Clinical Practice Guideline for Chronic Pain

The Committee for Clinical Practice Guideline for Chronic Pain

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Preface

A little over a year after the 16th International Association of the Study of Pain (IASP) Conference was held in Yokohama in 2016, it came to be recognized as a significant 'monument' to Japanese pain research and treatment. For the development of pain treatment, undoubtedly much research needs backing, including support for basic research, which pinpoints the pain mechanism, translational research, which leads to applications for future clinical practice, and also clinical research on new forms of treatment. There have been significant developments in pain research over the past 40～50 years. For example, the gate control theory of pain proposed by Melzack & Wall in 1965, Perl's research on nociceptor sensitization in 1976, and Basbaum and Field's (1979) research into the descending pain (sensitization) inhibitory system are particularly famous, and in the 1980s, Woolf and his colleagues proposed the concept of increased excitability of spinal cord neurons (central nervous system sensitization). In the late 1980s, Bennett et al., from the National Institutes of Health ('NIH'), published their neuropathic pain model, taking pain research into a new era. In addition, both the discovery of cloning opioid receptors and TRP channels in the 1990s were the results of molecular biology research methods and a massive number of papers and theories were spawned in the 20 years or so that followed and research into drug discoveries was also very active. However, with these new forms of research into explicating the pain mechanism, which led to the development of real drug discoveries and methods of treatment, some problems also arose. With 'pain' as our target, for various reasons, there were several difficulties with developing groundbreaking drug discoveries and new forms of treatment. Some of these issues, which we can cite here, include that : 1) 'pain' is a subjective sensation and is therefore difficult to quantify ; 2) pain is susceptible to psychological and emotional modification ; and 3) pain receptors often indicate plastic changes, making it difficult to analyze and comprehend. Despite these difficulties, thanks to the efforts and awareness-raising activities of a large number of pain clinicians and researchers around the world, we have seen significant changes and progress in pain treatment and clinical practice over the past few decades. As a result of the efforts of the IASP, WHO and a large number of other individuals and organizations, the current situation has completely changed since the time when IASP founder, Bonica, indicated the lack of interest in and understanding of cancer pain at the time. At the same time we have also been introducing multidisciplinary treatment by palliative care teams. In Japan which has been decades behind the times, there has been definite progress in the treatment of cancer pain and palliative care, meaning that a large number of patients are now being saved, and there is no doubt that what needs to be tackled next in clinical settings is non-cancer chronic pain, of which an immensely large number of people suffer. An enormous amount of national wealth is lost due to chronic pain and therefore

this needs to be tackled effectively. What is more, unless we deal with chronic pain, there is no way we can save individual patients. To date, the government has initiated administrative measures on a variety of diseases, including measures for cancer, life-style-related diseases, infectious diseases, mental disorders and intractable diseases, among others. However, a strategy for dealing with chronic pain diseases has been an area of inquiry, which seems to have slipped through the cracks. However, thanks to the efforts of a large number of people over the past 10 years, we are extremely delighted that countermeasures for dealing with chronic pain diseases have advanced to become a national project.

Against this backdrop, work is being conducted by the 'Research on Constructing a System for the Treatment and Education of Chronic Pain Problems' (Representative : Takahiro Ushida) under the Health, Labour and Welfare (MHLW) Promotional Reseach Grant. Furthermore, with the cooperation of the seven associations, which comprise the Pain Consortium, who tackle the diagnosis and treatment of chronic pain ('chronic pain') across the disciplines, we have been able to create the 'Clinical Practice Guideline for Chronic Pain' in line with the current situation in Japan. The seven associations which comprise the Pain Consortium are The Japanese Association for the Study of Musculoskeletal Pain, The Japanese Society of Orofacial Pain, The Japanese Association for the Study of Pain, The Japan Society of Pain Clinicians, The Japanese Association for the Study of Pain Rehabilitation, The Japanese Society for the Study of Chronic Pain, and The Japanese Society for the Study of Low Back Pain. The research team mentioned above, along with these seven societies and associations, have formed the core of the 'The Committee for Clinical Practice Guideline for Chronic Pain'. In making these guidelines, we have paid particular care to ensure that the contents are consistent with pain guidelines which have already been published in Japan (such as the 'Guidelines for Pharmacologic Management of Neuropathic Pain' and 'Guidelines for Prescribing Opioid Analgesics for Chronic Non-cancer Pain') and to improve its function as a reference book.

In closing, I wish to express my heartfelt gratitude to everyone from the promotional research grant research team at MHLW, all members belonging to the seven societies and associations, and in addition all members on the committee of the 'The Committee for Clinical Practice Guideline for Chronic Pain'.

March, 2018
President of the Japanese Society for the Study of Pain (JASP)
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Introduction

Pain is a warning signal from the living body and has an important meaning but if it is prolonged and becomes chronic, then it is subject to being treated as a disease. Chronic pain is a disease (pathological condition), which has an effect on the economy of our country. In many cases, each medical society or association creates its own guidelines outlining their own forms of treatment for these types of diseases. However, in many instances we fail to reach a consensus due to the different points of view of these associations and organizations. These guidelines, which have been compiled by a research team from the Japanese Ministry of Health, Labour and Welfare (MHLW), alongside seven pain-related societies and associations (The Pain Consortium), represent guidelines for the whole of Japan.

The purpose for making these guidelines for the management of chronic pain

These guidelines are a compilation of the opinions of medical practitioners, who are mainly involved in the examination and treatment of patients with chronic pain, on what they consider are the most effective and most useful forms of treatment in current practice. In order to refer not only to the doctors who are mainly involved in examining patients with chronic pain, but also first-line primary medical practitioners who often interact with regional citizens, rehabilitation staff who perform physiotherapy on patients suffering from pain, nursing staff who act as a liaison between the doctors and patients, and psychotherapy staff who provide counseling to patients with pain, among others, we prepare an extensive set of clinical questions (hereinafter 'CQ'). It is our hope that these guidelines will bring some light into the lives of patients suffering from chronic pain.

Our basic philosophy behind the making these guidelines for the management of chronic pain

Under the conduction of the research team from MHLW, we obtained the invaluable opinions of the Pain Consortium (The Japanese Association for the Study of Musculoskeletal Pain, The Japanese Society of Orofacial Pain, The Japanese Association for the Study of Pain, The Japan Society of Pain Clinicians, The Japanese Association for the Study of Pain Rehabilitation, The Japanese Society for the Study of Chronic Pain, and The Japanese Society for the Study of Low Back Pain) and related societies and associations (the Japan College of Fibromyalgia Investigation, The Japan Neurosurgical Society, The Japanese Headache Society, The Japanese Orthopaedic Association, the Japanese Society of Anesthesiologists the Japanese Society of Neurological Therapeutics, the Japanese Society of Psychosomatic Medicine [listed alphabetically]) in order to form a compilation of professional opinions from the whole of Japan. Furthermore, representatives

from patient groups also participated in general meetings. These guidelines were created in accordance with the '2014 and 2017 Guidebook for the Creation of Clinical Practice Guidelines' by MINDS, a project to promote the spread of evidence-based medicine (EBM) by the Japan Council for Quality Health Care (JCQHC), and the philosophy of AGREE II. In the general remarks in Chapter Ⅰ, we have mentioned such topics as the concept of chronic pain, its classification, diagnosis, and ways to evaluate treatment. In addition, we also mention multidisciplinary treatment, which has recently been a topic of much discussion. Ensuring that the guidelines conform with actual clinical practice, from Chapter II onwards, we have established some chronic pain CQs regarding the main forms of treatment currently being performed within Japan. There is a commentary on these CQs, and for each item, the search methods and the words searched for have been listed. As our top priority is on evidence, we have also decided to provide commentary on drugs and methods of treatment, which are not covered under the Japanese health insurance system. In order for the guidelines to form a consensus of opinion representing the whole of Japan, we have integrated the various guidelines issued by the seven associations of the Pain Consortium as well as the guidelines of related associations. However, as we have utilized the most recent evidence, some discrepancies have also arisen in certain CQ sections.

Patients for whom these guidelines for the management of chronic pain have been written and how to use these guidelines

These guidelines were written for adult patients suffering from chronic pain, not patients suffering from cancer pain or acute pain. However, it is our hope that cancer-bearing patients suffering from pain other than tumor-or metastasis-based pain will refer to these guidelines as well. As the main priority of these guidelines has been the provision of evidence, some of the drugs and methods mentioned are currently (as of March, 2018) ineligible for coverage under the Japanese health insurance system. However, with pharmacotherapy, we hope the readers will read the drug information thoroughly first, before undergoing treatment.

Acknowledgements

We wish to warmly thank Professor Kiyoshige Ohseto (specially-appointed Professor from the Department of Anesthesiology at Tokyo Medical University) for his invaluable opinions as an outside expert, all of the observing members for all of their guidance and advice, all of the various members from the seven member associations of the Pain Consortium, as well as all the members of the research team from the Ministry of Health, Labour and Welfare (MHLW) from the 'The Committee for Clinical Practice Guideline for Chronic pain', in addition to all members from related associations and members of patients groups, without whose help these guidelines could not have been created. Finally, we deeply thank Mr. Matthew James Mclaughlin for his excellent translation of the guidelines.

March, 2018
Health, Labour and Welfare Policy Research Grants (Research on chronic pain)
Research on Constructing a System for the Treatment and Education
of Chronic Pain Problems
The Committee for Clinical Practice Guideline for Chronic pain
Chairman Hisashi Date, MD, PhD
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Preparative Method of these Guidelines

The Committee for Clinical Practice Guideline for Chronic Pain

These guidelines are different from the guidelines issued by each individual society or association and were constructed by committee members selected from the Pain Consortium (Japanese Association for the Study of Musculoskeletal Pain, The Japanese Society of Orofacial Pain, The Japanese Association for the Study of Pain, The Japan Society of Pain Clinicians, The Japanese Association for the Study of Pain Rehabilitation, The Japanese Society for the Study of Chronic Pain, The Japanese Society for the Study of Low Back Pain) which is a conglomerate of pain-related societies and associations. The research team on 'Research on Constructing a System for the Treatment and Education of Chronic Pain Problems', Research on Chronic Pain, were the supervising editors who oversaw the creation of this document.

Basic component of these guidelines

The component of these guidelines followed alongside the 'Minds Handbook for Clinical Practice Guideline Development 2014 and 2017' with the contents itemized and its basic component consisting of CQs (clinical questions), answer, recommendation grades, levels of evidence, commentary and precautions. In some CQs where we thought the level of recommendation and quality of evidence were not necessary, we only provided an answer and commentary.

Preparation of clinical questions (CQs)

Members of the committee for preparing these guidelines composed drafts of CQs, and then an answer and commentary was created for each CQ based on what was agreed upon at the general meetings.

Levels of evidence

The 'Minds Handbook for Clinical Practice Guideline Development 2014 and 2017' was used to prepare the quality of evidence for treatments. We devised the answer section of the Q&A in the CQs, by adding the following overall evaluation of the systematic reviews of treatment outcomes.

For our summary of the total evidence in each CQ (overall quality of evidence for general outcomes), we made the following provisions based on the summary of the total evidence for creating a recommendation grade as described in 'Minds Handbook for Clinical Practice Guideline Development 2014 and 2017'.

A (Strong)：The estimated value of an effect is strongly reliable.
B (Moderate)：The estimated value of an effect is moderately reliable.
C (Weak)：The estimated value of an effect is somewhat reliable but limited.
D (Very weak)：The estimated value of an effect is hardly reliable.

Recommendation grade

Using the 'Minds Handbook for Clinical Practice Guideline Development 2014 and 2017', systematic reviews of the treatment outcomes were made for each CQ, after which we generalized the quality of evidence of the outcomes and as outlined below we used this as a basis for determining a recommendation grade.

Two recommendation strengths were displayed,

1 : intervention (non-intervention) strongly recommended,

2 : intervention (non-intervention) weakly recommended (proposed).

In cases where a strength of recommendation could not be determined, in cases where a clear recommendation could not be made, such as when members of the Committee failed to arrive at a consensus, then we displayed 'no clear evidence for recommendation.' At the end of the (CQ) answer, as mentioned above, we listed both the strength of recommendation, either a '1' or '2', as well as the quality of evidence (A, B, C, D). When making decisions, we also took into consideration the fact that even if the quality of evidence is low, when there is a large difference between the balance of benefits and risks (harms), it is still possible for the treatment to receive a strong recommendation, and even if the quality of evidence is high, the treatment might receive a weak recommendation, even when there is slight difference between the balance of health benefits and risks. As a general principle, we gave consideration to those treatments, which are covered under the scope of the Japanese health insurance system. However, even in instances where the treatment is not covered under our insurance system, we did give those treatment methods, considered to be effective in overseas settings and in terms of quality of evidence, a high recommendation grade. We utilized the modified Delphi method to determine the levels of recommendation. The contents created by each responsible party were peer-reviewed and polished, through cross-checking by the Committee members for these guidelines (Round 1). Based on the results, further refinements were made at the general meeting, which included patient representatives. These results were then reconsidered by each of the person in charge (Round 2) and then final decisions were ultimately made at the general meeting.

References searches and adoption

When running searches for references, as a general rule, we conducted searches by entering the key words, 'chronic pain' and 'CQ.' The scope of our search was in principle from 2005 up to October 2017. When searching for references, we used the search methods of PubMed, MEDLINE, Cochrane Database and Ichushi Web. We did also utilize some important reference materials from prior to 2005. Furthermore, references, which we judged to be important but not found through this search method, were searched by hand and added to the list.

Opinions from related societies & associations

Those concerned with the preparation of the guidelines ; members of the Board of Directors and Board of Trustees from the seven societies and associations of the Pain Consortium (Japanese Association for the Study of Musculoskeletal Pain, The Japanese Society of Orofacial Pain, The Japanese Association for the Study of Pain, The Japan Society of Pain Clinicians, The Japanese Association for the Study of Pain Rehabilitation, The Japanese Society for the Study of Chronic Pain, The Japanese Society for the Study of Low Back Pain) as well as members of the research team on 'Research for the Creation of a System Base for the Treatment and Education of Chronic Pain', Chronic Pain Research Project, solicited comments from The Japan College of Fibromyalgia Investigation, The Japan Neurosurgical Society, The Japanese Headache Society, The Japanese Orthopaedic Association, the Japanese Society of Anesthesiologists, The Japanese Society of Neurological Therapeutics, The Japanese Society of Psychosomatic Medicine [listed alphabetically] and the Association for the Support of Patients with Intractable Pain ('Goodbye−pain'). At the core member meeting, they decided which of these solicited opinions should be included herein or not and some revisions were made.

Conflict of interest

Our conflict of interest (COI) clause applies to all individuals involved in the preparation of these guidelines and in accordance with the COI regulations of the Japanese Association of Medical Sciences for those participating in the formulation of treatment guidelines, in the event where an amount exceeds the standard required for disclosure, we shall list the name of the committee member and the name of the corporation.

Indication for treatments

These guidelines were written for medical practitioners who are responsible for managing chronic pain, not for patients. However, we paid special attention to ensure that these guidelines would reflect the comments we receive from patients. When using these guidelines, we ask medical practitioners not to just simply glance at recommendation grade on each page but to consider performing or prescribing treatment only after thoroughly reading through the CQ text, summary and commentary. Another important point that we would like to make is that a large number of guidelines pertaining to chronic pain, created by the societies and associations specializing in each respective field, already exist. It is our wish that we continue to learn from and comprehend their latest knowledge before applying it to actual clinical practice.

Finally, we wish to clearly state that these guidelines have been created as a useful resource for managing chronic pain, and are not materials designed to be used for other situations such as lawsuits or litigation.

March, 2018
Health, Labour and Welfare Policy Research Grants (Research on chronic pain)
Research on Constructing a System for the Treatment and Education
of Chronic Pain Problems
The Committee for Clinical Practice Guideline for Chronic pain
Chairman Hisashi Date, MD, PhD
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Clinical Practice Guideline for Chronic Pain

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※ disclosure of Conflicts of Interest

CQ1 : What kind of condition is chronic pain?

IASP : International Association for the Study of Pain

Answer : International Association for the Study of Pain (IASP) defines chronic pain as, 'pain that extends beyond the expected period of healing or progressive pain due to non-cancer diseases.'

Commentary :

IASP defines chronic pain as 'pain that extends beyond the expected period of healing or progressive pain due to non-cancer diseases.'[1]. However, in Japan, it still has not been clearly defined. Previously, it referred generally to a pain condition persisting for more than six months since the time of onset but currently it often refers to (pain persisting for) three months or more due to factors such as improvement in pharmacotherapy. These guidelines do not define specifically designated illnesses as chronic pain illnesses and we have decided to consider it as a condition, based upon IASP's definition.

Another thing is that pain that persists for a long time can also involve psychosocial issues and therefore it is considered to be an incredibly complex condition[2].

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CQ2 : What kinds of classifications are there for chronic pain?

Answer : Chronic pain is classified for example by pain syndrome and by mechanism. Searching for the pain syndrome or mechanism leads to not only diagnosis but also treatment.

Commentary :

Chronic pain can be classified from a variety of different angles. When classifying by pain factors, there are nociceptive pain, neuropathic pain, psychosocial pain and others[1]. Psychosocial pain used to be called psychogenic pain but IASP does not call it psychogenic pain and because organic factors are involved, it has decided to call it psychosocial pain. When the pain becomes chronic, the cause is seldom due to one of these three and in many cases it is a complex mixed pain condition involving several causing factors.

IASP : International Association for the Study of Pain

IASP recommends seven classifications of chronic pain[2,3] to the ICD-11

Table 1-1 IASP Chronic Pain Classifications (Cited from Reference #2 and #3)

1. Chronic primary pain
   - 1.1. Widespread chronic primary pain (including fibromyalgia syndrome)
   - 1.2. Localized chronic primary pain (including nonspecific back pain, chronic pelvic pain)
   - 1.x. Other chronic primary pain
   - 1.z. Chronic primary pain not otherwise specified

2. Chronic cancer pain
   - 2.1. Chronic pain due to cancer and metastases [Note 1]
   - 2.2. Chronic chemotherapy-induced pain (primary parent : chronic neuropathic pain)
   - 2.3. Chronic pain due to cancer surgery (primary parent : chronic postsurgical and posttraumatic pain)
   - 2.4. Chronic pain due to radiotherapy
   - 2.x. Other chronic pain related to cancer
   - 2.z. Chronic cancer pain not otherwise specified

3. Chronic postsurgical and posttraumatic pain
   - 3.1. Chronic postsurgical pain
   - 3.2. Chronic posttraumatic pain
   - 3.x. Other chronic postsurgical and posttraumatic pain
   - 3.z. Chronic postsurgical and posttraumatic pain not otherwise specified

4. Chronic neuropathic pain
   - 4.1. Peripheral neuropathic pain
   - 4.2. Central neuropathic pain
   - 4.x. Other neuropathic pain
   - 4.z. Neuropathic pain not otherwise specified

5. Chronic headache and orofacial pain
   - 5.1. Chronic primary headaches*
   - 5.2. Chronic secondary headaches*
   - 5.3. Chronic orofacial pains †
   - 5.z. Headache and orofacial pain not otherwise specified*

6. Chronic visceral pain
   - 6.1. Chronic visceral pain from persistent inflammation
   - 6.2. Chronic visceral pain from vascular mechanisms
   - 6.3. Chronic visceral pain from obstruction / distension
   - 6.4. Chronic visceral pain from traction / compression
   - 6.5. Chronic visceral pain from combined mechanisms
   - 6.6. Chronic visceral pain referred from other locations
   - 6.7. Chronic visceral pain from cancer (primary parent : chronic cancer pain)
   - 6.8. Functional or unexplained chronic visceral pain (primary parent : chronic primary pain)
   - 6.x. Other chronic visceral pain
   - 6.z. Chronic visceral pain not otherwise specified

7. Chronic musculoskeletal pain
   - 7.1. Chronic musculoskeletal pain from persistent inflammation
   - 7.2. Chronic musculoskeletal pain from structural osteoarticular changes
   - 7.3. Chronic musculoskeletal pain due to disease of the nervous system (All neuropathic pain will be classified under4. Chronic neuropathic pain. Here, other chronic musculoskeletal pain originating from diseases of the nervous system, eg, spastic pain will be listed.)
   - 7.4. Chronic nonspecific musculoskeletal pain (primary parent : chronic primary pain)
   - 7.x. Other chronic musculoskeletal pain syndromes
   - 7.z. Chronic musculoskeletal pain not otherwise specified

Note 1 : "2.1. Chronic pain due to cancer and metastases" from the table refers to cancer pain but in Japan does not apply as a type of 'chronic pain.'

(Table 1-1). One of these items includes 'cancer pain' but the other items are all non-cancer pain and do not match with the classifications used in Japan [Note 1]. These items sometimes cover two items and this is recognized as multiple parenting[4].

multiple parenting：When classifying a disease with ICD-11, parenting allows us to classify it both the category of its primary location, and the category of its origin.

For the classification based on the mechanism causing chronic pain, we have assumed the concepts in Table 1-2[5]. The modality is also involved in these classifications and the stronger the psychosocial factors, the more frequently it becomes hard to treat.

Table 1-2 Acute Pain and Chronic Pain (Cited from Reference #5)

	Acute Pain	Chronic Pain	
		Chronic pain which is a repetition of acute pain Chronic pain which is protracted acute pain	Intractable chronic pain
Cause of pain	Stimulation of nociceptors	Stimulation of nociceptors	Functional changes in the central nervous system, modulation due to psychosocial factors
Duration	Does not exceed period for tissue repair	Slightly exceeds period for tissue repair	Exceeds period for tissue repair (three months≦)
Main accompanying symptoms	Hyperactive sympathetic nerves (Hyperacute period)	Insomnia, loss of appetite, constipation, Inhibition of living activities	Insomnia, loss of appetite, constipation, Inhibition of living activities
Main psychological symptoms	Anxiety	Depression, anxiety, catastrophizing	Depression, anxiety, catastrophizing

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CQ3：What are the characteristic symptoms and signs of patients with chronic pain?

Answer： Among patients with chronic pain, many display a variety of symptoms and signs apart from pain. As it is possible to reduce pain and expect an improvement in ADL in order to cope, it is necessary to not only cope with the pain but with the various symptoms and signs.

ADL：activity of daily living

Commentary：

Chronic pain patients exhibit a large number of symptoms and signs as the period of pain increases (Table 1-3).

Table 1-3 Non-pain Symptoms / Signs Exhibited by Patients with Chronic Pain

1. Cognitive / Emotional Factors Depression, anxiety, loss of appetite, anger, catastrophzing, fear
2. Physical Factors Sleeping disorders, decline in ADL（immobilization and disuse）
3. Social Factors Decline in level of social activity（time off work, school, loss of employment）, changes in family relationships, economical stress
4. Spiritual Factors Decline in feelings of self-worth, decline in self-efficacy
5. Other Factors Litigation, excessive expectations in medical institutions, dependence on treatment（medication）

Patients with chronic pain often display symptoms of depression but we have yet to conclude whether the stress from pain is triggering feelings of depression or whether a state of depression is triggering the pain as a physical symptom[1]. There has been some speculation that it may often be a depressive state as a reaction to the stress from the pain[2]. In actuality, it varies from case to case. It has been suggested that as the pain lingers, it becomes intractable and serious through a cyclical interaction with psychosocial factors. Furthermore, in cases where the pain becomes intractable, catastrophizing is often involved[3], and signs such as immobilization (disability) and disuse appear. As a result, this triggers a decline in ADL (Fig. 1-A). Therefore, an improvement in catastrophizing may lead to an improvement in the symptoms and signs of chronic pain patients[4].

pain catastrophizing：
An exaggerated negative perception of pain

When the pain persists over a long period of time, it affects one's work and academic life. A high percentage of both men and women losing their jobs, leaving school, having a break from their work or studies or changing jobs due

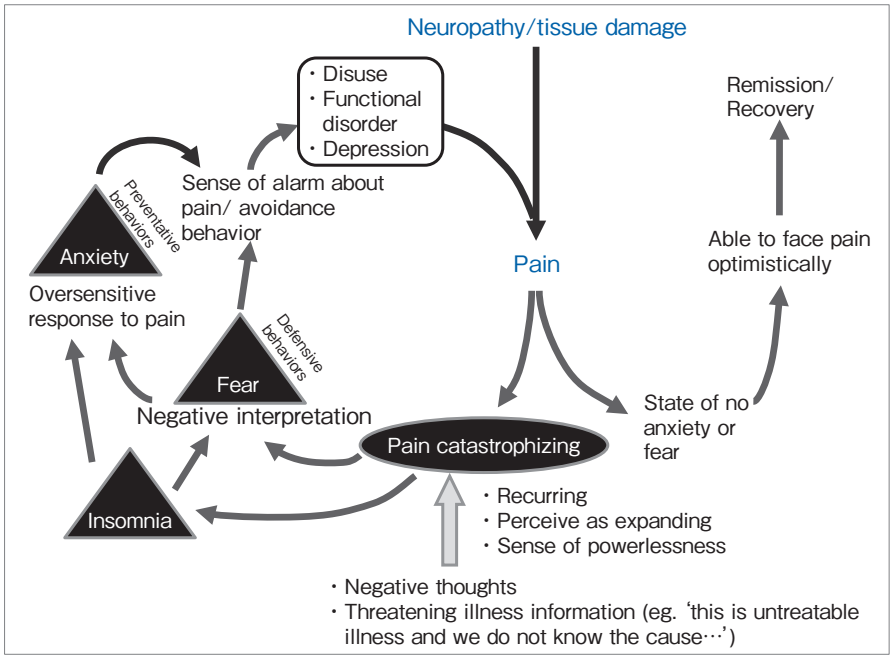

Fig. 1-A Pain Fear-Avoidance Model (Cited from reference #3, partly paraphrased)
As pain persists over a long period of time, it has been indicated that it becomes chronic and serious through a cyclical interaction of psychosocial factors.

to chronic musculoskeletal pain were reported[5]. Factors such as loss of employment can also lead to a decline in the quality of social activity, a deterioration in one's presence within the family and economical stress leads to a deterioration in perceptions of self-worth. Along with this, there is a decline in self-efficacy and there have been reports[6] that pain self-efficacy is positively correlated with health-related quality of life (HRQL/HRQOL) and negatively correlated with the level of lifestyle disability. Therefore, we can expect an improvement in pain and ADL through a cognitive change.

QOL：quality of life
HRQL：health-related quality of life

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CQ4 : What points need to be kept in mind when diagnosing chronic pain?

Answer : The most important thing when diagnosing chronic pain is having an accurate understanding of the patient's condition. Furthermore, diagnostic criteria have been established for each condition under the guidelines for pain diseases. Therefore, diagnosis should be made in accordance with these criteria.

Commentary :

Chronic pain not only involves organic factors but also often psychosocial factors as well, and various factors such as these make the condition incredibly complex[1]. When diagnosing chronic pain, which occurs due to various conditions, the most important thing is having an accurate understanding of the patient's condition. A method following what is called 'diagnostics' is used to do this (Fig. 1-B)[2]. That is to say, first of all the patient's condition can be inferred based on a detailed hearing of the patient's medical history and a physical examination. Next, the patient's condition can gradually be narrowed down

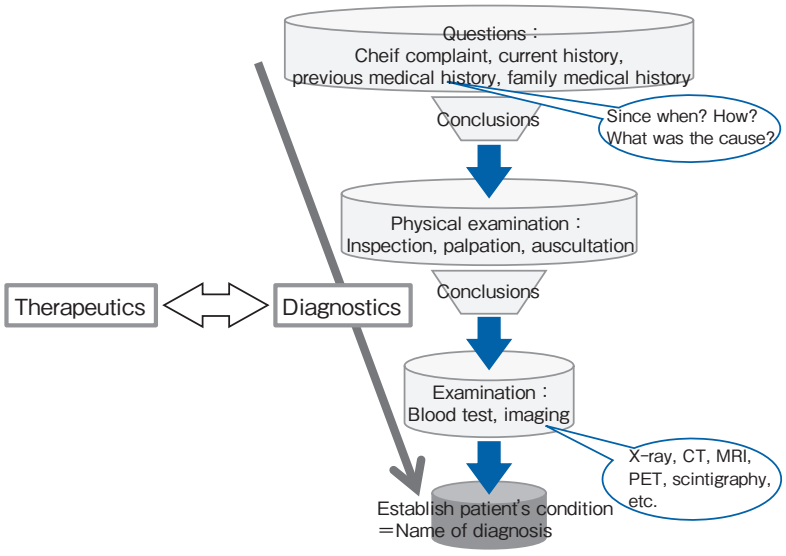

Fig. 1-B Method for Diagnosing Patients with Chronic Pain

by making full use of a variety of examinations (such as a blood test) based mainly around imaging (X-ray, CT, MRI, contrast studies etc.). Finally, judging whether the symptoms match with the examination findings is the basis of diagnostics ; a method to have an accurate understanding of the patient's condition. In this way, the reason why diagnostics is considered important is because the treatment should be based on an accurate understanding of the patient's condition. Under this series of processes, there is a possibility that it could be fatal if the condition is left unattended and it is therefore important not to overlook as 'red flag' conditions (such as malignant tumors) and conditions which may trigger severe symptoms (such as infectious diseases and traumatic illnesses).

In the guidelines on pain diseases published to date in Japan, diagnostic criteria have been established for each condition (Table 1-4) and diagnosis should

Table 1-4 Pain Diseases Indicated in the Guidelines According to the Japanese (October 2017 (current), as listed in 'Minds')

〔Muscle/Bone/Joint〕
- Guidelines for the Management of Rheumatoid Arthritis, Japan College of Rheumatology 2014
- Cervical Ossification of Posterior Longitudinal Ligament Diagnostic Guidelines 2011
- Cervical Spondylotic Myelopathy Diagnostic Guidelines 2015
- Guidelines on the Prevention and Treatment of Osteoporosis 2011 Edition
- Bone Metastasis
- Lateral Epicondylitis of the Humerus Diagnostic Guidelines
- Osteoarthritis of the Hip Diagnostic Guidelines
- Lumbar Disc Herniation Diagnostic Guidelines
- Low back Pain Diagnostic Guidelines 2012
- Lumbar Spinal Canal Stenosis Diagnostic Guidelines 2011

〔Pain Clinic〕
- Guidelines for the Interventional Pain Treatment
- Guidelines for the Pharmacologic Management of Neuropathic Pain Second Edition
- Guidelines for Prescribing Opioid Analgesics for Chronic Non-cancer Pain Second Edition

〔Brain/Nerves〕
- Chronic Headache Diagnostic Guidelines 2013
- Stereotactic and Functional Neurosurgery Treament Guidelines Second Edition

〔Dental/Oral〕
- Initial Treatment Diagnostic Guidelines for Patients with Temporomandibular Arthrosis
- Non-odontogenic Toothache Diagnostic Guidelines

〔Other〕
- Fibromyalgia Diagnostic Guidelines 2013

be conducted in accordance with these criteria.

When consulting patients with chronic pain, it is important not only to diagnose the pathology which causes chronic pain, but also to evaluate psychological factors such as anxiety, depression, and dissatisfaction which might modify the pain condition, as well as the actual lifestyles of the patients. A careful interview is the most important, but on the occasion of an evaluation, we recommend using evaluation tools such as psychology tests for confirming their validity and reliability.

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CQ5 : What points should be kept in mind when evaluating chronic pain patients?

Answer : There are some factors involved with chronic pain : such as 'nociceptive' ; 'neuropathic' ; 'psychosocial', and others. In many cases, these factors are intricately inter-related. Using a biopsychosocial model for the purpose of providing a multifaceted evaluation of chronic pain patients, we can get an overall (holistic) understanding of the patient's pain and on top of this, select the treatment and care best suited to each individual patient.

Commentary :

Generally speaking, if acute pain can be promptly alleviated, the patient's concern can also be promptly eliminated. However, with chronic pain, the psychological background or social background can have a large effect on the patient's pain. There are some factors related to chronic pain : such as 'nociceptive' ; 'neuropathic' ; 'psychosocial', and others,[1] but in many cases these factors coexist and are intricately related (**Fig. 1-C**). The purpose of providing a multifaceted evaluation of chronic pain patients using a biopsychosocial model is to have an overall (holistic) understanding of the patient's pain and on top of this, to select the treatment and care best suited to each individual patient.

In a multifaceted evaluation of chronic pain, the following points are important[2].

- **Strength, site, quality, progression, changes throughout the day, enhanc-**

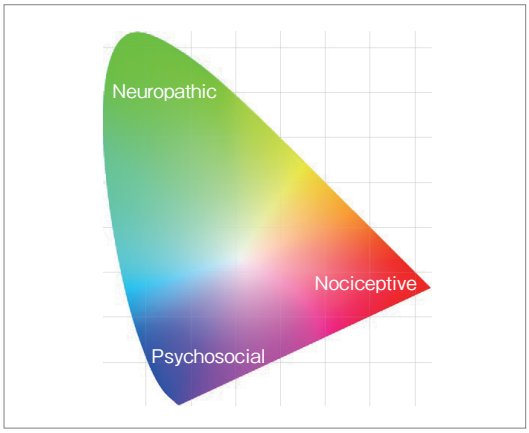

Fig. 1-C Pain Model Diagram
There are several factors involved in pain : 'nociceptive' ; 'neuropathic' ; 'psychosocial', and others.

Table 1-5 Main Questionnaires for Evaluating Psychological States such as Depressive State, Anxiety, Catastrophizing and Degree of Loss in ADL

Hospital Anxiety and Depression Scale (HADS)
Pain Catastrophizing Scale (PCS)
Beck Depression Inventory (BDI)
Center for Epidemiological Studies-Depression scale (CES-D)
State Trait Anxiety Inventory (STAI)
Hamilton Depression Rating Scale (HAM-D),
Hamilton Anxiety Rating Scale (HAM-A)
Fear-Avoidance Beliefs Questionnaire (FAB)
Pain Self-Efficacy Questionnaire (PSEQ)
Pain Disability Assessment Scale (PDAS)
Athens Insomnia Scale (AIS)
Self-rating Depression Scale (SDS)

ing factors and alleviating factors of pain : Understanding these points will serve as clues for sounding out the pain's pathology.

