Clinical Practice Guidelines for the Management of Chronic Pain

The Committee for Clinical Practice Guideline for the Management of Chronic Pain

The Japan Society of Acupuncture and Moxibustion
Japanese Association for the Study of Musculoskeletal Pain
Japanese Society of Orofacial Pain
The Japanese Headache Society
Japan College of Fibromyalgia Investigation
Japanese Association for the Study of Pain
Japan Society of Pain Clinicians
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

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Preface

Not just in the lives we lead every day, but in every respect, such as our academic and clinical activities, we have been largely affected by the COVID-19 pandemic in 2020 and as of February 2021, when this preface was written, although vaccinations have begun, we still cannot foresee at the present time what future restrictions will be like. Both various domestic and overseas conferences on pain which contribute towards pain research and the ongoing development of pain management have also been largely affected, forcing us to either cancel these conferences or hold them online. Under such circumstances, there is a large number of patients who are suffering from chronic pain and intractable pain through daily treatment and our activities need to continue to constantly make further advances forward. We are praying that our daily living situation will be restored as quickly as possible.

As mentioned in the preface to *Clinical Practice Guidelines for Chronic Pain*, published in 2018, research on pain has developed significantly over the past 40～50 years, during which time a rich diversity of attractive theories, among other publications, have been published, closing in on the mechanisms of pain and the causes of chronic pain. There have also been trials of drug discoveries based on what has been revealed about these mechanisms. Of course, new drugs have certainly brought about major developments and changes to the management of pain, many of which have been outlined in these guidelines. However, whether these new revelations about pain mechanisms have directly led to the development of actual drug discoveries and forms of treatment or not, still remains problematic. We are still unable to eschew the viewpoint that pain as a target is unlikely to lead to groundbreaking drug discoveries or forms of treatment, for various reasons. Some of these reasons include that pain is a subjective sensation and is therefore difficult to quantify, tends to undergo psychological and emotional embellishments, and our pain-receiving system tends to indicate changes in plasticity, making it difficult for us to analyze and understand it.

Despite the existence of these various challenges, thanks to the hard work of a large number of clinicians and researchers from all over the world, as well as campaigns to raise awareness, we have seen an incredible amount of change and progress in clinical pain management over the past decade. Japan, which used to be decades behind the West, has clearly made progress in the management of cancer pain and pain alleviation treatment, saving a large number of patients. Without any doubt, what we clinically need to tackle next is the extremely high number of patients suffering from chronic non-cancer pain. A vast amount of national wealth has been lost due to chronic pain, requiring us to tackle this issue effectively. Furthermore, it is not possible for us to save individual patients unless we deal with chronic pain. The Japanese government has implemented administrative policies on various types of illnesses, such as for treating can-

cer, lifestyle diseases, infectious disease, and mental illnesses, although the field of chronic pain disease has been left out like an air pocket. However, thanks to the hard work of a large number of people over the past decade and more, we are extremely delighted that measures on pain management are now being put forward as federal programs.

In this context, in 2018, 'Research on Constructing a System for the Treatment and Education of Chronic Pain Problems' was put forward as a part of Health, Labour and Welfare Policy Research (Research on Chronic Pain) (Research Representative : Takahiro Ushida, MD, PhD) and in cooperation with a pain consortium, comprised of 7 academic committees, tackling chronic pain across the various disciplines, they devised the 'Clinical Practice Guidelines for Chronic Pain.' In this revised edition, the guidelines were created under 'Research for the Uniform Accessibility to Chronic Pain Management Systems and Improved Healthcare Utilizing Pain Center Treatment Databases,' (Research Representative : Shoji Yabuki, MD, PhD), put forward by the MHLW Research Group as part of Health, Labour and Welfare Policy Research (Research on Chronic Pain), along with 8 academic societies and organizations belonging to the Union of Pain-related Associations in Japan (Japanese Association for the Study of Musculoskeletal Pain, the Japanese Society of Orofacial Pain, the Japanese Headache Society, 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 (JSSCP), and the Japanese Society of Lumbar Spine Disorders) in addition to representatives from two societies and organizations (the Japan Society of Acupuncture and Moxibustion, and the Japan College of Fibromyalgia Investigation (JCFI)) as well as other observers and those involved in chronic pain. We received positive feedback on the previous guidelines, more than we could have possibly ever imagined, from a large number of physicians and with this revised edition, we have been able to provide updates and improve sections that we had been unable to cover in the previous edition.

In closing, in creating these guidelines, we wish to take this opportunity to express our heartfelt gratitude to everyone from the MHLW Research Group, all doctors and physicians from the 10 societies and organizations, as well as everyone who was involved in the creation of this revised edition.

March, 2021
President of the Japanese Society for the Study of Pain (JASP)
President of the Hyogo College of Medicine
Koichi Noguchi, MD, PhD

Introduction

In 2020, the International Association for the Society of Pain (IASP) revised its definition of pain. Pain is "an aversive sensory and emotional experience typically caused by, or resembling that caused by, actual or potential tissue injury." There has been no change to the basic gist of what constitutes pain, but in the Japanese translation, we have emphasized "aversive (unpleasant) experience." Chronic pain, which is the subject of these guidelines, refers to 'pain that persists for a long time beyond the normal period required for healing trauma or disease that is the underlying cause of the pain.' As an unpleasant or aversive experience persists for a long period of time, it is easy for us to imagine how this adversely affects work, school and daily life.

A large number of guidelines on treating or managing diseases have been published to date, but there are hardly any guidelines on treating symptoms. In this context, the *Clinical Practical Guidelines for Chronic Pain* were published in 2018, eliciting a large response from its readers and this volume constitutes a revised edition of the 2018 edition.

Creation of the guidelines

The previous guidelines were created by experts from all over Japan, with contributions from 7 societies and associations : Japanese Association for the Study of Musculoskeletal Pain, Japanese Society of Orofacial Pain, Japanese Association for the Study of Pain, Japan Society of Pain Clinicians, 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. Although it was no easy task for these cross-disciplinary societies and associations to collaborate and accomplish something together, through the cooperation of these 7 societies and organizations, they were able to achieve something remarkable. However, due to the limited amount of time prior to publication, some aspects were unsatisfactory, such as citation analysis, deciding on evidence and determining the recommendation grades. This time round, in addition to the 7 previous societies and associations, the Japan Society of Acupuncture and Moxibustion, the Japanese Headache Society and Japan College of Fibromyalgia Investigation were also included, meaning that a total of 10 societies and associations have participated in this project. Representatives from patients' associations have also been included, and where necessary we have referred to their opinions as well. I believe that we have indeed created even deeper guidelines on chronic pain, encompassing a wider representation from all over Japan. In addition, learning from the past, our physicians involved in the creation of these guidelines undertook workshops held by the Japan Council for Quality Health Care Minds Guidelines Center (also known as 'Minds'). They were able to learn about the current methods and policies for creating guidelines before proceed-

ing with the creation of these guidelines. Furthermore, it was most reassuring to hear the opinions of specialists from Minds on a variety of different occasions.

Our basic philosophy behind the creation of these guidelines

When making these guidelines, we discussed what kinds of chronic pain we would address and decided to address adult chronic pain, but not chronic cancer pain. Moreover, we created items on frequently-occurring diseases, deciding to create guidelines that would be even more helpful for our readers. We have assumed that our readers would consist of medical practitioners involved in treating or managing patients with chronic pain. As a wide variety of specialists from various professions are involved in the management of chronic pain, we have aimed for something useful not only for physicians but for other medical staff as well. There are various forms of chronic pain treatment that are being implemented. We think that medical practitioners are choosing a treatment method that they themselves believe matches with the patient. However, unfortunately evidence has not always been established across the board. We have emphasized evidence in these guidelines. As there is a wide variety of patient diseases, points of evaluation and patient background, there were many CQs in which we were unable to summarize information through meta-analysis. In these cases, we conducted qualitative synthesis and decided on a level of evidence, keeping in mind our effort to make it helpful to readers. There were more than a few instances in which high-quality helpful research papers were only available overseas. This does not necessarily mean that all of the results from these overseas research papers match and conform with the management of chronic pain in Japan. In meetings during which we decided upon a recommendation grade, we emphasized these points as well during our discussion. In the CQs, there are cases where the recommendation grade is not high, even though the (quality of) evidence is, and vice versa. We kindly ask readers to understand that this is a result of our efforts to make the guidelines match and conform with the situation in Japan.

