ?

The number of RCTs investigating efficacy for cervical and lumbar radiculopathy is very limited. It is unknown if there are any drugs which are more effective than antidepressants, Ca^{2+} channel $\alpha_2\delta$ ligands and opioids.

The level of recommendation and the summary of overall evidence : 2D

Comments :

The anti-epileptic drug, topiramate, is effective for lumbar radiculopathy. However, it is currently not recommended for the treatment of radiculopathy due to adverse effects and low treatment continuation rate due to adverse effects¹⁾.

Reference

- 1) Khoromi S, Patsalides A, Parada S, et al : Topiramate in chronic lumbar radicular pain. J Pain. 2005 ; 6 : 829–836 [\[1b\]](#)

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