- **Psychological state** : There are many cases of patients suffering from a combination of a depressive state, feelings of anxiety, a negative cognitive state called 'catastrophizing', feelings of fear, angry emotions, feelings of low self-efficacy, feeling dissatisfied and feeling distrust. There is a questionnaire used for screening the patient's psychological state. (Table 1-5).

pain catastrophizing : An exaggerated negative perception of pain

- **How one spends the day, degree of loss in ADL** : Due to a fear of exercise, patients with chronic pain spend the whole day sleeping, and it is frequently a cause of falling into a vicious cycle of immobilization and a cause of insomnia. There is a need to assess what kind of treatment and care

should be chosen, depending on the degree of loss in ADL.

- **Family structure and situation** : Among patients with chronic pain, there are various family conflicts, tension between siblings, family pathologies such as breakdowns in contact or communication within the family and the level of satisfaction with one's married life are sometimes involved in the persistence or aggravation of the existing symptoms. In cases where the living environment provides a low supporting function from the family, self-efficacy is low, and in some cases patients lapse into a state of alexithymia, in which one cannot convey one's feelings to others. Early developmental history is considered to be one of the major factors in the onset of chronic pain.
- **Illnesses and clinical conditions in the field of psychiatry** : Frequently-cited illnesses and clinical conditions in the field of psychiatry, which are related to pain chronicity include somatization disorder, dysthymic (pain) disorder, depressive disorder, bipolar disorder, developmental disorder, dementia, and substance-related disorder.
- **Employment history, job details and conditions** : If people change jobs over and over again, it is suspected that they may be socially maladjusted. In cases of patients who are having difficulty finding employment due to their pain, the main goal of treatment is to improve their employment situation, on the assumption that information on the patient's current condition and progress is being shared between the patient and the medical practitioner. In patients with chronic pain, their relationships with others at work, work-related stress, physical burden, loss of employment, and level of satisfaction with what they do at work often contribute towards the persistence or aggravation of their existing symptoms. On top of the patient's own predisposing factors, in cases where the patient is on leave from his/her job, it is also very important to consider the possibility that some type of social factors may also be involved, such as what is causing mental stress at work or in the occupation, whether he/she is absent or on leave from work, the type of employment, the the possibility of dismissal from the job, the current income situation and information related to his/her future prospects.
- **Compensation and litigation** : When the initial cause of the pain is a traffic accident or work accident, we find out whether this person is receiving compensation or not. If the patient is the victim of an accident, what is called the 'victim's awareness' can make the pain become chronic.
- **Changes in sleeping, eating, weight** : Depressive states or conditions of stress cause changes to one's sleep and appetite. Therefore, it is important to question patients on their sleeping and appetite history .

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CQ6 : What are the purposes and ultimate goals of chronic pain management ?

Answer : As non-organic factors are larger components of chronic pain than organic factors, it is difficult to establish a pain-free condition. Reducing pain is one of the purposes and ultimate goals of chronic pain management but not the leading goal. Medical practitioners should manage chronic pain while trying to minimize adverse events induced by the treatment and it is important to improve the patient's QOL and ADL actions.

QOL : quality of life
ADL : activity of daily living

Commentary :

Acute pain is a warning, notifying the body of injury and often reacts to the the short-term administration of analgesics and conservative treatment. On the other hand, with chronic pain, non-organic factors such as central sensitization and cognition of the nervous system are larger components of this pain than organic factors. With chronic pain, even though injury as organic factor is repaired, the body is unnecessarily releasing this warning[1)].

IASP : International Association for the Study of Pain

The treatment purpose and ultimate goals vary depending on the fundamental illness at its onset and the components of the pain. IASP defines chronic pain as 'pain that persists beyond normal tissue healing time, and progressive non cancer pain' and is generally a pain which persists for three months or more[2)]. However, even if the pain persists for longer than three months, a protracted pain disease also exists (for example trigeminal neuralgia, headache illnesses such as migraine and cluster headache, and rheumatoid arthritis) in order for the cause of this pain to persist. A larger number of these illnesses are due to organic factors rather than non-organic factors so pharmacotherapy tends to have a rapid effect on them. Therefore, as the treatment purpose and ultimate goals are different from other forms of chronic pain, they are excluded from the eligible illnesses under the chronic pain treatment guidelines in every country[1,3)].

As mentioned above, a larger number of components of chronic pain are non-

organic factors rather than organic factors and therefore there is much distress with treatment. The Guidelines for the Treatment of Chronic Pain[4] by ASA and ASRA, cite the following four items as their treatment purposes objectives and ultimate goals.

① Optimize pain control, recognizing that a pain-free state may not be attainable ;
② Enhance functional abilities and physical and psychologic well-being ;
③ Enhance the quality of life of patients ;
④ Minimize adverse outcomes.

In this way, we must manage pain while minimizing adverse outcome (side effects) induced by treatment and improving the patient's QOL and ADL are the purposes and ultimate goals of chronic pain management.

As chronic pain patients have been suffering from pain for a long time, they tend to expect that their medical practitioner can help completely remove their pain. Of course, reducing pain is one of the goals but it should not be the leading goal. Before commencing pain treatment, the medical practitioner should explain and convince the patient that the goal of pain treatment is 'at best to reduce strong pain to around a moderate level'[1]. In the management of chronic pain, going against patient's expectations, generally functional improvement comes first rather than a reduction in pain. Therefore, it is important to educate patients on this distinction, to avoid persistent and unrealistic expectations for an elusive cure, where none exists[1].

There are various methods to treat chronic pain such as pharmacotherapy, interventional therapy, psychotherapy, and therapeutic exercise but these are more effective when integrated, not implemented individually. All methods of management should focus on functional recovery as the leading goal, rather than simply reducing pain, and evaluations of the treatment's efficacy are achieved through reports on functional improvement[1]. The management goal of chronic pain should not be vague but directly associated with the problematic symptoms (such as insomnia and hypoactivity) identified in each patient and preferably these should be realistic and achievable to the patient (such as a reduced number of times the patient wakes up during the night, and managing household chores by oneself)[5].

The medical practitioner should set the treatment goal and determine the treatment strategy with the patients, and it can be considered a success if there is functional improvement and some degree of reduced pain after commencing treatment. However, in cases where there is no response to treatment or the condition deteriorates, the medical practitioner needs to re-assess the components of the patient's pain and needs to change the treatment policy. Pain is ultimately subjective and with chronic pain in particular, it will be influ-

ASA : American Society of Anesthesiologists
ASRA : American Society of Regional Anesthesia and Pain Medicine

enced by the patient's cognition, emotions and environmental factors. Furthermore, as time progresses and as a result of changes in the environment surrounding the patient, complaints about pain also change frequently. A patient's complaint about pain is one form of pain behavior but is not the pain itself. External gain such as money and compensation are large factors affecting pain behavior. Therefore, the medical practitioner must carefully observe whether these kinds of factors are involved or not [1].

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CQ7 : What kind of treatment is multidisciplinary treatment?

Answer : Multidisciplinary treatment is an integrated and multifaceted form of treatment, in which specialists from a large number of fields and occupations collaborate with a common goal in mind : to treat patients.

Commentary :

In multidisciplinary treatment, a multidisciplinary case conference is held and a liaison case council is launched by different types of professionals, such as physicians, nurses, mental health professionals, and physiotherapists in order to develop a comprehensive understanding of a patient's pain and associated problems, and decide on recommendations for treatment. After the conference, all staff work together to provide treatment[1], and the multidisciplinary treatment consists of the following five components : [2-7]

1. Intervening to weaken the effect that pain is having on the functional aspects of their daily life ;
2. Training based on cognitive-behavioral therapy (CBT), in which patients are educated and provided guidance on acquiring ways to change their

patterns of thought, which can have a negative effect on their reactions to pain ;

3. Step-by-step physical exercise (exercise therapy) ;
4. Pharmacotherapy ;
5. Interventional treatment.

Multidisciplinary treatment is when specialists from various fields and occupations exchange their opinions openly, from a diverse number of viewpoints, sharing background information on patients, their pain conditions, as well as their goals for treatment and providing treatment in accordance with the five components mentioned above.

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Table 2 Drugs Used in Chronic Pain Treatment

Drug name	Method of administration	Dosage/Directions for usage	Applicable diseases	Adverse events/ Precautions for usage	Ref.
NSAIDs (only characteristic drugs have been listed)					
Diclofenac	oral, suppository	25~100 mg/day	osteoarthritis, low back pain, cervicobrachial syndrome, periarthritis scapulohumeralis, other general pain	gastrointestinal tract disturbance, renal dysfunction, edema, cardiovascular event, asthma	CQ8 (p.190)
Ibuprofen	oral	600 mg/day			
Loxoprofen	oral	60~180 mg/day			
Celecoxib	oral	200 mg/day			
Acetaminophine					
Acetaminophine	oral	600~4,000 mg/day	general pain	digestive symptoms, liver/renal dysfunction	CQ9 (p.193)
An extract from inflamed cutaneous tissue of rabbits inoculated with Vaccinia virus					
An extract from inflamed cutaneous tissue of rabbits inoculated with Vaccinia virus	oral	4 tablets (16 unit)/day	postherpetic neuralgia, low back pain, ervicobrachial syndrome, periarthritis scapulohumeralis, osteoarthritis	nausea, eruption	CQ10 (p.196)
	injection	3.6 Unit intravenous injection, intramuscular injection, subcutaneous injection	low back pain, cervicobrachial syndrome, symptomatic neuralgia, Itch with the skin disease	drowsiness, eruption	
Antidepressants					
Tricyclic antidepressants					
Amitriptyline	oral	initial dose : 10~25 mg/day maintenance dose : 10~100 mg/day	depression, enuresis, peripheral neuropathic pain	drowsiness, dizziness, fatigue, nausea, dipsia	CQ14 (p.211)
Imipramine	oral		depression, enuresis		CQ15 (p.214)
Nortriptyline	oral		depression		
Clomipramine	oral		depression, enuresis, emotional cataplexy accompanying narcolepsy		
	injection	initial dose : 25 mg/day maintenance dose : 25~75 mg/day	depression		
Tetracyclic antidepressants					
Maprotiline	oral	initial dose : 10 mg/day maintenance dose : 30~75 mg/day	depression	unknown	CQ15 (p.214)
Selective serotonin re-uptake inhibitors (SSRI)					
Paroxetine	oral	initial dose : 10~20 mg/day maintenance dose : 10~40 mg/day	depression, panic disorder, obsessive-compulsive disorder (OC), social anxiety disorder (SAD)	drowsiness, dizziness, fatigue, nausea, dipsia	CQ15 (p.214)
Escitalopram	oral	initial dose : 10 mg/day maintenance dose : 10~20 mg/day	depression, social anxiety disorder (SAD)	drowsiness, dizziness, fatigue, nausea, dipsia	
Sertraline	oral	initial dose : 25 mg/day maintenance dose : 25~100 mg/day	depression, panic disorder, posttraumatic stress disorder (PTSD)	unknown	
Fluvoxamine	oral	initial dose : 25~50 mg/day maintenance dose : 50~150 mg/day	depression, social anxiety disorder (SAD), obsession	nausea, dipsia, constipation,	
Serotonin-noradrenaline re-uptake inhibitors (SNRI)					
Duloxetine	oral	initial dose : 20 mg/day maintenance dose : 40~60 mg/day	depression, fibromyalgia, diabetic neuropathy, chronic low back pain, osteoarthritis of the knee	nausea, drowsiness, dipsia, headache, fatigue	CQ13 (p.207)
Milnacipran	oral	initial dose : 25 mg/day maintenance dose : 25~60 mg/day	depression	dipsia, nausea, vomiting, drowsiness	CQ15 (p.214)
Venlafaxine	oral	initial dose : 37.5 mg	depression	nausea, abdominal discomfort, somnolence	
Other antidepressants					
Mirtazapine	oral	initial dose : 15 mg/day maintenance dose : 15~30 mg/day	depression	drowsiness, fatigue, dipsia, constipation	CQ15 (p.214)
Trazodone	oral	initial dose : 25 mg/day maintenance dose : 25~50 mg/day	depression	drowsiness, fatigue, dipsia, constipation	

Drug name	Method of administration	Dosage/Directions for usage	Applicable diseases	Adverse events/ Precautions for usage	Ref.
Antiepileptic drugs					
Pregabalin	oral	initial dose : 50～150 mg/day maintenance dose : 300～600 mg/day	neuropathic pain, fibromyalgia	drowsiness, dizziness, weight gain, edema	CQ11 (p.200)
Gabapentin	oral	initial dose : 400～600 mg/day maintenance dose : 600～1,800 mg/day	intractable epileptic seizure	drowsiness, dizziness	CQ12 (p.204)
Carbamazepine	oral	initial dose : 200～400 mg/day maintenance dose : 600～1,200 mg/day	trigeminal neuralgia epileptic seizure, bipolar disorder	drowsiness, dizziness, rash, cytopenia	
Sodium valproate	oral	400～1,200 mg/day	prevention of migraine, epileptic seizure, bipolar disorder	drowsiness, dizziness, liver disease, pancreatitis	
Lamotrigine	oral	initial dose : 25 mg/day maintenance dose : 50～200 mg/day	epileptic seizure, bipolar disorder	toxic epidermal necrolysis, Stevens-Jonson syndrome	
Topiramate	oral	initial dose : 50 mg/day maintenance dose : 50～200 mg/day	epileptic seizure	drowsiness, weight gain, closed-angle glaucoma	
Anticonvulsant					
Baclofen※1	oral	initial dose : 5～15 mg/day maintenance dose : 15～30 mg/day	spastic paralysis	drowsiness, dizziness, weakness, nausea, vomiting	CQ12 (p.204)
NMDA receptor antagonists					
Ketamine	injection	single dose 0.5 mg/kg (gradually administered over 30 minutes) maintenance dose : 5～20 mg/hr※2	general anaesthesia at time of surgery, investigation, procedure	nightmares, excitement, nausea, vomiting, respiratory and circular depression, abuse, misuse	CQ16 (p.217)
Dextromethorphan	oral formula	maintenance dose : 30～45 mg/day	cough	drowsiness, dizziness, nausea, vomiting	
Memantine	oral formula	initial dose : 5 mg/day maintenance dose : 10～20 mg/day	Alzheimer-type dementia	dizziness, nausea, vomiting	
Antianxiety agents					
Etizolam	oral	initial dose : 0.5～1.5 mg/day maintenance dose : 0.5～3.0 mg/day	neuropathy, depression, anxiety/strain/depression/ sleep disorder in psycho-physiologic disorder, cervical spondylosis, low back pain, muscle contraction headache	drowsiness, dizziness, relaxes the muscles, dependency	CQ17 (p.220)
Clonazepam	oral	initial dose : 0.5～1 mg/day maintenance dose : 0.5～3/day	epilepsy	drowsiness, dizziness, closed-angle glaucoma, relaxes the muscles	
Alprazolam	oral	initial dose : 0.4～1.2 mg/day maintenance dose : 0.4～2.4 mg/day (not use over 1.2 mg/day in elderly person)	anxiety/strain/depression/ sleep disorder in psycho-physiologic disorder	drowsiness, dizziness, closed-angle glaucoma, relaxes the muscles	
Diazepam	oral	initial dose : 2～10 mg/day maintenance dose : 4～15 mg/day	anxiety/strain/depression in psychophysiologic disorder, muscle cramps in the cerebrospinal disease	drowsiness, dizziness, closed-angle glaucoma, relaxes the muscles	
Opioid analgesics					
Tramadol	oral formula	initial dose : 50～100 mg/day maintenance dose : 50～300 mg/day	chronic pain, cancer pain	drowsiness, dizziness, nausea, vomiting, constipation	CQ18 (p.224)
Tramadol/ Acetaminophen pill (T/A pill)	oral formula	initial dose : 75～150 mg/day maintenance dose : 150～300 mg/day※3	chronic pain, post-dental treatment pain	drowsiness, dizziness, nausea, vomiting, constipation	
Buprenorphine patch	patch (for 7 days)	initial dose : 0.12 mg/day maintenance dose : 0.12～0.48 mg/day	osteoarthritis chronic low back pain	drowsiness, dizziness, nausea, vomiting	CQ19 (p.228)
Morphine	oral formula (quick-release formula)	initial dose : 10～30 mg/day maintenance dose : 30～90 mg/day※4	chronic pain, cancer pain	nausea, vomiting, constipation, respiratory depression, psychological dependence, abuse, misuse	CQ20 (p.232)
Fentanyl patch	patch (for 1 day or 3 days)	initial dose : 12.5～25 μg/hr maintenance dose : 5～37.5 μg/hr	chronic pain, cancer pain	nausea, vomiting, constipation, respiratory depression, psychological dependence, abuse, misuse	

※1 Consider the usage for trigeminal neuralgia when carbamazepine can not be used.
※2 Caution that the risk of neuropsychiatric symptoms increases in dose-dependent manner.
※3 Initial dosage and maintenance dosage indicate amounts including tramadol.
※4 The upper limit is 90 mg/day but it is better to use a dosage of up to 60 mg/day.

CQ8 : Are nonsteroidal anti-inflammatory drugs effective in managing chronic pain?

NSAIDs : nonsteroidal anti-inflammatory drugs

Answer : Nonsteroidal anti-inflammatory drugs (NSAIDs) have an analgesic effect and improve motor function in musculoskeletal pain, and can also be effective when applied topically to relieve pain caused by osteoarthritis (OA). There has been no high-quality research conducted on its analgesic effects on neuropathic pain and therefore the use of NSAIDs is not recommended. It has been recognized as effective in preventing and improving headache, orofacial pain and migraine and therefore NSAIDs should be considered. We do not recommend NSAIDs for fibromyalgia. When administering NSAIDs, careful attention must be paid to any adverse events and long-term use without any clear purpose in mind should be avoided.

Summary of recommendation grades and overall evidence :

Musculoskeletal pain : 1A (Use is strongly recommended)
Neuropathic pain : 2D (Non-use is weakly recommended)
Headache/Orofacial pain : 2B (Use is weakly recommended)
Fibromyalgia : 2C (Non-use is weakly recommended)

Commentary :

Musculoskeletal pain

In systematic reviews verifying the efficacy of NSAIDs on chronic low back pain[1], there was a minor improvement in motor function and analgesic effect, in comparison with a placebo but no difference in efficacy according to the type of NSAIDs has been found. Furthermore, as the period of observation is short in randomized control trials (RCT) which are the object of analysis, the long-term safety of administering NSAIDs is unknown.

RCT : randomized controlled trial

In 'Noninvasive treatments for acute, subacute and chronic low back pain : A clinical practice guideline' published in 2017 by the American College of Physicians[2], it was first recommended to conduct non-pharmacotherapy on chronic pain such as rehabilitation and therapeutic exercise. Pharmacotherapy is then recommended and the first-line drug is NSAIDs, if non-pharmacotherapy does not have a sufficient effect.

According to a systematic review verifying the efficacy of the analgesic effect of NSAIDs on OA[3], the efficacy of NSAIDS was confirmed in 76 RCTs in comparison with a placebo. When these data were analyzed, at the current stage, it appears that 150mg of diclofenac, taken orally, is the most effective improving motor function and pain.

In addition, in a systematic review verifying the efficacy of celecoxib[4], when 36 RCTs were analyzed, it appeared that celecoxib was slightly effective in im-

proving motor function and pain, in comparison to a placebo and conventional NSAIDs.

According to a systematic review verifying the efficacy of applying topical NSAIDs[5], both diclofenac and ketoprofen were found to be significantly superior in terms of analgesic effect, compared with a placebo, with a number needed to treat (NNT) of 9.8 and 6.9, respectively. However, apart for this, there has been no other evidence indicating its efficacy on chronic pain.

NNT : number needed to treat (the number of patients who need to be treated for one of them to benefit compared with a control)

According to the 'OARSI Guidelines' on OA, announced by the Osteoarthritis Research Society International (OARSI) in 2014[6], based on the assumption that pharmacotherapy and non-pharmacological therapy are used concomitantly in the management of OA, oral NSAIDs under pharmacotherapy are recommended but OA has also been recognized outside of the knee, and in the case where moderate complications are also present, it is recommended that highly selective NSAIDs, in particular cyclooxygenase-2 (COX-2) be used. When severe complications have been recognized, we strongly urge that NSAIDs not be used. We recommend topical use of NSAIDs only in cases of knee OA, irrespective of whether complications are present or not.

OARSI : Osteoarthritis Research Society International

OA : Osteoarthritis

COX-2 : cyclooxygenase-2

Neuropathic Pain

In a systematic review verifying the efficacy of NSAIDs on neuropathic pain[7], two RCTs were subjected to analysis but quality of the evidence was low, and so they were unable to draw any conclusions about the efficacy of NSAIDs. For each of the patients' conditions, there was one RCT[8] on postherpetic neuralgia (PHN) but this study is unsuitable for considering efficacy because it was conducted on COX-2 selective inhibitor which is not used in clinical settings. At the current stage, no high-quality evidence indicating the efficacy of NSAIDs on neuropathic pain exists.

Headache/Orofacial Pain

American Academy of Neurology (AAN) and the Quality Standards Subcommittee of American Headache Society (AHS) state that fenoprofen, ibuprofen, ketoprofen and naproxen are effective as treatments in early phases of migraine. Flurbiprofen is probably effective but aspirin and indomethacin are not really effective[9]. In recent reviews, amongst patients with migraine from eight RCTs who took between 50～650mg of oral aspirin, they reported a decrease in the frequency of migraines when 325mg of oral aspirin or more was administered[10]. Based on these facts, we recommend the use of NSAIDs for migraine. However, we advise caution because continuous and excessive use of NSAIDs over a long period of time sometimes induce medication overuse headache (MOH).

AHS : the American Headache Society

Fibromyalgia

In a systematic review verifying the efficacy of NSAIDs on fibromyalgia,[11]

upon analysis of six RCTs, no significant difference in analgesic effect was recognized between four types of NSAIDs (etoricoxib, ibuprofen, naproxen, tenoxicam) and the placebo and as there was a wide variation in the results, the evidence level is low. Therefore, under our guidelines we do not recommend the administration of NSAIDs for fibromyalgia.

Precautions：

The typical side effects of NSAIDs are gastrointestinal ulcer, renal dysfunction, cardiovascular events and asthma. For elderly or high-risk patients, we would consider administering COX-2 highly selective celecoxib, and to prevent gastrointestinal ulcer, we would consider administering proton pump inhibitor (PPI) and misoprostol. When administering NSAIDs, careful attention must be made to a risk assessment of the patient and side effects, and it is important to avoid long-term use without any clear aim in mind and to limit its use to the short term.

PPI：proton pump inhibitor

Dosage and directions for usage are shown in **Table 2** [Note 2].

Note 2：refer to p.188

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Database	Cochrane library, PubMed
Period	2005–2017
Words searched by the combination with 'chronic pain'	NSAIDs, low back pain, osteoarthritis, neuropathic pain, postherpetic neuralgia, diabetic neuropathy, trigeminal neuralgia, orofacial pain, migraine, chronic headache, fibromyalgia
*Notes	Out of these, we mainly searched for systematic review, RCT and selected the references by considering its contents and avoiding any overlap.

CQ9：Is acetaminophen effective in managing chronic pain?

Answer： In terms of musculoskeletal pain, acetaminophen for managing chronic low back pain is eligible for coverage under the Japanese health insurance system, and due to its high level of safety as well, we recommend the administration. There is no high-quality study, which has investigated its analgesic effects on neuropathic pain and so we do not recommend the administration. However, in headache and orofacial pain, it has been recognized as effective in improving infrequent episodic tension-type headache (IETTH) and migraine and therefore we recommend that it be administered. Its effects on fibromyalgia remain unclear.

Close attention must be paid however, as there is a higher possibility of the patient developing liver disorders when administered high dosages.

Summary of recommendation grades and overall evidence：

Musculoskeletal pain：1A (Use is strongly recommended)

Neuropathic pain：2D (Use is weakly recommended)

Headache/Orofacial pain：1A (Use is strongly recommended)

Fibromyalgia：2C (Use is weakly recommended)

Commentary：

Musculoskeletal pain

According to a systematic review verifying the efficacy of acetaminophen on low back pain[1], it is not recognized as effective in improving the quality of life (QOL) in acute low back pain, and no high-quality RCTs indicating the efficacy of acetaminophen on sub-acute pain and chronic pain exist. Furthermore, according to recent RCTs on non-specific chronic low back pain[2], celecoxib had significantly higher analgesic effect than acetaminophen.

RCT：randomized controlled trial

Results of the efficacy of acetaminophen on osteoarthritis (OA) vary depending on the RCTs. There have been reports that slow-release acetaminophen (1,950～3,900 mg/day)[3], and a combination of 3,000mg/day of acetaminophen and therapeutic exercise[4], significantly improved pain and joint function, compared with the placebo. On the other hand, there have also been reports that 3,000～4,000 mg/day of acetaminophen did not have a significant effect, com-

NSAIDs：nonsteroidal anti-inflammatory drugs

pared with the placebo[5,6]. According to systematic reviews analyzing placebo-controlled RCTs including these[7,8], the efficacy of acetaminophen was very low and was limited to a short period of time. Furthermore, it found that compared with nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen had significantly lower analgesic effect and there was no difference in levels of safety.

In this way, recently the efficacy of acetaminophen on musculoskeletal pain has been questioned, mainly in Western countries. In light of the results of these systematic reviews, some physicians are of the opinion that the positioning of acetaminophen under the treatment guidelines for musculoskeletal pain needs to be revised[7]. In actual fact[9], under the 'Noninvasive treatments for acute, subacute, and chronic low back pain：A clinical practice guideline'[9] released by the American College of Physicians in 2017, Acetaminophen is not recommended under pharmacotherapy irrespective of whether it is for acute or chronic pain.

However, as acetaminophen has a high level of safety and is administered with high frequency for managing chronic musculoskeletal pain in Japan, under the 'guidelines for low back pain'[10] its efficacy is considered, and is a first-line drug, along with NSAIDs, for chronic low back pain. In addition, as it is covered under the Japanese health insurance system for managing chronic low back pain, we also recommend that it be administered under these guidelines.

Neuropathic pain

There are no RCTs which meet the set criteria related to the efficacy of acetaminophen and therefore we have no grounds on which to indicate a recommendation grade[11].

Headache/Orofacial pain

Depending on the frequency of headache, tension-type headaches are classified into infrequent episodic (less than once a month), frequent episodic (1～14 times a month) and chronic (more than fifteen times a month). Among these types, in a systematic review related to the analgesic effects of acetaminophen on infrequent episodic tension-type headache (IETTH)[12], when 1,000 mg of acetaminophen was administered per dosage, it was more effective than the placebo but there was no significant difference when 500 mg was administered per dosage. There are few RCTs related to the analgesic effects of acetaminophen on frequent episodic and chronic tension-type headache (TTH). In a systematic review related to migraine[13], a single dosage of 1,000 mg of acetaminophen had a significant analgesic effect, compared with the placebo and when a single dosage of 1,000 mg of acetaminophen was used in combination with metoclopramide, it provided an analgesic effect equivalent to that of 100 mg of sumatriptan.

Fibromyalgia

No RCTs indicating the efficacy of acetaminophen alone on fibromyalgia exist. A placebo-controlled RCT study on patients with fibromyalgia complaining of moderate pain or worse, reported a significant decrease in the degree and pressure points of pain after taking a tramadol-acetaminophen tablet (T/A tablet)[14], However, these are unreliable grounds to indicate the efficacy of acetaminophen.

Precautions：

Dosage and directions for usage are shown in Table 2 Note 3.

Note 3：refer to p.188

Under many of the guidelines to date, acetaminophen has been a first-line drug for general pain diseases, for the reasons that it has few side effects and is highly safe. However, in high dosages, patients are at increased risk of liver damage. In many cases of hepatic failure, the cause was an overdose of acetaminophen[5,16]. As an unexpected overdose may occur through the concomitant use of drugs contained within acetaminophen (such as common cold remedies and opioid analgesic compounds), we advise caution when increasing the dosage or in cases of long-term administration.

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Database	Cochrane Library, PubMed
Period	2005–2017
Words searched by the combination with 'chronic pain'	acetaminophen, paracetamol, low back pain, osteoarthritis, neuropathic pain, postherpetic neuralgia, diabetic neuropathy, trigeminal neuralgia, orofacial pain, migraine, chronic headache, fibromyalgia
*Notes	Out of the words searched, we searched mainly for systematic review, RCT, and selected references by considering their details and tried to avoid any overlap. As for those with few search results, we used references prior to 2004 which were considered important (References 6, 14)

CQ10 : Is an extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus effective in managing chronic pain?

An extract from inflamed cutaneous tissue of rabbits. inoculated with vaccinia virus

Answer : There is some evidence indicating that an extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus is effective on chronic musculoskeletal pain and neuropathic pain, and therefore we recommend that it be administrated. Evidence indicating that it be recommended to manage headache, orofacial pain and fibromyalgia is scarce but because there are no severe adverse events and it is highly safe, it should be considered as an alternative option in cases where patients fail to react to standard treatment.

Summary of recommendation grades and overall evidence :

Musculoskeletal Pain : 2B (Use is weakly recommended)

Neuropathic pain : Postherpetic neuralgia : 1B (Use is strongly recommended)

Neuropathic pain other than above : 2C (Use is weakly recommended)
Headache/Orofacial pain : 2D (Use is weakly recommended)
Fibromyalgia : 2D (Use is weakly recommended)

Commentary :

An extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus is a type of drug containing non-protein type biologically active substances extracted from the inflamed cutaneous tissue of rabbits, which have been inoculated with the vaccinia virus. It exhibits analgesic effects through activation of the descending pain inhibitory system, anti-inflammatory action, inhibiting the release of excitatory neuropeptides, inhibiting the excitation of sympathetic nerves, improving blood flow, and neuroprotective action, and in other ways[1]. It is a highly safe formulation and researchers have not found any severe adverse events such as disturbance of the gastrointestinal tract, kidney damage, cardiovascular events or asthmatic attacks.

Musculoskeletal pain

Clinical trials conducted in Japan indicate that an extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus is effective on chronic pain due to various musculoskeletal pain diseases. In a randomized controlled trial (RCT) conducted on 121 patients suffering from low back pain, this drug was shown to be effective on subjects who were orally administered four tablets a day (administered twice/day), compared with a placebo group[2]. It was also shown to be effective in another placebo-controlled RCT study on patients with cervico-omo-brachial syndrome[3]. However, in another RCT study in which they compared the effects of the extract with indomethacin on patients with periarthritis scapulohumeralis and osteoarthritis (OA) of the knee, they did not find any significant difference in analgesic effect between the two groups, and no difference in their levels of safety[4]. However, in both RCTs, patients' symptoms were not caused by the same disease and therefore the methods for evaluating improvement of symptoms and drug utility are vague, and so the level of evidence is slightly weak.

RCT : randomized controlled trial

Neuropathic Pain

As for its effect on neuropathic pain, a placebo-controlled RCT conducted in Japan on 228 subjects suffering from postherpetic neuralgia (PHN) indicated the efficacy of the extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus. Compared with the placebo-controlled group, there was a significant improvement in pain in the group which continued to take four tablets/day (taken twice/day) continuously over four weeks[5]. In addition, a small-scale preliminary study indicated that administering the extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus reduced peripheral

neuropathy due to oxaliplatin in 80 patients undergoing chemotherapy for colorectal cancer[6]. Furthermore, in a case series study on 36 patients with painful diabetic neuropathy (PDN) who were orally administered with the extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus continuously for eight weeks, spontaneous pain and numbness improved in 65% of the subjects[7].

As seen above, as the usefulness of the extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus for managing postherpetic pain has been firmly established, it is a second-line drug under the 'Guidelines for the pharmacologic management of neuropathic pain, second edition'[8] released by the Japan Society of Pain Clinicians. As there are few adverse events and it has high tolerability, we recommend its use for neuropathic pain.

Headache/Orofacial pain

There are no RCTs, either in Japan or abroad, which have investigated the efficacy of an extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus on headache and orofacial pain. There are several case studies which have shown its efficacy on headache and orofacial pain and in Japan, there are some case series indicating its efficacy on tension-type headache (TTH) and migraine[9,10], but the evidence indicating its efficacy is weak. However, as an extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus displays almost no severe adverse events and is a highly safe formulation, it is worth considering as an alternative in cases where patients fail to react to standard treatment.

Fibromyalgia

No RCTs investigating the efficacy of extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus on fibromyalgia exist either in Japan or abroad. There are some instances of case reports here and there, which claimed that it was effective on fibromyalgia pain but the evidence indicating its efficacy is weak. However, as there are almost no severe adverse events and it is highly safe, one could consider using these extracts as an alternative in cases where a highly recommended drug has poor effects on patients with fibromyalgia.

Precautions：

In RCTs and cases series on an extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus in the past, results have shown that there are extremely few adverse events and it is highly safe. However, even though it is unclear how frequently this occurred, there have been reports of severe adverse events such as shock, anaphylactic-type symptoms, liver dys-

function and jaundice and therefore caution is advised when using this agent. Furthermore, in cases where it has proven to be ineffective on patients, even after administering it for four weeks, one needs to be careful not to administer it without any clear purpose in mind[11].

Dosage and directions for usage are shown in Table 2 Note 4.

Note 4：refer to p.188

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Database	Cochrane Library, PubMed, Ichushi Web
Period	1970 – 2017
Words searched by the combination with 'chronic pain'	neurotropin, low back pain, osteoarthritis, neuropathic pain, postherpetic neuralgia, diabetic neuropathy, trigeminal neuralgia, orofacial pain, migraine, chronic headache, fibromyalgia (Cochrane Library, PubMed) an extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus, neurotropin, pain, low back pain, cervico-omo-brachial syndrome, osteoarthritis (OA), neuropathic pain, postherpetic neuralgia (PHN), diabetic neuropathy, headache, orofacial pain, facial pain, fibromyalgia (Ichushi Web)
*Notes	From these results, we searched mainly for systematic review, RCT, clinical study, and clinical trial and selected the references. In addition to this, we also referred to the Guidelines for the Pharmacologic Management of Neuropathic Pain (Second Edition), published by the Japan Society of Pain Clinicians, and drug information of Neurotropin®.