Methods utilized

First of all, what we kindly ask from our readers is not to just look at the evidence and recommendation grades and nothing else. Please make sure to read our answers and commentary. Some may feel something odd about the evidence and recommendation grades provided in our CQs, depending on the type of profession, specialty, and the level of experience of the individual reader, but we believe readers should be able to understand the reasons and justifications for why a certain recommendation grade has been listed. In some cases, the recommendation for the same type of treatment may vary depending on the CQ. There are also some instances in which the results of research papers which have focused on chronic pain in general (overall chronic pain) and those which have focused on specific diseases are different. As we have provided a

summary of these, in a certain sense, it is natural for the evidence and recommendation grades to vary. We would like our readers to first refer to these guidelines and conduct or implement treatments and diagnoses that are recommended and which have accumulated a high amount of evidence. However, each individual patient has a different background and underlying causes for their pain. Ultimately, the medical practitioner will choose a treatment method that (s)he thinks is best suited to the patient. This is because the medical practitioner attending to the patient knows that patient best. After considering the information contained in these guidelines, if our readers then think about what would be best for their particular patients, then the makers of these guidelines will feel that their efforts have been rewarded.

Acknowledgements

These guidelines were created thanks to the cooperative efforts of a large number of people. We received a large number of useful public comments from everyone belonging to the societies and associations. Thank you very much. I would especially like to acknowledge the efforts and hard work of Dr. Hisashi Date from the Sendai Pain Clinic, as the committee leader in successfully completing these guidelines which encompass all of Japan. There were some discussions in which it seemed like we had reached a deadlock, but Dr. Date skillfully brought these members together and pushed onwards. Thank you sincerely.

Furthermore, I also cordially wish to thank Mr. Yukio Morita who checked and edited the manuscript from its incipient stages, Dr. Masako Watanabe of the Publication Department of Medical Books, Shinko Trading Company (Ltd.), Mr. Matthew McLaughlin who translated the original Japanese manuscript, which underwent numerous changes, into English, and Ms. Kyoka Ito from the Department of Orthopaedic Surgery, School of Medicine, Fukushima Medical University, who has worked behind the scenes as the secretariat supporting this project.

It is our sincere wish that these guidelines will prove to be useful for everyone involved in the management of chronic pain and in future if some issues arise, we hope that our next revised edition will offer even better guidelines including the latest available evidence.

March, 2021
Health, Labour and Welfare Policy Research Grants (research on chronic pain)
Research for the Uniform Accessibility to Chronic Pain Management Systems and Improved Healthcare Utilizing Pain Center Treatment Databases
Research Representative : Shoji Yabuki, MD, PhD

Preparative Method of these Guidelines

The Committee for Clinical Practice Guidelines for Chronic Pain

These guidelines act as a second volume, continuing on from *Clinical Practice Guidelines for Chronic Pain*, published in 2018. This volume features not only treatments for chronic pain but also a discussion of diagnosis, assessment and typical chronic pain illnesses. Just like with the previous volume, *Clinical Practice Guidelines for Chronic Pain*, these guidelines are different from the various guidelines issued by the societies and associations, as they have been constructed by the Committee for Clinical Practice Guidelines for Chronic Pain, which is comprised of specialists from various pain-related medical occupations and departments, and executed under the supervision of the MHLW Research Group, as 'Research for the Uniform Accessibility to Chronic Pain Management Systems and Improved Healthcare Utilizing Pain Center Treatment Databases.'

Basic structure of these guidelines

The structure of these guidelines was itemized in accordance with the medical-information service, 'Minds Handbook for Clinical Practice Guideline Development 2017,' adopting the basic structure of clinical questions (CQs), answers, recommendation grades, level of evidence, and commentary. For those CQS where we thought level of evidence and recommendation grades were not necessary, we have limited our discussion to answers and commentary only.

Preparation of clinical questions (CQs)

The clinical questions were devised from the debate and discussion conducted through 'Plenary Sessions of the Committee for Clinical Practice Guidelines for Chronic Pain' (Plenary Sessions), comprised of members of the committee responsible for creating these clinical practice guidelines (CPG), academic experts from Minds (observers), nursing representatives, and representatives from patient associations.

In our previous Clinical Practice Guidelines for Chronic Pain, we decided to conduct evaluations by dividing the recommendation grades for CQs on pharmacotherapy into 'Musculoskeletal Pain,' 'Neuropathic Pain,' 'Headache/Orofacial Pain,' and 'Fibromyalgia Pain' (of the 7 IASP categories for chronic pain (Table A-1), we excluded the 4 categories of 'Cancer Pain', 'Post-surgical / Traumatic Chronic Pain' and 'Chronic Visceral Pain'). However, in these guidelines, as evaluations were made according to the main disease categories of chronic pain and also because some drugs did not fit or match with these categories, we decided on a recommendation grade through a holistic evaluation of the drugs.

Searching for citations

In line with the CQs that had been selected, our CPG committee in cooperation with our systematic review team ran searches for references and citations. In principle, searches ranged from between 2005 to 2020. In our search for references, our method was to utilize MEDLINE, Cochrane and the NPO Japan Medical Abstracts Society to extract citations listed in each CQ. With important references, we incorporated citations from prior to 2005 and if the references were deemed to be important, we searched for them manually and added them to the selection.

Levels of evidence

With the levels of evidence for the CQs, we conducted a systematic review of each outcome, with the 5 important outcomes in mind for each CQ, and referred to for example the assessment sheet on the overall evidence of each research paper, their SoF (summary of findings), and evidence to decision (EtD) frameworks and following the 'Minds Handbook for Clinical Practice Guideline Development 2017,' we made decisions after taking into consideration the discussion and debate that took place in the Plenary Sessions.

The summations (overall strength of evidence regarding the general outcomes) of the overall evidence for each CQ are as follows:

- **A (high)**: We are very confident that the effect of the study reflects the actual effect;
- **B (moderate)**: We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different;
- **C (low)**: The true effect may differ significantly from the estimate;
- **D (very low)**: The true effect is likely to be substantially different from the estimated effect.

Determining a recommendation grade

Recommendation grades were determined after taking into consideration a balance between benefits (benefits, profits, usefulness) and risks (harm, disadvantages). In principle, forms of treatment that are covered under the scope of the Japanese health insurance system are considered but we decided to also recommend forms of treatment that were not covered by health insurance if they were believed to be useful overseas or based on the evidence.

When deciding on a recommendation grade, votes were cast in the Plenary Session, and we determined the grade when we reached a consensus rate of 80% or higher. If votes did not reach a 80% consensus result, we would hold another discussion in a Plenary Session and cast a second round of votes. In cases where we failed to obtain 80% consensus or higher, even after 3 rounds of voting (in cases where we had trouble agreeing on the same point of view in the Plenary Session), we then assigned a "no rec-

ommendation" grade and also listed the final voting results. Furthermore, in cases where there were no high-quality research papers, and we could not decide on a strength of recommendation, we assigned a "no recommendation" grade and also listed the consensus rate. Therefore, in cases of "no recommendation," in some cases, we had a consensus rate of 80% or higher, but we were unable to decide upon a recommendation grade due to insufficient evidence, and in some cases where several recommendation grades were listed with the consensus rate, we were unable to agree upon a unified point of view at the Plenary Session.

The way we listed the strength of our recommendations was conducted in accordance with the 'Minds Handbook for Clinical Practice Guideline Development 2017,' and are as follow.

1：(Non-)implementation is strongly recommended；
2：(Non-)implementation is weakly recommended.

Opinions from related societies & associations

This time we solicited public comments from the presidents, trustees, and members of the 10 pain-related societies and associations who were involved in the creation of the guidelines (The Japan Society of Acupuncture and Moxibustion, the Japanese Association for the Study of Musculoskeletal Pain, the Japanese Society of Orofacial Pain, The Japanese Headache Society, Japan College of Fibromyalgia Investigation, Japanese Association for the Study of Pain, Japan Society of Pain Clinicians, Japanese Association for the Study of Pain Rehabilitation, Japanese Society for the Study of Chronic Pain, and the Japanese Society of Lumbar Spine Disorders). We also solicited public comments from the Japanese Society of Neurological Therapeutics, Japanese Society of Psychosomatic Medicine, the Japanese Orthopaedic Association, The Japan Neurosurgical Society, and the Japanese Society of Anesthesiologists. We judged whether to accept or reject the opinions we had received during the Plenary Session and added some revisions to certain sections.

Conflict of interest (COI)

All members who were involved in the creation of these guidelines were subject to potential conflict of interest and in accordance with the regulations on conflict of interest as outlined in the "the Policy of Conflict of Interest (COI) in Medical Research" guidelines by the Japanese Association of Medical Sciences (JAMS), in cases where information disclosure standards were exceeded, we have listed the names of the corporation or names of the committee members.

Indications for treatments

When devising these guidelines, we consciously tried to make them easy to utilize for a large number of chronic pain-related medical practitioners, nursing representatives

and patient association representatives also participated in this project and therefore we have consciously tried to reflect many of their comments as well.

When using these guidelines, we ask medical practitioners not to just read the recommendation grades ; we ask you to read through the CQ main text, answers, and commentary sufficiently before considering whether, for example, to implement or prescribe. We would also greatly appreciate it if you could also refer to the guidelines issued by the various related societies and associations. Finally, we would like to clearly state that these guidelines are something to be of clinical use for chronic pain and not something to be used as materials for example in a court of law.

The Committee for Clinical Practice Guidelines for Chronic Pain
Chairman Hisashi Date, MD, PhD

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※ Disclosure of Conflicts of Interest

Note a：※ A-6：Eli Lilly Japan, A-7：① Kyocera, ② Stryker Japan, ③ Hosoki Hospital, ④ Kubokawa Hospital, ⑤ Suzaki Kuroshio Hospital, ⑥ Kochi Takasu Hospital, ⑦ Fujiwara Hospital, ⑧ Atago Hospital, ⑨ Shiragikuen Hospital , ⑩ Nangoku Chuo Hospital, ⑪ Maeda Hospital

Note b：A-6：① Teijin-Frontier, ② Dai-ichi Life Foundation, ③ IASP・JASP・Pfizer, A-8：① Nippon Zoki Pharmceutical, ② Ayumi Pharma, ③ Ono Pharma, ④ SOMPO Japan, ⑤ MS & AD InterRisk Research & Consulting,Inc, ⑥ Chugai Pharma, ⑦ The Association for Preventive Medicine of Japan, ⑧ Shionogi Pharma , ⑨医療データサイエンティスト医療 AI 機器開発機構 , ⑩ MTG

Note c：A-1：シーエックスサービス, A-4：① Daiichi-Sankyo, ② Ayumi Pharma, ③ Eisai, ④ MSD, ⑤ Mochida Pharma, ⑥ Janssen Pharma, ⑦ Mundipharma, A-6：① P Mind, ② Asahi-kasei, Pfizer, A-8：Nippon Zoki Pharmceutical

Chapter A. Overview : CQ A-1～CQ A-5

CQ A-1 : What kind of condition is chronic pain ? (How do we define “chronic pain” ?)
CQ A-2 : What kinds of classifications are there for chronic pain ?
CQ A-3 : What are the characteristics of patients with chronic pain ?
CQ A-4 : What are the purposes and ultimate goals of chronic pain management ?
CQ A-5 : Is there a placebo effect in chronic pain management ?

A. Overview

CQ A-1 : What kind of condition is chronic pain ? (How do we define 'chronic pain' ?)

Answer : Chronic pain refers to 'pain that persists or recurs for more than 3 months, or pain that continues beyond the normal period required for healing.'

Commentary :

The International Association for the Study of Pain ('IASP') defines pain as "an aversire sensory and emotional experience typically caused by, or resembling that caused by, actual or potential tissue injury."[1]. Chronic pain refers to pain that typically persists for a period of three months or more, or pain that continues beyond the normal period required for healing. On the other hand, because chronic pain persists beyond the regular period of time of an acute disease or the appropriate length of time required for tissue to heal, some believe that it follows no particular length of time. These guidelines do not define specifically designated illnesses as chronic pain illnesses and we have decided to consider it as a condition, based upon the IASP's definition.

Pain sensitization (peripheral sensitization and central sensitization) is involved in the pathology of chronic pain and its mechanism is believed to be caused by changes in nerve plasticity through repetitive stimulation.

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

IASP : International Association for the Study of Pain

pain sensitization : A condition of exacerbated reactivity of nociceptive neurons to standard input and reaction to input below the normal threshold

peripheral sensitization : A condition of exacerbated reactivity of peripheral nociceptive neurons to a receptive field stimulus and reduced threshold

central sensitization : Exacerbated reactivity of central nervous system nociceptive neurons to standard centripetal input or that below the threshold

plasticity : Originally a term from physics, meaning when an extra external force is applied, it is unable to go back to the original state even after the force disappears. With regards to nerves, through repetitive stimulation, the functions of the sensitive nerves cannot be restored even after the stimulus disappears and a sensitized state persists

mixed pain condition

CQ A-2 : What kinds of classifications are there for chronic pain ?

Answer : Chronic pain is classified for example by pain syndrome and mechanism. Evaluating the pain syndrome or mechanism leads to both diagnosis and treatment.

Commentary :

Chronic pain has several classifications. When classifying by pain factors, there are nociceptive pain, neuropathic pain, psychosocial pain and others[3]. When the pain becomes chronic, its cause is seldom exclusively due to one of these three factors and in many cases it is a complex mixed pain condition involving several causative factors.

Table A-1 IASP Chronic Pain Classifications (ICD-11) (Cited from References #4 and #5)

1. Chronic primary pain
   - 1.1. Widespread chronic primary pain (including fibromyalgia syndrome)
   - 1.2. Localized chronic primary pain (including non-specific low 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 A1]
   - 2.2. Chronic chemotherapy-induced pain
   - 2.3. Chronic pain due to cancer surgery
   - 2.4. Chronic pain due to radiotherapy
   - 2.x. Other cancer-related chronic pain
   - 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 indicated
5. Chronic headache and orofacial pain
   - 5.1. Chronic primary headaches
   - 5.2. Chronic secondary headaches
   - 5.3. Chronic orofacial pain
   - 5.z. Chronic headache and orofacial pain not otherwise indicated
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 mechanism
   - 6.6. Chronic visceral pain referred from other locations
   - 6.7. Chronic visceral pain from cancer
   - 6.8. Functional or unexplained chronic visceral 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 diseases of the nervous system
   - 7.4. Chronic non-specific musculoskeletal pain
   - 7.x. Other chronic musculoskeletal pain
   - 7.z. Chronic musculoskeletal pain not otherwise specified

※ As the ICD-11 is revised regularly, readers should refer to the lastest version

Note A1 : "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 A-2 Acute Pain and Chronic Pain, Intractable Chronic Pain (Cited from Reference #7)

	Acute Pain	Chronic Pain	
		Chronic pain which is a repetition of acute pain Chronic pain which is protracted chronic pain	Intractable chronic pain
Cause of pain	Stimulation of nociceptors	Stimulation of nociceptors	Functional changes in 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 (3 months <)
Main accompanying symptoms	Hyperactive sympathetic nerves (Hyperacute period)	Sleeping disorders, loss of appetite, constipation, inhibition of daily living activities	Sleeping disorders, loss of appetite, constipation, inhibition of daily living activities
Main psychological symptoms	Anxiety	Depression, anxiety, catastrophizing	Depression, anxiety, catastrophizing

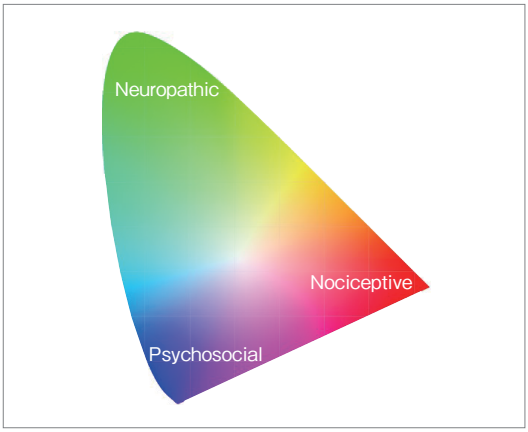

Figure A-1 Pain Model Diagram (Cited from Reference #8)
There are 3 factors related to pain : 'nociceptive' : 'neuropathic' : and 'psychosocial'.

IASP : International Association for the Study of Pain

multiple parenting

IASP recommends seven classifications of chronic pain to the ICD-11[4,5] (Table 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]. Sometimes an item overlaps with another item and this is recognized as multiple parenting[6].