CQ11：Is pregabalin effective in managing chronic pain?

Answer： Pregabalin is recommended as a first-line drug for managing neuropathic pain as a whole. Analgesic efficacy of pregabalin on fibromyalgia has been proven when administered at high doses. As there are few high-quality RCTs on the efficacy of pregabalin on musculoskeletal pain (e.g. arthritic pain, low back and lower extremity pain) and headache/orofacial pain, the recommendation grade for these diseases is low. However, for trigeminal neuralgia patients allergic to carbamazepine and for neuropathic pain clearly derived from trigeminal nerve disorder, use of pregabalin under the management of a specialist is recommended. Adverse effects such as drowsiness and lightheadedness are common, therefore patients should start on a low dosage, according to their age and gender, and the dosage should be titrated. Particular care is required with elderly patients.

Summary of recommendation grades and overall evidence：

Musculoskeletal pain：2C (Use is weakly recommended)

Neuropathic pain：1A (Use is strongly recommended)

Headache/Orofacial pain：2C (Use is weakly recommended)

Fibromyalgia：1A (Use is weakly recommended)

Commentary：

Musculoskeletal pain

In a non-randomized controlled trial on lumbar and cervical radiculopathy which had persisted for six months or more, the groups which had been administered pregabalin alone and pregabalin in combination showed significantly higher analgesic effects than the group which did not use pregabalin [1]. However, in a RCT study targeting patients with sciatic nerve pain, pregabalin

(starting dose of 150 mg/day, gradually increased to a maximum dose of 600 mg/day) did not have significantly greater analgesic effects, compared with the placebo[2]. This study subjects included a large number of patients experiencing sciatic nerve pain in the acute stage of less than three months since onset and therefore it is hard to say that the results reflect the effects of pregabalin on chronic radicular pain. Further high-quality RCTs about the effects of pregabalin on radicular pain are required. Out of the musculoskeletal pain in Japan, low back pain is a common symptom with a high incidence rate. As low back pain has a mixture of nociceptive, neuropathic and psychosocial factors, it is assumed that using several types of drugs in combination with their different acting mechanisms is effective. In a RCT targeting patients with low back and lower extremity pain, pregabalin administered in combination with celecoxib displayed significantly higher analgesic effects than when pregabalin alone or celacoxib alone was administered[3]. In another RCT on low back and lower extremity pain, buprenorphine patch used in combination with pregabalin showed significantly higher analgesic effects than when buprenorphine patch alone was administered[4]. In both RCTs, many of the subjects included patients with elements of neuropathic pain, and therefore we think the results reflect the analgesic effects of pregabalin on neuropathic pain. At the current stage, there are no significant reports indicating the efficacy of pregabalin on back pain unaccompanied by lower extremity pain (i.e. back pain with few elements of neuropathic pain). Chronic arthritic pain due to osteoarthritis of the knee is a typical disease of nociceptive pain but in recent years, it has been suggested that increased pain or protracted pain due to central sensitization is involved and there are quite a few instances of patients who also display neuropathic pain-type symptoms[5]. In a RCT targeting chronic arthritic pain of the knee, meloxicam administered in combination with pregabalin displayed significantly higher analgesic effects than when meloxicam alone or pregabalin alone was used[6]. We need to compile even more data on the efficacy of pregabalin in managing chronic arthritic pain.

Neuropathic pain

There is much research indicating that pregabalin produces a higher analgesic effect than the placebo on neuropathic pain, including postherpetic neuralgia (PHN), painful diabetic neuropathy, painful polyneuropathy and post-spinal cord injury pain. Therefore, pregabalin is highly effective on neuropathic pain[7]. Regarding neuropathic pain as a whole, including the above diseases, when the outcomes were a 50% reduction in pain or more compared with the baseline, which was prior to treatment, the number needed to treat (NNT) and number needed to harm (NNH) were 7.7 and 13.9, respectively, when subjects were administered 300～600 mg of pregabalin[7].

NNT：number needed to treat
(the number of patients who need to be treated for one of them to benefit compared with a control)

NNH：number needed to harm
(the number of patients who need to be exposed to a risk factor to cause harm to one patient)

Headache/Orofacial pain

There are no RCTs investigating the efficacy of pregabalin in preventing migraine. In non-odontogenic toothache, although there are few RCTs investigating the efficacy of pregabalin, when neuropathic pain elements are strong, pregabalin can be used as a first-line drug, in the same way as when other neuropathic pain is present in other parts of the body[8]. For trigeminal neuralgia cases who are allergic to carbamazepine and for neuropathic pain clearly derived from trigeminal nerve disorder, use of pregabalin under the management of a specialist is recommended[9].

Fibromyalgia

In the several RCTs on fibromyalgia, pregabalin was not effective at doses of 150 mg/day[10], but provided significant analgesic effects at dosages of 300 mg/day or more, compared with the placebo[11–13]. The NNT for outcomes in which pain was reduced by 50% or more were 14 (300 mg/day), 9.7 (450 mg/day) and 11 (600 mg/day), respectively[14]. The NNH for doses of 300～600 mg/day was between 5.7～9.0, and the higher the dosage, the poorer the tolerability[14]. In a RCT targeting Japanese patients with fibromyalgia, 450 mg/day of pregabalin showed higher analgesic effect and improvement in sleep quality, compared with the placebo[15]. Considering the NNT and NNH, doses of 300～450 mg/day of pregabalin for fibromyalgia are considered appropriate in terms of efficacy and tolerability.

tolerability：the degree to which overt adverse effects of a drug can be tolerated by a patient.

Precautions：

Dosage and directions for usage are shown in **Table 2** [Note 5].

Note 5：refer to p.189

A long-term domestic study targeting patients with painful diabetic neuropathy who had participated in domestic Phase 3 clinical trials, investigated the occurrence of adverse events when patients were administered between 150～600 mg/day of pregabalin over 52 weeks. The overall side-effect incidence rate was 87%, which included drowsiness (28%), weight gain (27%), dizziness (26%), and edema (19%). The level of severity of drowsiness and dizziness ranged from light to moderate, but tended to appear at an early stage and would often reduce over the course of the year. The incidence rate of severe complications was extremely low[16]. The same results were obtained with the domestic long-term study targeting patients with fibromyalgia[17].

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Database	Cochrane Library, PubMed
Period	2005～2017
Words searched by the combination with 'chronic pain'	pregabalin, low back pain, osteoarthritis, neuropathic pain, postherpetic neuralgia, diabetic neuropathy, trigeminal neuralgia, orofacial pain, migraine, chronic headache, fibromyalgia
*Notes	Out of these words, we searched mainly for systematic review, RCT, and selected references by considering their details and by trying to avoid any overlap.

CQ12 : Are antiepileptic drugs effective in managing chronic pain?

Answer : Similar to pregabalin, gabapentin is recommended as a first-line drug for neuropathic pain, but at the current stage, from the perspective of health insurance coverage, gabapentin is off label for neuropathic pain in Japan. There are few high-quality RCTs about the efficacy of other antiepileptics (e.g. carbamazepine, lamotrigine, lacosamide, topiramate, sodium valproate) on chronic pain diseases (e.g. neuropathic pain, fibromyalgia, musculoskeletal pain, orofacial pain). Although antiepileptics can be used as an alternative when a drug with a high recommendation grade was not effective, great caution is needed when using them, as there can be some severe adverse effects. Regarding the preventive effect of sodium valproate and topiramate on migraine, a certain evaluation has been obtained and the recommendation grade is high.

RCT : randomized controlled trial

Summary of recommendation grades and overall evidence :

1) Gabapentin
   - Musculoskeletal pain : No clear evidence for recommendation
   - Neuropathic pain : 1A (Use is strongly recommended)
   - Headache/Orofacial pain : No clear evidence for recommendation
   - Fibromyalgia : No clear evidence for recommendation

2) Carbamazepine
   - Musculoskeletal pain : No clear evidence for recommendation
   - Neuropathic pain : 2C (Use is weakly recommended)(excluding trigeminal neuralgia)
   - Headache/Orofacial pain : trigeminal neuralgia : 1A (Use is strongly recommended)
   - Other headache/orofacial pain : No clear evidence for recommendation
   - Fibromyalgia : No clear evidence for recommendation

3) Sodium valproate
   - Musculoskeletal pain : No clear evidence for recommendation
   - Neuropathic pain : 2B (Use is weakly recommended)
   - Headache/Orofacial pain : 1A (Use is strongly recommended)(as a preventative medicine for migraine)
   - Fibromyalgia : No clear evidence for recommendation

4) Lamotrigine
   - Musculoskeletal pain : No clear evidence for recommendation
   - Neuropathic pain : 2B (Use is weakly recommended)
   - Headache/Orofacial pain : Trigeminal neuralgia: 2D (Use is weakly recommended)
   - Other headache/orofacial pain : No clear evidence for recommendation
   - Fibromyalgia : No clear evidence for recommendation

5) Topiramate

Musculoskeletal pain : No clear evidence for recommendation

Neuropathic pain : 2C (Use is weakly recommended)

Headachie/Orofacial pain : 1A

(Use is strongly recommended) (as a preventative medicine for migraine)

Fibromyalgia : No clear evidence for recommendation

Commentary :

1) Gabapentin

There are many RCTs indicating gabapentin's higher analgesic effect, compared with the placebo, on neuropathic pain such as postherpetic neuralgia (PHN), painful diabetic neuropathy, painful polyneuropathy and post-spinal cord injury pain[1]. Regarding neuropathic pain as a whole, including the above diseases, the NNT and NNH of 1,800～3,600 mg/day of gabapentin were 6.2 and 25.9, respectively, for outcomes in which pain was reduced by 50% or more compared with the baseline, which was prior to the commencement of treatment. It has both a high efficacy and high tolerability[1]. There are no high-quality RCTs on fibromyalgia[2]. In a RCT on low back pain with accompanying radicular pain, significantly higher analgesic effect was obtained in the group which used a combination of gabapentin (2,400 mg/day) and standard treatments such as physiotherapy and the oral administration of NSAIDs, than in the group which only used these standard treatments[3]. There are no RCTs targeting low back pain without radicular pain. Regarding the efficacy of gabapentin on orofacial pain, there is only one RCT on patients with chronic pain in the masticatory muscle. In this RCT, gabapentin (300 mg/day) displayed significantly higher analgesic effects[4]. Further studies are required to clarify the efficacy of gabapentin on fibromyalgia, low back and lower-extremity pain as well as orofacial pain.

NNT : number needed to treat
(the number of patients who need to be treated for one of them to benefit compared with a control)

NNH : number needed to harm
(the number of patients who need to be exposed to a risk factor to cause harm to one patient)

2) Carbamazepine

It has been established that carbamazepine is effective on trigeminal neuralgia[5]. On the other hand, there are few reports on its efficacy on other forms of neuropathic pain, apart from trigeminal neuralgia. In addition, it has an NNH of 5.5 and low tolerability, therefore, its recommendation grade against neuropathic pain other than trigeminal neuralgia is low[1]. Some of the side effects from carbamazepine include dizziness, lightheadedness, aplastic anaemia, granulocytopenia, toxic epidermal necrolysis (TEN), and Stevens-Jonson syndrome. When managing trigeminal neuralgia, in cases where carbamazepine alone is unable to provide sufficient analgesic effect, or when carbamazepine cannot be used due to old age or side effects, the use of baclofen should be considered Note 6.

TEN : toxic epidermal necrolysis

Note 6 : refer to p.189

3) Sodium valproate

The results of RCTs on the efficacy of 1,000～2,400 mg/day of sodium valproate on neuropathic pain vary from one study to the next[6-8]. There are no RCTs on fibromyalgia, low back and lower-extremity pain or arthritic pain. There are some severe side effects such as hepatic dysfunction, drug-induced pancreatitis (aggravated when used in combination with topiramate), and teratogenesis, and therefore its recommendation grade is low. In several RCTs on its efficacy in preventing migraine, the consistent results were obtained and it has been evaluated as a preventative drug which reduces the frequency of headache[9].

4) Lamotrigine

In the results of several RCTs on neuropathic pain, the efficacy of lamotrigine varies from one study to the next[1]. There are no high-quality RCTs on other chronic pain diseases (e.g. fibromyalgia, low back and lower-extremity pain, arthritic pain) and so there is no evidence for which we can recommend it. In trigeminal neuralgia, although its analgesic effect is low, it can be used, although weakly recommended, as an analgesic option under the management of a specialist in patients who are resistant to or allergic to carbamazepine[10-12]. Side effects of lamotrigine include some severe skin problems such as toxic epidermal necrolysis (TEN) and Stevens-Jonson syndrome.

5) Topiramate

There are few RCTs on chronic pain diseases and the results of the efficacy of topiramate vary from one study to the next[1]. In a RCT study on radiculopathy, there was no significant difference in analgesic effect between 400 mg/day of topiramate and the placebo[13]. It has an NNH of 6.3, with a low tolerability. Therefore, it has a low recommendation grade for chronic pain diseases. On the other hand, there are several RCTs on migraine, which showed that when patients were administered 50～200 mg/day of topiramate reduced the numbers of headache attacks and painkiller use, and improved QOL[14]. Therefore, in the same way as with sodium valproate, it is recommended as a first-line drug to prevent migraine. Adverse events include drowsiness, weight loss and closed-angle glaucoma.

Precautions：

Dosages, precautions for usage and adverse events for each drug are shown in Table 2 [Note 7].

Note 7：refer to p.189

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Database	Cochrane Library, PubMed
Period	2005–2017
Words searched by the combination with 'chronic pain'	anticonvulsant, valproate, lamotrigine, topiramate, low back pain, osteoarthritis, neuropathic pain, postherpetic neuralgia, diabetic neuropathy, trigeminal neuralgia, orofacial pain, migraine, chronic headache, fibromyalgia
*Notes	Out of these words, we mainly searched for systematic review, RCT, and selected references by considering their details and by trying to avoid any overlap. As for those words with few search results, we selected references prior to 2004 which were considered important (References 5, 6, 7)

CQ13 : Is duloxetine effective in managing chronic pain?

Answer : There is much evidence that duloxetine is effective on neuropathic pain, chronic low back pain, osteoarthritis, and fibromyalgia, and is therefore recommended. One thing to be careful of when using duloxetine is that we should cautiously judge whether to administer the drug or not after considering the possibility that it may cause mental states such as suicidal thoughts, suicidal attempts, hostility and aggressiveness.

Summary of recommendation grades and overall evidence :

Musculoskeletal pain : 1A (Use is strongly recommended)

Neuropathic pain : 1A (Use is strongly recommended)

Headache/Orofacial pain : 2C (Use is weakly recommended)

Fibromyalgia : 1A (Use is strongly recommended)

Commentary :

SNRI : serotonin-noradrenaline re-uptake inhibitor

Duloxetine is one of the serotonin-noradrenaline re-uptake inhibitors (SNRI), is safer and easier to use than amitriptyline, and is a better option for patients with heart disease. It is believed that the analgesic mechanism of duloxetine induces an activation of the descending pain inhibitory system (DPIS).

Musculoskeletal pain

RCT : randomized controlled trial

ACP : The American College of Physicians

There are some RCT studies on duloxetine and chronic low back pain[1-3], and even in the systematic reviews, it is strongly recommended. According to the guidelines of the American College of Physicians (ACP), in three RCTs in which patients were administered 60 mg/day of duloxetine over the short period of 12～13 weeks, there was a mild improvement in pain, and only in one RCT was there a large number of patients whose pain was reduced by 50%. In three RCTs, there was an improvement in functional disorders but in one RCT the quality of life (QOL) did not improve. It is reported that duloxetine increases the possibility of nausea as a side effect. However, in reports on pharmacotherapy for low back pain, in many of the reports the period of observation was short and the effects of treatment ranged from moderate to low. Therefore, further investigation is required.

There are some RCTs on osteoarthritis of the knee and osteoarthritis of the hip[7-9], and in some systematic reviews[10-11] and it was strongly recommended. According to the analysis of two RCTs on osteoarthritis of the hip in which patients were administered 60～120 mg/day of duloxetine over thirteen weeks[10], the NNT was seven patients, when the study was set to have a therapeutic effect of reducing pain by 30% or more or by 50% or more as well as an improvement in physical function. The adverse events were nausea, fatigue and constipation and the NNH was 16, 17, and 18, respectively.

NNT : number needed to treat
(the number of patients who need to be treated for one of them to benefit compared with a control)

NNH : number needed to harm
(the number of patients who need to be exposed to a risk factor to cause harm to one patient)

Neuropathic pain

According to systematic reviews, the NNT is 6.4 when SNRIs are used, which mainly includes duloxetine, and therefore it is considered a first-line drug for treating neuropathic pain.[12]

There are also some RCTs indicating the analgesic effects of duloxetine for pain and numbness due to diabetic neuropathy[13-18], and chemotherapy-induced peripheral neuropathy (CIPN) from cancer[19]. Furthermore, it has also shown to have analgesic effects on peripheral neuropathy accompanying multiple sclero-

sis (MS)[20] and central post-stroke pain (CPSP)[21], but they are case-series study reports, so it needs to be evaluated in future.

Headache/Orofacial pain

There are only case studies on chronic pain (migraine, tension-type headache)[22-23], so its efficacy is limited.

Fibromyalgia

There are some RCTs on duloxetine and fibromyalgia[24-27], and also some systematic reviews[28-29], which have confirmed the effectiveness of the treatment and an improvement in QOL. When patients were administered 60～120 mg/day of duloxetine, the therapeutic effects on fibromyalgia were reported to be a further improvement in psychological symptoms rather than analgesic effect[28].

Precautions：

Dosage and directions for usage are shown in Table 2 Note 8.

Note 8：refer to p.188

In clinical tests conducted in our country, in order to inhibit the onset of side effects in the early stages of administration, treatment should begin at 20 mg/day, and 1～2 weeks later, the dosage should be increased to the ideal dose (maintenance dose) of up to 40～60 mg/day. By administering a dosage of 40～60 mg / day, the patient will receive analgesic effects in the first week after commencing a course of duloxetine[11]. According to systematic reviews in the Cochrane Database, within the twelve weeks of the observation period, the degree of pain improved by 50% or more in patients administered with 40 mg, 60 mg and 120 mg of duloxetine, compared with the placebo. However, there was no recognizable correlation between the level of dosage and the level of improvement. Furthermore, physical function items evaluated on the SF-36 significantly improved as well, compared with the placebo. The frequency of side effects was not significant compared with the placebo (duloxetine：12.6%, placebo：5.8%) but 12.6% of the patients had discontinued oral administration of the drug due to side effects[27]. The adverse events, which stopped the oral administration of duloxetine were nausea, dipsia, diarrhea, headache, drowsiness, dizziness and insomnia. Infrequent symptoms also included attempted suicide, severe liver damage, metrorrhagia, a rise in blood pressure and difficulty urinating[8].

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Database	Cochrane Library, PubMed
Period	2005～2017
Words searched by the combination with 'chronic pain'	duloxetine, low back pain, osteoarthritis, neuropathic pain, postherpetic neuralgia, diabetic neuropathy, trigeminal neuralgia, orofacial pain, migraine, chronic headache, fibromyalgia
*Notes	Out of these words, we mainly searched for systematic review, RCT, and selected references by considering their details and by trying to avoid any overlap. As for those words with few search results, we selected references prior to 2004 which were considered important. (Reference 16).

CQ14 : Is amitriptyline effective in managing chronic pain?

Answer : In musculoskeletal pain, amitriptyline is not effective with chronic pain but it can be effective on upper extremity pain. It is effective and is the most effective drug for neuropathic pain. With chronic headaches, it also acts to prevent tension–type headache (TTH) and migraine. Amitriptyline is also effective in helping to treat idiopathic odontalgia (atypical odontalgia) and burning mouth syndrome (BMS). It has analgesic effects on fibromyalgia.

BMS : burning mouth syndrome

Summary of recommendation grades and overall evidence :

Musculoskeletal pain : 2B (Use is weakly recommended)

Neuropathic pain : 1A (Use is strongly recommended)

Headache/Orofacial pain : 2A

(Use is weakly recommended)(tension–type headache (TTH) and migraine)

Fibromyalgia : 2B (Use is weakly recommended)

Commentary :

Amitriptyline has significant analgesic effects on chronic pain, compared with the placebo. It has been revealed that the analgesic properties of amitriptyline act through a different mechanism from that of antidepressants. Amitriptyline can also be used in lower dosages than the dosage indicated for antidepressants to act and it has also been revealed that it shows analgesic effects within a short period of time. The main analgesic-acting mechanism is the activation of the descending pain inhibitory system (DPIS) via the action of serotonin-noradrenaline reuptake inhibitors, and NMDA receptor antagonists and Na^+ channel blockers are also involved[1].

NMDA : N-methyl-D- aspartic acid

Musculoskeletal pain

In a systematic review of musculoskeletal pain[2], the American College of Physicians (ACP)[3] said that amitriptyline has little analgesic effect on chronic low back pain. In a review in 2017, it claimed that it does have analgesic effects on musculoskeletal diseases including low back pain and upper extremity pain[4]. There has been one RCT each on low back pain and upper extremity pain and as there are few cases on upper extremity pain, there is limited evidence.

RCT : randomized controlled trial

Neuropathic pain

Amitriptyline is effective in providing analgesic effect on neuropathic pain, regardless of the variety of diseases and pathologies such as postherpetic neuralgia[5-6], post-traumatic nerve injury pain[7], pain and numbness due to diabetic neuropathy[8-9], and central poststroke pain[10]. In a systematic review published in 2005, the number needed to treat (NNT) neuropathic pain with amitriptyline was the lowest at 3.6[11]. In the 'Guidelines for the Pharmacologic Management of Neuropathic Pain, Revised 2nd Edition' by the Japan Society of Pain Clinicians[12], they claimed it is effective, as it is one of the most effective drugs for neuropathic pain. However, in a systematic review, amitriptyline was said to have limited efficacy on neuropathic pain even though amitriptyline has been used for many years clinically to treat neuropathic pain. Therefore, one needs to give it some consideration when judging its efficacy[13].

NNT : number needed to treat
(the number of patients who need to be treated for one of them to benefit compared with a control)

Headache/Orofacial pain

In order for amitriptyline to have a preventative effects on tension-type headache (TTH), it is recommended that a patient should orally take 10～100 mg before sleeping, and in order to reduce the onset of side effects, one should start by orally taking 10～25 mg. One needs to consider any improvement in symptoms and the patient's whole physical condition before increasing the dosage[14]. Amitriptyline decreases the frequency of migraines, compared with a placebo but there is a high possibility that the patient will have to stop taking it orally due to adverse events[15]. In addition, according to systematic reviews

on its effects on idiopathic odontalgia (atypical odontalgia) and burning mouth syndrome (BMS)[16–18], both amitriptyline and nortriptyline, another tricyclic antidepressant, are effective. However, the number of observations and diagnostic criteria differ greatly between reports, so future study is necessary.

Fibromyalgia

According to a systematic review on fibromyalgia, amitriptyline is effective if the patient takes 25 mg/day over a short-term period (less than 6～8 weeks) but its efficacy at high dosages (50 mg/day) or over a long period of time exceeding 8 weeks is unknown[19].

Precautions：

Dosage and directions for usage are shown in Table 2 Note 9.

Note 9：refer to p.188

The adverse events of amitriptyline are mainly anitcholinergic problems such as dipsia and constipation. In elderly patients, there have been reports of increased cases of patients falling over with doses of 75 mg or more and increased cases of sudden cardiac death with doses of 300 mg or more. Amitriptyline should be started at low doses and used cautiously[20,21].

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Database	Cochrane Library, PubMed
Period	2005～2017
Words searched by the combination with 'chronic pain'	amitriptyline, low back pain, osteoarthritis, neuropathic pain, postherpetic neuralgia, diabetic neuropathy, trigeminal neuralgia, orofacial pain, migraine, chronic headache, fibromyalgia
*Notes	Out of these words, we mainly searched for systematic review, RCT, and selected references by considering their contents and by trying to avoid any overlap. As for those words with few search results, we selected references prior to 2004 which were considered important (References 5, 6, 8, 9, 10).

CQ15 : Are other types of antidepressants effective in managing chronic pain?

RCT : randomized controlled trial

Answer : Apart from amitriptyline and duloxetine, there have been few high-quality RCTs on antidepressants, and their recommendation grades are low. They can be used as an option for patients in which standard treatment was not effective.

Summary of recommendation grades and overall evidence :

Musculoskeletal pain : 2C (Use is weakly recommended)
Neuropathic pain : 2C (Use is weakly recommended)
Headache/Orofacial pain : 2C (Non-use is weakly recommended)
Fibromyalgia : 2B (Use is weakly recommended)

Commentary :

Musculoskeletal pain

In chronic pain, there are few RCTs on tricyclic antidepressants (imipramine,

nortriptyline, clomipramine), tetracyclic antidepressants (maprotiline), selective serotonin reuptake inhibitors (SSRI) (paroxetine) and drugs such as trazodone. Even if such reports exists, the scope of research is small and the level of evidence is low[1–2]. They report that apart from duloxetine, other antidepressants were ineffective[1]. Furthermore, according to the guidelines of the American College of Physicians (ACP)[3], there have been few RCTs on escitalopram and only one clinical research study in which no difference in analgesic effect was reported between it and duloxetine, also a serotonin–noradrenaline reuptake inhibitor (SNRI), meaning there is little evidence.

SSRI：selective serotonin reuptake inhibitor

SNRI：serotonin-noradrenaline re-uptake inhibitor

ACP：The American College of Physicians

Neuropathic Pain

RCTs have indicated that the tricyclic antidepressants imipramine[4], clomipramine[5–6] and nortriptyline[7–8] have an analgesic effect but both the number of eligible patients and the period of observation were short so there is little on the evidence level. How the tricyclic antidepressants are used differently is clomipramine is the only one of the tricyclic antidepressants which is administered intravenously and is used in cases where something fast-acting is expected or oral administration is ineffective [6]. On the other hand, nortriptyline is the main metabolite of amitriptyline and has fewer adverse events than amitriptyline. There have been RCTs on its analgesic effects but with few eligible patients and over a short period of observation so there is little on the evidence level. Nortriptyline is not used as a first-line drug with neuropathic pain but can be used in cases where the other tricyclic antidepressants are ineffective[8].

In RCTs, venlafaxine has been described as having analgesic effects on neuropathic pain but there is little high-quality research and according to the systematic reviews in the Cochrane Database[9] it is poorly evaluated. In Japan, there have been few instances of prescribing it for neuropathic pain so it is difficult to evaluate its efficacy.

With paroxetine which is an SSRI[10], escitalopram[11] and milnacipran which is an SNRI[12], there have been RCTs on each that they are effective on neuropathic pain but the number of eligible patients used was small and therefore the level of evidence is low.

Headache/Orofacial Pain

According to systematic reviews related to its preventive action on migraine[13], SSRIs (sertraline) and SNRIs (venlaflaxine) do not act to prevent migraine. Even in systematic reviews on tension-type headache (TTH)[14], there was no difference in strength or frequency of onset of TTH with SSRIs (citalopram, sertraline, paroxetine, fluvoxamine) and SNRIs (venlaflaxine), in comparison with the placebo.

With chronic pain, both SSRIs and SNRIs were ineffective in the prevention

of migraine and TTH.

Fibromyalgia

The efficacy of mirtazapine[15], and milnacipran which is an SNRI[16] on fibromyalgia have been indicated but SSRIs (citalopram, paroxetine) have proven ineffective[17].

Precautions：

Dosages, precautions when using and adverse events for each drug are shown in Table 2 [Note 10].

Note 10：refer to p.188

Caution is advised when administering large dosages of SSRIs or a multidrug regimen of SSRIs, or the concomitant use of tramadol drugs which run the risk of causing serotonin syndrome.

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Database	Cochrane Library, PubMed
Period	2005-2017
Words searched by the combination with 'chronic pain'	antidepressants, low back pain, osteoarthritis, neuropathic pain, postherpetic neuralgia, diabetic neuropathy, trigeminal neuralgia, orofacial pain, migraine, chronic headache, fibromyalgia
*Notes	Out of the words searched, we focused mostly on systematic review, RCT and chose references in consideration of their contents and to avoid any overlap. Regarding those with few search results, we adopted those references prior to 2004 which were considered important (References 5, 6, 10)

CQ16 : Are NMDA receptor antagonists effective on chronic pain?

NMDA : N-methyl-D-aspartic acid
RCT : randomized controlled trial

Answer : There have been few RCTs which indicate significantly higher analgesic effects of NMDA receptor antagonists (ketamine, dextromethorphan, memantine) on chronic pain compared to the placebo, and therefore the recommendation grade is low. Since NMDA receptor antagonists act on the central nervous system and have psychotropic effects such as causing hallucinations, sufficient consideration is necessary for its use.

Summary of recommendation grades and overall evidence :

1) Ketamine

Musculoskeletal pain : 2D (Use is weakly recommended)
Neuropathic pain : 2C (Use is weakly recommended)
Headache/Orofacial pain : 2D (Use is weakly recommended)
Fibromyalgia : 1C (Non-use is strongly recommended)

2) Dextromethorphan

Musculoskeletal pain : 2D (Non-use is weakly recommended)
Neuropathic pain : 2C (Use is weakly recommended)
Headache/Orofacial pain : 2D (Non-use is weakly recommended)
Fibromyalgia : 2D (Non-use is weakly recommended)

3) Memantine

Musculoskeletal pain : 2D (Non-use is weakly recommended)
Neuropathic pain : 2C (Non-use is weakly recommended)
Headache/Orofacial pain : 2C (Use is weakly recommended)
Fibromyalgia : 2C (Use is weakly recommended)

Commentary :

Central sensitization of the spinal cord and brain play a major role in the intensification and protraction mechanism of chronic pain. As the activation of NMDA receptors is considered to be involved in central sensitization, much attention has been given to NMDA receptor antagonists as an analgesic strategy against chronic pain. However, contrary to this expectation, there have been few clinical trials indicating its efficacy. Moreover, it has poor tolerability, therefore its recommendation grade is low. There have been several RCTs examining the efficacy of NMDA receptor agonists on neuropathic pain, while there have been few studies on musculoskeletal pain such as low back pain and arthritis. As ketamine has not been manufactured as an oral formula, it is essential to be administered intravenously under medical supervision, and there is also the heavy burden of hospitalization or visiting hospital as an outpatient. Furthermore, it carries the risk of illegal misuse or abuse, therefore sufficient care is required to ensure that it is not used in these ways. The efficacy of memantine, which is indicated for Alzheimer's disease, has been suggested in RCTs targeting migraine and fibromyalgia, but further clinical research needs to be made.

1) Ketamine

Ketamine is approved as a general anesthetic, and is only available through intravenous or intramuscular administration. In 2007, ketamine was designated as a narcotic under the 'Narcotics and Psychotropics Control Law'. Compared with the dosage used for general anaesthesia, it displays analgesic effects at lower dosages when used for the purpose of alleviating pain. There are several RCTs on various forms of chronic pain such as central pain, post-spinal cord injury pain, postherpatic neuralgia (PHN), migraine, complex regional pain syndrome (CRPS), fibromyalgia, and traumatic cervical syndrome[1].

CRPS : complex regional pain syndrome

Although ketamine provides short-term analgesic effects only while being administered intravenously[2,3], reports on its long-term effects after discontinuation are limited. Some RCTs targeting CRPS and post-spinal cord injury pain showed that, when ketamine was administered continuously or intermittently (but daily) for 4～14 days, analgesic effects remained, even several weeks after discontinuation[4-6]. Based on these results, a single dose of ketamine cannot be expected to provide an analgesic effect longer than the period of its administration, while prolonged continuous or intermittent administration could provide analgesic effects, for a moderate period of time, even after discontinuation. However, as it has a higher risk of affecting the central nervous system (psychotropic action), cardiovascular system (tachycardia, high blood pressure), and causing hepatic disorder, it should be used as an alternative only in cases where other analgesic treatments for chronic pain were ineffective.

2) Dextromethorphan

Dextromethorphan is approved as an antitussive drug. Out of the two RCT studies which indicated the efficacy of dextromethorphan on painful diabetic peripheral neuropathy[7,8], one of the studies indicated the efficacy of dextromethorphan (with an average dosage of 381mg/day), although the sample size was very small. In the other study, dextromethorphan (30～45 mg/day) administered concomitantly with quinidine (30 mg/day) displayed a significantly higher analgesic effect, compared with the placebo. In a RCT study on postherpetic neuralgia (PHN), it was found to be ineffective.

3) Memantine

Memantine is approved as a drug to treat Alzheimer's Disease. It has few side-effects such as psychotropic effect and the safety of long-term administration of memantine has been established. The main adverse events are dizziness and nausea. Several RCTs targeting postherpetic neuralgia, painful diabetic peripheral neuropathy and phantom limb pain showed that the analgesic effect of memantine was not significant compared with the placebo[9-11]. In RCTs targeting fibromyalgia, memantine (20 mg/day) displayed significant analgesic effects compared with the placebo, and also improved overall function, depression and quality of life (QOL)[12]. There are no RCTs on low back pain. In a RCT on migraine, the number of migraines, the severity of the migraines and the number of days absent from work due to migraine significantly decreased in the subjects who were administered with memantine (10 mg/day), compared with the placebo group[13]. In a RCT on tension-type headache (TTH), memantine (40 mg/day) was found to be effective on female patients[14].

Precautions：

Dosage and directions for usage for each drug, precautions for usage and side effects etc. are shown in Table 2 [Note 11].

Note 11：refer to p.188

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Database	Cochrane Library, PubMed
Period	2005–2017
Words searched by the combination with 'chronic pain'	NMDA antagonist, low back pain, osteoarthritis, neuropathic pain, postherpetic neuralgia, diabetic neuropathy, trigeminal neuralgia, orofacial pain, migraine, chronic headache, fibromyalgia
*Notes	Out of the words searched, we searched mainly for systematic review, RCT and selected the references by considering their contents and to avoid any overlapping. As for those with few search results, we adopted references prior to 2004 which were considered important (References 3, 7, 9, 10, 11)

CQ17 : Are antianxiety agents (benzodiazepine type drugs) effective in managing chronic pain?