For the classification based on the mechanism causing chronic pain, we have assumed the concepts in Table 2[7] and Figure 1[8]. The modality is also involved in these classifications and the stronger the psychosocial factors, the more frequently it becomes difficult to treat.

Table A-3 Factors which are related to Main Non-pain Symptoms / Signs Exhibited by Chronic Pain Patients

1. Cognitive / Emotional Factors
   Depression, anxiety, loss of appetite, anger, catastrophizing, 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, economic stress
4. Spiritual Factors
   Decline in feelings of self-worth, decline in self-efficacy
5. Other Factors
   Litigation, excessive expectations from medical institutions, dependence on treatment (medication)

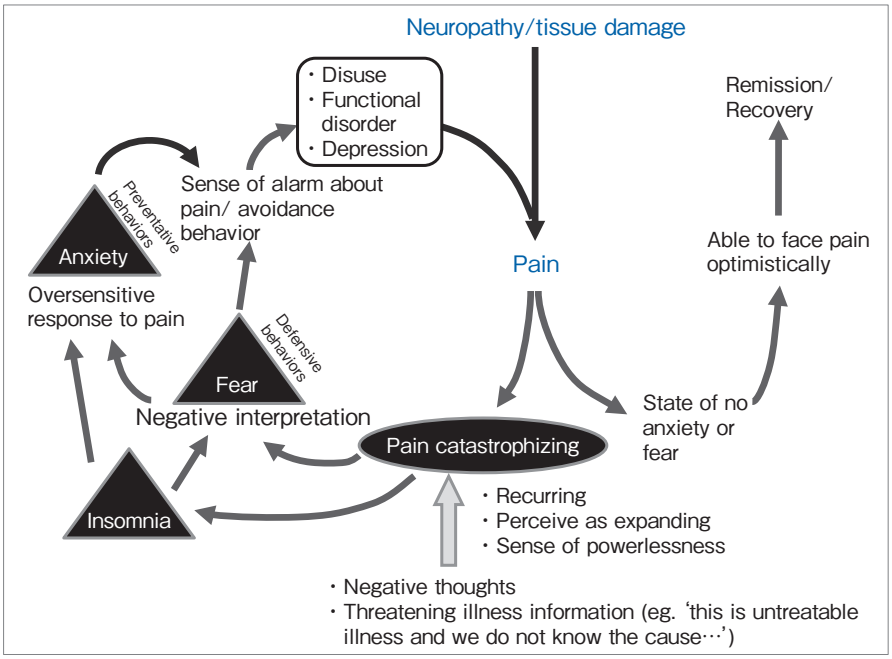

Figure A-2 Fear-avoidance model of pain (Partly cited from Reference #11)
This shows how pain becomes intractable and serious through a cyclical interaction with psychosocial factors as the pain lingers.

CQ A-3 : What are the characteristics of patients with chronic pain ?

Answer : Among patients with chronic pain, many display a variety of symptoms and signs apart from pain.

Commentary：

Chronic pain patients exhibit a wide variety of symptoms and signs as the duration of pain increases (Table A-3). Depression is a typical symptom. Conclusions have yet to be reached on whether the stress caused by pain is triggering feelings of depression or whether a state of depression is triggering the pain as a physical symptom[9]. When the pain lingers, it becomes intractable and serious through a cyclical interaction with psychosocial factors. As the fear-avoidance model of pain illustrates, when the pain becomes intractable, it often involves catastrophizing[10]. In this way, signs such as immobilization and disuse appear, triggering a decline in activities of daily living (ADL) (Figure A-2)[11]. When pain persists over a long period of time, it affects one's work and academic life. Factors such as loss of fixed employment can also lead to a decline in the quality of social activity, a deterioration in one's sense of belonging in the family and economic stress leads to a deterioration in perceptions of self-worth. As a result, this leads to a vicious cycle of a decline in quality of life (QOL) and the occurrence of lifestyle disorders[12].

ADL：activities of daily living

QOL：quality of life

CQ A-4：What are the purposes and ultimate goals of chronic pain management？

Answer： It is difficult to attain a pain-free condition in patients with chronic pain. Reducing pain is one of the purposes and ultimate goals of chronic pain management but not the primary goal. The goal of medical practitioners should be to manage chronic pain while at the same time improving the patient's QOL and ADL.

QOL：quality of life

Commentary：

The IASP defines chronic pain as "pain that persists longer than the expected period of time required to treat an illness or disease"[13]. There are no clear guidelines on duration but it is generally considered to be pain that persists for three months or more. In addition to a wide variety of organic factors involved in chronic pain, non-organic factors, such as psychosocial factors, and central sensitization and cognition of the nervous system are also largely involved. Therefore, it is extremely difficult to completely rid patients of a pain in which these complex factors overlap.

IASP：International Association for the Study of Pain

The Guidelines for the Treatment of Chronic Pain[14] by ASA and ASRA cite the following four items as their treatment purposes and ultimate goals.

ASA：American Society of Anesthesiologists

ASRA：American Society of Regional Anesthesia and Pain Medicine

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

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

Medical practitioner should set the treatment goals with their patients and confirming the degree to which these goals are attained is important to obtain sound treatment outcomes. Therefore, feasible, positive and specific treatment goals are set. Furthermore, psychological factors that modify pain such as depression, anxiety and dissatisfaction and a behavioral assessment should be conducted and if necessary, an emotional approach should be adopted to reduce these factors. In any case, in order to have a diversity of expression to reflect aspects such as the patient's living circumstances regarding pain, his/her behavioral patterns and individual character, we are required to set treatment goals that are finely tailored to each individual case. External gains such as money and compensation are major factors affecting pain behavior. Therefore, the medical practitioner must exercise caution when observing whether or not such factors might be involved[15].

CQ A-5 : Is there a placebo effect in chronic pain management ?

Answer : A large number of previous papers indicate that there is a placebo effect in the management of chronic pain.

Commentary :

The 'placebo effect' is a phenomenon by which a patient feels effects such as an improvement in his/her symptoms through an intervention that is essentially believed to be medically ineffective (including administering medication, intravenous injection, surgery, various forms of intervention, and alternative medicine).

The placebo effect has come to be widely known following reports from the 1950s[16]. Pain is a subjective experience to the patient and it is believed that a large percentage of placebo effects can be accounted for by treatments that have the purpose of alleviating pain. However, before the placebo effect itself was able to be considered as something which brings about the effect of alleviating pain, it first had to go through a long history of being treated as something of a nuisance[17]. There have also been some reports that have cast doubt on the actual placebo effect[18]. However, recently, some researchers believe in actively utilizing the placebo effect in the treatment of pain[17,19,20].

In clinical settings, placebos are used to judge the effect of many analgesics and in many research studies, including randomized controlled trials (RCTs), they have acknowledged its analgesic effects[21]. One research study also reported that a placebo arthroscopy (a surgical procedure) had the same effect as a synovectomy[22].

RCT : randomized controlled trial

The trust relationship between a medical practitioner and patient contributes to enhanced patient willingness and increased placebo effect[23]. There have also been some meta-analysis reports that patient expectation in treatment can positively affect pain alleviation[24].

In terms of its mechanism, some placebo effects act as naloxone antagonists so it is believed that the placebo effect is conveyed via endogenous brain opioids[25-27]. In addition, research studies using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) suggest that the descending pain inhibitory system may be implicated with analgesic effects due to a placebo[28]. Moreover, in patients where the placebo proved to be effective, reports indicated asymmetry in the emotional regions of the cerebral cortex limbic system and an increase in the sensory area of the cerebral cortex[29]. As seen above, there is a large number of research reports that are trying to scientifically determine the placebo mechanism.

fMRI：functional magnetic resonance imaging

PET：positron emission tomography

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Chapter B. Diagnosis & Evaluation

: CQ B-1～CQ B-11

CQ B-1 : What points need to be kept in mind when diagnosing or evaluating patients with chronic pain ?
CQ B-2 : What kinds of tests are conducted to diagnose and evaluate patients with chronic pain ?
CQ B-3 : Is a quantitative evaluation of physical function and activity useful for evaluating the condition of chronic pain ?
CQ B-4 : Is the quantitative sensory test (QST) useful for assessing the condition of chronic pain?
CQ B-5 : Is thermography useful for evaluating chronic pain ?
CQ B-6 : Is there a test that is useful as a biomarker for chronic pain ? (brain function, brain blood flow, blood, saliva, cerebrospinal fluid etc. ?)
CQ B-7 : What scales are used to diagnose and evaluate chronic pain ?
CQ B-8 : Is the evaluation of pain intensity useful for chronic pain ?
CQ B-9 : Is the evaluation of neuropathic pain useful for chronic pain ?
CQ B-10 : Is the evaluation of ADL/QOL useful for chronic pain ?
CQ B-11 : Is psychosocial evaluation useful for chronic pain ?

B. Diagnosis & Evaluation

CQ B-1 : What points need to be kept in mind when diagnosing or evaluating patients with chronic pain ?

Answer : An important point when diagnosing chronic pain patients is having an accurate understanding of the patient's condition and confirming whether any highly urgent diseases are present or not. The patient's pain needs to be assessed holistically so that it leads to suitable treatment and care for each individual patient.

Commentary :

The most important thing when diagnosing chronic pain is taking the patient's history on their pain (including chief complaints, a history of their current illness, case history, family history, duration of pain, intensity of pain, pain patterns, aspects and characteristics of their pain) and also conduct a physical examination (visual inspection, percussion, palpation, auscultation, neurological findings such as muscular strength, sensation or reactions). In addition, where necessary, blood tests, diagnostic imaging, and neurological exams should be conducted to determine the root cause of the pain and its pathology. In particular, attention should be paid to whether any underlying conditions such as inflammatory diseases and malignant tumors

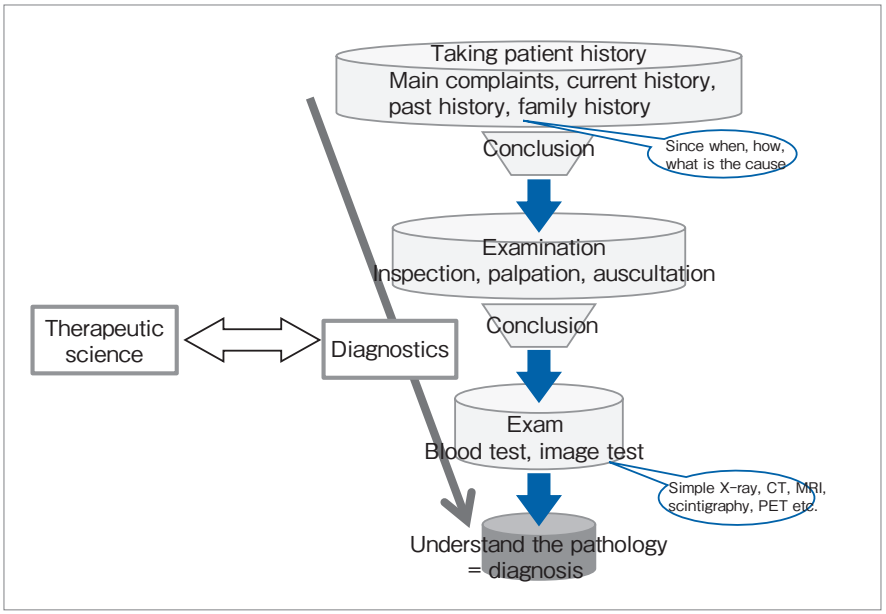

Figure B-1 Method for diagnosing patients with chronic pain

are present when proceeding with the diagnosis. (Figure B-1) . Even when seeing chronic pain patients over time, when new symptoms emerge, physical examinations and where necessary tests must be conducted to confirm the primary disease requiring treatment and any underlying pathologies that had not been apparent before.[1,2)]

On the other hand, chronic pain can be divided into factors based on the pain mechanism such as 'nociceptive', 'neuropathic' and 'psychosocial.'[1)]. However, in many cases chronic pain is not caused by a single mechanism ; these factors coexist and are intricately interrelated. Therefore, in order to select the suitable treatment and care required for each individual patient, there is need for a multifaceted evaluation based on a biopsychosocial model. The items illustrated in Table B-1 are necessary for a multifaceted evaluation[3)]. Doctors needs to conduct an overall (holistic) evaluation of chronic pain patients.

Table B-1 Multifaceted Evaluation of Chronic Pain

1.	Intensity, site, nature of pain, patterns, progression, changes throughout the day, enhancing and alleviating factors of pain
2.	Psychological state : A questionnaire is used to take patient history regarding matters such as anxiety, depression, angry emotions, fear, feelings of low self-efficacy, a negative cognitive state called 'catastrophizing', feelings of unfairness, feelings of distrust etc.
3.	How one spends the day, degree of impairment in ADL, current sleeping habits
4.	Development history, family history, family structure and current situation
5.	Illnesses and clinical conditions in the field of psychiatry
6.	History of substance dependence
7.	Academic background, employment history, job details and conditions
8.	Compensation and litigation
9.	Exercise habits
10.	Changes in diet and weight

CQ B-2 : What kinds of tests are conducted to diagnose and evaluate patients with chronic pain ?

Answer : It goes without saying that when diagnosing patients with chronic pain, one needs to take a detailed history and tests in order to have an accurate understanding of the patient's condition. However, because pain is a subjective experience, much evaluation is conducted using an evaluation form (questionnaire)[4)] Note B1. In recent years, a variety of tests have been conceived and developed in order to objectively evaluate patients with chronic pain but at the current stage, there is insufficient evidence regarding its usefulness. Therefore, we expect this to be verified in future.

Note B1 : Refer to B-7

Table B-2 Examination & Testing for Diagnosing Chronic Pain

Taking history	History of disease & treatment, past injury, accidents, history of surgery, pre-existing conditions, employment history, history of absence from work, family history, family make-up, compensation, litigation
Visual examination	Abnormal posture, gait disorder, edema, muscular atrophy, involuntary movement, Abnormal perspiration, changes in skin tone, presence of rash
Palpation	Tender points, muscle tension, psychroesthesia, sensations of heat
Neurological test	Dermatome,existence of sensation abnormalities [hypoesthesia, hypersensitivity, allodynia] muscular strength, deep reflex, pathological reflex
Blood test	Blood cell count, CRP, protein fractionation, electrolytes, sugar metabolism, liver & kidney function, others
Imaging tests	X-ray, CT, MRI / MRA, ultrasound, scintigraphy etc.
Electrophysiological test	Peripheral nerve conduction velocity test, electromyogram, electroencephalogram

Commentary :

1) Diagnosing pain in patients with chronic pain

In many cases, patients have been suffering from pain over a long period of time, have taken tests and received diagnoses from other facilities and have undergone treatment. In order to avoid being misled by the diagnosis pronounced at other hospitals and clinics, doctors need to re-examine patients once again for an accurate pathology and disease. In order to do this, patient history, a visual examination and palpation need to be conducted in fine detail as well as neurological tests on cranial, sensory and motor nerve, perception, muscular strength and reflexes, pain provocation tests, range of motion (ROM) tests (on joints), if necessary, blood test, imaging tests (X-ray, CT, MRI, ultrasound, scintigraphy) , and electrophysiological tests (nerve conduction test, and electromyogram (EMG) etc.) should also be conducted (Table B-2)[5]. Careful attention needs to be paid to primary diseases that should be immediately treated such as malignant diseases, infections, bone fractures and neuromuscular diseases and if necessary, it is also important to consult a specialist about them. On the other hand, with chronic pain, evaluations should proceed not only based on the anatomical changes obtained from these tests but also by taking into account the multiple factors involved in each individual patient.

2) Attempts to Objectively Evaluate Chronic Pain Patients

Attempts are being made to objectively evaluate chronic pain patients. Thermography, which can visually catch a patient's body surface temperature, allows us to measure the temperature on skin. This is used to investigate the differences be-

tween a healthy side and the afflicted side, as well as changes in temperature at the site of disease over time. However, skin temperature is prone to be affected by the temperature of the (surrounding) environment. Therefore, caution is required when comparing changes over time[6] Note B2. A perception/pain quantitative analytical device and current perception threshold (CPT) measuring devices are commercially available in the attempt to try and objectively measure the strength of pain. Quantitative sensory testing (QST) is a quantitative evaluation method of psychophysically evaluating subjective pain, using static QST that investigates the sensory receptivity of peripheral nerves to each form of stimulus, and dynamic QST that investigates changes in pain perception repeatedly from a physical nociceptive stimulus at (or near) the site of pain and at a site away from the site of pain[7] Note B3. With evaluations of pain by quantitatively measuring physical function and physical activity Note B4, attempts are being made to shed light on pain through brain function imaging tests such as MRI and PET. We have begun to understand phenomena such as the atrophy of gray matter from chronic pain on MRI, and that the default mode network (network of brain activity at rest) changes due to a chronic pain state[8–10]. Research is also being conducted in which blood, saliva and spinal fluid are being tested to reveal the biomarkers that can serve as indicators to evaluate pain Note B5.