RCT : randomized controlled trial

Answer : There are few high–quality RCTs on the efficacy of antianxiety agents (benzodiazepines) on chronic pain diseases (musculoskeletal pain, neuropathic pain, headache/orofacial orofacial pain, fibromyalgia), therefore the recommendation grade is low. The use of benzodiazepine is considered as an adjunctive option for chronic pain patients who are resistant to other medication.

Summary of recommendation grades and overall evidence :

Musculoskeletal Pain : 2C (Use is weakly recommended) (etizolam)

Neuropathic Pain : 2C (Use is strongly recommended) (clonazepam)

Headache/Orofacial Pain : 2B (Use is weakly recommended)
(TTH : etizolam, alprazolam
Orofacial pain : diazepam, clonazepam)

Fibromyalgia : 2C (Use is weakly recommended)

Commentary :

Among drugs that can be classified as antianxiety agents, we will only explain the efficacy of benzodiazepine. It is assumed that the analgesic effect of benzodiazepine is mainly in mediating the activation of $GABA_A$ receptors. It is often used to alleviate insomnia which accompanies chronic pain, to reduce psychological stress, and to relax muscles. There are reports that concomitant use of NSAIDs with benzodiazepine could provide higher analgesic effect than single use of NSAIDs. However, they are addictive, therefore there is much debate over their long-term usage. In addition, using benzodiazepine concomitantly with opioid analgesics heightens the risk of dependence so this should be avoided.

GABA : γ (gamma)-aminobutyric acid reuptake inhibitor

Musculoskeletal Pain

As benzodiazepines are effective as a muscle relaxant, they are used for low back pain and stiff shoulders. There have been reports[1,2] suggesting that etizolam, which was a benzodiazepine developed in Japan, might be effective on cervical spondylosis and low back pain but there are no high-quality RCTs. In systematic reviews on pain associated with rheumatoid arthritis, there exist several RCTs comparing benzodiazepine with a placebo, benzodiazepine with NSAIDs, as well as the concomitant use of benzodiazepine/NSAIDs with NSAIDs but in each case, benzodiazepine was not shown to be effective[3].

Neuropathic Pain

In a RCT related to the analgesic effects of amitriptyline, lorazepam and a placebo on postherpetic neuralgia (PHN), there was a lower percentage of patients who felt significant analgesic effects in the lorazepam group (0.5～6 mg/day) than in the amitriptyline group (12.5～150 mg/day) but it was about the same as the placebo group[4]. There have been reports suggesting an analgesic effect of clonazepam, as an adjuvant therapy, on neuropathic pain due to cancer[5]. However, at the current stage, there are no RCTs on the efficacy of clonazepam on neuropathic pain and therefore further clinical research is required[6].

Headache/Orofacial pain

In a RCT study on tension-type headache (TTH), in female subjects, the con-

comitant use of etizolam and NSAIDs was more significantly effective in alleviating headache and its accompanying neck and shoulder pain than using NSAIDs alone[7]. Similarly, in another RCT, alprazolam had a higher analgesic effect on TTH compared with the placebo[8]. There are quite a few reports on its efficacy on TTH but there is a need for even higher-quality RCTs.

The results of the efficacy of benzodiazepine on orofacial pain vary from study to study. In a RCT related to the efficacy of diazepam on chronic orofacial pain, diazepam administered in combination with ibuprofen and diazepam administered alone had higher analgesic effects compared with administering ibuprofen alone and the placebo[9]. In a RCT on stomatalgia, the oral local administration of clonazepam (1 mg) displayed significantly higher analgesic effects compared with the placebo. In this study, the patient does not swallow the pill but it is placed for several minutes in the vicinity of the site of pain in the mouth, after which the subject spits out the pill[10]. In another RCT on burning mouth syndrome (BMS), clonazepam (0.5 mg/day) displayed significantly higher analgesic effect than the placebo[11]. In an RCT related to the efficacy of diazepam on temporomandibular joint syndrome, it did not have significantly higher analgesic effects compared with the placebo[12]. Similarly, clonazepam didn't have significantly higher analgesic effects on temporomandibular joint syndrome compared with the placebo[13].

BMS：burning mouth syndrome

Fibromyalgia

In a RCT related to the analgesic effects of alprazolam on fibromyalgia, Ibuprofen used in combination with alprazolam displayed significantly higher analgesic effects compared with the placebo but this was not the case when alprazolam alone was administered[14]. In a different RCT, tenoxicam (discontinued in Japan) used in combination with bromazepam showed a recognizable significant improvement in overall symptoms, compared with when tenoxicam alone was used[15]. However, in this research study, tenoxicam used in combination with bromazepam and tenoxicam used alone showed no recognizable significant effect in improving the symptoms, when compared with the placebo.

Precautions：

Dosage, possible adverse events and precautions for usage are shown in Table 2 Note 12.

Note 12：refer to p.189

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Database	Cochrane Library, PubMed
Period	2005–2017
Words searched by the combination with 'chronic pain'	benzodiazepine, low back pain, osteoarthritis, neuropathic pain, postherpetic neuralgia, diabetic neuropathy, trigeminal neuralgia, orofacial pain, migraine, chronic headache, fibromyalgia
*Notes	Out of these words searched, we searched mainly for systematic review, RCT and chose the references by considering their contents and to avoid any overlapping. For those which returned few search results, we selected the references prior to 2004 which were considered important 2004 (References 4, 5, 8–10, 13–15). Furthermore, with etizolam which was developed in our country, On Ichushi Web (by the Japan Medical Abstracts Society) we searched for 'etizolam' and 'chronic pain' and selected those references, which were considered important. (References 1, 2)

CQ18：Is tramadol effective in managing chronic pain?

Note 13：Tramadol is classified as opioid analgesics [weak]

Answer： Tramadol[Note 13] is recognized as having analgesic effects on musculoskeletal pain, and effective in improving motor function. It has also been confirmed to have analgesic effects on neuropathic pain, such as painful diabetic neuropathy and postherpetic neuralgia (PHN) as well as effective in improving QOL. Furthermore, it is also possible that it might be useful on pain caused by fibromyalgia. Its effect on headache/orofacial pain has not been confirmed.

QOL：quality of life

However, the efficacy and safety of its long-term administration remains unclear and therefore this should be avoided.

Summary of recommendation grades and overall evidence：

Musculoskeletal pain：1B (Use is strongly recommended)

Neuropathic pain：1B (Use is strongly recommended)

Headache/Orofacial pain：No clear evidence for recommendation

Fibromyalgia：2C (Use is weakly recommended)

Commentary：

Musculoskeletal pain

According to a systematic review of fifteen RCTs which considered the efficacy of opioid analgesics on chronic pain[1], tramadol (150～300 mg/day) was significantly superior in its analgesic effects and its effectiveness in improving motor function than the placebo. Furthermore, tramadol (200 mg/day) and celecoxib (400 mg/day) displayed the same degree of analgesic effect. Tramadol had the same analgesic effect and was as effective as a motility stimulant as antidepressants. Furthermore, tramadol-acetaminophen oral tablets (T/A tablets) have been indicated as effective on chronic low back pain, and significantly improved pain and QOL, compared with the placebo[2]. In another RCT, numerical rating scale (NRS) and Self-Rating Depression Scale (SDS) significantly improved in patients with chronic low back pain and comorbid depression when taking T/A tablets, compared with NSAIDs[3].

NRS：numerical rating scale
SDS：Self-Rating Depression Scale

In three RCT studies related to osteoarthritis[4,5,6], on patients with knee osteoarthritis or hip osteoarthritis suffering from moderate pain or worse, they reported that 8～12 weeks administration of sustained-release tramadol brought about a significant improvement in analgesic effects, physical function and sleep, compared with the placebo. Furthermore, according to a systematic review which summarized eleven RCTs of the administration of tramadol (including T/A tablets) on osteoarthritis[7], tramadol (average dosage of 201.4 mg/day) significantly improved analgesic effects and motor function, compared with the placebo. However, as the patient drop-out rate due to adverse events was 12.5%, and as the average period of observation for the RCTs was 35 days,

three months at the most, the results only showed that it is effective over a short period of time.

Neuropathic Pain

As for neuropathic pain, tramadol significantly improved the pain from painful diabetic neuropathy[8], postherpetic neuralgia (PHN)[9], and post-spinal cord injury[10], compared with the placebo. According to a systematic review summarizing six RCTs (including cancer pain) which verified the efficacy of tramadol on neuropathic pain[11], tramadol had a number needed to treat (NNT) of 4.4 and high analgesic effects compared with the placebo. However, overall, due to factors such as a small sample population and diverse types of pain, it was concluded that the evidence of tramadol's efficacy on neuropathic pain was low, both in terms of quality and quantity.

NNT：number needed to treat
(the number of patients who need to be treated for one of them to benefit compared with a control)

Headache/Orofacial Pain

As for research into the efficacy of tramadol on headache and orofacial pain, RCT studies on acute pain and postsurgical pain exist but there are some occasional case reports on chronic pain. No high-quality RCTs exist.

Fibromyalgia

In a RCT investigating the efficacy of tramadol on fibromyalgia[12], the degree of pain and the number of points of tenderness significantly decreased in the group administered orally with a T/A tablet, compared with the placebo group. However, while the drop-out rate due to adverse events was 2% in the placebo group, it was as high as 19% in the T/A tablet group. According to a systematic review announced in 2016 however[13], while it recognizes the efficacy of tramadol to some degree, it is not for its effect as an opioid analgesic but infers that it is effective as an SNRI. There is no clinical research evidence supporting the efficacy and safety of opioid analgesics on fibromyalgia.

We are far from having a sufficient understanding of the causes and pathology of fibromyalgia and currently many also suffer from psychiatric disorders concomitantly. Administering opioid analgesics in such patients, runs the high risk of causing psychological dependence. Therefore, under our guidelines, if one is considering the administration of opioid analgesics, we only propose the use of tramadol, which has a low risk of patients forming a dependence on it, while simultaneously consulting a pain specialist, and limiting administration to a short period of time.

Out of the opioid analgesics, tramadol is highly safe and there have been very few incidences of psychological dependence[14]. However, in many of the RCTs, the period of observation was short (three months or less) and they described a patient drop-out rate of around 10～20% due to adverse events such as nausea and vomiting. In a placebo-controlled open-label trial, testing the continual administration of sustained-release tramadol over one year on 1,052

patients with chronic non-cancer pain, 795 patients (approximately 76%) dropped out due to reasons such as adverse events[15]. Due to this and other reasons, the efficacy and safety of tramadol over the long-term have not been established and it is best to be discontinued after a relatively short period of time[16]. Therefore, long-term administration should be conducted only while consulting a pain specialist.

Precautions：

Currently in Japan, tramadol formulas, which can be administrated for chronic pain are orally disintegrating tablets (ODT) (25 mg, 50 mg), sustained-release tablets over a 24-hour period (100 mg) as well as tramadol (37.5 mg)/acetaminophen (325 mg) tablets.

As mentioned in the drug information, administration of tramadol should begin with 100～150 mg per day but considering the patient's age and build, the dosage should start small and then be gradually increased. In the same way as with other opioid analgesics, when a course of tramadol is begun, adverse events such as nausea, vomiting, drowsiness and constipation become severe so appropriate treatments need to be taken in accordance with the symptoms at the time. The clinical effective limit of tramadol is 300 mg/day and even if the dosage is increased beyond this, an improvement in analgesic effect cannot be expected.

Tramadol is metabolized into M1 by CYP2D6, a drug-metabolizing enzyme of the liver, and M1 exhibits the main analgesic effect. Activity of the CYP2D enzyme varies from person to person and the analgesic effect of tramadol is weaker in people where the enzyme has low activity. Therefore, when the expected analgesic effect is not obtained even after gradually increasing the dosage, we should consider changing to another drug on the assumption that this is possibly due to low-enzyme activity. When switching over to an opioid analgesic, such as morphine, one should begin with a smaller dosage rather than an equivalent reduced dosage.

Furthermore, tramadol acts as a monoamine reuptake inhibitor and as it can also act like an SNRI at the same time, it activates the descending pain inhibitory system and displays analgesic effects and is effective on neuropathic pain. However, when administrated in combination with drugs which act to increase serotonin, such as duloxetine, one needs to be careful that it does not lead to the onset of serotonin syndrome.

If tramadol is reduced or discontinued suddenly, there is a risk that it may cause withdrawal or serotonin syndrome, so it is best to gradually reduce the dosage to 1/4～1/2 of a daily dosage, administered every 2-3 days.

Dosage and directions for usage are shown in Table 2 [Note 14].

Note 14：refer to p.189

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Database	Cochrane Library, PubMed
Period	2005–2017
Words searched by the combination with 'chronic pain'	tramadol, low back pain, osteoarthritis, neuropathic pain, postherpetic neuralgia, diabetic neuropathy, trigeminal neuralgia, orofacial pain, migraine, chronic headache, fibromyalgia
*Notes	Out of these words searched, we mainly searched for systematic review, RCT, and selected references by considering their contents and by avoiding any overlap. As for those words with few search results, we used references prior to 2004 which were considered important. (References 8, 9, 12, 14)

CQ19：Are buprenorphine patches effective in managing chronic pain?

Note 15：Buprenorphine is classified as opioid analgesics [moderate]

QOL：quality of life

Answer： Buprenorphine [Note 15] patches have a high analgesic effect on musculoskeletal pain and are expected to bring about an improvement in quality of life (QOL). As for neuropathic pain, it has the possibility of being effective on conditions such as painful diabetic neuropathy. Furthermore, its effect on headache/orofacial pain and fibromyalgia has not been confirmed. Another point is that at the current stage, buprenorphine patches are only eligible for coverage under the Japanese health insurance system for chronic low back pain and osteoarthritis.

Even in senior patients, it has few severe adverse events such as respiratory depression, has high tolerability and its efficacy and safety if administered over a long period of time has also been confirmed but it is relatively likely for patients to suffer from nausea and vomiting.

Summary of recommendation grades and overall evidence：

Musculoskeletal pain：1B (Use is strongly recommended)

Neuropathic pain：2C (Use is weakly recommended)

Headache/Orofacial pain：No clear evidence for recommendation

Fibromyalgia：1D (Non-use is strongly recommended)

Commentary：

Musculoskeletal pain

There are many RCTs, which indicate the effectiveness of buprenorphine patches on musculoskeletal pain and the level of evidence is also high.

RCT：randomized controlled trial

In six RCTs on chronic low back pain[1–6] there was a significant improvement in analgesic effect, motor function, sleep and QOL in the group which used buprenorphine patch (5～40 μg/hr), compared with the placebo group. The period of observation was 4～12 weeks, and the drop-out rate due to side-effects was around 20%. In two of these RCTS, buprenorphine patch was continued up to six months after the end of the observation period, and an improvement in pain and motor function persisted[3,4].

There is one RCT on osteoarthritis and in the buprenorphine patch group (5～20 μg/hr), pain improved significantly at four weeks, compared with the placebo group[7]. In another RCT which compares one group administered with sustained-release tramadol (75～400 mg) and one group administered with buprenorphine patch (5～20 μg/hr), analgesic effects were recognized in both groups and the percentage of subjects who terminated treatment due to adverse events was 29.2% in the sustained-release tramadol group, while it was low at 14.5% in the buprenorphine patch group. The number of patients who wished to continue receiving treatment with the same agent was also higher in the buprenorphine patch group[8].

With musculoskeletal pain, managing patients experiencing moderate or worse levels of pain due to the insufficient effects of non-pharmacologic therapy or non-opioid analgesic pharmacotherapy, one should prescribe this after assessing certain factors such as the patient's background.

Neuropathic Pain

Buprenorphine patch can be effective on neuropathic pain but there are almost no high-quality RCTs and the level of evidence is low.

In a systematic review of the Cochrane Database, there have been reports on the effects of buprenorphine on neuropathic pain[9], but in all eleven research studies which were candidates for inclusion, as the quality of the research was low, they were excluded from analysis and its efficacy was not discussed. In terms of a RCT which verifies the efficacy of buprenorphine patch on neuropathic pain, there exists only one on painful diabetic neuropathy and in this RCT, analgesic effect was significantly higher in the buprenorphine patch group (5～40 μg/hr) than in the placebo group, and analgesic effect was approximately 30% above the baseline. However, approximately 40% of the patients in the buprenorphine patch group dropped out of treatment due to adverse events such as nausea, vomiting and constipation, which is a low tolerability result[10]. Furthermore, in an open-label trial on buprenorphine patch's effect on neuropathic pain, they reported a significant improvement in pain due to sciatic neuralgia, protracted post-surgical shoulder joint pain, and postherpetic neuralgia (PHN) eight weeks after the trial[11].

Headache/Orofacial Pain

There are some sporadic cases of research investigating the efficacy of buprenorphine patch on headache and orofacial pain but no high-quality RCTs exists.

Fibromyalgia

No RCT indicating the efficacy of buprenorphine patch on fibromyalgia exists. Furthermore, under the guidelines of various American societies and academies, the long-term administration of opioid analgesics [strong] for fibromyal-

gia is not recommended, as it is less effective than other forms of treatment in improving QOL and analgesic effect. As a result of this and other factors, under our guidelines, just like with opioid analgesics [strong], we do not recommend using buprenorphine patch in cases of fibromyalgia.

There is little risk of respiratory depression with buprenorphine patch[12], and reports have not recognized a significant difference in efficacy or safety when comparing patients 65 years or older with patients under 65 years of age[13], and so it is also safe to use with elderly patients. As for its long-term use, in long-term open-label trials conducted in Japan[14,15] high-frequency (10%+) adverse events included nausea, itchiness at the patch site, constipation, vomiting and drowsiness but few adverse events were severe and therefore it is considered to have a high level of safety.

Precautions：

Currently in Japan, buprenorphine patches are changed once a week and it is a 5 mg, 10 mg, and 20 mg drug, releasing 0.12 mg, 0.24 mg, and 0.48 mg of buprenorphine per day, respectively. To secure its safety, only doctors who have undergone an e-learning course and have received permission are able to prescribe the drug. As mentioned on the drug information, it applies in cases of chronic pain associated with osteoarthritis and low back pain which are difficult to treat with non-opioid analgesics, and limited only to musculoskeletal chronic pain. Dosages should start at 5 mg, and in cases where it provides insufficient analgesic effect, dosages can be increased by a minimum of 5 mg/week, up to a maximum of 20 mg/week. In cases where it becomes difficult to continue administration due to adverse events, either after commencing or after raising the dosage, administration should be terminated promptly or a lower dosage should be administered. When the analgesic effect obtained is insufficient, even after raising the dosage, one should consider changing to another drug.

Clinically speaking, it is a full μ-opioid receptor agonist, with no ceiling effect in its analgesic potential and it is not considered a problem if used in combination with other opioid analgesics. In addition, compared with other opioid analgesics, it produces few severe adverse events such as respiratory depression and as it can be used even in patients with impaired renal function without reducing the dosage, it is also easy to use on elderly patients.

Note 16：refer to p.189

Dosage and directions for usage are shown in Table 2 [Note 16].

Adverse events to be cautious of are nausea and vomiting and if necessary, antiemetics such as prochlorperazine and metoclopromide can be used in combination. In addition, caution is advised with the concomitant use of benzodiazepine type agents, muscle relaxants and alcohol as this may cause respirato-

ry depression. Furthermore, as it is a patch, sometimes itchiness or rash around the site where the patch is placed can become a problem.

Buprenorphine is metabolized by CYP3A4, a drug-metabolizing enzyme of the liver, so one should be careful of the drug having a stronger or weaker action, when used in combination with agents which cause drug interactions.

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Database	Cochrane Library, PubMed
Period	2005–2017
Words searched by the combination with 'chronic pain'	buprenorphine, transdermal, low back pain, osteoarthritis, neuropathic pain, postherpetic neuralgia, diabetic neuropathy, trigeminal neuralgia, orofacial pain, migraine, chronic headache, fibromyalgia
*Notes	Out of these words searched, we searched mainly for systematic review, RCT and selected references by considering their contents and to avoid any overlap. As for words with few search results, we selected references prior to 2004 which were considered important (Reference 11). We also used 2 important references (References 14, 15) by searching 'Buprenorphine, dermal' on Ichushi Web (Japan Medical Abstracts Society).

CQ20 : Are opioid analgesics [strong] effective in managing chronic pain?

Answer : Opioid analgesics [strong] provide short-term analgesic effect on musculoskeletal pain and are effective in improving motor function but its long-term effects and level of safety remain unclear. As for neuropathic pain, they are effective over the short-term on each type of patient condition but have a low tolerability to adverse events and as psychological dependence is a concern if administered over the long term it is recommended that only those patients who have been specially selected by a pain specialist should be administered with opioid analgesics [strong]. Furthermore, there is no evidence indicating the efficacy and level of safety of opioid analgesics [strong] on headache/orofacial pain and fibromyalgia.

Summary of recommendation grades and overall evidence :

Musculoskeletal pain : 2B (Use is weakly recommended)
Neuropathic pain : 2B (Use is weakly recommended)
Headache/Orofacial pain : 2D (Non-use is weakly recommended)
Fibromyalgia : 1D (Non-use is strong recommended)

Commentary :

At the current stage, the only opioid analgesics [strong] [Note 17], which are available for chronic non-cancer pain in Japan, are morphine formulations (morphine hydrochloride powder and morphine hydrochloride tablets) and fentanyl formulations (fentanyl 1-day patch, 3-day patch). We will now explain the efficacy of using morphine and fentanyl patches in managing chronic pain.

Note 17 : morphine formulations and fentanyl formulations are classified as opioid analgesics [strong]

Musculoskeletal pain

In 'Noninvasive treatments for acute, subacute, and chronic low back pain: A clinical practice guideline from the American College of Physicians' released by the American College of Physicians (ACP) in 2017[1], they first recommend non-pharmacological therapy for chronic low back pain, such as therapeutic exercise and rehabilitation, and if the effects proved to be insufficient, pharmacotherapy is recommended. In pharmacotherapy, nonsteroidal anti-inflammatory drugs (NSAIDs) are the first-line drug, tramadol and duloxetine are second-line drugs and opioid analgesics [strong] are third-line drugs. In cases where the first-line and second-line drugs are ineffective, opioid analgesics [strong] can be used after considering the patient's condition and if the benefits outweigh the risks.

ACP : The American College of Physicians

NSAIDs : nonsteroidal anti-inflammatory drugs

In RCTs regarding each individual opioid analgesic [strong] on chronic low back pain, one showed that fentanyl patches were effective in providing analgesic effect compared with the placebo[2] and in another study[3], researchers showed that fentanyl patches had similar analgesic effects to morphine. In addition, according to a systematic review of fifteen RCTs verifying the efficacy of opioid analgesics on chronic low back pain, opioid analgesics [strong] produced a stronger improvement in pain and motor function than the placebo. However, considering that with many of the drugs, 20% of the patients or more dropped out of treatment due to adverse events and the period of observation was short at under fifteen weeks, its long-term efficacy remains unclear[4].

RCT : randomized controlled trial

Both morphine[5] and fentanyl patches[6] displayed significant analgesic effects on osteoarthritis in placebo-controlled studies. In a systematic review which broadly verified the efficacy of opioid analgesics on osteoarthritis[7], the analgesic effects of opioid analgesics drop at the cut-off point of one month, and there is no discernible interrelation between the dosage administered and analgesic effects and its effect in improving motor function and there is little evidence of its long-term efficacy and levels of safety. In addition, as fentanyl patches are superior in terms of analgesic effect, there have also been reports that the symptoms of osteoarthritis can progress in a short period of time so caution is advised[8].

Neuropathic Pain

There are many RCTs indicating the efficacy of opioid analgesics [strong] on neuropathic pain. They show that morphine is effective on postherpetic neuralgia (PHN)[9,10], painful diabetic neuropathy[10], post-traumatic peripheral neuropathic pain [11,12], and lumbar radiculopathy[13], while fentanyl patches are effective on postherpetic neuralgia (PHN), CRPS and persistent postsurgical pain[14]. However, in systematic reviews of these agents, their tolerability to adverse events and their long-term effects and level of safety remain unclear, so the

CRPS : complex regional pain syndrome

level of evidence is said to be low[15,16,17].

There is a risk of dependence on, or abuse of opioid analgesics [strong], so considering that that its long-term effects and level of safety have not been firmly established, as a first-line drug for neuropathic pain, administration of drugs such as Ca^{2+} channel $\alpha_2\delta$ ligands, serotonin/noradrenaline reuptake inhibitors (SNRI), tricyclic antidepressants and pregabalin should be prioritized[18].

SNRI：serotonin/ noradrenaline reuptake inhibitors

Headache/Orofacial Pain

There is no evidence from clinical research supporting the efficacy and level of safety of opioid analgesics [strong] on headache and orofacial pain.

Fibromyalgia

Overseas, a large number of patients with fibromyalgia are currently prescribed with opioid analgesics [strong] but there are many cases in which prescription was terminated as a result of side effects, dependence or abuse. In large-scale studies, the administration of opioid analgesics [strong] over the long term is shown to lead to poor outcomes[19,20]. There is no evidence from clinical research supporting the efficacy and level of safety of opioid analgesics [strong] on fibromyalgia. Therefore, the use of opioid analgesics [strong] for fibromyalgia is not recommended.

Precautions：

The way of thinking when it comes to administering opioid analgesics to manage chronic non-cancer pain differs largely from when it involves cancer pain (pain which is directly caused by cancer).

As The Japan Pain Society of Clinicians (JPSC) has outlined a detailed explanation of this in its 'Guidelines for Prescribing Opioid Analgesics for Chronic Non-cancer Pain, Second Edition'[21], we would like to refer to it. In the guidelines listed above, some of the important points mentioned are：

① The purpose of treatment with opioid analgesics is to alleviate pain and improve quality of life (QOL)

② Opioid analgesic treatment shall be limited to only those patients who are at a low risk of things such as dependence and abuse

③ Treatments of some kind should be considered for typical side-effects of opioid analgesics such as nausea, vomiting, constipation and drowsiness.

④ The dosage of opioid analgesics shall be kept to the bare minimum required amount, with no more than 60 mg/day of oral morphine hydrochloride at a reduced quantity and a limit of 90 mg/day.

⑤ The standard period of treatment for opioid analgesics [strong] is three months and at the maximum period of six months, one should consider discontinuing administration of the drug or reducing its dosage.

In the 'CDC Guideline for Prescribing Opioids for Chronic Pain' released in

CDC: Centers for Disease Control and Prevention

2016' [22], weighing up the balance of risks and benefits as well as the suitability of the method of treatment should be reassessed at least every three months, while patients are undergoing treatment with opioid analgesics. We also share the same basic way of thinking, which includes that the dosage upper limit for a reduced quantity of oral morphine hydrochloride should be 90 mg/day.

Dosage and directions for usage are shown in Table 2 [Note 18].

Note 18：refer to p.189

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Database	Cochrane Library, PubMed
Period	2005–2017
Words searched by the combination with 'chronic pain'	opioids, morphine, fentanyl, transdermal, low back pain, osteoarthritis, neuropathic pain, postherpetic neuralgia, diabetic neuropathy, trigeminal neuralgia, orofacial pain, migraine, chronic headache, fibromyalgia
*Notes	Out of these words searched, we mainly searched for systematic review, RCT and selected references by considering their contents and to avoid any overlap. Regarding those which returned few results, we used those references prior to 2004 which were considered important (References 5, 9, 12). In addition, we referred to the guidelines published by the Japan Society of Pain Clinicians, regarding the current usage of opioids for chronic non-cancer pain in Japan (References, 18, 21)

CQ21 : Is Kampo medicine effective in managing chronic pain?

Answer : At present there is little evidence regarding the effect and safety level of Kampo medicine in managing chronic pain, and therefore this issue remains unclear.

Summary of recommendation grades and overall evidence :

Musculoskeletal pain : 2D (Use is weakly recommended)
Neuropathic pain : 2D (Use is weakly recommended)
Headache/Orofacial pain : 2C (Use is weakly recommended)
Fibromyalgia : 2D (Use is weakly recommended)

Commentary :

Kampo medicine is a traditional form of medicine in Japan that originated in China, and it is based on the accumulation of numerous experiences from long

ago. It is a system of treatment based upon a unique theory, and Kampo medicine is what is used for this treatment. In principle, the use of Kampo medicines are based on eligible patient conditions according to the Kampo diagnosis, or what is called 'proof'. This is also described in the package inserts of these extract preparations for medical treatment as "important basic precautions". Under the health care services covered by the health insurance system of Japan, not only can doctors use high-quality extract formulations for medical treatment, but it is also possible for them to use natural remedies in powder or pill form, as well as decoctions consisting of natural remedies.

The administration of Kampo medicines for chronic pain is widely seen in daily consultations, and there are quite a few reports on its efficacy. Some typical examples include goshajinkigan for chronic low back pain[1], yokukansan for neuropathic pain[2], shakuyakuzanzoto for algospasm of the leg[3,4], kamishoyosan for glossalgia[5], and keishikajutsubuto and bushi powder for postherpetic neuralgia (PHN)[6]. However, up to the present there has been almost no high-quality clinical research conducted on the efficacy of kampo formulas targeting a large number of cases of chronic pain, meaning that at the current stage we are unable to clearly demonstrate their effects or levels of safety.

There have only been a few reports on patients suffering from chronic headache for whom 'goshuyuto' was effective. In one such study, patients were randomly allocated into a 'goshuyuto' group and a placebo group, and it was reported that the number of days on which they suffered from a headache decreased in the 'goshuyuto' group[7]. The design of this study was slightly unusual, considering the 'goshuyuto proof', but it can be said that it showed the preventive effects of goshuyuto on chronic headache. Furthermore, there have been some forward-looking randomized blind comparison tests, which positively investigated the therapeutic value of boiogito with shuchi-bushi powder and loxoprofen sodium over a ten-year period of osteoarthritis. While it was claimed that boiogito with shuchi-bushi powder provided a better level of improvement in ADL (pain from passive exercise, spontaneous pain, oppressive pain, ballottement of the patellae, soft-tissue swelling, local heat, chronic pain scores and health-related QOL scores)[8], many details still remain unclear, and therefore further investigation is required. In addition, although reports have indicated the analgesic effects of 'tsumura' powdered aconite root, the tests were not blinded and were not conducted against control drugs, and therefore serious evaluations are still necessary[9].

Pseudoaldosteronism from glycyrrhizae radix, drug-induced interstitial pneumonia and drug-induced liver injury from scutellariae radix, excessive β stimulus action from ephedrae herba, aconitine poisoning from aconiti tuber, and mesenteric phlebosclerosis from gardeniae fructus are some of the known side-

effects from Kampo medicine. When administering Kampo medicines, we should also have an interest in the natural remedies from which they are made. Furthermore, there are some combinations which raise the risk of causing adverse events, similar to when steroidal drugs, loop diuretics and glycyrrhizae radix are used in combination, so caution is advised concerning the interactions between drugs used in combination.

In addition, in recent years, there have been reports that the administration of goshajinkigan aggravated chemotherapy-induced peripheral neuropathy (CIPN)[10], and therefore careful attention needs to be paid to the possibility that Kampo medicine might worsen the targeted symptoms.

As the effects and safety levels of Kampo medicines on chronic pain have not yet been established, it is important to judge their efficacy in each individual case in fine detail and continue this evaluation in terms of whether it has caused adverse events or not. In addition, Kampo medicines should not be administered for a long time without a clear purpose in mind.

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Database	Cochrane Library, PubMed, Ichushi Web
Period	2005–2017
Words searched by the combination with 'chronic pain'	herbal medicine, traditional Japanese medicine, traditional Chinese medicine, kampo medicine (Cochrane Library, PubMed,) Kampo medicine (Ichushi Web)
*Notes	Out of these words searched, we mainly searched for RCT and case series, and in addition we conducted hand research for the most recent academic papers, and from research which used Kampo extraction formulas which can be used under the scope of what is covered by the health system in Japan, we selected references by considering the quality of the research details.

CQ22 : Are interlaminar epidural injections effective in managing chronic pain?

Answer : Interlaminar epidural injections are mainly useful for spinal diseases and in particular it is useful to administer steroids for radiculopathy due to lumbar or cervical disc herniation.

Summary of recommendation grades and overall evidence :

1) Lumbar spine disease

Steroid injection for radiculopathy due to lumbar disc herniation : 1A (Execution is strongly recommended)

Interlaminar epidural injections and caudal epidural injections for lumbar spinal canal stenosis, discogenic pain : 1B (Execution is strongly recommended)

Caudal epidural injections for failed back surgery syndrome (FBSS) : 2C (Execution is weakly recommended)

2) Cervical/thoracic spine disease

Steroid injection for radiculopathy due to cervical disc herniation : 1A (Execution is strongly recommended)

Interlaminar epidural injections for cervical spinal canal stenosis, discogenic pain : 1B (Execution is strongly recommended)

Interlaminar epidural injections for failed back surgery syndrome (FBSS) : 2C (Execution is weakly recommended)

3) Prevents the transition to postherpetic neuralgia (PHN) in patients with herpes zoster : 2C (Execution is weakly recommended)

4) Execution using fluoroscopy, ultrasound guide : 1C (Execution is strongly recommended)

Commentary :

Epidural injections are an interventional therapy frequently used to manage pain. Here we will discuss interlaminar epidural injections and caudal epidural injections, while transforaminal epidural injections will be described as a nerve root block on the following CQ.

Furthermore, it is important to constantly judge the effects of treatment and not administer these injections repetitively without a set intention.

1) Lumbar spine disease

RCT : randomized controlled trial

In a systematic review of the seventeen randomized controlled trials (RCTs) related to the efficacy of lumbar interlaminar epidural injections on lumbar diseases, and fourteen RCTs related to caudal epidural injections, there is evidence indicating efficacy[1]. However, the majority of these RCTs are not placebo-controlled, and instead they compare the drugs patients were injected with (whether a steroidal drug had been added or not) and the method of approach.