Note B2 : Refer to B-5

QST : quantitative sensory testing

Note B3 : Refer to B-4

Note B4 : Refer to B-3

Note B5 : Refer to B-6

CQ B-3 : Is a quantitative evaluation of physical function and activity useful for evaluating the condition of chronic pain ?

Answer : Because physical function and physical activity are deeply involved in the condition of chronic pain, conducting a specific evaluation of these factors will extract issues and serve as indicators for making the suitable choice for treatment, intervention and management and their efficacy so it is useful for evaluating the condition of chronic pain.

Commentary :

As the fear-avoidance model of pain indicates, physical function and physical activity are deeply involved in the development and exacerbation of chronic pain and have a strong influence over not only pain but also ADL and QOL. Therefore, evaluating the physical function and activity in chronic pain patients is important for understanding their pathological condition[11]. To be more specific, evaluation forms (questionnaires) investigating patient-based outcomes are used Note B6, which measure and evaluate actual physical function, exercise performance and the amount of physical activity.

When evaluating physical function and exercise performance, it is recommended

ADL : activities of daily living

QOL : quality of life

Note B6 : Refer to B-10

to evaluate muscular strength, range of joint motion, balance function, movement capabilities and ADL-related factors[11,12]. To be more specific, there is the one-legged standing (OLS) test and one-legged hop for evaluating patients' balance functions. The Time Up and Go (TUG) and the 10 Meter Walk Test (comfortable walking speed and maximal walking speed) are widely used to asses movement capabilities. In addition, there is the Six Minute Walk Test to assess exercise tolerance and for assessing ADl-related performance, there are for example the 30-Second Chair Stand Test and the Stair Climb Test.

IPAQ : International Physical Activity Questionnaire

For evaluating the amount of physical activity, there are questionnaires such as the International Physical Activity Questionnaire (IPAQ)[13,14] and Physical Activity Scale for the Elderly (PASE)[15,16] to investigate activity within the home, work-related activity, movement, leisure activity and non-active time. IPAQ is designed for adults (15～69 years old) whereas PASE is for elderly patients. Also when evaluating the actual physical activity measured, the utilization of activity recording instruments such as activity meters and pedometers are recommended for measuring data such as time of activity, non-active time, number of steps and walking distance.

CQ B-4 : Is the quantitative sensory test (QST) useful for assessing the condition of chronic pain?

QST : quantitative sensory testing

Answer : The quantitative sensory test (QST) indicates the different characteristics between patients with chronic pain and healthy subjects and there are many clinical research studies that indicate its usefulness. However, the QST results provide insufficient evidence for categorizing the chronic pain pathology or for deciding on a method of treatment.

Commentary :

The QST is one form of psychophysical methods and can be broadly divided into static QST and dynamic QST[17]. Static QST is a test that investigates the 'condition' of receptivity, mainly in the peripheral nerves and serves as an indicator for somatic sensations such as tactile and vibratory perception, heat and cold as well as serving as a pain perception threshold such as with pressure pain and heat/cold pain. On the other hand, the dynamic QST is a test that serves as an indicator of the 'function' of pain modulation in locations above the peripheral nerves, and consists of temporal summation of pain (TSP) and conditioned pain modulation (CPM). The TSP is an indicator for the sensitization of abnormalities, like wind-up, in the ascending pain transmission system, whereas the CPM serves as an indicator that reflects dysfunctions in the descending pain inhibitory system.

TSP : temporal summation of pain
CPM: : conditioned pain modulation

① Knee osteoarthritis

In knee osteoarthritis, researchers have indicated the possibility that pressure pain threshold and TSP are related to the degree of severity of pain symptoms. However, there is insufficient evidence indicating its relationship with the cold pain threshold[18] . In addition, some studies have shown that CPM was reduced in patients with knee osteoarthritis compared with healthy subjects[18]. With the prognostic predictions using QST, one study showed that in cases indicating a clear decline in CPM, analgesic effects were low[19], in cases of exacerbated TSP, pain tended to be protracted after prosthetic joint replacement surgery[20], and in cases showing a recognizable decline in the pressure pain threshold over a wide area, patients' response to exercise therapy as a form of treatment was low[21].

② Non-specific chronic low back pain

Systematic reviews comparing the QST values for non-specific chronic low back pain with healthy subjects showed a decline in the pressure pain threshold in remote sites including the upper and lower limbs, and exacerbated TSP in the lumbar area. However, there are few reports related to CPM and in addition, there is a lack of uniformity among the protocols, meaning that a fixed point of view has not yet been obtained[22].

③ Fibromyalgia

Cases of fibromyalgia have a lower heat pain threshold than healthy subjects, with reports that their cut-off value is a sensitivity of 39.1 ℃, with a sensitivity of 63.5%, and specificity of 78.9%. The cut-off value for CPM is −1.0 (amount of change in VAS) with a sensitivity of 45.7% and specificity of 78.9%[23]. Furthermore, in systematic reviews comparing TSP and CPM with healthy subjects, they indicated exacerbated TSP, and reduced CPM but there is an extremely small number of research studies using them as tools in diagnosing fibromyalgia and for making prognostic predictions meaning it does not provide us with conclusive evidence[24].

In this way, there have been various reports on chronic pain patients regarding a reduced heat pain threshold[18,22,23], exacerbated TSP, reduced CPM and dysfunction[18,22,24,25]. On the other hand, systematic reviews that considered the correlations between factors such as CPM, pain intensity and impaired function were unable to establish a significant correlation between them[25]. Therefore, at the current stage, we have been unable to ascertain the validity of QST (especially dynamic QST) as a clinical and experimental pain biomarker. Future research needs to strongly focus on for example establishing a standardized measuring method[25,26] and multiple verifications, which incorporates several forms of QST (for example ones that are TSP and CPM based).

CQ B-5 : Is thermography useful for evaluating chronic pain ?

Answer : Thermography measures the distribution of temperature on the surface of the body using infrared light and is one type of physiological method that displays data visually. In chronic pain, it is used to assess the degree of severity of the primary illness and the effects of treatment. However, in terms of the usefulness of thermography, there is insufficient evidence for it to be used to give a definite diagnosis of chronic pain and for classifying its level of severity. At the current stage, we expect randomized controlled trials (RCTs) to be conducted using it in future on a variety of illnesses and pathologies.

RCT : randomized controlled trial

Commentary :

To date, there have been several observational studies that conducted exploratory evaluations of changes in skin temperature using thermography as an indicator of pathologies and outcomes for some diseases, while no RCTs had verified the usefulness of thermography.

As vasomotor disturbances and changes in skin temperature occur in complex regional pain syndrome (CRPS) due to the impaired function of sympathetic nerves, thermography has long been utilized as an auxiliary diagnostic tool. The IASP's criteria[27] for assessing CRPS includes the differences in skin temperature between the affected and contralateral areas. In a joint multicenter study[28] that examined 296 CRPS patients following the IASP's diagnostic criteria, researchers utilized infrared thermography imaging to assess the difference in skin temperature (ΔT) between the affected limb and non-affected limb. The average ΔT ± standard deviation (SD) was -0.72 ± 1.65 ℃. The ΔT was under 1 ℃ in 131 patients, failing to achieve the assessment criteria ($\Delta T > 1$ ℃) advocated by the IASP[29]. Furthermore, there has been no correlation between the duration of symptoms and ΔT. With CRPS, it cannot be used to assess skin temperature on regular occasions but some are of the opinion that it should be used to measure body temperature when the sympathetic nerves are stimulated when conducting whole-body cooling. However, there are limits to its usefulness in actual clinical conditions[30]. Therefore, for the purpose of making a diagnosis, the diagnostic accuracy of using a thermography alone need to be considered[31].

CRPS : complex regional pain syndrome
IASP : International Association for the Study of Pain

There exist some observational studies on herpes zoster, investigating the changes in skin temperature according to the stage of the disease, in its acute phase, sub-acute phase, and chronic phase[32].

There have been reports on low back pain (LBP) and tension type headache in which the site of pain matched with the site of skin temperature abnormality[33]. Furthermore, skin blood flow increases through treatment interventions such as rehabilitation and trigger point injections and some reports have assessed its effects

as a treatment[34].