Regarding lumbar spine diseases, there are two RCTs on the use of caudal epidural injections for treating radiculopathy due to lumbar disc herniation and five RCTs on interlaminar epidural injections have been described and in both cases, they have strong evidence of its long-term efficacy. There are high-quality RCTs on both caudal epidural injections[2] and epidural injectons[3] for lumbar spinal canal stenosis indicating their long-term efficacy and there have also been reports of the long-term effects of caudal epidural injections[4] and epidural injections[5] on discogenic pain. Caudal epidural injections are also effective on failed back surgery syndrome[6]. Differences in efficacy as a result of the different approaches used in caudal and interlaminar epidural injections have not been shown[7].

There is much debate over which drug should be administered to the patient. There is strong evidence suggesting that the use of steroid with local anaesthetic for treating lumbar disc herniation is more effective than using local anaesthetic alone[8], but there was also a meta-analysis indicating that there was no advantage of administering steroid drugs to treat other diseases[9]. In clinical settings, if the cause of pain is suspected to be inflammation around the nerve root/spine, steroid can be added to local anesthetic but we recommend that it not be used without a set purpose.

2) Cervical/thoracic spine disease

Similarly, in cervical spine diseases, the efficacy of cervical interlaminar epidural injections were displayed in a systematic review of eight RCTs[1], and in particular, in a systematic review of five studies on radiculopathy as a result of cervical disc herniation, there is evidence indicating its long-term efficacy[10]. Even though the evidence is weak, it has also been indicated that it can be useful for treating spinal canal stenosis, discogenic pain, and cervical post-surgery pain [11]. There are few reports on thoracic diseases but it is believed to have the same kind of efficacy[12].

PHN : postherpetic neuralgia

3) Prevents the transition to postherpetic neuralgia (PHN) in patients with herpes zoster

There have been indications of its efficacy as a treatment for clearly reducing the pain from herpes zoster. However, in terms of its effects for preventing its transition to PHN, a form of chronic pain, while there is a RCT on the efficacy of a continuous epidural block[13], there has also been a RCT that a single dose of epidural steroid injections was not effective in its prevention[14]. Epidural injections have a limited effect on PHN.

There are no other reports with high-quality evidence on other forms of chronic pain, and therefore its efficacy remains unknown.

4) Execution using fluoroscopy, ultrasound guide

In investigations using fluoroscopy, intravascular entry was detected in 0.5%

of lumbar and 4.1% of cervical epidural injections, and dural puncture was observed in a total of 0.5% of the procedures[15]. It can have greater efficacy and safety if confirmed on epidurogram, and although a lumbar one is not essential, it should be done under fluoroscopy as much as possible. When performing cervical interlaminar epidural injections, as there have been reports of fatal complications with transforaminal epidural injections through the intravascular injections of particulate steroid, it is essential to make a caudal puncture between the $C_{6/7}$ laminae, and conduct a fluoroscopy in real time[1]. There have also been reports of ultrasound-guided procedures. There is a RCT which claims that ultrasound-guided caudal epidural injections had approximately the same efficacy as a block performed under fluoroscopy[2], and there is also a RCT which states that by confirming the laminae to be punctured and their depth by conducting a scan before performing epidural injections, it had approximately the same efficacy as a block performed under fluoroscopy[16]. There is no risk of radiation exposure and to raise safety and efficacy, we recommend that it be performed under the guidance of ultrasound rather than procedures based only on landmarks.

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Database	PubMed, MEDLINE, Cochrane Library
Period	2010–2017
Words searched by the combination with 'chronic pain'	epidural injection
*Notes	We searched for 'chornic pain' and 'epidural block' on Ichushi. We narrowed down our search by guidelines, RCT, maintenance and systematic review, and focused on the most recent academic papers. References 13 and 14 were not from our search method but have been added because of their importance.

CQ23 : Are nerve root block/transforaminal epidural injections effective in managing chronic pain?

Answer : Nerve root blocks are mainly effective on lumbar diseases, and in particular steroid injections are effective on radiculopathy due to disc herniation.

Summary of recommendation grades and overall evidence :

1) Nerve root block for the purpose of diagnosis : 2B (Execution is weakly recommended)

2) Lumbar spine disease

Nerve root block using steroid on lumbar disc herniation : 1A (Execution is strongly recommended)

Nerve root block on lumbar spinal canal stenosis : 1B (Execution is strongly recommended)

3) Cervical spine disease : 2C (Execution is weakly recommended)

4) Herpes zoster pain : 2D (Execution is weakly recommended)

Commentary：

In Japan, nerve root block is a technique of puncturing into the nerve sheath and some think that it is different from transforaminal epidural injections but this concept is not consistently agreed upon. Under the scope of our search for these guidelines, nerve root block is used in some papers as a diagnostic block and in most of the research where treatment was the objective, they discussed transforaminal epidural injections but as they have been unable to clearly distinguish between the two, we will treat them as the same technique.

1) Nerve root block for the purpose of diagnosis

In a systematic review[1] of fifteen academic papers investigating the efficacy of diagnostic nerve root block performed for the purpose of identifying the impaired nerve root, they found that it had limited effects. Considering its adverse events, we recommend it only under limited conditions such as high-grade diagnosis prior to operation, in cases where disc herniation is present in several sites.

2) Lumbar spine diseases

In a systematic review[2] of eighteen RCTs on transforaminal epidural injections, they indicated its efficacy on lumbar spine diseases. There is strong evidence indicating its long-term efficacy on radiculopathy due to disc herniation, and there are some small-scale RCTs indicating the superiority of transforaminal epidural injections over caudal epidural injections and interlaminar epidural injections[3,4]. Long-term effects have also been described for lumbar spinal canal stenosis but there have been no high-quality RCTs on discogenic pain in the low back and failed back surgery syndrome (FBSS). Regarding the agent patients are injected with, administration of steroid for radiculopathy due to lumbar disc herniation is effective but there is some debate over whether the addition of steroid for other patient conditions has a superior effect or not. Careful consideration needs to be given to whether administration of steroid is applicable or not, taking into account the adverse events.

3) Cervical spine diseases

Although rare, there have been reports of severe complications with cervical transforaminal epidural injections [5]. The mechanism is apparently a brain stem and spinal cord infarction mainly through the intravascular injection of particulate steroid. Other possibilities include vasospasm due to the puncture needle. As a result, there have been few high-quality RCTs in recent years.
In a review of cervical radiculopathy, in five papers its efficacy (analgesic effect and avoidance of surgery) was indicated but the evidence was limited and we recommend performing the interlaminar approach for which there is even stronger evidence[6]. When performing cervical transforaminal epidural injections, particulate steroid is not used, and one needs to confirm the images of

the injected contrast media in real time on fluoroscopy.

In reports comparing the ultrasound guide method with the fluoroscopy method for cervical radiculopathy, in one RCT they reported similar efficacy up to twelve weeks later[7] and although conducted retrospectively, there is a report[8] that it had similar long-term effects one year later.

It remains unclear whether attempts to increase the safety of fluoroscopy conducted in real time, ultrasound guide and injection of nonparticulate steroid would reduce the risk of severe complications or not. On the one hand, there are some severe complications due to the interlaminar approach such as accidental dural puncture, spinal cord damage, and epidural hematoma/abscess and there is no evidence indicating that it is superior to the transforaminal approach which takes safety into consideration. As it is predicted that transforaminal epidural injections will show specifically more analgesic effects than interlaminar epidural injections, we need to continue to consider its usage by examining cautiously its applicability when performing this technique.

4) Herpes zoster pain

There are no high-quality RCTs related to herpes zoster pain but in terms of thoracolumbar, it is predicted to have similar or better effects to interlaminar epidural injections, and therefore is recommended to the same degree.

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Database	PubMed, MEDLINE, Cochrane Library
Period	2005-2017
Words searched by the combination with 'chronic pain'	transforaminal epidural injection, nerve root block
*Notes	We searched for 'chronic pain' and 'root block' on Ichushi. We narrowed down our search by guidelines, RCT, meta-analysis and systematic reviews, and focused on the most recent academic papers. Reference 8 was not through our search method but we added it due to its importance.

CQ24 : Are medial branch block and facet (zygapophyseal) joint injection effective in managing chronic pain?

Answer : Medial branch block is an essential procedure for diagnosing chronic neck pain, back pain and low back pain originating from the facet (zygapophyseal) joints. Furthermore, if performed under an accurate diagnosis, medial branch block has short-term and long-term effectiveness for treating chronic neck pain, back pain and low back pain originating from the facet (zygapophyseal) joints. Facet (zygapophyseal) joint injection is widely performed in order to diagnose and treat chronic neck pain, back pain and low back pain originating from the facet (zygapophyseal) joints but evidence indicating its utility is limited.

Summary of recommendation grade and overall evidence :

1) Medial branch block

Diagnosis of chronic neck pain, back pain, low back pain originating from facet (zygapophyseal) joints : 1B (Execution is strongly recommended)

Treatment of chronic neck pain, back pain, low back pain originating from facet (zygapophyseal) joints : 1B (Execution is strongly recommended)

2) Facet (zygapophyseal) joint injection

Diagnosis of chronic neck pain, back pain, low back pain originating from facet (zygapophyseal) joints : 2D (Execution is weakly recommended)

Treatment of chronic neck pain, back pain, low back pain originating from facet (zygapophyseal) joints : 2C (Execution is weakly recommended)

Commentary :

1) Medial branch block

Previous guidelines[1,2] describe that the prevalence of chronic facet pain is 36～67% in chronic neck pain, 34～48% in chronic back pain and 15～45% in chronic low back pain (often classified as non-specific low back pain). The mechanism of pain originating from the facet (zygapophyseal) joints has not

been completely clarified. Although there are various opinions about the diagnostic criteria, the diagnostic medial branch block to confirm pain relief is currently positioned as the gold standard procedure for the diagnosis of facet pain. The facet (zygapophyseal) joints are innervated by medial branches of dorsal rami. There are many studies which have investigated medial branch block for the diagnosis of chronic pain originating from the facet joints. Guidelines based on systematic review[2], have recommended that facet pain be diagnosed with the criterion standard of 75% or greater pain relief, and also recommended confirming reproducibility of the efficacy of the diagnostic medial branch block by performing it twice.

There were five non-placebo-controlled RCTs (1 cervical, 1 thoracic, 3 lumbar spine) which investigated the effectiveness of medial branch block for treating chronic facet pain[3-7]. The study on lumbar spine[7], showed that repeated medial branch block with corticosteroid and local anesthetic has equivalent long-term effects in comparison with medial branch radiofrequency thermocoagulation which is supported by much evidence. Other studies also reported similar effects of medial branch block regardless of whether corticosteroids were used or not. There were some two-year follow-up studies on neck pain, thoracic pain and low back pain [3,4,6]. The authors described that the patients in the studies experienced significant pain relief for two years, requiring approximately five to six treatments with an average relief of 14～19 weeks per episode of treatment. Furthermore, in these studies, diagnostic medial branch block was performed strictly for adequate patient enrollment in the studies. Therefore, we concluded that medial branch block, based on an accurate diagnosis, was an effective way to manage chronic neck pain, back pain and low back pain originating from facet (zygapophyseal) joints, both over the short-term and long-term.

RCT : randomized controlled trial

2) Facet (zygapophyseal) joint injection

Facet (zygapophyseal) joint injection (intraarticular injection) has also been performed as a diagnostic procedure for chronic pain originating from the facet joints, but there are no high-quality studies investigating its usefulness in the diagnosis of facet pain.

There are seven non-placebo-controlled RCTs (2 cervical, 5 lumbar spine) investigating the effectiveness of facet joint injection for treating chronic facet pain[8-14]. Studies on the cervical spine have shown conflicting results; in a study where the procedure was found to be ineffective[8], the only subjects investigated were whiplash-injury patients, while in a study in which the procedure was effective[9], there were some problems with how subjects were assigned into treatment and control groups and with evaluation. Studies on lumbar spine have also shown conflicting results. Results on the effectiveness of facet joint

injection were inconclusive because the injected agents or the subjects varied from one study to the next. In a systematic review[15] and a set of guidelines[2], authors evaluated that the evidence of facet joint injection for treating chronic facet pain was limited for both cervical and lumbar spine. In general, facet joint injection is often performed for acute pain or acute exacerbation of chronic pain originating from facet joints. Therefore, we need further studies evaluating the effectiveness of facet (zygapophyseal) joint injection for acute exacerbation of chronic facet pain.

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Database	PubMed, MEDLINE, Cochrane Library
Period	2005–2017
Words searched by the combination with 'chronic pain'	facet block, facet blocks, facet joint block, facet joint blocks, zygapophyseal joint block, zygapophyseal joint blocks, medial branch block, medial branch blocks, facet injection, facet injections, facet joint injection, facet joint injections, zygapophyseal joint injection, zygapophyseal joint injections, medial branch injection, medial branch injections
*Notes	We searched for 'chronic pain' ('facet joint injection' or 'medial branch block') on Ichushi. We narrowed it down by RCT, meta–analysis and systematic review and focused on the most recent academic papers. We searched for References 1, 3–5, 8, 10–15 by hand search and as they are important they were added.

CQ25 : Is stellate ganglion block effective in managing chronic pain?

SGB : stellate ganglion block

Answer : Stellate ganglion block (SGB) is often used, in clinical settings, for the purpose of alleviating pain for example in the head and neck area and upper extremities and there are many reports indicating its efficacy. However, there is no high–quality evidence except with complex regional pain syndrome (CRPS).

Summary of recommendation grades and overall evidence :

1) CRPS in the upper extremities : 2B (Execution is weakly recommended)
2) Preventing the transition to postherpetic neuralgia (PHN) in patients with herpes zoster : 2C (Execution is weakly recommended)
3) Pain due to peripheral vascular disease in the upper extremities, sympathetically maintained pain (SMP) following cervical spine surgery, cluster headache, various pains in the head and neck area : 2D (Execution is weakly recommended)

Commentary :

SGB is a type of nerve block widely used in other diseases apart from chronic pain such as in the head and neck area and in the upper extremities as well as vascular disorders in the upper extremities and facial paralysis.

1) CRPS in the upper extremities

There are several reports indicating the efficacy of CRPS in the upper extremities. A placebo-controlled double-blind study on a small number of subjects[1] indicated the utility of SGB. In a report targeting 22 patients with CRPS type I in the upper extremities[2], a significant improvement in pain and range of movement (ROM) of the wrist due to SGB was recognized and the improvement was more significant in the group with a shorter period of time (28 weeks or less, average 17.0±6.3 weeks), between onset of pain until treatment by SGB began, than in the group with a longer period of time (29 weeks or more, average 49.8±17.6 weeks). Furthermore, in cases where 16 weeks or more had passed since onset or skin blood flow had decreased by over 22% in comparison with normal subjects, there have been reports that SGB had low effects and there is a correlation between the effects of treatment and how early on treatment by SGB begins. Furthermore, in a comparison of a case series claiming that continual SGB is effective on patients with CRPS[4], a landmark method[5] and a method under fluoroscopy[6], there have been reports of a case series indicating the superiority of a method under ultrasound guidance, a case series indicating the efficacy of radiofrequency thermocoagulation[7] and reports on cases indicating the effects of the pulsed radiofrequency method[8]. In a review announced in 2011[9], the effects of SGB on CRPS was evaluated as 2B+(One or more RCTs, while methodologically flawed, demonstrated effectiveness. Benefits closely balanced with risk and burdens : Positive recommendation). Furthermore, there have also been several case reports indicating its efficacy on facial CRPS[10-12].

ROM : range of movement

2) Preventing the transition to postherpetic neuralgia (PHN) in patients with herpes zoster

There are reports indicating the efficacy of SGB on postherpetic neuralgia (PHN)[13] and, negative reports[14] as well. In a double-blinded RCT on the possibility of preventing the transition from acute-stage herpes zoster to postherpetic neuralgia[15], they targeted 64 patients (50 years old or more) with acute-stage herpes zoster and found that the frequency of transitions to PHN was significantly lower.

PHN : postherpetic neuralgia

3) Pain due to peripheral vascular disease in the upper extremities, sympathetically maintained pain (SMP) following cervical spine surgery, cluster headache, various pains in the head and neck area

There have been reports elsewhere indicating its efficacy on pain due to peripheral vascular disease in the upper extremities[16], sympathetically maintained pain (SMP) following cervical spine surgery[17], There have also been reports indicating its efficacy on cluster headache[18], and reports indicating the efficacy of radiofrequency thermocoagulation[19] on various types of pain, for example in the head and neck area but no high-quality RCTs exist.

RCT : randomized controlled trial

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Database	PubMed, MEDLINE, Cochrane Library
Period	2005–2017
Words searched by the combination with 'chronic pain'	stellate ganglion block, cervical sympathetic block
*Notes	We searched for 'chronic pain' and 'stellate ganglion block' on Ichushi. We narrowed down our search by RCT, meta-analysis and systematic review and focused on the most recent academic papers. References 1–17 and 19 were not a result of our search method but were added due to their importance.

CQ26 : Is sympathetic ganglion block effective in managing chronic pain?

Answer : Thoracic sympathetic ganglion block and lumbar sympathetic ganglion block have often been used in clinical settings for the purpose of alleviating pain from impaired blood flow, complex regional pain syndrome (CRPS), and pain due to sympathetically maintained pain (SMP), and there are also many reports indicating its efficacy. However, there is little high-quality evidence.

CRPS : complex regional pain syndrome
SMP : sympathetically maintained pain

Summary of recommendation grades and overall evidence :

1) Thoracic sympathetic ganglion block

CRPS in the upper extremities : 2B (Execution is weakly recommended)

Pain due to vascular disorders of the upper extremities, post-traumatic syndrome, postherpetic neuralgia, failed spinal surgery syndrome : 2D (Execution is weakly recommended)

2) Lumbar sympathetic ganglion block

Pain due to vascular disorders in the lower extremities : 1B (Execution is strongly recommended)

Lower extremity CRPS, failed spinal surgery syndrome, sympathetically maintained pain (SMP), diabetic neuropathy, lumbar spinal stenosis : 2D (Execution is weakly recommended)

Commentary :

In the management of chronic pain, sympathetic ganglion block is often used in clinical settings for the purpose of alleviating pain due to vascular disorders and pain involved in the sympathetic afferent pathways. We have established a separate CQ about stellate ganglion block, and in this CQ, we will discuss thoracic sympathetic ganglion block and lumbar sympathetic ganglion block.

1) Thoracic sympathetic ganglion block

Thoracic sympathetic ganglion block is used for example to treat CRPS, postherpic neuralgia (PHN), phantom breast pain and pain due to vascular disorders in the upper extremities. They have experienced cases where it was effective in clinical settings in the past but evidence on its efficacy is limited. In a RCT investigating the effects of thoracic sympathetic ganglion block on 36 subjects with CRPS[1], in the group of patients who had undergone thoracic sympathetic ganglion block, the strength of pain twelve months later, the McGill Pain Questionnaire scores, the Neuropathic Pain Symptom Inventory values and the Hospital Anxiety and Depression Scale (HADS) were significantly lower. Furthermore, in a study targeting 51 patients with chronic pain of the upper extremities (CRPS, post-traumatic syndrome, PHN, failed spinal surgery syndrome) they reported that the thoracic sympathetic ganglion block had shown to be highly effective, especially in patients in which onset had occurred within the last year[2]. In a controlled study on the effects of percutaneous thoracic sympathetic ganglion high-frequency thermocoagulation on vascular disorders of the upper extremities[3], they compared 50 subjects with Raynaud's disease who had been classified into two groups ; those who underwent conventional T_2 and T_3 high-frequency thermocoagulation and those who only underwent T_2 thermocoagulation as well being administered with an injection of 6% phenol. In both groups, they recognized a significant reduction in pain, a rise in skin temperature in the upper extremities and an improvement in QOL but outside of the duration of the procedure, there was no recognizable significant difference. There have been reports indicating the efficacy of thoracic sympathectomy by open thoracotomy[4], but no high-quality RCTs exist. There have also been reports on thoracoscopic sympathectomy[5,6] but were unable to conclude that it was sufficiently effective over the long term. As seen above, evidence is insufficient and even in a systematic review conducted in 2011[7], they have not reached any definite conclusions on its efficacy.

PHN : postherpetic neuralgia

video associated endoscopic thoracic sympathectomy

2) Lumbar sympathetic ganglion block

In clinical settings, lumbar sympathetic ganglion block is often used for the purpose of alleviating pain due to blood flow disorders of the lower extremities and pain from SMP but there is little high-quality evidence. In terms of managing pain, there have been reports indicating its efficacy in diagnosing SMP as a diagnostic block[8]. There is a RCT indicating the efficacy of lumbar sympathetic block for pain due to vascular disorders of the lower extremities[9]. Studying 41 ischemic limbs, they compared a group undergoing chemical lumbar sympathetic block from phenol with a placebo-controlled group administered with a local anaesthetic, and found that pain six months later had significantly improved in the phenol block group. There are several other reports in-

SMP : sympathetically maintained pain

dicating the efficacy of chemical lumbar sympathetic block[10,11]. As for diabetes, there have been reports that blocks using phenol were useful on diabetic lower-limb ischemia[12], several reports that they had reduced pain and promoted the healing of ulcers[13,14], and in recent years, it has alleviated intractable pain accompanying diabetic neuropathy and improved QOL[15]. There are no RCTs which have investigated the effects of lumbar sympathetic block on lumbar spinal canal stenosis. As for reports which have shown its efficacy, there is one report indicating the possibility of its effectiveness on cases of cauda equina lesion of short-term duration[16] and it had an effective rate of 48.4% in 62 cases of lumbar spinal canal stenosis, had a high effective rate in cases who also felt cold in their lower limbs, and there are also reports of a recognizable improvement in intermittent claudication[17]. There are no RCTs which have investigated the effects of a lumbar sympathetic ganglion block on CRPS but there are several reports indicating its efficacy[18-19]. In a review released in 2016[20], on the effect of lumbar sympathetic ganglion block using a local anaesthetic on CRPS, they were unable to conclude that it was effective. Apart from this, there have also been reports indicating its efficacy on neuropathic pain[21], SMP[21-23], lower-limb pain[24], and pain due to rectal tenesmus.

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Database	PubMed, MEDLINE, Cochrane Library
Period	2005–2017
Words searched by the combination with 'chronic pain'	sympathetic nerve block
*Notes	We searched for 'chronic pain' and 'sympathetic block' on Ichushi. We then narrowed down by guidelines, RCT, meta-analysis, and systematic review and focused on the most recent academic papers. References 1 and 3–25 were not through our search method but were added because of their importance.

CQ27 : Is a trigger point injection effective in managing chronic pain?

Answer : There is not enough evidence to conclude that a trigger point injection is effective but there is evidence of its efficacy over the short-term. As long as experienced specialists perform the procedure, it is relatively safe and easy. Thus it can be used to help treat chronic pain. When used, it is necessary to consider which drug to use and how frequently it should be administered.

Summary of recommendation grades and overall evidence : 2C (Execution is weakly recommended)

Commentary :

TPI : trigger point injection

A systematic review of fifteen RCTs investigating the utility of a trigger point injection (TPI) in treating chronic pain, including various diseases, was unable to reach a conclusion due to the small sample sizes used and lack of methodological uniformity (such as eligibility, site of injection, type and dosage of drug used, volume and number of injections etc.)[1]. A systematic review of RCTs with placebo drugs showed no difference in effectiveness by injected drug (local anaesthetic, steroid, botulinus toxin) and dry needling (procedure in which patient is punctured, not injected with the drug)[2]. Use of a local anaesthetic is expected to have alleviative effects on pain at the injection site. As there is no strong evidence recommending the use of a steroid or botulinus toxin, we need to consider issues such as their side effects and patients being ineligible for insurance coverage. A systematic review of nineteen RCTs showed the efficacy of TPI on the trigger point for myofascial pain syndrome (MPS)[3], but they reported that it was mostly short-term effects. There are also reviews of cases of MPS in which TPI had displayed short-term effects but who also had received long-term effects through the injection of botulinus toxin[4], but this usage is not covered under the Japanese insurance system and therefore we cannot recommend it. A review of three RCTs on chronic pain, including tension-type headache (TTH)[5], showed that it was effective over the short-term. According to a systematic review of eighteen RCTs on chronic low back pain[6],

MPS : myofascial pain syndrome

they indicated no difference in reduction in pain or improvement in function compared with a placebo injection and so there is insufficient evidence to draw a conclusion[7]. There is a systematic review in which TPI through local anaesthetic (local steroid injection) was useful not only for the diagnosis of acute cutaneous nerve entrapment syndrome (ACNES) but also helped reduce pain over the long-term[8]. However, with only one RCT to date, the evidence is low.

ACNES：anterior cutaneous nerve entrapment syndrome

It is a widely-performed procedure in clinical settings and is believed to be highly safe but when performed, we must constantly be evaluating its effects and we should not continue to aimlessly administer it over the long-term.

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Database	PubMed, MEDLINE, Cochrane Library
Period	2005-2017
Words searched by the combination with 'chronic pain'	trigger point injection
*Notes	We searched for 'chronic pain' and 'trigger point block' on Ichushi. We narrowed our search down by guidelines, RCT, meta-analysis and systematic review and focused on the most recent academic papers.

CQ28 : Is radiofrequency denervation effective in managing chronic pain?

Answer : Radiofrequency denervation (RF), is an effective treatment on chronic neck and low back pain originating from facet (zygapophyseal) joints, chronic hip, low back and buttock pain originating from sacroiliac joint, and trigeminal neuralgia. It is possibly also effective on ischemic pain in the extremi-

RF：radiofrequency thermocoagulation/denervation

ties, complex regional pain syndrome (CRPS), and chronic knee pain due to knee osteoarthritis, however there is limited evidence on its effectiveness.

Summary of recommendation grades and overall evidence :

1) **Chronic neck and low back pain originating from facet (zygapophyseal) joints : 1A** (Execution is strongly recommended)
2) **Chronic hip, low back and buttock pain originating from sacroiliac joint : 2B** (Execution is weakly recommended)
3) **Trigeminal neuralgia : 1B** (Execution is strongly recommended)
4) **Ischemic pain in the extremities, complex regional pain syndrome (CRPS), and chronic knee pain due to knee osteoarthritis : 2C** (Execution is weakly recommended)

Commentary :

1) Chronic neck and low back pain originating from facet (zygapophyseal) joints

RCT : randomized controlled trial

Facet (zygapophyseal) joints are innervated by the medial branches of the dorsal rami. There were four RCTs comparing the effectiveness of radiofrequency denervation (RF) of medial branches of the dorsal rami with sham therapy (needle insertion without RF) for chronic low back pain originating from facet joints, three studies[1,3,4] describing its short-term and long-term effectiveness, and one study[2] reporting that it was ineffective. Furthermore, eleven systematic reviews and one set of guidelines[16], which were reported after 2005, supported the short-term and the long-term effectiveness of the medial branch RF for chronic low back pain originating from facet joints[5-15]. There is one RCT comparing the effectiveness of medial branch RF with sham therapy for chronic cervical pain originating from facet joints, which indicated the short-term and the long-term effectiveness of the medial branch RF[17]. Moreover, six systematic reviews[6,8,9,13,18,19] and one set of guidelines[16], which were reported after 2005, supported the short-term and the long-term effectiveness of the medial branch RF for chronic cervical pain originating from facet joints.

2) Chronic hip, low back and buttock pain originating from the sacroiliac joint

There were two RCTs which compared the effectiveness of RF of S_{1-3} lateral branches of the sacral nerves and L_5 (+L_4) medial branches of the dorsal rami with sham therapy for chronic hip, low back and buttock pain originating from the sacroiliac joint (sacroiliac joint complex). They described the short-term and the long-term effectiveness of the sacroiliac joint RF[20,21]. In these studies, they used cooled radiofrequency system which is not currently approved in Japan. A study comparing the effectiveness of conventional RF with cooled RF[22], showed similar effects for both treatments. Furthermore, since 2005, there

have been six systematic reviews[11,23-27] and one set of guidelines[16], on chronic hip, low back and buttock pain originating from the sacroiliac joint (sacroiliac joint complex), and although they supported the effectiveness of cooled RF on the medial branch of the dorsal ramus and the posterior branches of the sacral nerves, they mentioned that further research was required.

3) Trigeminal neuralgia

In the treatment of trigeminal neuralgia, RF is performed on the Gasserian ganglion (trigeminal ganglion) and the trigeminal nerves (supraorbital nerve, supratrochlear nerve, maxillary nerve, infraorbital nerve, mandibular nerve, and mental nerve). In the studies regarding Gasserian ganglion RF for trigeminal neuralgia, there was no RCT comparing the effectiveness of it with sham therapy. In four relevant RCTs without sham therapy, they compared the effects of different methods of needle guidance[28], different approaches of radiofrequency treatment (vs Gasserian ganglion pulsed radiofrequency (PRF)[29], vs supraorbital nerve RF[30]), and different treatment time of combined PRF[31]. These studies showed that despite a high incidence of dysesthesia, Gasserian ganglion RF was an effective treatment with a high success rate. In studies on trigeminal nerve peripheral branch RF for trigeminal neuralgia, there was no RCT comparing the effectiveness of it with sham therapy. In one relevant RCT, they compared its effects with Gasserian ganglion RF. This study showed that supraorbital nerve RF displayed similar effects to the Gasserian ganglion RF for first division trigeminal neuralgia[30]. Furthermore, since 2005, there has been one systematic review[32] and four sets of guidelines[33-36] on the effects of RF on trigeminal neuralgia. In the systematic review[32], as there was poor evidence to compare the effectiveness of interventional treatments for trigeminal neuralgia, they stated that they were unable to conclude whether interventional treatments including RF were effective or not. In the guidelines on trigeminal neuralgia management[33], they concluded that Gasserian ganglion RF was an effective treatment, the effectiveness of trigeminal nerve peripheral branch RF on trigeminal neuralgia has been evaluated as insufficient, and the early application of interventional treatments including RF might be recommended in pharmacotherapy-resistant patients. In the guidelines for interventional treatment of neuropathic pain[34], they were unable to draw conclusions about the effectiveness of interventional treatments including RF for trigeminal neuralgia because of the small amount of high-quality evidence. However, they mentioned that it should be considered for pharmacotherapy-resistant cases. Even in the guidelines on pharmacotherapy for neuropathic pain including trigeminal neuralgia[35], they recommend considering interventional treatments including RF in cases where first-line drugs such as carbamazepine prove to be ineffective.

4) Ischemic pain in the extremities, complex regional pain syndrome (CRPS), and chronic knee pain due to knee osteoarthritis

Other reported indications of RF for chronic pain, apart from those already mentioned above, are thoracic and lumbar sympathetic RF for CRPS and ischemic pain in the extremities, and genicular nerve RF for chronic knee pain due to knee osteoarthritis. We have excluded intradiscal radiofrequency thermocoagulation for discogenic low back pain from this CQ, as strictly speaking it does not qualify as a nerve block. In RCTs verifying the effects of a thoracic and lumbar sympathetic RF for ischemic pain in the extremities and CRPS, there was no study compared with sham therapy. With thoracic sympathetic RF for Raynaud's syndrome of the upper extremities, there was a study comparing the effect of RF monotherapy with RF + phenol injection treatments[36], and with lumbar sympathetic RF for lower-limb CRPS, there was a study comparing the effect of RF with phenol block[37] ; both studies showing the long-term analgesic effects of RF. There was also one RCT comparing the effectiveness of genicular nerve RF with sham therapy for chronic knee pain due to knee osteoarthritis. This study described that genicular nerve RF improved pain and activities of daily living (ADL) over the long-term compared with sham therapy[38]. These RF treatments have been insufficiently evaluated in systematic reviews and guidelines, and while it is possible that RF treatments are effective, it is supported by limited evidence.

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Database	PubMed, MEDLINE, Cochrane Library
Timing	2005-2017
Words searched by the combination with 'chronic pain'	radiofrequency
*Notes	We searched for 'chronic pain' and 'radiofrequency denervation' on Ichushi. We narrowed down our search by RCT, meta-analysis, and systematic review, and focused on the most recent academic papers. References 1-7, 9, 10, 13-15, 17-31, 33-37 were searched by hand and were added due to their importance.

CQ29 : Is pulsed radiofrequency treatment effective in managing chronic pain?

Answer : Pulsed radiofrequency (PRF) treatment has been reported as a highly safe and effective tool to manage chronic cervical radiculopathy, postherpetic neuralgia (PHN) and chronic shoulder joint pain in the short and long term (at least for three months), and therefore PRF should be selected to manage these pain conditions. Radiofrequency thermocoagulation (RF) is also thought to be the prioritized form of treatment for managing pain deriving from the lumbar facet joints and idiopathic trigeminal neuralgia. Further investigation is needed to indicate its efficacy for other pain conditions (such as lumbar radiculopathy and occipital neuralgia, cervicogenic headache, and chronic knee joint pain), optimal duration of application, and parameters.

PRF : puled radiofrequency

PHN : postherpetic neuralgia

RF : radiofrequency thermocoagulation/ denervation

Summary of recommendation grades and overall evidence :

1) Radiculopathy
   - Cervical radiculopathy : 1A (Execution is strongly recommended)
   - Lumbar radiculopathy : 2C (Execution is weakly recommended)
2) Herpes zoster-associated pain
   - PHN : 1A (Execution is strongly recommended)
   - Preventing transition to PHN (herpes zoster pain) : 2C (Execution is weakly recommended)
3) Chronic shoulder joint pain : 1B (Execution is strongly recommended)
4) Patient conditions in which RF is prioritized (pain deriving from the lumbar facet joints, idiopathic trigeminal neuralgia) : 2B (Execution is weakly recommended)
5) Occipital neuralgia, cervicogenic headache, chronic knee joint pain] : 2C (Execution is weakly recommended)

ZAP : zoster-associated pain

Commentary :

There are several randomized controlled trials (RCTs) and prospective comparative studies demonstrating the efficacy of PRF for chronic pain. In particular, recent meta-analysis and systematic reviews revealed that performing PRF once for patients with cervical radiculopathy, PHN, and chronic shoulder joint pain, was a highly safe way to provide pain relief for at least twelve weeks. Therefore, we propose that PRF should be selected mainly for management of the chronic pain conditions listed above. However, there is no evidence for the optimal duration, target and parameters of PRF, so it warrants further investigation in future.