Researchers have acknowledged that in chronic pain that comes with impaired blood flow such as from thromboangiitis obliterans and arteriosclerosis obliterans, there is a decline in skin temperature due to reduced blood flow. Furthermore, thermography is used to assess the effects of sympathetic nerve block and to confirm improvements in impaired blood flow.[35].

CQ B-6：Is there a test that is useful as a biomarker for chronic pain？(brain function, brain blood flow, blood, saliva, cerebrospinal fluid etc. ?)

Answer： At the current stage, there are no verified biomarkers that can be used to detect the prevention, early diagnosis, or relapses of chronic pain. However, there are reports on tests that could potentially be considered according to each disease.

Commentary：

In randomized controlled trials (RCTs) conducted since 2010, several biomarkers have been used, in an explorative manner, as indicators for the treatment outcome of chronic pain.

RCT：randomized controlled trial

In a systematic review that considered the effects of exercise therapy on chronic pain, blood-based biomarkers were used as indicators of outcomes in 4 RCTs[36]. As chronic pain is thought to be a malfunction of the immune system, proinflammatory and anti-inflammatory markers were used. In research that introduced exercise therapy on patients with knee osteoarthritis (OA), researchers observed a reduction in Interleukin-6 (IL), a proinflammatory cytokine, and also tumor necrosis factor (TNF)α-receptors 1 and 2[37,38]. In addition, in a research study examining the effects of exercise therapy on subjects with low back pain, showed found that catechol-O-methyltransferase (COMT) genes and single nucleotide polymorphism (SNP) were related to pain, anxiety and depression[39].

knee OA：knee osteoarthritis

There have been no RCTs or systematic reviews on biomarkers in the saliva for chronic pain, only 2 case control research studies and a pilot research study[40,41].

A systematic review on CRPS reported an increase in the concentration of IL-1β and IL-6 and a decrease in soluble intercellular adhesion molecule-1 (sICAM-1)in the cerebrospinal fluid of CRPS patients[42].

No systematic reviews exist on the relationship between chronic pain and brain blood flow but there have been reports of 2 RCTs[43,44]. There have been numerous reports on the relationship between changes in functional connectivity and severity of pain and psychological factors in various chronic pain patients using functional magnetic resonance imaging (fMRI), but the usefulness of fMRI as a biomarker

fMRI：functional magnetic resonance imaging

have yet to be established[45,46].

A systematic review on proton magnetic resonance spectroscopy (^{1}H-MRS) that could quantitatively measure the level of neurometabolites (glutamic acid, γ-aminobutyric acid) indicated that ^{1}H-MRS is expect to develop as a biomarker by improving measurement techniques[47].

In addition, a meta-analysis that assessed the relationship between the length patterns of the third finger, and OA and chronic joint pain reported that the Type-3 pattern (the ring finger > the index finger) was related to symptomatic knee and hand OA and indicated the possibility of adopting it as a non-invasive biomarker for identifying the risks of such diseases[48].

CQ B-7 : What scales are used to diagnose and evaluate chronic pain ?

Answer : Since chronic pain involves multiple factors, it is hard to assess it by an unified scale. Scales that diagnose and evaluate chronic pain include ones for the intensity and nature of pain, dysfucntion, ADL/QOL, and pain affect/cognition, which are used in accordance with the objectives.

Commentary :

At the current stage, there is no single scale that has been certified as being able to express actual pain itself[49]. In particular, chronic pain includes multiple factors so currently the situation is that a diverse range of scales are being used in combination to diagnose and evaluate pain (Table B-3). However, each indicator records pain over time so patients are able to evaluate how their pain changes and the effects of treatment[3]. When utilizing the scales, attention must be paid to how they might be influenced by age, culture, language, cognitive ability or communication ability. As a basic premise, one should choose a scale which is easy for patients to comprehend, and of which reliability and validity has already been tested[50]. In addition, one should listen attentively to patients' complaints and at the same time observe their behaviors and attitudes ; it is necessary to integrate all the information that is useful for making a decision about the treatment policy.

CQ B-8 : Is the evaluation of pain intensity useful for chronic pain ?

Answer : Pain intensity is one of the most general items used in clinical evaluations. Self-reports from patients are widely used as a method to evaluate the pain and evaluation tools including for example the visual analogue scale (VAS), numerical rating scale (NRS), verbal rating scale (VRS) and the Faces Pain Scale-Re-

Table B-3 Pain-related Questionnaires & Scales

1. Pain Intensity ・NRS : numerical rating scale ・VAS : visual analogue scale ・FRS : Wong-Baker Faces pain rating scale
2. Nature of Pain ・MPQ : McGill Pain Questionnaire ・SF-MPQ : Short-Form McGill Pain Questionnaire ・Pain drawings
3. Neuropathic Pain ・Neuropathic Pain Screening Questionnaire ・painDETECT ・Spine painDETECT ・DN4 : the Douleur Neuropathique en4 questions ・NPSI : Neuropathic Pain Symptom Inventory ・LANSS : the Leeds Assessment of Neuropathic Symptoms and Signs / S-LANSS : Short versions of the LANSS ・NPQ : Neuropathic Pain Questionnaire
4. Evaluation of Dysfunction (illness / site specific evaluation) ・DASH : Disabilities of the Arm, Shoulder and Hand ・WOMAC : Western Ontario and McMaster Universities Osteoarthritis Index ・JOACMEQ : Japanese Orthopaedic Association Cervical Myelopathy Evaluation Questionnaire ・JOABPEQ : Japanese Orthopaedic Association Back Pain Evaluation Questionnaire ・RDQ : Roland-Morris Disability Questionnaire ・ODI : Oswestry disability index ・NDI : Neck disability index ・HIT-6 : Headache Impact Test ・DC / TMD : Questionnaires from Diagnostic Criteria for Temporomandibular Disorders ・DC / BMS : Questionnaires from Diagnostic Criteria for Burning Mouth Syndrome
5. Evaluation of ADL / QOL ・BPI : Brief Pain Inventory related items ・MPI : Multidimensional Pain Inventory related items ・PDAS : Pain Disability Assessment Scale ・SF36 : Short-Form36-Item Health Survey ・EQ-5D : EuroQol5 Dimension
6. Evaluation of Pain Affect / Cognition ・HADS : Hospital Anxiety and Depression Scale ・STAI : State-Trait Anxiety Inventory ・BDI : Beck Depression Inventory ・POMS : Profile of Mood States ・PCS : Pain Catastrophizing Scale ・TSK : Tampa scale for kinesiophobia ・FABQ : Fear-Avoidance Beliefs Questionnaire ・BS-POP : Brief Scale for Psychiatric Problems in Orthopaedic Patients ・PSEQ : Pain Self-Efficacy Questionnaire ・MPI : Multidimensional Pain Inventory ・SCL-90 R : Symptom Check List 90 Revised

vised (FPS-R). It is recommended to not only evaluate intensity of pain in chronic pain examinations, but to include it alongside other evaluation items and conduct a comprehensive evaluation.

Commentary :

Because pain is an internal and personal experience, self-reports are currently accepted as a form of measurement of pain, in a wide sense. Intensity of pain is the most general item in clinical evaluations of pain[51].

VAS : visual analogue scale
NRS : numerical rating scale
VRS : verbal rating scale
FPS-R : face pain scale-revised

VAS, NRS, VRS and FPS-R are widely used as scales to represent intensity of pain. Of these, VAS and NRS have a strong correlation and both are considered to be superior to VRS[52]. Writing materials are not necessary to measure using NRS and methods such as phone interviews and asking patients to directly type in responses into a computer database can also be handled. In systematic reviews[53,54] comparing the usefulness and practicality of each respective scale, when evaluating intensity of pain in a one-dimensional manner, NRS is believed to be the easiest one to use in terms of sensitivity, convenience and a high level of compliance.

VAS is hard to comprehend compared with other scales and in particular, suitable results are unobtainable in elderly patients. On the other hand, as it is a continuous scale, it is possible to use it for comparing data.

Just like with VRS, NRS and VAS, there is a strong correlation with other scales[53]. VRS utilizes adjectives to represent different levels of pain and because respondents have to read the whole list included on the scale, it is more time-consuming than other methods but it has an equal or superior level of compliance to other methods. Because the expressions used in VRS might sometimes be interpreted differently by individual respondents and as it depends on the circumstances (for example, pre-and post-surgery comparisons, and comparisons between respondents etc.), it may not be suitable for comparing two phenomena or events.