RCT : randomized controlled trial

1) Radiculopathy

In a double-blinded RCT[1] on PRF for cervical radiculopathy, the PRF group

DRG : dorsal root ganglion
VAS : visual analogue scale

(eleven cases), in which subjects underwent PRF on the dorsal root ganglion (DRG), showed significantly better outcomes with regard to the global perceived effect and pain intensity (visual analogue scale, VAS) than the sham group (twelve cases) over a six-month period. In contrast, a placebo-controlled double-blinded RCT on PRF for lumbar radiculopathy[2] compared the DRG-PRF group (sixteen cases) and the placebo group (fifteen cases) over a three-month period, and reported no significant difference. Furthermore, a systematic review in 2016[3] investigating the efficacy of PRF for the management of pain associated with different spinal conditions, concluded that while the use of PRF on the DRG is effective in cases of cervical radiculopathy, further investigation into its efficacy on lumbar radiculopathy is required. Moreover, in a meta-analysis conducted in 2015 on the efficacy of PRF for neuropathic pain[4], as they had analyzed the efficacy of PRF for neuropathic pain without classifying cases into cervical or lumbosacral radiculopathy, they were unable to show whether PRF was effective for the management of radiculopathy or not. As seen above, performing PRF once on the DRG could be effective for cervical radiculopathy over the long-term (for at least three months). However, further investigation into its efficacy for lumbosacral radiculopathy is required.

2) Herpes zoster-associated pain

There is one placebo-controlled double-blinded RCT on thoracic PHN. In this study of PHN[5], they compared the group (48 cases) who underwent PRF on the peripheral nerve (intercostal nerve) with the group who underwent a sham treatment (48 cases) over a six-month period[5], and demonstrated a significant improvement in pain intensity (VAS), physical function and QOL (SF-36). Furthermore, a meta-analysis of twelve RCTs on the efficacy of PRF for neuropathic pain[4], showed PRF to be effective on PHN and a safe form of treatment. In a retrospective study[6] targeting 58 patients with ZAP who underwent PRF on DRG, they reported a significantly lower intensity of pain (numerical rating scale, NRS) in the group of subjects (29 cases) who underwent PRF in an acute phase (90 days or less) than those subjects (29 cases) who underwent PRF in a chronic phase (90 days or more). Overall, we could say PRF is a recommended treatment for PHN. Further investigation is required on differences in its effects according to the site where PRF is performed, and in its efficacy on herpes zoster-associated pain from the acute phase to the subacute phase.

NRS : numerical rating scale

3) Chronic shoulder joint pain

According to a systematic review[7] discussing five RCTs which investigated the effects of PRF on chronic shoulder joint pain, PRF on the suprascapular nerve was effective on chronic shoulder joint pain for at least twelve weeks, and showed high safety because no complications were reported. In a RCT on

adhesive capsulitis[8], a group (21 cases) who underwent twelve weeks of rehabilitation as well as PRF on suprascapular nerve reported a significantly higher improvement in VAS and restricted range of motion (ROM) of the shoulder joint, compared with a group (21 cases) who only underwent rehabilitation. In a single-blinded RCT on patients with shoulder joint pain persisting for three months or more, they compared a group who underwent PRF on the suprascapular nerve (25 cases) with a group who were administered with an intra-articular steroid (20 mg of triamcinolone) injection (25 cases) and reported almost the same results for VAS and shoulder joint function between the two groups up to 12 weeks later[9].

4) Patient conditions in which RF is prioritized (pain deriving from the lumbar facet joints, idiopathic trigeminal neuralgia)

Regarding pain deriving from the lumbar facet joints and idiopathic trigeminal neuralgia, they reported less effects with PRF, than with a conventional nerve block using RF[3,10]. On the other hand, by using PRF in combination with RF, they also reported a lower frequency of complications due to nerve damage and shorter time until recovery[11]. Therefore, using PRF is suitable in some cases.

5) Occipital neuralgia, cervicogenic headache, chronic knee joint pain

There are a large number of studies[12] indicating the efficacy of PRF for pain conditions such as occipital neuralgia, cervicogenic headache and chronic knee joint pain. However, there are few studies of high-quality and because the existing evidence remains unclear, PRF has only been given a weak recommendation. On the other hand, because the temperature at the needle tip under PRF is maintained below 42℃, there is a low possibility of nerve damage, and there have been no reports of complications to date. Therefore, overall we can say that PRF is a highly safe tool for chronic pain management[12] and in clinical settings, nothing has prevented the use of PRF for the conditions mentioned above but further research is also desirable.

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Database	PubMed, MEDLINE, Cochrane Library
Period	2005-2017
Words searched by the combination with 'chronic pain'	pulsed radiofrequency
*Notes	We searched for 'pulsed radiofrequency' on Ichushi. We then narrowed our search down by RCT, meta-analysis and systematic review, and focused on the most recent academic papers and uncovered 42 references on chronic pain. Reference 6 is a report on pain between the acute and sub-acute stages but we have added it because we judged that it was important.

CQ30 : Are spring-coil catheters, and epiduroscopy effective in managing chronic pain?

Answer : Treatment using spring-coil catheter is effective on chronic low back and lower-limb pain. The only reports of its efficacy on chronic cervicobrachial pain are observational studies and so as its level of safety has not been established, careful judgment about its applicability is necessary. Treatment using epiduroscopy is highly useful on the adhesion of the epidural space as a cause of chronic low back and lower-limb pain and useful in diagnosing the site which is highly responsible for the pain. It is highly effective in treating lumbar failed back surgery syndrome (FBSS) but there is insufficient evidence of its effects on lumbar spinal canal stenosis, and lumbar disc herniation.

Summary of recommendation grades and overall evidence :

1) Spring-coil catheter

Chronic low back and lower-limb pain : 1B (Execution is strongly recommended)

Chronic cervicobrachial pain : 2C (Execution is weakly recommended)

2) Epiduroscopy

Lumbar FBSS : 2B (Execution is weakly recommended)

Lumbar spinal canal stenosis, other, intractable low back and inferior-limb pain : 2C (Execution is weakly recommended)

Commentary :

1) Spring-coil catheter

Epidural neuroplasty and epidural adhesiolysis by spring-coil catheter, and epidural adhesiolysis by epiduroscopy, are forms of interventional therapy for pain such as low back and inferior-limb pain and cervicobrachial pain as accompanying pain which is not responding to conservative medical treatment.

In a systematic review and meta-analysis released in 2016 on spring-coil catheters[1], they reported strong evidence of the effect of epidural neuroplasty and epidural adhesiolysis on chronic intractable low back and inferior-limb pain. Patients with chronic radiculopathy, improved significantly at three months, six months, and twelve months in terms of their Oswestry Disability Index (ODI) scores and VAS scores, compared with the placebo treatment (an indwelling catheter was placed under the skin, and patients were injected with normal saline solution)[2]. In a report on patients with chronic low back and inferior-limb pain, the VAS scores as well as the ODI scores significantly decreased after three months in the epidural neuroplasty group in contrast to the group that underwent physiotherapy, and at twelve months after the procedure, these results persisted[3]. In patients with lumbar FBSS, compared with patients who received caudal epidural injection (steroid), VAS had improved significantly at one week, one month and six months[4]. There is a report in which NRS and ODI had significantly improved at three months, six months, and twelve months, in comparison with caudal epidural injection (a local anaesthetic and steroid and 0.9%[w/v] sodium chloride solution [saline])[5], and a report showing a significant improvement in NRS up to two years later and a significant improvement in ODI up to one year later[6]. In a study on patients with spinal canal stenosis, NRS and ODI significantly improved at three months, six months and twelve months, in comparison with caudal epidural injection (a local anaesthetic and steroid and 0.9%[w/v] sodium chloride solution [saline])[7]. In this way, we can see strong evidence regarding low back and inferior-limb pain but due to differences in what is covered under the insurance system overseas and in Japan, we need to consider that there are differences

VAS : visual analogue scale

NRS : numerical rating scale

in the drugs used. There is an observation study reporting its efficacy on cervicobrachial pain[8] and another report on its efficacy on sub-acute stage cervicobrachial pain[9]. However, these are only observation studies and as there are no RCT reports, its effects and level of safety remain unclear. Therefore, we are waiting for further research to be conducted.

2) Epiduroscopy

Epiduroscopy has high diagnostic value, and compared with lumbar MRI, it allows us to make a diagnosis of adhesion to the epidural space as a cause of intractable chronic low back and lower-extremity pain and also the site which is highly responsible for the pain. In a report on 78 cases of patients with lumbar FBSS, while they reported diagnosis of approximately 16% of cases of adhesion to the same site by MRI, in approximately 90% of the cases, adhesion was recognized on epiduroscopy, and additionally, they reported that they could diagnose the site which was responsible for the pain[10]. According to a report in 2005 on the effects on patients with intractable chronic low back and lower-extremity pain (many of which were FBSS patients), in a RCT comparing adhesiolysis by epiduroscopy with caudal block[11], by epiduroscopy they were able to diagnose with certainty the site responsible for the pain, and by administering patients with local anaesthetic and steroid after adhesiolysis of the site, patients experienced a significant alleviation of pain for over six months or more. In another observational study released in 2014 on 114 patients with FBSS[12], in which they compared the effects of an epiduroscopy and a transforaminal epidural injection, six months later[12], there was a significant recognizable improvement in low back NRS and lower-extremity NRS and ODI in the epiduroscopy group, compared with prior to the procedure and its rate of efficacy was higher than in the group administered with a transforaminal epidural injection. Furthermore, epiduroscopy was more effective in patients who had undergone decompression surgery than in spinal fusion surgery.

Also, there are several reports which have shown the efficacy of epiduroscopy on lumbar FBSS[13-15], and a report indicating its efficacy on chronic sciatic nerve pain[16]. In an observational study[17] released in 2004 on the effects of adhesiolysis by epiduroscopy in patients with lumbar spinal canal stenosis, adhesiolysis by epiduroscopy was performed on patients with lumbar spinal canal stenosis who failed to respond to conservative medical treatment, and they reported a significant improvement in pain within one year for those with low back pain, within one year for those with lower-extremity pain of the nerve-root type and within three months for those of the cauda-equina type. At the current stage, there are no reports on the evidence of effects of epiduroscopy on lumbar disc hernia. In a systematic review and meta-analysis released in 2016[1], they said that the amount of evidence supporting adhesiolysis by epi-

duroscopy is currently limited, and therefore mentioned the need to accumulate high-quality data on its technical issues and applicability.

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Database	PubMed, MEDLINE, Cochrane Library
Period	2005–2017
Words searched by the combination with 'chronic pain'	Racz catheter, epidural neuroplasty, epidural adhesiolysis, epiduroscopy, endoscopic adhesiolysis
*Notes	We searched for 'chronic pain' and 'Racz catheter' on Ichushi. We narrowed down our search by RCT, meta-analysis, systematic review and review but there were no references which applied. References 1–9 were not based on our search method but were added due to their importance. We searched for 'chronic pain' and 'epiduroscopy' on Ichushi. We narrowed our search down by guidelines, RCT, meta-analysis and systematic review, and focused on the most recent academic papers. References 2017 were not based on our search method were added due to their importance.

CQ31 : Is spinal cord stimulation effective in managing chronic pain?

SCS : spinal cord stimulation

FBSS : failed back surgery syndrome

PDPN : painful diabetic peripheral neuropathy

Answer : Spinal cord stimulation (SCS) has a unique analgesic mechanism, based on neuromodulation, which has the value of being trialed on patients with chronic pain in which other forms of treatment proved to be insufficient. In particular, its utility on patients with failed back surgery syndrome (FBSS), peripheral vascular disorders, and painful diabetic peripheral neuropathy (PDPN) has been indicated. It is different from other forms of interventional therapy in that it is not directly invasive on the site of pain and in that it is a reversible form of treatment. These are the advantages of spinal cord stimulation.

Summary of recommendation grades and overall evidence :

1) Failed back surgery syndrome (FBSS) : 1B (Execution is strongly recommended)

2) Peripheral vascular disorders : 1B (Execution is strongly recommended)

3) Painful diabetic peripheral neuropathy (PDPN) : 2B (Execution is weakly recommended)

CPSP : central post-stroke pain

4) Central post-stroke pain (CPSP) : 2C (Execution is weakly recommended)

5) Pain in the extremities due to multiple sclerosis : 2C (Execution is weakly recommended)

6) Post-spinal cord injury pain : 2C (Execution is weakly recommended)

CRPS : complex regional pain syndrome

7) Complex regional pain syndrome (CRPS) type Ⅰ : 2C (Execution is weakly recommended)

CRPS type Ⅱ : 2D (Execution is weakly recommended)

8) Phantom limb pain : 2C (Execution is weakly recommended)

9) Postcervical spine surgery cervico-omo-brachial pain : 2D (Execution is weakly recommended)

10) Brachial plexus avulsion injury : 2D (Execution is weakly recommended)

11) Postherpetic neuralgia : 2D (Execution is weakly recommended)

PHN : postherpetic neuralgia

12) Angina pectoris : 2D (Execution is weakly recommended)

Commentary :

1) Failed back surgery syndrome (FBSS)

There are six RCTs on FBSS, which have reported on the efficacy of tonic stimulation[1,2], the efficacy of burst stimulation[3], the efficacy of 10kHz high-frequency stimulation[4,5], and the efficacy of adaptive stimulation[6]. In a report comparing a group of patients who had undergone surgery again with a group who had undergone SCS, they claimed that it was more effective in the SCS group than in the group who had undergone surgery again[1]. In a RCT on a large number of facilities, they compared SCS with conservative forms of medical treatment, and reported a greater amount of pain relief, a larger improvement in quality of life (QOL) and a higher level of satisfaction in the SCS group than in the conservative medical treatment group[2]. With conventional tonic stimulation, they reported a sufficient level of efficacy but expect that the newer stimulation methods, which are burst stimulation and high-frequency stimulation, will have an even greater efficacy.

RCT : randomized controlled trial

adaptive stimulation : When the patient change positions, the stimulation level is automatically adjusted.

QOL : quality of life

2) Peripheral vascular disorders

There is a systematic review on a total of 444 patients from six reports on pain of the extremities due to peripheral vascular disorders[7]. The limb salvage rate one year after SCS was 83%, they recognized that pain had been alleviated and the dosages of analgesics had been significantly decreased. They reported that conservative medical treatments were ineffective, could not be applied for revascularization, that it could be applied in cases of ulcers which were 3cm in size or less, and that a transcutaneous partial pressure of oxygen (Tc_{PO_2}) of 10～30 mmHg was a selecting indicator for patients.

3) Painful diabetic peripheral neuropathy (PDPN)

There are two RCTs on pain of the extremities due to painful diabetic peripheral neuropathy (PDPN). In one study, 60 patients were enrolled and were randomly allocated into either a SCS group or a control group. After six months, the VAS scores in the SCS group had decreased from 73 to 31 but in the control group, there was no recognizable change from 67 to 67[8]. In the other RCT, 22 patients underwent test stimulation of SCS, and seventeen patients received an implant. Eleven out of these seventeen subjects (65%) reported a reduction in pain of 50% or more, which persisted for up to two years later[9].

4) Central post-stroke pain (CPSP)

There was a retrospective study on central post-stroke pain, which reported that it had been effective in seven subjects out of 30[10], and also another which report that it had been effective in three subjects out of 45 (7%)[11]. Although the efficacy rate is not high, before conducting invasive treatments such as deep brain stimulation (DBS) and motor cortex stimulation (MCS), it could be given some consideration as a form of treatment.

DBS : deep brain stimulation
MCS : motor cortex stimulation

5) Pain in the extremities due to multiple sclerosis (MS)

SCS : spinal cord stimulation

In a retrospective research study, out of 410 subjects who underwent SCS, seventeen subjects suffered from lower-extremity pain due to multiple sclerosis (MS), and fifteen of these subjects experienced a 50% or greater relief in pain over the long-term[12]. There is not a high level of evidence but it could be given some consideration when no other analgesic methods are available.

6) Post-spinal cord injury

In a retrospective research study on post-spinal cord injury, twelve subjects with incomplete spinal cord injury underwent SCS, and they reported that their NRS scores decreased from 9.9 to 3.6[13]. There is not a high level of evidence but it could be given some consideration when no other analgesic methods are available.

NRS : numerical rating scale

7) Complex regional pain syndrome (CRPS)

There are retrospective studies and RCTs on CRPS type Ⅰ. One group underwent a combination of SCS and physiotherapy while the other group only underwent physiotherapy. Six months later, while the level of pain in the SCS group had decreased in NRS by 2.4, it had increased in the physiotherapy group by 0.2. Therefore they reported[14] that it had significantly decreased in the SCS group. Two years later they had the same kind of results[15], but three years later, four years later, and five years later, there was no recognizable difference between the two groups[16]. There are only several case series on CRPS type Ⅱ suggesting the efficacy of SCS, so the level of evidence is not high. We can expect SCS to be effective on CRPS type Ⅰ but it is possible that it does not provide long-term effects. Currently studies are being conducted on whether burst stimulation and high-frequency stimulation improve efficacy or not[17]. We need to exercise careful judgment when it comes to its applicability for CRPS type Ⅱ.

8) Phantom limb pain

A systematic review has reported on its efficacy on phantom limb pain[18] but in each of these reports, the number of subjects is small and therefore the quality of evidence is not high.

9) Post-cervical spine surgery cervico-omo-brachial pain

There is a case series on post-cervical spine surgery cervico-omo-brachial

pain. Five subjects suffering from cervico-omo-brachial pain after cervical fusion according to a previous approach, underwent SCS, and four of these subjects reported pain relief of up to 70～90%[19]. It is possible that SCS might be effective on cervical pain and upper-limb pain following cervical spine surgery but there is no high quality evidence.

10) Brachial plexus avulsion injury

There are some retrospective research studies on brachial plexus avulsion injury[20,21]. Four subjects suffering from brachial plexus avulsion injury underwent a SCS trial and in all cases experienced alleviation of pain and therefore they underwent an implant procedure. Up to nine months following the procedure, their pain gradually became lighter and they reported a reduction in NRS scores, from a score of 9 prior to the procedure to 5.9 in the ninth-month following the procedure[20]. There is little high-quality evidence but it is possible that it is effective on upper-limb pain due to brachial plexus avulsion injury, and it should be given some consideration before patients undergo invasive treatments such as dorsal root entry zone lesion (DREZ).

DREZ : dorsal root entry zone lesion

11) Postherpetic neuralgia

There is prospective study on postherpetic neuralgia (PHN). 28 patients with PHN underwent SCS, and 23 subjects (82%) reported a significant improvement in pain[22]. The efficacy rate is not high but SCS could be given some consideration when no other analgesic methods are available.

12) Angina pectoris

Although this treatment is not eligible for coverage under the Japanese health insurance system, there have been reports on the efficacy of SCS in treating angina pectoris. In a review on treating patients with intractable angina pectoris, SCS decreased the number of angina pectoris attacks and was reported as a useful method for improving patient's QOL[23].

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severe angina pectoris : What does the evidence say? Future Cardiol 2011 ; 7 : 825–833

Database	PubMed, MEDLINE, Cochrane Library
Period	2005–2017
Words searched by the combination with 'chronic pain'	spinal cord stimulation
*Notes	We searched for 'chronic pain' and 'spinal cord stimulation' on Ichushi. We narrowed our search down by RCT, meta-analysis, systematic review and review and focused on the most recent academic papers. References 2, 4, 7–17, 19–23 were not from our search method but were added due to their importance.

CQ32 : Are intradiscal therapies effective in managing chronic pain?

Answer : An intradiscal steroid injection has limited efficacy on discogenic low back pain. There are several forms of intradiscal therapies, which are limited, but have been shown to be effective.

Summary of recommendation grades and overall evidence :

1) Diagnostic discography : 2C (Execution is weakly recommended)

2) Lumbar intradiscal steroid injection : 2C (Execution is weakly recommended)

3) Intradiscal therapies : 2C (Execution is weakly recommended)

Commentary :

1) Diagnostic discography

Injection into the lumbar intervertebral disc is used to diagnose discogenic low back pain and assumes that at the time of injection, inducement of pain is positive. According to the diagnostic standards[1] of the International Association for the Society of Pain (IASP), it is useful with analgesic effects by using a local anesthetic, can be continued for a suitable amount of time, and as long as it induces no pain by injection into adjoining intervertebral discs, it has high diagnostic value[2]. It can also be useful as a pre-surgical test[3]. There is some debate over its accuracy for diagnosis and furthermore, as it has been suggested that it may possibly help advance degenerative changes in the disc[4], its applicability needs to be given careful scrutiny. There have been almost no reports on thoracic intervertebral disc injections[5] but there is a review of 41 studies related to cervical intervertebral disc injections[6] and each one indicates its limited diagnostic effects.

IASP : International Association for the Study of Pain

2) Lumbar intradiscal steroid injection

As a form of treatment, there is a review[7] denying the efficacy of injecting steroid into the lumbar intervertebral disc with strong supporting evidence. On the other hand, there is also a RCT[8] indicating its short-term efficacy on discogenic low back pain accompanying modic changes in the vertebral body

RCT : randomized controlled trial

on MRI. It has limited applicability for the period of activity of discogenic low back pain accompanying inflammation of the endplate.

3) Intradiscal therapy

Intradiscal therapy is an intervention, in which a cannula is punctured into the intervertebral disc percutaneously, under fluoroscopy, but is shown to be of limited efficacy as there are few high-quality RCTs.

Percutaneous discectomy reduces intradiscal pressure by removing the nucleus pulposus. It has been shown to have therapeutic effects especially on the contained type of disc herniation which means herniated disc material remains below the posterior longitudinal ligament without leaking into epidural space (a disc protrusion and subligamentous extrusion). Automated percutaneous lumbar discectomy (APLD) is a system developed in 1985 with an automated suction-cutting device using pistons which removes the nucleus pulposus. There are no RCTs about it but there are many observational studies. In a review of nineteen studies[9], they showed that it was effective in 80% of cases out of a total of 5,515 patients one year later. Percutaneous disc decompression (PDD) is a system which uses an "Archimedian screw" to remove the nucleus pulposus, and uses a cannula with an outside diameter of 15mm, making it easy to perform with precision. In a review of three observational studies, which does not include any RCTs, they recognize its short-term and long-term effects, but evidence is limited[10].

PLDD : percutaneous laser disc decompression

Percutaneous laser disc decompression (PLDD) is a procedure for reducing intradiscal pressure. It reduces the volume of the area by vaporizing the nucleus pulposus watery material through laser irradiation. In a review of fifteen observational studies, they indicated its short-term and long-term efficacy on intervertebral disc hernia but there are no RCTs on it so evidence is limited[11].

IDET : intradiscal electrothermal treatment

Intradiscal electrothermal treatment (IDET) is performed on lumbar discogenic pain. A flexible heating element is inserted through a cannula and in a circular fashion alongside the annulus of the disc and the catheter's coil is placed on the site of lesion of the posterior annulus. Radiofrequency denervation (RF) is performed via the coil, causing changes in the nerves of the annulus and thereby reducing pain. In a recent review, there were two RCTs. In one of these studies, it was effective over the short-term in 40% of cases but in the other study, it did not prove to be effective, even though the level of evidence was low. In addition, there have been six observational studies, in which four of them it was found to be effective, one in which it was found to be negative and in the remaining study, the results were inconclusive. To sum up these studies, it is weakly recommended[12].

New interventions are also being trialed. There is a procedure, which has been named annulo-nucleoplasty, using radio waves. It uses one cannula to

surgically remove the nucleus pulposus with the aid of forceps and using a probe with a bent tip it performs nucleus ablation and annular modulation. In addition to the contained type of disc herniation, it is considerd to have shown its efficacy on low back pain due to degenerative intervertebral disc and there is an observational study in which it proved to be effective up to one year later[13]. Intradiscal pulsed radiofrequency (PRF), is a procedure, which brings pain relief by placing an active tip in the middle of the intervertebral disc and supplying RF. Its analgesic mechanism is unknown, but it is considered to be highly safe as it does not cause damage due to heat or tissue damage and there are several observational studies, which have reported on it. Fukui et al.[14], exposed exposed subjects, diagnosed with intervertebral lumbar disc pain, with PRF under discography, for 15 minutes and reported that it showed analgesic effects up to twelve months later. In future, we would like to see an accumulation of evidence on these types of procedures.

It is hard to conduct controlled studies on intradiscal therapies and although there is insufficient evidence, in cases in which conservative medical treatment proved to be ineffective, we might consider performing this treatment after careful deliberating its applicability. Regarding radiculopathy due to intervertebral disc herniation, contained type of disc herniation has good applicability but prior to procedure, as the quality of evidence is low, we recommend performing diagnostic blocks such as nerve root block and discography. As discogenic low back pain is hard to diagnose, through conducting discography in addition to the MRI findings on intervertebral disc degeneration, we need to clarify the lesions responsible and also properly differentiate other causing factors as well.

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Database	PubMed, MEDLINE, Cochrane Library
Period	2005–2017
Words searched by the combination with 'chronic pain'	lumbar discography
*Notes	We narrowed our search down by guidelines, RCT, meta–analysis and systematic review, and focused on the most recent academic papers. There are various procedures for intervertebral disc treatment so we ran a search for these one–by–one on PubMed.

CQ33 : Are intra–articular injections effective in managing chronic pain?

Answer : Evaluations of the effects of intra–articular steroid injection on osteoarthritis of the knee (knee OA) are uneven. It is effective over the short–term and long–term on adhesive capsulitis (periarthritis scapulohumeralis) and using steroid injection in combination with physiotherapy may possibly improve its efficacy. Its effects should be constantly evaluated and it is important not to continue injections over the long–term, without a particular purpose in mind. There are some RCTs showing that an intra–articular hyaluronic acid injection is effective on knee OA and adhesive capsulitis. However we cannot say that there is high–quality evidence and therefore more evidence needs to be compiled in future in order to draw conclusions. It is also useful to use an ultrasound device.

RCT : randomized controlled trial

Summary of recommendation grades and overall evidence :

1) Knee OA

Intra-articular steroid injection : 2C (Execution is weakly recommended)

Intra-articular hyaluronic acid injection : 2C (Execution is weakly recommended)

2) Adhesive capsulitis

Intra-articular steroid injection : 2C (Execution is weakly recommended)

Intra-articular hyaluronic acid injection : 2C (Execution is weakly recommended)

Subacromial bursa steroid injection : 2C (Execution is weakly recommended)

Commentary :

In this CQ, we will discuss intra-articular injections on knee OA and adhesive capsulitis. There are many RCTs and meta-analyses on the efficacy of intra-articular injection on knee OA and adhesive capsulitis.

1) Knee OA

In the 'Osteoarthritis Research Society International (OARSI) guidelines'[1], they compared the effects of intra-articular steroid injection into the knee with intra-articular hyaluronic acid injection into the knee in patients with knee OA, and concluded that the early-stage pain-suppressing effects of the intra-articular steroid injection into the knee were higher than those from the intra-articular hyaluronic acid injection into the knee. In contrast, in a meta-analysis comparing the longer-term effects of both, they reported that from twelve weeks onwards, intra-articular hyaluronic acid injection into the knee displayed more significant pain-suppressing effects than an intra-articular steroid injection into the knee[2]. In a meta-analysis of twelve studies on OA, in which they compared both injections[3], they concluded that over the short-term (within one month), an intra-articular steroid injection into the knee showed more significant analgesic effects than an intra-articular hyaluronic acid injection into the knee, but, on the contrary, over the longer term of six months or more, an intra-articular hyaluronic acid injection into the knee showed more significant effects. There was no significant difference between the two groups in terms of the number of times analgesics were used on an as-needed basis or in terms of range of motion (ROM) of the joint. This indicates that an intra-articular steroid injection may be effective over the short-term while an intra-articular hyaluronic acid injection may be effective over the long-term. On the other hand, there is a systematic review[4] which showed no significant difference over the short-term in pain-suppressing effects with an intra-articular steroid injection into the knee[4], and so there is an uneven perception of its effects.

The 'OARSI guidelines'[1] have also discussed the safety of intra-articular steroid injection into the knee and there is a RCT[5] which showed a recognizable reduction in cartilage due to regular intra-articular steroid injection into the

knee, and therefore steroid injections should be limited to single doses in cases where symptoms are strong and should not be administered regularly.

In a meta-analysis[6] investigating the effects of intra-articular hyaluronic acid injection into the knee, compared with the placebo, the degree of effect from the intra-articular injection into the knee was small but from 4 ～ 24 weeks, it showed significant pain-suppressing effects. In a single-blinded RCT on the effects of intra-articular hyaluronic acid injection into the knee and intra-articular steroid injection into the knee on patients with OA, there was a significant improvement in VAS scores in the hyaluronic acid group and a recognizable improvement in knee function scores as well[7]. In addition, there are dozens of RCTs investigating the efficacy of intra-articular hyaluronic acid injection into the knee but due to a lack of uniformity among the research studies (drug dosage used, molecular weight of the agent, period of administration, outcomes), we cannot say that there is high-quality evidence indicating its efficacy and safety. Furthermore, in Japan, there are many instances in which intra-articular hyaluronic acid injection is administered, starting with mild cases, for the purposes of joint protection, whereas overseas it is recommended in severe cases and therefore the treatment environment varies to a large degree. We need to accumulate evidence unique to Japan. When administering an intra-articular knee injection, we need to constantly assess its effects and it should not be continuously administered over the long-term without a particular purpose in mind.

VAS：visual analogue scale

2) Adhesive capsulitis

According to the Guidelines of the American Physical Therapy Association (APTA)[8], they found that a combination of intra-articular steroid injection into the shoulder along with range of motion (ROM) exercises on the joint and stretching was more effective over the short-term (4 ～ 6 weeks) in terms of pain and functional improvement of adhesive capsulitis, than just ROM exercises of the joint and stretching alone. In a systematic review[9] of five RCTs related to the efficacy of intra-articular shoulder steroid injection on adhesive capsulitis, they compared the effects of an intra-articular shoulder steroid injection with an intra-articular shoulder 0.9%[w/v] sodium chloride solution [saline]) injection. In four out of the five papers, they administered a single dose and in the other 1 study they administered a total of three doses every other week. They showed that over the short-term (0～8 weeks), an intra-articular shoulder steroid injection had more significant pain-suppressing effects but there was no difference at 9～24 weeks after administration. Furthermore, intra-articular shoulder steroid injection showed a more significant improvement in passive shoulder range of motion (ROM) but this significant difference was only temporary. Due to the small number of subjects used and the lack of uni-

formity between the research studies, we need more high-quality RCT studies in order to show its efficacy. In a systematic review[10] of 9 RCTs regarding the effects of intra-articular shoulder steroid injection + physiotherapy, and either at-home exercises or physiotherapy alone, there was a recognizable improvement in reduction of pain and improved movement at 6 weeks and at 6 months in the group which was also administered with an intra-articular shoulder steroid injection. In addition, in a systematic review of eight studies comparing the effects of an intra-articular shoulder steroid injection with an intra-articular shoulder saline injection solution on frozen shoulder, they showed that intra-articular shoulder steroid injection may possibly be more effective over the short-term and medium-term[11]. However, in each of these reports, subjects were often administered with a single dose and so there is a need for high-quality RCTs related to the frequency of injections. As we saw with knee OA, single doses should be limited to only when symptoms are strong and it should not be administered regularly.

In a forward-looking study which compared the efficacy of a subacromial bursa steroid injection with an intra-articular shoulder steroid injection on frozen shoulder, they reported a significant improvement in pain over the short-term in the group administered with an intra-articular shoulder steroid injection but over the long-term there was no recognizable significant difference and there was no difference with range of motion (ROM) of the joint[12]. In a RCT which compared the efficacy of intra-articular shoulder steroid injection, subacromial bursa steroid injection and intra-articular shoulder saline injection on frozen shoulder, there was a significant improvement in range of motion (ROM) of the joint and pain in the group administered with an intra-articular shoulder saline injection one month later but they reported no significant difference at three months and six months after administration[13]. We might possibly recognize the short-term effects of subacromial bursa steroid injection but there is no high-quality evidence. Just like with knee OA, administration should be limited to single doses in cases where symptoms are strong and should not be administered regularly.

In a systematic review[14] of intra-articular shoulder hyaluronic acid injection, they investigated three RCTs but due to a lack of uniformity between the research studies, the evidence is insufficient.

Furthermore, in a systematic review of intra-articular joint injections performed under ultrasound guidance, they reported an improvement in accuracy and efficacy[15].

As with knee OA, we need to constantly assess the effects when it is performed and it should not be continuously administered over the long-term without a particular purpose in mind.

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Database	PubMed, MEDLINE, Cochrane Library
Period	2005–2017
Words searched by the combination with 'chronic pain'	osteoarthritis, intra-articular corticosteroid, frozen shoulder, shoulder
*Notes	We narrowed our search down by guidelines, RCT, meta-analysis and systematic review and focused on the most recent academic papers. References 1–3, 5–8, 10–15 which were not found using our search method, we searched for by hand and were added due to their importance.

CQ34：Is psychoeducation effective in managing chronic pain?

Answer： There is low-quality evidence that the execution of psychoeducation alone is effective on chronic pain but we do recommend the basics of psychoeducation as a psychological approach.

Summary of recommendation grades and overall evidence：1C (Execution is strongly recommended)

Commentary：

Within a psychological approach to chronic pain, the most fundamental principle is psychoeducation. This psychoeducation is defined as "conveying the correct knowledge and information about diseases which are hard for the patient to accept, considering the psychological aspects, and educating them and assisting them with coping methods for their issues." In other words, psychoeducation is already included with various types of psychological treatments, and it would be safe to say that there is no psychological approach which does not include psychoeducation. For this reason, unfortunately, there is almost no research which has assessed the effects of psychoeducation alone. On the other hand, there are cases in which psychoeducation has been used as an active control group for actual treatment when investigating the effects of other psychological approaches. For example, the Cochrane Review on chronic pain patients includes research which used educational programs as a control group in order to see the effects of cognitive behavioral therapy (CBT)[1]. However, there are few high quality research studies which have clearly showed the effects of psychoeducation.

In a Cochrane Review on cervical pain, irrespective of whether symptoms of radiculopathy were present or not, they evaluated psychoeducation, including what is so-called the 'Neck School', in which subjects were educated on increasing the amount of physical activity and were educated on pain and stress coping, but in each case the effects were refuted[2]. However, there was only a small number of applicable research papers, and therefore they mentioned the future need for research on specified educational programs. Furthermore, even in other Cochrane Reviews on cervical pain, the educational effects of the level of daily activity, stress coping, the ergonomical approach, and self-care approach, did not prove to be effective[3]. However, in a RCT on a 12-minute video education on patients with traumatic cervical syndrome, they reported that the pain had reduced by the time of six months follow-up, and physical dysfunction had been prevented and in the Cochrane Review, they evaluated this as a high-quality study[4]. In addition, in a RCT on a short-term educational program of primary care on low back pain, they reported that although it had

stress coping：ストレス対処行動

RCT：randomized controlled trial

had a small effect on pain, physical dysfunction and catastrophizing, the effects did persist for a six-month period[5]. Furthermore, some have also presented a unique form of treatment in which an educational textbook on pain is read out for patients with low back pain[6]. Although we cannot call it general psychoeducation, there was also a systematic review of neuroscience educational programs on pain[7]. In this review, they assessed that this program had effects on pain and physical dysfunctions.

As mentioned above, although there is evidence of no considerable effects of conducting psychoeducation alone for managing chronic pain, we must also consider the fact that there is a lack of uniformity, for example in terms of which diseases are targeted and their educational procedures, but realistically because they clearly act as the foundations for other types of psychotherapy (the psychological approach), we have decided that they be recommended.

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Database	Cochrane Library, PubMed
Period	2004-2017
Words searched by the combination with 'chronic pain'	psychoeducation, pain education
*Notes	From these results, we selected references by focusing mainly on systematic reviews, and RCTs.

CQ35：Is behavioral therapy effective in managing chronic pain?

Answer： The various methods of behavioral therapy (relaxation method, self-monitoring, communication skills, graded behavioral activation etc.) are generally recommendable as a basis for chronic pain management. However, researchers have found that behavioral therapy only has a small effect on mood in chronic pain, may possibly have short-term effects on intensity of pain, but in some cases there is no difference between its effects and those from group therapeutic exercise over the mid- to long-term. It has been incorporated as an element within the utility of cognitive behavioral therapy (CBT) and is also utilized in clinical settings.

CBT：cognitive behavioral therapy

Summary of recommendation grades and overall evidence：1B (Execution is strongly recommended)

Commentary：

In a Cochrane Review on psychological interventions on adult patients with chronic pain, excluding those with headache, they mainly investigated the effects of behavioral therapy and CBT, but there were few RCTs on behavioral therapy for each outcome, with around 1～5 only, and generally they did not find any significant difference[1]. In a study comparing behavioral therapy with regular treatment, investigating intensity of pain, lifestyle dysfunction, mood and catastrophizing, they found that it only had a small short-term effect on mood.

In a Cochrane Review on the effects of behavioral therapy on chronic low back pain, they investigated three therapies classified as behavioral therapy；operant therapy, cognitive therapy, and respondent therapy (progressive muscle relaxation [PMR] and biofeedback therapy). Over the short-term, operant therapy was more effective in improving chronic low back pain, compared with a waiting-list group of patients. General behavioral therapy was also more effective than standard treatment (physiotherapy, in both low back pain classes and medical treatment together or individually) over the short-term in terms of its effects on reducing low back pain but over the long-term, they did not find any difference. With each combination of operant therapy, cognitive therapy or behavioral therapy, they found almost no difference in their effects on improving pain over the short- to mid-term. Over the long-term, they found almost no difference between behavioral therapy and group therapeutic exercise in terms of improvement in pain and reduction in symptoms of depression. Even when behavioral therapy was added for patients undergoing hospitalized rehabilitation, they did not find that it had any increased effects as compared with when patients underwent hospitalized rehabilitation alone[2].

In a Cochrane Review on Internet-based interventions offering behavioral therapy or CBT to children, they found that, although the quantity and quality of the research conducted was insufficient, over the short-term it reduced headache and the intensity of complex pain in young children and adolescents but they did not find that it had an effect in improving physical function[3].

In order to advance evidence-based practice, Division 12 of the American Psychological Association (APA) (clinical psychology) compiled a list of effective interventions (limited to those which were supported by actual experimental studies) for specified diseases and disabilities ; a list which they are continually updating[4]. The items for chronic pain on this list included, 'fibromyalgia', 'chronic low back pain', 'rheumatic disease', 'headache' and 'general pain' as low-ranked items, and below is an outline of their recommendations[5].

APA : American Psychological Association

For fibromyalgia (FM), we strongly recommend multi-component [components (1)～(3)] CBT, which is adapted to the varied symptom domains. These multi-components comprise : (1) education about FM including the nature of the disorder and the role patients can play in its management ; (2) symptom self-management skills targeting pain, fatigue, sleep, cognition, mood, and functional status ; and (3) life style change promoting skills targeting barriers to change, unhelpful thinking styles, and long-term maintenance of change. This includes the approaches of behavioral therapy, which are relaxation therapy, graded behavioral activation, pleasant activity scheduling, sleep hygiene, communication skills, self-monitoring, skill rehearsal, and social reinforcement.

FM : fibromyalgia

Behavioral therapy and CBT are strongly recommended for chronic low back pain. This includes behavioral therapy approaches such as time-contingent pacing, spouse involvement and reinforcement of adaptive responding, use of quotas and goals for gradual return of functioning, relaxation approaches such as progressive muscle relaxation (PMR) and biofeedback therapy, self-monitoring, skill rehearsal, and social reinforcement.

Multi-component [(1)～(3)] CBT is strongly recommended for rheumatic disease. These multi-components comprise : (1) education about the nature of pain, options for treatment, and the importance of patients playing an active role in pain management ; (2) symptom self-management skills targeting pain, affect, cognition, and functional status ; (3) promotion of life style change and relapse prevention. This encompasses the approaches of behavioral therapy, which include relaxation therapy, graded behavioral activation, pleasant activity scheduling, communication skills, self-monitoring, skill rehearsal and social reinforcement.

Multi-component CBT is strongly recommended for chronic headache. Researchers claim that through the addition of cognitive coping skills for pain to relaxation therapy, it alleviates headache more than just when relaxation ther-

TTH : tension-type headache

apy alone is conducted, especially in the case of tension-type headache (TTH). As for vascular headaches, such as migraine, it remains unclear whether there is any value in adding cognitive skills to relaxation, or not. This relaxation includes behavioral therapy approaches such as progressive muscle relaxation (PMR), visual imagery (visualization) method, biofeedback therapy and also mindfulness.

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Database	Cochrane Library, PubMed
Period	2005-2017
Words searched by the combination with 'chronic pain'	behavioral therapy, operant therapy
*Notes	Based on these search results, we focused mainly on systematic review, RCT, and selected the references. We also referred to the *APA Presidential Task Force on Evidence-Based Practice : Evidence-based practice in psychology*.

CQ36 : Is cognitive-behavioral therapy effective in managing chronic pain?

Answer : Based on a large amount of research, cognitive-behavioral therapy (CBT) is recognized as having small-medium effects on chronic pain and we can say that it is an intervention, which we can recommend overall. However, there are some cases where little research has been done or the effects were not recognized, depending on the site of disease, how long the effects persist and what it was being compared against.

CBT : cognitive behavioral therapy

Summary of recommendation grades and overall evidence : 1A (Execution is strongly recommended)

Commentary :

1) Overall effects

RCT : randomized controlled trial

Many RCTs have already been conducted on the overall effects of CBT on chronic pain and systematic reviews have been made based on them. In a Co-

chrane Review on face-to-face psychological interventions on patients with chronic pain, excluding headache, compared with standard treatment, CBT had a small recognizable effect, over the short-term, on improving the intensity of pain and quality of life (QOL), and a moderate-level effect on improving mood and catastrophizing[1]. These effects are limited, compared with other active forms of treatment but it did have a small recognizable effect on QOL and catastrophizing. Over the long-term, they confirmed that it had a small effect in improving QOL and mood. In a systematic review on adult patients with chronic migraine, they showed that CBT contributed to an improvement in symptoms[2].

QOL : quality of life

There is also a Cochrane Review on face-to-face psychotherapy on children[3]. CBT showed small short-term and long-term effects on improving the intensity of headache and QOL. However, it only displayed small short-term effects in improving anxiety and did not have any short-term or long-term effects in improving symptoms of depression. In patients with chronic pain other than headache, CBT showed medium-level effects in improving intensity of pain and QOL over the short-term, but did not have long-term effects.

Although they point out that the number and quality of research studies on cases of CBT offered through the Internet is insufficient, at the present stage, generally it has displayed similar results to face-to-face treatments.[4,5].

In a research study on South-East Asians, including Japanese people, although in terms of quantity and quality it has been pointed out as insufficient compared with studies undertaken in the West, in a systematic review on South-East Asian patients suffering from chronic pain, CBT displayed low- to moderate-level effects in improving intensity of pain, QOL, symptoms of depression and anxiety[6].

Therefore, CBT on chronic pain has low- to medium-level effects over the short-term in various facets, and over the long-term, even though its effective aspects are limited, it does have a small recognizable effect and therefore, we can say that it is an effective intervention for chronic pain overall.

2) By site of disease and name of disease

In a RCT comparing mindfulness-based stress reduction (MBSR) and CBT with standard multidisciplinary chronic pain management on patients with chronic low back pain, the percentage of patients who experienced an improvement in the level of irritation felt towards pain and their QOL after 26 weeks was both statistically and clinically more significant in the CBT and MBSR groups, which were around the same level[7]. In a different RCT, they found that the MBSR group showed a better short-term improvement than the CBT group in catastrophizing and in avoiding their own pain. But in terms of self-efficacy towards their pain and accepting internal experiences for what they

MBSR : mindfulness based stress reduction

were, over the short-term CBT and MBSR had similar effects and over the long-term, both were equally effective also in improving their tendencies to avoid pain and catastrophizing[8]. In a systematic review investigating the long-term effects of CBT on chronic low back pain, there was a small improvement in activities of daily living (ADL) and pain intensity in the group which underwent CBT, compared with the group which didn't undergo treatment and compared with the group which received active treatment in accordance with the guidelines, there was a large improvement in ADL and a medium-level improvement in the intensity of pain in the CBT group[9]. There is a RCT which showed more of an improvement in pain intensity and catastrophizing in subjects where CBT was not provided face-to-face but in a group, compared with those who received standard multidisciplinary chronic pain management[10]. Based on the above, we can say that CBT is recommendable for chronic low back pain. Under the 'Clinical Practice Guidelines for the Management of Chronic Low back Pain' in Japan, CBT is recommended[11].

ADL：activities of daily living

In a systematic review of CBT on fibromyalgia, while there was no short-term or long-term improvement in intensity of pain, fatigue, sleep and health-related QOL, there was a small short-term improvement in symptoms of depression, and a large short-term and long-term effect on improving patient's sense of self-efficacy for their pain[12]. In a different systematic review, a meta-analysis investigated the effects of psychotherapy on fibromyalgia, and found that psychotherapy had a small but definite effect on sleep, symptoms of depression, QOL and catastrophizing. In addition, they reported that CBT was particularly effective in comparison with other forms of psychotherapy[13]. After that, a Cochrane Review which investigated the short-term and long-term effects of CBT on patients with fibromyalgia, from children through to adults, was released and they reported that over the short-term it had a small effect on intensity of pain, negative mood, and QOL and over the long-term, it had a small- to medium-size effect on intensity of pain, negative mood and ADL[14]. In the 'Guidelines on the Treatment of Fibromyalgia'[15] in Japan, CBT was given a strong recommendation due to the long duration required to perform CBT and also due to the small number of facilities where it is actually offered.

HRQL/HRQOL：health-related QOL reduction

In a Cochrane Review of CBT's effects on chronic neck pain, even though the quality of evidence is low, they found that subjects who had undergone CBT, compared with subjects who had currently not undergone treatment, experienced a medium-level improvement in intensity of pain and ADL and a large improvement in QOL over the short-term[16]. However, compared with subjects who underwent other forms of active treatment, although there was only a small effect on kinesiophobia over the long-term, it was not effective in improving intensity of pain or ADL over the short-term and over the long-

term. There were no particular effects found on subjects who underwent CBT and another form of treatment concomitantly. Based on the above, it remains uncertain whether conducting CBT on patients with chronic cervical pain has clinical value or not.

In a Cochrane Review of the effects of psychotherapy on chronic neuropathic pain, only two research studies matched the eligibility criteria[17]. However, one of these studies investigated the effects of CBT on patients with spinal cord injury, by comparing its effects before and after treatment[18] and they found a long-term improvement in intensity of pain, ADL, anxiety and level of activity.

In a Cochrane Review of the effects of non-pharmacological therapy on patients with somatoform disorders (somatic symptom disorder), fourteen out of the 21 studies which matched the eligibility criteria were related to CBT, and compared with subjects who did not undergo treatment, there was definitely an effect, although the reduction in physical symptoms was small, and its long-term effects were also confirmed[19]. However, there was no difference in comparison with other forms of active treatment.

As seen above, in terms of the efficacy of CBT according to the site of injury or the name of the disease, there are differences in the quality and quantity of research that has already been done and in some cases there were no visible effects.

3) The concomitant use of other interventions

Researchers have also investigated the effects of other forms of treatment in combination with CBT. In a research study on patients with chronic low back pain, they compared a group of patients who underwent general therapeutic exercise with a group of patients who underwent general therapeutic exercise in addition to CBT. In both groups, there was a visible improvement in intensity of pain and ADL, compared with the baseline but at twelve weeks after treatment had been concluded, there was a greater improvement in intensity of pain and ADL in the group which had undergone CBT[20].

A review showed that in the perioperative period of patients who had undergone spinal fusion surgery for chronic low back pain, they were able to obtain even better results, in many aspects, by dealing with psychological risk factors using CBT[21].

In an RCT study on patients with chronic low back pain currently being treated with opioid analgesics, they implemented a composite group program, using meditation and CBT specially designed for chronic low back pain. Compared with the control group, intensity of pain and pain hypersensitivity to a heat stimulus improved in the group which underwent CBT[22].

As seen above, not only when CBT is implemented alone, but also when it is

used in combination with various existing interventions, we can say that it is effective. However, as we saw with chronic cervical pain above, in some cases CBT did not have any additive effects, when used in combination with other forms of treatment[16].

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Database	Cochrane Library, PubMed
Period	2009-2017
Words searched by the combination with 'chronic pain'	cognitive behavioral therapy, psychological intervention, CBT
*Notes	From these results, we searched mainly for systematic review, randomized controlled trial, and selected the references. Then, we added 2 known guidelines related to domestic chronic pain.

CQ37 : Is mindfulness as proposed in the third wave of cognitive-behavioral therapy effective in managing chronic pain?

Answer : Mindfulness-based intervention may be effective on chronic pain in improving intensity of pain, the degree of depression symptoms, dysfunction, and quality of life (QOL).

QOL : quality of life

Summary of recommendation grades and overall evidence : 1A (Execution is strongly recommended)

Commentary :

Mindfulness refers to 'paying attention in a particular way : intentionally, in the present moment, and non-judgmentally.' This state of mind is trained through mindfulness meditation and, as a result, our ability to objectively and non-judgmentally notice our own sensations, thoughts and emotions, and other things improves. Through doing this, it has been suggested that one's ability to

endure physical and psychosocial stress improves. There are many reports claiming that mindfulness based interventions are effective on chronic pain. A systematic review[1] of 38 RCTs was conducted comparing groups of subjects who underwent a mindfulness-based intervention for chronic pain (mindfulness-based stress reduction [MBSR], mindfulness-based cognitive therapy [MBCT], and other programs based on mindfulness) with a control group (waiting-list group, group only undergoing usual treatment, patient education/support group). According to this review, within 4～60 weeks follow-up, although the degree of effect was small, the intensity of pain and the degree of depression symptoms as well as physical and mental QOL had significantly improved in the group undergoing mindfulness-based intervention compared with the control group. The evidence of improvement of depression symptoms was evaluated as high, and improvement of mental QOL was evaluated as medium. They reported some disparity in the results on improvement of pain intensity and physical QOL and so the evidence was low. Although investigations on dysfunction tend to show improvement, no significant difference was obtained when compared with the control group. Only four RCTs were used for the investigation, far too few to generalize the results. In an investigation into the different effects that each of the three above mentioned types of mindfulness-based interventions had on pain intensity, no significant difference between the methods was found. Seven RCTs investigated adverse events arising due to the implementation of mindfulness, but no severe events were reported. However, at the current stage of research into mindfulness, findings on adverse events are insufficient and therefore further investigation is needed.

MBSR：mindfulness based stress reduction
MBCT：mindfulness based cognitive therapy

RCT：randomized controlled trial

A systematic review of RCTs was conducted, investigating the effects of mindfulness-based intervention on several specific forms of pain diseases. In systematic reviews of the effects of MBSR on chronic low back pain[2,3] compared with standard treatment/patient education, a significant short-term improvement in the MBSR group was found in terms of pain intensity and dysfunction, even though the degree of effect was small. In a review[4] of the effects of MBSR on headache, it was claimed that there was a moderate-level effect in the group that underwent mindfulness-based intervention and that it significantly reduced the intensity of pain, compared with a group undergoing standard treatment. A review[5] of a group of subjects with irritable bowel syndrome (IBS) reported that a moderate-level effect was seen in a group that underwent mindfulness-based intervention and that there was a significant improvement in intensity of pain, symptom severity, and symptom-related QOL compared with a waiting-list/support only group. Systematic reviews of its effects on fibromyalgia have been reported by a German group[6] and by the Cochrane Musculoskeletal Group[7]. According to the German group, in six RCTs

that compared standard treatment and patient education, MBSR was effective in providing a short-term improvement in pain intensity and QOL, but they claimed that there was no difference over the long-term. The Cochrane Musculoskeletal group reported that mindfulness-based intervention did not significantly improve intensity of pain, depression symptoms, or physical function in comparison with standard treatment. Thus, the findings of the studies conducted on fibromyalgia are too unclear for generalization and therefore we are unable to draw any conclusions at this stage. However, researchers have implied its effectiveness on chronic low back pain, headache, and irritable bowel syndrome (IBS).

To compare the second wave of CBT, which has the largest amount of evidence among the psychological approaches to chronic pain, with MBSR, there is a high-quality RCT[8] that compared the effects of MBSR, CBT, and standard treatment on chronic low back pain. At 26 weeks follow-up, subjects in both the MBSR and CBT groups showed a significant improvement in pain intensity and disability compared with the standard-treatment group. However, no significant difference was found suggesting that MBSR is as useful as CBT.

In light of the above, it is possible that mindfulness-based intervention could be a useful alternative to conventional CBT.

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Database	Cochrane Library, PubMed
Period	2005–2017
Words searched by the combination with 'chronic pain'	mindfulness, mindfulness-based stress reduction, MBSR, mindfulness-based cognitive therapy, MBCT, pain, headache, irritable bowel syndrome, fibromyalgia, arthritis
*Notes	From these search results, we searched mainly for systematic review, randomized controlled trial and selected the references.

CQ38 : Is acceptance and commitment therapy under the third wave of cognitive-behavioral therapy effective in managing chronic pain?

RCT : randomized controlled trial
ACT : acceptance and commitment therapy

Answer : A large number of RCTs have indicated that acceptance and commitment therapy (ACT) has small- to medium-level efficacy, as an evaluation item in the treatment of chronic pain. In particular, it may possibly have a large effect on psychological flexibility and dysfunctions due to pain and therefore we can say that it is a recommendable form of intervention.

Summary of recommendation grades and overall evidence : 1A (Execution is strongly recommended)

Commentary :

Acceptance and commitment therapy (ACT) is a form of psychotherapy in which we do not spend the majority of our time and effort on removing pain or unpleasant thoughts or emotions related to pain but realizing that existing with this unpleasant phenomenon is a normal state for human beings, and ACT will support patients live the life they wish.

There have been over 20 RCTs[1] which have shown the efficacy of ACT on chronic pain, and two meta-analyses have been conducted[2,3]. According to one of these meta-analyses[2], patients who had undergone ACT treatment showed a small improvement in intensity of pain, degree of depression symptoms, and dysfunction, immediately after treatment, compared with a group of subjects who underwent standard treatment or a group of subjects on a waiting-list and also it had a medium-level effect in improving patients' degree of pain interference and their degree of anxiety. In addition, in this research study, within 2～6 months follow-up, they indicated that the level of improvement in intensity of pain, degree of depression symptoms, and quality of life (QOL) had increased. Furthermore, they demonstrated that it had a large effect on improving the level of pain interference in particular. They also indicated that the level of improvement in anxiety and dysfunction had been maintained at around the same level. In addition, in another meta-analysis[3], they found that compared with subjects who had undergone standard treatment and subjects on a waiting list, ACT had a medium-level effect directly after treatment on

patients' acceptance of pain, a large effect on their psychological flexibility, a medium-level effect on improving their anxiety and depression symptoms, and a small effect on dysfunction. Furthermore, within 3～6 months follow-up, they showed that it had had a small effect on intensity of pain and dysfunction.

CBT has the largest amount of strong evidence on chronic pain. The amount of effect by the second wave of CBT[4] and the amount of effect by the third wave of CBT (mindfulness)[5] on chronic pain is almost the same but compared with the second wave of CBT, the third wave tends to show persistent effects at the time of follow-up (2 ～ 6 months after treatment). Furthermore, within the third wave of CBT, ACT has tended to show a larger amount of effect[2] than interventions based on mindfulness meditation (mindfulness based stress reduction [MBSR] and mindfulness based cognitive therapy [MBCT]). Therefore, ACT might possibly be the most effective psychological approach to chronic pain at the current stage. However, in a RCT directly comparing the second wave of CBT and MBSR[5], and in another RCT directly comparing the second wave of CBT with ACT[6], they did not find any significant difference in pain or other outcomes and therefore it is unclear which of these three is better than the others.

CBT : cognitive behavioral therapy

MBSR : mindfulness based stress reduction

MBCT : mindfulness based cognitive therapy

In order to promote evidence-based actual cases, Division 12 of the American Psychological Association (clinical psychology), has compiled a list of effective interventions (limited to those supporting experimental studies) against specific diseases and disabilities, and is updating them consecutively[7]. As for chronic pain items on this list, 'fibromyalgia', 'chronic low back pain', 'rheumatic disease', 'headache' and 'chronic pain in general' are low-ranked items. For one of these items ; chronic pain in general, they only recommend ACT. For the other items, they recommend conventional behavioral therapy or CBT[8].

Just like with ACT and mindfulness, dialectical behavior therapy (DBT) was developed under the third wave of CBT, and is a comprehensive cognitive-behavioral therapy developed as a form of intervention specifically for borderline personality disorder (a personality disorder in which sufferers are accustomed to harming themselves, and while within clinical psychology this requires the largest amount of effort, it is also extremely hard to obtain therapeutic effects). RCTs on the effects of DBT on chronic pain have not been conducted but in cases of intractable fibromyalgia or protracted chronic pain, there is a tendency for some patients with personality disorders to also be suffering from a history of abuse or trauma. There is a neuroscience case study report[9] on the effects of DBT on pain and we are waiting for further research to be conducted in future.

DBT : dialectical behavior therapy

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Database	Cochrane Library, Pubmed
Period	2005-2017
Words searched by the combination with 'chronic pain'	acceptance and commitment therapy, ACT
*Notes	From these search results, we focused mainly on systematic review, RCT for our selection. Furthermore, we also referred to the APA Presidential Task Force on Evidence-Based Practice : Evidence-based practice in psychology.

CQ39 : Is hypnotherapy effective in managing chronic pain ?

Answer : There is evidence indicating that hypnotherapy is effective on chronic pain. If patients are undergoing treatment from a therapist who has received an education on hypnotherapy, it is recommended.

Summary of recommendation grades and overall evidence : 2B (Execution is weakly recommended)

Commentary :

Clinical hypnosis for chronic pain, is a method of treatment which uses trance (state of modified consciousness). Its mode of action is known to be related to the several neurophysiological mechanisms in the experience of pain[1].

A meta-analysis[2] concluded that hypnosis has medium-level effects on chronic pain.

Below we will cite some hypnosis-related RCTs on various diseases. Compared with a control group which just underwent relaxation, hypnosis significantly improved pain in patients with temporomandibular arthritis and reduced the number of times patients were awakened by their pain during night[3]. Furthermore, hypnosis also significant improved pain in patients with persistent orofacial pain, compared with a control group which only underwent relaxation, and the area of the pain site also decreased[4]. In a research study on fibromyalgia, they compared a group undergoing pharmacotherapy alone with a group undergoing cognitive-behavioral therapy (CBT), and a group undergoing a combination of CBT and hypnotherapy. In this research study, sensory and emotional aspect of pain improved more significantly in the CBT group and the CBT and hypnotherapy combined group than the pharmacotherapy alone group, but there was no difference between the two former groups[5]. In another research study on osteoarthritis (OA) of the knee and osteoarthritis (OA) of the hip, pain had improved by standardized hypnosis, compared with a group of patient on a waiting list, by three months follow-up, and hypnosis had helped reduce the number of times patients had to use analgesics[6]. Next, in a research study on patients with chronic pain due to spinal cord injury, they reported a significant reduction in pain due to hypnosis, compared with biofeedback thrapy[7]. However, a Cochrane Review claims that there is no evidence indicating that self-hypnosis is effective on post-spinal cord injury chronic pain[8]. In addition, the effects of hypnosis on non-cardiogenic chest pain were found to be significantly higher in terms of the overall level of improvement of pain, compared with supportive psychotherapy[9]. None of the other reports are RCTs and although there is a low level of sufficient evidence, they are investigating the clinical effects of hypnosis on chronic headache and chronic low back pain. In a systematic review on its effects on irritable bowel syndrome (IBS) in children, although hypnotherapy was more effective than standard treatment, they mentioned that it is difficult to verify the effect size of hypnotherapy[10].

As mentioned above, hypnotherapy is effective on chronic pain overall and we conclude that, if conducted properly, it is recommended for patients who are undergoing treatment by a therapist who has received an education on hypnosis. However, this therapy is not standardly performed yet in Japan, and so we hope that it will spread as an important treatment methodology for chronic pain.

RCT：randomized controlled trial

CBT：cognitive behavioral therapy

IBS：irritable bowel syndrome

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Database	Cochrane Library, PubMed
Period	2004–2017
Words searched by the combination with 'chronic pain'	hypnosis, hypnotic state
*Notes	Based on these search results, we focused mainly on systematic reviews, and RCTs and selected the references. We also selected some academic papers conducted before our period which we believed to be important (Reference 6.)

CQ40：Is general therapeutic exercise effective in managing chronic pain?

Answer： Compared with rest and guidance on daily living, therapeutic exercise alone is effective on chronic pain and dysfunction. On the other hand, it is not clear if there are any differences in effect depending on the type of exercise.

Summary of recommendation grades and overall evidence：

1) Chronic low back pain：1A (Execution is strongly recommended)

2) Osteoarthritis (OA) of the knee：1A (Execution is strongly recommended)

3) Chronic cervical pain：1B (Execution is strongly recommended)

Commentary：

1) Chronic low back pain

RCT：randomized controlled trial

In a quantitative systematic review of RCTs investigating the effects of general therapeutic exercise, such as stretching, aerobic exercise and muscle-strengthening exercise on chronic low back pain[1,2], they reported[1] that it was more effective in terms of reducing pain, and improving dysfunction and quality of life (QOL), compared with a waiting-list group of patients and a group not undergoing treatment[1]. On the other hand, there are also some reports[2] claiming that it has no recognizable effect. However, comparing a group which underwent general therapeutic exercise with a group which did not undergo treatment, researchers recognized that in the group which underwent therapeutic exercise, it had been effective in reducing pain and improving dysfunction. Furthermore, they also reported[2] its effects on improving pain and dysfunction at follow-up, twelve months post-treatment[2]. One thing that should be pointed out is that depending on the type of exercise implemented, there have been reports of adverse events such as low back pain.

QOL：quality of life

2) Osteoarthritis (OA) of the knee

As for its effects on osteoarthritis (OA) of the knee[3], they have found that general therapeutic exercise is effective in reducing pain and improving dysfunction. Furthermore, researchers have also shown that an individually-formulated exercise program was more effective in reducing pain over the long-term than a group exercise program[3].

As for the differences in efficacy depending on the method of exercise used, they found that land-based muscle strengthening exercise and aerobic exercise were effective in reducing pain and improving physical function[4-6]. There have also been claims that aquatic muscle-strengthening and aerobic exercises slightly reduced pain[7]. However, differences in therapeutic effect depending on the type of exercise used remain unclear[7]. It should also be pointed out that with some forms of exercise, there have been reports of adverse events, such

as aggravated knee pain[3].

3) Chronic cervical pain

Compared with a waiting-list group, supervised multimodal exercises (range of motion [ROM] exercises and muscle-strengthening exercises) have shown to be effective in reducing pain for patients suffering from chronic cervical pain[8]. Furthermore, they found that a combination of strengthening the muscles around the neck region and stretching had a large effect over the short-term and a slight effect over the long-term in reducing pain, and reported that muscle-strengthening exercises and stabilization exercises for the muscles around the neck region were effective in improving pain and dysfunction[9]. On the other hand, some reports have also shown that high-frequency muscle-strengthening exercise had no effect on reducing pain and improving dysfunction, when compared with non-supervised stretching[10,11].

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Database	MEDLINE, CINAHL, PEDro
Period	2010–2017
Words searched by the combination with 'chronic pain'	guideline, meta-analysis, RCT, randomized controlled, chronic pain treatment, exercise, aerobic, resistance, isometric, stabilization, tai chi, yoga, Pilates, qigong
*Notes	From these search results, we focused mainly on searching for systematic reviews, RCT and selected the references.

CQ41：Is exercise, other than general therapeutic exercise, effective in managing chronic pain？

MCE：motor control exercise

Answer： Motor control exercise (MCE) is effective on chronic pain and dysfunction, compared with general therapeutic exercise. Yoga, Tai Chi, Qigong (breathing exercises), and the Pilates method are also effective on chronic pain compared with general therapeutic exercise, such as aerobic exercise and muscle-strengthening exercise. However, the difference in their effects compared with other forms of exercise is unknown.

Summary of recommendation grades and overall evidence：

1) Motor control exercises：1B (Execution is strongly recommended)
2) Yoga：2B (Execution is weakly recommended)
3) Tai Chi：2B (Execution is weakly recommended)
4) Qigong (breathing exercises)：2C (Execution is weakly recommended)
5) Pilates Method：2C (Execution is weakly recommended)
6) Radio calisthenics (TV calisthenics)：2D (Execution is weakly recommended)

Commentary：

1) Motor control exercises

RCT：randomized controlled trial

Motor control exercises (MCE) are a form of training designed to improve muscle function in the deep muscles of the trunk, such as the transverse abdominal, the internal oblique, and multifidus muscles for the purpose of improving the stability of the spine. In a quantitative systematic review of RCT studies on its effects on chronic low back pain[1], they found that compared with general therapeutic exercise, short-term (six weeks～fow months) and medium-term interventions (4～8 months) were more effective in improving pain and physical function. Furthermore, compared with a group who did not undergo treatment and those who underwent patient education, researchers found[2] that it was more effective in improving pain and physical function, too. On the other hand, there was also a study[3] that compared MCE with general exercise, such as aerobic exercise, muscle-strengthening exercise and stretching, and they reported that there was not much difference in effect. There was no recognizable difference in pain alleviation, compared with spinal manipulative

therapy but they did find that it was effective in improving physical function. However, when MCE was combined with general therapeutic exercise, there was no difference in its effect on improving pain, compared with therapeutic exercise alone[4,5].

2) Yoga

In an RCT study on its effect on chronic low back pain, compared with general care, they found that by doing yoga (Iyengar Yoga) for three months or six months, it was effective in reducing pain and improving physical function[6]. Compared with general therapeutic exercise, there have been claims that it is effective in reducing pain but the level of evidence for this is low[1,7-10]. Additionally, in a quantitative systematic review of RCTs, compared with patient education, at twelve weeks (short-term follow-up) and at twelve months after intervention (long-term follow-up), there was a slight improvement in pain and physical function through yoga[11].

As for its effects on chronic cervical pain[12], and osteoarthritis (OA) of the knee[13], yoga (Iyengar Yoga, Hatha Yoga) has been shown to be effective in reducing pain.

3) Tai Chi

In some RCTs[1, 14-16], compared with a waiting-list group, they found that patients with chronic low back pain experienced a moderate improvement in pain and a slight improvement in physical function through Tai Chi. Compared with jogging and walking backwards, they found that by 6 months after intervention, Tai Chi had had a slight effect on reducing pain and improving physical function[1].

In a quantitative systematic review[17] of RCT studies and cluster RCTs[16], they found that compared with patient education and a group which did not undergo treatment, a 20-week 'Sun Style Tai Chi Program' was effective in reducing pain[16,17] and improving physical function[17] in patients with knee osteoarthritis (OA).

4) Qigong (breathing exercises)

Compared with general therapeutic exercise, such as aerobic exercise, muscle-strengthening exercise and stretching, they did not find that Qigong had a significant difference on reducing pain in patients with chronic low back pain but it did have a recognizable effect on improving physical function[18].

As for its effects on cervical pain, in a quantitative systematic review of RCTs, they found that compared with a waiting-list group, it was effective over the short-term and mid-term in reducing pain but was not effective in improving physical function[19].

5) Pilates method

To give a general overview of several RCTs on the effect of Pilates method

on chronic low back pain, compared with a combination of patient education and physical activity, there are some RCTs which showed that it had a slight effect on reducing pain at the conclusion of treatment, and some RCTs in which it was not shown to be effective, and so a definite conclusion on its effects has yet to be reached[20]. Compared with the McKenzie method[21], and general exercise (aerobic exercise, stretching and muscle-strengthening etc.)[22], they did not find a significant difference in pain reduction. On the other hand, in a quantitative systematic review of RCTs, compared with a supervised exercise program and exercise using equipment, it was found to be effective over the short-term in improving pain and function without adverse events[23].

6) Radio calisthenics (TV calisthenics)

Radio calisthenics (TV calisthenics) is something, which has been developed and passed down only in Japan, is well known among Japanese people and is therefore a familiar form of exercise to them. It is a form of aerobic exercise which extensively uses the whole body and if all exercises cannot be completed in the standing position, people can choose to conduct as much exercise as they can, for example through alternative methods such as in the sitting position. In addition, as it is a simple and safe form of exercises, which can be performed by anybody, anytime and anywhere, we recommend that it be implemented.

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Database	MEDLINE, CINAHL, PEDro
Period	2010–2017
Words searched by the combination with 'chronic pain'	guideline, meta–analysis, RCT, randomized controlled trial, chronic pain treatment, exercise, aerobic, resistance, isometric, stabilization, tai chi, yoga, Pilates, qigong
*Notes	From these results, we ran a search and selected the references.

CQ42 : Are physical modalities effective in managing chronic pain?

Answer : There is a lack of evidence indicating that physical modalities are effective on chronic pain and dysfunction and therefore we do not actively recommend implementation.

Summary of recommendation grades and overall evidence :

1) Thermotherapy : 2D (Non-execution is weakly recommended)
2) Cryotherapy : 2D (Non-execution is weakly recommended)
3) Therapeutic ultrasound therapy : 2C (Non-execution is weakly recommended)
4) Transcutaneous electrical nerve stimulation (TENS) : 2C (Non-execution is weakly recommended)
5) Low-level laser therapy (LLLT) : 2C (Execution is weakly recommended)
6) Traction therapy : 2D (Execution is weakly recommended)

Commentary :

1) Thermotherapy

Short-wave diathermy

Two clinical research studies have reported[1,2] that shortwave diathermy in which deep heating is performed by irradiation with shortwaves had a slight effect in reducing pain in patients with chronic low back pain but in both studies, their control group settings and blinded tests were conducted insufficiently so the quality of evidence is low.

balneotherapy / spa therapy

No difference in reduction of pain or improvement of physical function for a group of patients with osteoarthritis (OA) of the knee was found between a placebo-controlled group and a group of patients with OA of the knee who underwent shortwave diathermy[3]. However, compared with a placebo group (in which tap water was used), they found a difference in its effect on reducing pain when patients underwent balneotherapy (hot spring bathing containing minerals), and even at six months follow-up after the conclusion of treatment, they found that it was effective in reducing pain[4]. Compared with home exercises, they found that it had a slight effect in reducing pain[5,6] but looking at the individual RCTs, there are issues with a lack of uniformity between the results and small sample sizes used and therefore the quality of evidence is low[6].

2) Cryotherapy

Compared with a group which did not undergo treatment, they found that cryotherapy was effective in improving muscle strength in patients with OA of the knee, but they did not find any effect on reducing pain[7].

3) Therapeutic ultrasound therapy

Compared with a placebo-controlled group, they did not find that therapeutic ultrasound therapy was effective in reducing pain in patients with chronic low back pain[8]. Researchers also did not find any effect in reducing pain, when

comparing it with general exercise[8]. Furthermore, when they compared a combination of therapeutic ultrasound therapy and therapeutic exercise with therapeutic exercise alone, they did not find that it was effective in reducing pain[8].

It was found to be effective in reducing pain in patients with OA of the knee[9]. As for the therapeutic ultrasound conditions, they found that it was effective in reducing pain under low-intensity conditions (<1 W/cm^2) and under pulsed mode[10]. Furthermore, compared with continuous mode, they have shown that the effects obtained from pulsed mode persist for a longer time after treatment has been concluded, but in each individual RCT the methodology used was of poor quality and on top of this, the sample size used was small and so the quality of evidence is low[11]. On the other hand, in a quantitative systematic review[12], compared with the placebo-controlled group, they did not find that it was effective in reducing pain, and so we have yet to reach a consensus on the effects of therapeutic ultrasound therapy.

4) Transcutaneous electrical nerve stimulation (TENS)

Compared with a placebo group, they found that TENS was not effective in reducing pain and improving dysfunction in patients with chronic low back pain[13] and chronic cervical pain[14].

In a quantitative systematic review of its effects on OA of the knee, they found that it was effective in reducing pain but people have pointed out the low quality of the analytical methods used in each individual RCT and so the quality of evidence is low. In recent years, there was an RCT study which found that compared with a placebo group and a group which did not undergo treatment, TENS did not have an effect on reducing pain[15].

5) Low-level laser therapy (LLLT)

LLLT : Low level laser treatment

In a quantitative systematic review, they found that compared with a placebo-controlled group, LLLT was effective in reducing pain in patients with chronic low back pain[16] and chronic cervical pain[14]. However, each of the RCTs on chronic cervical pain contained a high level of statistical variation and so the quality of evidence is low[17]. In two reports comparing the effects on chronic low back pain in a group of patients who underwent a combination of LLLT and therapeutic exercise with a group of patients who underwent placebo irradiation and therapeutic exercise, they verified its effects at three months follow-up and showed that it was effective in producing a weak reduction in pain[18,19]. However, the quality of evidence in these reports is low.

In a systematic review on the effects of LLLT on OA of the knee, they did not find that it had a recognizable effect in improving pain and dysfunction either at immediately after the conclusion of treatment or at follow-up[20]. In an RCT which compared the effects on chronic cervical pain of a combination of

LLLT and therapeutic exercise with a combination of placebo irradiation and therapeutic exercise, they showed that there was no effect in both cases, immediately after treatment[21].

6) Traction

Compared with a group that received a placebo treatment and a group which did not undergo treatment at all, they found that traction had a slight effect in improving pain in patients with chronic low back pain without symptoms of radiculopathy[22].

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Database	MEDLINE, CINAHL, PEDro
Period	2010–2017
Words searched by the combination with 'chronic pain'	systematic review, meta analysis, guideline, cryotherapy, icing, crymotherapy, ice pack, cooling, cryoanalgesia, cold therapy, thermotherapy, heat therapy, thermal therapy, shortwave, microwave, paraffin, hotpack, hot-pack, spa therapy, balneotherapy, balneology, hot-spring therapy, infrared therapy, infrared, mud bath, shock wave therapy, short-wave therapy, YAG laser, diode laser, diathermy, low level laser, laser therapy, low-level laser therapy, LLLT, low-level light, phototherapy, electrical stimulation, TENS, electrotherapy, transcutaneous electrical nerve stimulation, muscular electrical stimulation, electrical muscle stimulation, middle frequency stimulation, electric stimulation, EMS, neuromuscular electrical stimulation, NMES, transcranial electrical stimulation, TES, functional electrical stimulation, FES, interferential current, magnetic therapy, magnetic stimulation, ultrasound, ultrasonic, traction, vibration
*Notes	We ran a search based on these results and selected the references.

CQ43 : Is manipulative therapy effective in managing chronic pain?

Answer : There is insufficient evidence showing that manipulative therapy is effective on chronic pain and dysfunction, and so we cannot say that it is more effective than other conservative forms of medical treatment and therefore we do not actively recommend its implementation.

Summary of recommendation grades and overall evidence :

1) Spinal manipulation, mobilization : 2C (Non-execution is weakly recommended)

2) Massage : 2C (Execution is weakly recommended)

Commentary :

1) Spinal manipulation, mobilization

Regarding the effects of spinal manipulation and mobilization on rotator cuff injury, researchers found weak evidence[1] that there was no difference in its effects from medium- to long-term interventions on pain, shoulder joint function (for example active abduction range of motion), and quality of life (QOL) compared with steroid injection, therapeutic exercise, arthroscopic subacromial decompression, dietary instruction, acupuncture, supplements, and the internal administration of nonsteroidal anti-inflammatory drugs (NSAIDS).

QOL : quality of life

NSAIDs : nonsteroidal anti-inflammatory drugs

Compared with a control group, researchers found that manipulative therapy alone, and in combination with therapeutic exercise displayed weak short-term effects (less than three months) on pain and dysfunction in patients with osteoarthritis (OA) of the hip but there was weak evidence that there was no difference in effect over the medium- to long-term (four months or more)[2,3].

There are no good-quality interventional grounds for its effects on pain, range of motion (ROM) limitations, and orofacial dysfunction in patients with temporomandibular disorder and therefore its effects are unknown[4].

As for its effects on cervicogenic headache, it was found to have a weak interventional effect on intensity and frequency of pain, compared with traditional physiotherapy and a placebo treatment[5].

Compared with sham manipulation, it was found to have short-term analgesic effects on non-specific low back pain[6]. Furthermore, by combining manipulative therapy with another active treatment (for example therapeutic exercise), they found that, compared with just implementing the intervention alone, it was effective in improving pain and dysfunction one month later, three months later, and twelve months later[7]. However, due to issues with sample sizes and their blinded tests, as well as differences in method, frequency and period of intervention used, and a lack of uniformity among the results, it is difficult to undertake a meta-analysis. As there were only a few studies which have been analyzed, careful attention needs to be paid with interpreting the findings. Furthermore, there have also been reports of complications, including adverse events such as local malaise and fatigue, vertebral body fracture, neuropathy due to intervertebral disc herniation, stroke and headache, and vertebral artery dissection[8,9].

2) Massage

According to the clinical treatment guidelines of the Ottawa Panel in 2012[10]

on the effects of massage on chronic cervical pain, it remains unclear whether it has long-term effects or not and there is low evidence supporting this treatment.

As for its effects on sub-acute to chronic low back pain, they found medium-level evidence that, compared with manipulation, therapeutic exercise, relaxation, acupuncture, and physical modalities (TENS etc.), it has weak analgesic effects and improved function over the short-term[11,12]. Furthermore, when massage is combined with therapeutic exercise, exercise and patient education, and standard treatment, they found weak evidence that these produce superior analgesic effects over the short-term than when each of these methods are used alone[11].

As for its effects on fibromyalgia, researchers found that it tended to produce a short-term improvement in pain, sleep and well-being, without side effects, in comparison with standard treatment, a combination of standard treatment plus phone call patient consultations, TENS and sham TENS, and progressive muscle relaxation[13]. However, because the massaging method, amount of intervention, results displayed and methods of analysis were unclear in a large number of the previous studies and as it is difficult to remove the bias, the scientific grounds are limited and therefore we cannot prove that it has therapeutic effects on fibromyalgia.

TENS：transcutaneous electrical nerve stimulation

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Database	MEDLINE, CINAHL, PEDro
Period	2010-2017
Words searched by the combination with 'chronic pain'	guideline, systematic review, meta-analysis, manual therapies, manual therapy, manipulation, spinal manipulation, massage
*Notes	We ran a search based on these results and selected the references.

CQ44 : Is the introduction of cognitive behavioral therapy and education into rehabilitation and its application to treatment effective in managing chronic pain?

CBT : cognitive behavioral therapy
(For more details related to CBT, refer to CQ34)

Answer : Introducing the theory of cognitive behavioral therapy (CBT) into rehabilitation is expected to improve its effectiveness. Within rehabilitation, while CBT can be effective in improving pain, physical dysfunction and a patient's psychological state when implemented alone or in combination, for example, with patient education and exercise, it is unclear whether its effects differ from those of other forms of treatment. On the other hand, when patient education is implemented independently, its effects are poor in comparison with other forms of treatment but when used additively with other forms of treatment, we expect that it enhances the therapeutic effects for patients.

Summary of recommendation grades and overall evidence :

1) Cognitive behavioral therapy (CBT) : 1B (Execution is strongly recommended)

2) Patient education : 1B (Execution is strongly recommended)

Commentary :

1) Cognitive behavioral therapy (CBT)

Compared with a waiting-list group and a group which did not undergo treatment, researchers showed that CBT had a medium-level effect on improving pain and a slight improvement on physical function in patients with chronic low back pain, although the level of evidence was low[1-3]. Furthermore, compared with a waiting-list group and a group which did not undergo treatment, although operant therapy did reduce pain slightly, there was no difference in

its effect on improving dysfunction[1-3]. When CBT was used in combination with other forms of treatment (such as education, problem-solving training, coping techniques, images, relaxation, cognitive pain control, and exercise), similar to when CBT was used alone, it was found to have medium-level effects on reducing pain, in comparison with a waiting-list group and a group which did not undergo treatment, but it remains unclear whether it has a different effect on improving dysfunction or not[1-3]. In a treatment which combined CBT with therapeutic exercise, researchers found that it had a small effect on improving physical function, compared with total disc replacement and lumbar fusion, but over the long-term, it had approximately the same level of improvement on pain and physical function as lumbar fusion[4]. In addition, a combination of CBT and therapeutic exercise was found to be more effective in improving pain and physical function than general physiotherapy[4].

As for its effects on chronic cervical pain, compared with a group which did not undergo treatment, it was found to be effective on improving pain and physical function over the short-term, and effective on improving quality of life (QOL), but they did not find a clear difference in its effects on improving kinesiophobia and stress[5]. It remains unclear whether it is effective in improving pain and physical function over the short-term and mid-term, compared with other treatments[5]. However, it does improve kinesiophobia over the mid-term and over the short-term it is more effective in improving depression than other types of treatment[5], indicating its effects on psychosocial factors. Furthermore, they have not found whether CBT used in combination with other types of treatment (invasive treatment, pharmacotherapy, physiotherapy, therapeutic exercise, and manipulative therapy) has a clearly different effect on improving pain and physical function than other types of treatment, or not[5]. On the other hand, researchers have shown that compared with other types of treatment, it is effective in improving pain over the short-term in patients with sub-acute cervical pain but it remains unclear whether there is a clear difference in its effects on improving physical function and psychosocial factors, or not. However, as researchers have shown[5] that it is more effective than manipulative therapy in improving pain and physical function over the long-term, we expect it to be effective in preventing chronic pain.

QOL : quality of life

2) Patient education

Patient education, when implemented in isolation, does not have any different effects on the various forms of chronic pain over the short-term and mid-term in terms of improving pain, physical function, and psychosocial factors (catastrophizing, self-efficiency, depression)[6].

Yoga[2,3,7] and mindfulness[3,8,9] are more effective than education in improving pain and physical function in patients with chronic low back pain but over

the long-term, researchers did not find a clear difference between yoga and education in terms of how much they improved pain[2,3,7].

Compared with multimodal care, patient education has low costs but only a small effect on patients with acute to sub-acute cervical pain, without any accompanying neurological symptoms, but the therapeutic effects of implementing patient education alone, remain unclear[10-12]. Similarly, in patients with acute to sub-acute cervical pain with accompanying neurological symptoms, it remains unclear whether patient education alone is effective or not and researchers have not found[10,11] it to be effective compared with physical modalities, supervised exercise and massage conducted in isolation. Therefore, an intervention using patient education alone in the acute phase is insufficient in preventing chronic cervical pain.

Therefore, patient education can be effective when used additively with other types of treatment[10,11]. On patients with acute to sub-acute cervical pain, researchers have shown that it can be effective in reducing pain when used in combination with for example range of motion (ROM) exercises and manipulation, mobilization, and short-term progressive muscle relaxation[10]. Furthermore, education using videos has also been effective in reducing pain when used in addition to urgent care[10,11], and by using it additively in the acute stage of treatment, we expect that this will lead to a rapid reduction in pain and prevent chronic cervical pain. However, there have also been claims that physical modalities including self-care are more effective than oral advice provided to patients on one occasion[10,11]. Similarly with chronic cervical pain, it is recommended[10] that patient education be used in combination with other types of treatment (ROM exercises, muscle strengthening exercise, yoga, multimodal care, massage, physical modalities, drugs etc.) and a program which combines self-management based on an educational booklet has shown to be as effective as multimodal physiotherapy[10,11].

When it comes to the details and methods of patient education, it is recommended that patients are educated on their pain symptoms at the beginning of treatment, given an outline of the treatment plan and supported with their decision-making[13]. It is also important to give patients a feeling of reassurance by explaining to them the predictions for recovery[11,12] and also educate them on the efficacy of maintaining their activity level[10-12]. Comparing the effects of patient education according to the contents of the education program, neurophysiological education on pain, has shown to be more effective than other forms of education, in bringing about an immediate improvement in dysfunction and a medium-term improvement in catastrophizing thoughts in patients with chronic pain[6]. However, it remains unclear whether the contents of the education program have a different effect on improving the patient's feelings

about their own health and social function, or not[6]. In elderly patients as well, it remains unclear whether the contents of education programs have a different effect on improving their pain and physical dysfunctions, or not[6].

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Database	MEDLINE, PubMed, PEDro
Period	2010-2017
Words searched by the combination with 'chronic pain'	guideline, meta-analysis, RCT, randomized controlled trial, chronic pain treatment, lecture, CBT, cognitive behavioral therapy, behavioral medicine approach, behavior management, pacing, lifestyle management
*Notes	We ran a search based on these results and selected the references.

CQ45：Is orthotic therapy/taping effective in managing chronic pain ?

Answer： Even though there is insufficient evidence on the therapeutic effects of lumbar fixing belts and taping on chronic low back pain, there have been no reports of adverse events or side effects. Rather than benefits, as cervical collars have side-effects such as immobilization, and a decline in self-efficacy, we do not recommend them for cervical pain derived from whiplash-associated disorders (traumatic cervical syndrome), regardless of whether neurological symptoms are present or not.

Summary of recommendation grades and overall evidence：

1) Lumbar fixing belt, corset：No clear evidence for recommendation
2) Taping：No clear evidence for recommendation
3) Cervical collar：No clear evidence for recommendation

Commentary：

1) Lumbar fixing belt, corset

There is insufficient evidence to judge the therapeutic effects of lumbar fixing belt and corset on chronic low back pain[1]. While the evidence is low, they did not find a difference in effect on pain and function at the eighth week and third month between patients who underwent stretching alone and patients who did stretching with a lumbar fixing belt fastened[1]. Furthermore, when they compared a lumbar fixing belt with physical modalities, there was not a clear difference between their effects[2-4].

Like with other forms of rehabilitation and psychotherapy, while the evidence is low, there are no reports of serious adverse events due to the use of a lumbar fixing belt[5-9].

2) Taping

Kinesio taping, in which mainly the site of pain is radially taped, did not show any different effect compared with lumbar taping (taped on the horizontal axis), at the fifth week and twelfth week[10,11]. There were also reports[12,13], which showed with low evidence that compared with exercise, kinesio taping did not show any difference in effect on pain and dysfunction in patients with chronic low back pain and whiplash-associated disorders (WAD).

WAD：whiplash-associated disorders (traumatic cervical syndrome)

3) Cervical collar

As for its effects on WAD, in cases where there are no neurologic findings within three months after injury, we do not recommend a cervical collar, and patient education, which incorporates for example range of motion (ROM) exercise, is important. In cases where neurologic findings are present, in addition to patient education, it is important to conduct phased muscle-strengthening training of the neck muscles under supervision. In any case, cervical collars are

not effective and therefore not recommended. Furthermore, even when neurologic findings are present after injury, a cervical collar is not recommended and in the event that neck pain persists for three months or longer after injury and neurologic findings are present, the patient should undergo tests and treatment. There is one bias RCT with low evidence conducted on patients with neck pain persisting for up to three months or more after injury and with neurologic findings present, in which a multimodal program of therapeutic exercise and patient education, conducted individually over the short-to long-term, had similar therapeutic effects[15,17].

As for its effects on cervical radiculopathy within one month of onset, by using a combination of a semi-hard cervical collar and rest, in addition to neck-muscle strengthening training conducted twice a week, over a six-week course under supervision, it was found to have similar effects to at-home stretching, muscle-strengthening training, and relaxation[14].

However, as cervical collars have the latent risk that they might cause detrimental effects such as iatrogenic disorders, inactivity, poor physical health, and a lack of self-efficacy, they are not recommended[15-17]. In addition, they are also not recommended from the logical viewpoint that their harmful effects outweigh their benefits[18].

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Database	MEDLINE, CINAHL, PEDro
Period	2010–2017
Words searched by the combination with 'chronic pain'	guideline, meta-analysis, RCT, randomized controlled trial, chronic pain treatment, rehabilitation, physical therapy, physiotherapy, noninvasive therapies, nonpharmacological therapies
*Notes	We ran a search based on these results and selected the references.

CQ46 : Is multidisciplinary rehabilitation effective in managing chronic pain?

Answer : Multidisciplinary rehabilitation consists of not only a rehabilitation therapist but also a team of various medical practitioners who provide support in executing a rehabilitation program, towards achieving a common goal. Compared with general pain care and regular rehabilitation, as multidisciplinary rehabilitation is more effective in reducing pain and dysfunction in patients with chronic pain, it is recommended.

Summary of recommendation grades and overall evidence : 1A (Execution is strongly recommended)

Commentary :

Multidisciplinary rehabilitation is a form of rehabilitation performed by a team of medical practitioners who work in several different specialized fields. It can also be called multidisciplinary biopsychosocial rehabilitation, but the program contents and the types of medical occupations of which the team is comprised are not clearly defined. Therefore, there has been variance[1] in the details of multidisciplinary rehabilitation conducted in each RCT.

bio-psycho-social rehabilitation

RCT : randomized controlled trial

In a systematic review[1] on the effects of multidisciplinary rehabilitation on chronic low back pain persisting for twelve weeks or longer, compared with general pain care and regular rehabilitation (therapeutic exercise, physical modalities, manipulative therapy), they positively evaluated its effects on pain, dysfunction and helping patients return to work. Compared with general pain care and regular rehabilitation, pain had improved through multidisciplinary rehabilitation at three months after intervention and at twelve months after intervention, compared with prior to intervention. Dysfunction (evaluated by the Roland-Morris Disability Questionnaire [RDQ]) had also improved three months after intervention. In each case, it was unclear whether it was effective in helping patients return to work. In light of these results, a systematic review[1] concluded that there was high evidence indicating its effect on pain and dysfunction. The results were the same in other systematic reviews[2,3]. In addition, there are some other RCTs[4,5] which have reported that it was effective in preventing pain from becoming chronic in patients suffering from low back pain in the sub-acute phase.

RDQ : Roland-Morris Disability Questionnarie

According to a systematic review[6] on its effects on adult fibromyalgia, they recommend that treatment is multifaceted and multidisciplinary and listed the level of evidence as 'A1' (RCT meta-analysis) and gave a recommendation grade of 'A' (implementation is strongly recommended). Furthermore, multidisciplinary treatment improved pain and dysfunction (evaluated by the Fibromyalgia Impact Questionnaire [FIQ]) more than treatments conducted independently[6]. To be more specific, a non-pharmacological form of treatment should be prioritized, and among non-pharmacological treatments, the largest evidence exists for therapeutic exercise and cognitive behavioral therapy (CBT). As these treatments improved FIQ scores which evaluate pain and dysfunction, researchers state that multidisciplinary treatment including these should first be conducted and if this fails to alleviate pain and other symptoms, then it is okay to use pharmacotherapy[6]. Furthermore, some guidelines[7] have stated that the principles of self-management, using multidisciplinary treat-

FIQ : Fibromyalgia Impact Questionnaire

ment, should be incorporated when treating fibromyalgia.

Considering the above, we hope that multidisciplinary rehabilitation is spread throughout Japan.

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Database	MEDLINE, CINAHL, PEDro
Period	2010–2017
Words searched by the combination with 'chronic pain'	guideline, meta-analysis, randomized controlled trial, chronic pain treatment, rehabilitation, physical therapy, physiotherapy, noninvasive therapies, nonpharmacological therapies
*Notes	We ran a search based on these results and selected the references.

CQ47：What does the multidisciplinary team for chronic pain management consist of？ And what are the roles of its staff members?

Answer： A multidisciplinary treatment team consists of a wide variety of specialists from various fields and occupations such as doctors (physicians and psychiatrists and psychosomatic medical practitioners), dentists, nurses, clinical psychologists, physiotherapists and occupational therapists, pharmacists, managerial dieticians, social workers, and psychiatric social workers. Each team varies from institution to institution but in many cases, it fundamentally consists of doctors, nurses, physiotherapists, and clinical psychologists.

Commentary：

A multidisciplinary team for managing chronic pain consists of doctors, dentists, nurses, physiotherapists, occupational therapists, clinical psychologists, pharmacists, managerial dieticians, social workers, and psychiatric social workers . Each respective member of staff has an understanding of chronic pain from the biopsychosocial model and it is important that they make the most use of their knowledge and skills from their own specialty, when making evaluations and conducting treatment interventions[1–9].

Physicians such as orthopaedic surgeons, anaesthesiologists (pain clinic), rehabilitation doctors, neurologists and dentists etc.

Physicians evaluate biological pathophysiology. They also carry out the necessary tests and make a diagnosis on the pathology, manage the prescription of drugs, treat biological pathologies and undertake patient education.

Psychiatrists, Psychosomatic medical practitioners

They evaluate psychosociological, psychosomatic, and psychiatric pathologies, diagnose psychiatric diseases and treat these diseases.

Nurses

They listen carefully to patients' concerns and complaints, take and assess patients' medical history, collect data on vital signs, assist with tests and treatment as well as provide patient education, including for the patients' families, and guidance on lifestyle habits.

Physiotherapists

They run tests on and evaluate musculoskeletal function, realign the musculoskeletal system, teach patients self-care such as stretching, analyze one's work and lifestyle environment and provide physical realignment for this, and undertake physiotherapy education.

Occupational therapists

They train patients on the actions they need to take in order to lead a hindrance-free daily life.

Clinical psychologists

They provide psychosocial evaluations, counseling and patient education.

Pharmacists

They evaluate drug prescriptions such as when many drugs are being used in combination, provide suitable advice to doctors about drugs, and provide drug education for patients.

Managerial dieticians

They revise meals (nutrition), which form the basis of people's lives, and provide patient education to make them improve this.

Social workers

They provide patients with advice on things such as being accepted by the social security system for when they, for example, experience a reduction in income due to a leave of absence.

Psychiatric social workers

Psychiatric social workers assist patients suffering from mental health issues by helping them solve problems in their daily lives, and advising them on activities which will help them participate in society. They act as a liaison between the patients' healthcare and regional lifestyles.

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CQ48 : Is multidisciplinary treatment effective on chronic pain?

Answer : There is at least medium-level evidence which clearly shows the efficacy of multidisciplinary treatment on chronic pain.

Summary of level of recommendation and overall evidence : 1B (Execution is strongly recommended)

Commentary :

According to a systematic review from 2008 on multidisciplinary treatment, compared with a waiting-list group of patients and a group of patients who underwent regular treatment, there was strong evidence that multidisciplinary treatment was effective on chronic pain (chronic low back pain and fibromyalgia). Furthermore, there is at least medium-level evidence that multidisciplinary treatment was effective in comparison with physiotherapy, which included discussions held with the patients, and non-multidisciplinary treatment such as patient education. There is also medium-level evidence indicating that hospitalization programs are more effective than outpatient programs. In this report, cognitive behavioral therapy (CBT) was the main form of treatment conducted under multidisciplinary treatment. With outpatient programs, the duration of treatment was between 4 ～ 15 weeks, while with hospitalization programs, it was between 3～8 weeks. For doctors, part of this involves belonging to a treatment team, and their role is to manage and decrease dosages of drugs, and provide information on the pathophysiology behind the formation of chronic pain. In an investigation of the individual treatment contents, it was unclear whether there was a variance in treatment contents[1] or not. In a report of a meta-analysis which compared the methods of treating chronic pain, they did not find a clear difference in pain and dysfunction among three groups which used a combination of physiotherapy, behavioral therapy and psychotherapy[2]. However, strictly classifying the treatment content of these three groups is difficult. In a meta-analysis of multidisciplinary treatment conducted on patients who were on leave of absence due to chronic pain, multidisciplinary treatment was found to be clearly useful in helping them return to work[3]. In a meta-analysis of intensive multidisciplinary treatment using bio-psychosocial rehabilitation, they found strong evidence that it was effective on physical function due to chronic low back pain. There was also medium-level evidence of its effects on pain[4]. In a systematic review on treatment of headache accompanying cervical pain, researchers showed that therapeutic exercise was essential, and multidisciplinary treatment was useful[5]. As for the costs incurred by multidisciplinary treatment, as the contents of the multidisciplinary treatment and the health insurance system in each country is different,

bio-psycho-social rehabilitation

this needs to be investigated in future[6].

There are no RCTs in Japan, but there are several case reports, which have reported on the efficacy of multidisciplinary treatment[7,8].

RCT：randomized controlled trial

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Database	Cochrane Central Register of Controlled Trials, PubMed, EMBASE, etc
Period	2005～2017
Words searched by the combination with 'chronic pain'	RCTs, multidisciplinary, interdisciplinary, patient care team, back pain, fibromyalgia, chronic pain syndrome, physical / behavioral / psychological / combined intervention, spinal pain, chronic, RCT, back pain, rehabilitation, return to work, sick leave, work injury, disability pension
*Notes	We ran a search based on these results and selected the references.

CQ49：Is group cognitive behavioral therapy (teaching group education behavior) effective on chronic pain?

Answer： With the management of chronic pain, group cognitive behavioral therapy (CBT) has approximately the same effects (medium-level efficacy) as individual treatment. On the other hand, from a cost-effectiveness perspective,

group treatment programs are clearly superior to individual treatment.

Summary of recommendation grades and overall evidence : 1B (Execution is strongly recommended)

Commentary :

A meta-analysis has medium-level evidence that group cognitive behavioral therapy is effective in treating chronic pain[1]. When they investigated the effects of a multidisciplinary program, which had incorporated both cognitive behavioral therapy and physiotherapy, conducted over several weeks, on individuals and groups, they found a significant improvement in both cases. The individual multidisciplinary program and the group multidisciplinary program had approximately the same efficacy[2,3]. In addition, in other research reports in which RCTs were conducted, they reported that group treatment programs were more effective than standard treatments but they did not find a significant difference when comparing them with multidisciplinary programs conducted by individual patients[4,5]. However, from a cost-effectiveness perspective, group treatment programs are clearly superior. In Japan, although it was not a RCT research study, there was one report that group multidisciplinary treatment was effective[6].

RCT : randomized controlled trial

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1) Scascighini L, et al : Multidisciplinary treatment for chronic pain : A systematic review of interventions and outcomes. Rheumatology 2008 ; 47 : 670-678
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Database	Cochrane Central Register of Controlled Trials, PubMed, EMBASE, etc
Period	2006～2017
Words searched by the combination with 'chronic pain'	RCTs, multidisciplinary, interdisciplinary, patient care team, back pain, fibromyalgia, chronic pain syndrome
*Notes	We ran a search from these results and selected the reference.

CQ50 : How should we begin multidisciplinary treatment in managing chronic pain?

Answer : When commencing multidisciplinary treatment on chronic pain, healthcare professionals from each discipline who are involved in multidisciplinary treatment, need to acquire anatomical and physiological knowledge on the perception of pain. They also need to have an understanding of the psychosocial factors which can have an effect on pain perception, and after they have an understanding of the fundamental principles of pain treatment, it is important that they have a shared awareness of treating patients along the lines of a biopsychosocial model.

Commentary :

When commencing multidisciplinary treatment, there is a need to bring together practitioners from various medical specialties who are both knowledgeable and willing to treat patients suffering from chronic pain. Furthermore, it goes without saying that healthcare professionals from various disciplines who are involved in multidisciplinary treatment need to have knowledge of the area of their respective specialty, an understanding of anatomical and physiological knowledge, the psychosocial factors which can have an effect on pain perception, and need to continue to have a sound understanding of the basic principles of pain treatment. As for the areas of expertise practiced by other practitioners participating in multidisciplinary treatment, one needs to have a sound understanding of what kind of basic treatment interventions they are conducting within multidisciplinary treatment as a whole[1,2]. On top of this, it is also necessary to have a shared awareness of conducting treatment along the lines of a biopsychosocial model. Therefore, they need to share their philosophies, work duties and treatment goals and need to secure enough time and space in order to be able to discuss how to put these things into practice adequately. As for treating individual patients, healthcare professionals from each discipline involved in multidisciplinary treatment need to have an understanding of the patients' backgrounds, the pathology of patients with chronic pain, the treatment plans, the treatment methods and types, as well as the overall ultimate aims and also need to be unified when proceeding with treatment.

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CQ51：What are the purposes and ultimate goals of multidisciplinary treatment for chronic pain?

Answer： The purpose of multidisciplinary treatment is to improve the patient's physical and emotional function, and its ultimate goal is to bring about an overall improvement in quality of life (QOL)[Note 19].

Note 19：refer to p.182
QOL：quality of life

Commentary：

The degree to which we are able to improve QOL varies from patient to patient and so prior to treatment, we need to conduct a multidisciplinary evaluation of the factors causing the patient's pain and then decide on the ultimate goals.

In general pain syndromes such as chronic low back pain, it is difficult to completely remove the pain but when patients try to stop moving as little as possible in order to avoid the pain, physical function sharply declines out of disuse. If patients are dominated by their pain, their emotional function also becomes impaired and their overall QOL declines. Therefore, a purpose of chronic pain treatment is, first of all, to improve their physical function, and even if there is pain, by making them experience some degree of activity, they are able to regain their confidence. As a result of this, they are able to recover their emotional function, which had been impaired by their pain[1–3]. By enacting control over their pain through pharmacotherapy and control over their physical function through therapeutic exercise, our final goals for the treatment is to create a situation in which patients become independent in their everyday lives, and fulfill the roles (jobs) they can do by themselves. It is possible to foster independence among elderly patients and patients with developmental brain disorders by using a support system such as a regional comprehensive support center. We could also consider using administrative services, such as hiring social workers. Furthermore, in cases where patients are on leave of absence from their jobs or have left their jobs due to pain, our ultimate goal is also to improve their physical and emotional functions up until the time when they are able to return to work or find new employment.

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