FPS-R is recommended for children or patients who have limited language abilities[53].

There are several research reports that have investigated the minimal clinically important changes (MCID) of each scale in cases of chronic pain disease. A study reported an MCID was of approximately 20mm[55] on the VAS in patients with chronic low back pain, and another reported that an MCID was 2 points decrease (or 30% reduction)[56] on the NRS in chronic pain patients who were treated with pregabalin. In a study on patients with chronic musculoskeletal pain, they reported a 1 point decrease (or 15% decrease) in NRS as an MCID[57], and on top of this, in the same research study, a 2 point, or 33% decrease on the NRS matched with a patient's improved condition which was "far greater" (than compared with before).

Compared with NRS, VAS, VRS and FPSR have been reported to be more influenced factors other than pain intensity, such as pain-related interference and dis-

comfort[58].

When evaluating the intensity of pain, there is a possibility that the current pain data we are getting from the above scales are not accurately reflecting the overall pain of the patients. Scales such as the Brief Pain Inventory (BPI) and Graded Chronic Pain Scale (GCPS) are designed to self-report the maximum, minimum and average pain intensity during a fixed period of time (for example over the past 24 hours or over the past 1 week)[53].

Although the scales above are widely used in clinical settings, in chronic pain care, there are no research studies that investigate the usefulness of evaluating pain intensity. When evaluating chronic pain, it is recommended that doctors do not just evaluate pain intensity but make a comprehensive judgement by incorporating other evaluation factors as well.

CQ B-9 : Is the evaluation of neuropathic pain useful for chronic pain ?

Answer : In chronic pain care, evaluation of neuropathic pain is useful for deciding on a treatment policy. Screening questionnaires are utilized to identify patients who might be suffering from neuropathic pain. A diagnosis of neuropathic pain is ascertained through taking patient history, conducting a neurological examination and tests to diagnose neurological disease and lesions, following an algorithm.

Commentary :

Various factors are implicated when chronic pain arises. As the treatment policy for neuropathic pain is different from that of other diseases and pain, it is necessary to confirm the presence or absence of neuropathic pain in order to have the appropriate treatment[59].

The screening questionnaire is used to distinguish between patients who have neuropathic (especially non-specific) pain. For example, there is the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) and the Short Version of the LANSS (S-LANSS), Neuropathic Pain Questionnaire (NPQ), Douleur Neuropathique Pain Questionnaire (DN4), painDETECT, ID Pain[59], and the reliability and validity of each respective questionnaire has been proven but each of them is supported by a low amount of evidence[60]. Each questionnaire has been translated into many languages, and Japanese versions have been developed for the LANSS, DN4, and PainDETECT questionnaires. In Japan, they have developed the Neuropathic Pain Screening Questionnaire[61] and Spine painDETECT for evaluating spinal disease-derived neuropathic pain.[62]

Although a screening questionnaire is useful in terms of how it simply distinguishes between patients who have neuropathic pain and those who do not, there

is no information on the questionnaire the clinical course of pain and the sensory examination is either extremely simplified or an abbreviated version. Therefore, the screening questionnaire should be utilized as the first stage in the diagnostic process and when the results do suggest neuropathic pain, it is recommended that doctors take patient history and perform neurological tests in order to confirm the presence (or absence) of neurological legions or disease[63]. The Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the study of Pain (IASP) have displayed a diagnostic algorithm mainly based on nerve lesions and disease[64], and so we recommend taking patient history, conducting neurological examinations and confirmation tests stage by stage, when proceeding with a diagnosis (Figure B-2).

IASP : International Association for the Study of Pain

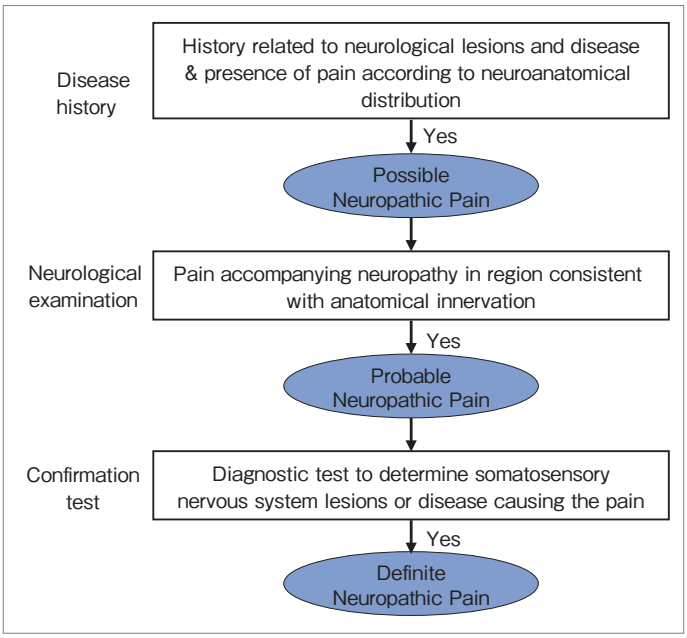

Figure B-2 Flowchart of Neuropathic Pain Scoring
(Cited from References #5)

Evaluation or assessment questionnaires are also used as a tool to complement the screening questionnaire. Evaluation questionnaires either provide a numeric value or categorization for the syndrome of neuropathic pain patients and include for example the Neuropathic Pain Scale (NPS), Neuropathic Pain Symptom Inventory (NPSI), Short-form McGill Pain Questionnaire 2 (SF-MPQ-2), and Pain Quality Assessment Scale (PQAS). Of these, the reliability and validity of the Japanese translation of the NPSI and SF-MPQ-2 have been certified. Evaluation questionnaires can be utilized for understanding the syndrome and characteristics of pa-

tients with neuropathic pain and also for assessing their responses to therapy or treatment and there are reports that they are a more accurate reflection of pain syndromes, rather than a measurement of pain intensity in neuropathic pain[65].

CQ B-10 : Is the evaluation of ADL/QOL useful for chronic pain ?

Answer : Patients who suffer from chronic pain have limited physical activity due to their fear of pain. It goes without saying that the ultimate goal of chronic pain treatment is not just alleviating the pain but also an improvement in ADL and QOL. Therefore, evaluating ADL/QOL as well as evaluating the severity of pain are useful for evaluating treatment outcomes. When evaluating ADL/QOL that accompanies pain, there is an evaluation of chronic pain in general and a disease-specific evaluation, so it is recommended that doctors select a combination of evaluation methods depending on the disease or condition.

ADL : activities of daily living
QOL : quality of life

Commentary :

The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) which was designed by US pain specialists, have indicated 4 domains that can serve as indicators for clinical trial outcomes on chronic pain treatment : pain intensity, physical function, mental function and general overall level of improvement[11]. The alleviation of pain through treatment of chronic pain is not necessarily associated with an improvement in physical function ; evaluations of ADL, QOL and social engagement are also important for evaluating in a wider sense the efficacy of treatment. Most evaluations of ADL/QOL use patient self-reported scales, an evaluation of chronic pain in general, and also disease-specific evaluations that correspond to the particular site of pain or disease. In terms of the evaluation of chronic pain in general, the Brief Pain Inventory[66,67], Multidimensional Pain Inventory related items[68], the Pain Disability Assessment Scale[69], and the related items of the 36-Item Short Form Health Survey (SF-36)[67,70] are widely used to evaluate treatment intervention outcomes. On the other hand, for patients with low back pain, not just comprehensive evaluations discribed above, but disease-specific evaluations such as the Roland-Morris Disability Questionnaire and Oswestry Disability Index, are often used to evaluate treatment outcomes[67,71]. When using a patient self-reported scale, doctors should use questionnaires in which the reliability and validity of the Japanese version has been certified and approved. Furthermore, after taking into consideration the site of the patient's pain or disease and considering their cognitive ability and burden, it is recommended that doctors evaluate them using a combination of comprehensive and disease-specific evaluations.

CQ B-11 : Is psychosocial evaluation useful for chronic pain ?

Answer : There is a strong relationship between chronic pain and psychological function. Psychological changes such as anxiety, depression and anger can arise due to pain. On the other hand, the degree of psychological distress and negative thoughts can be a predictor for the prognosis of chronic pain. Therefore, psychosocial evaluation are useful for predict the prognosis of treatment and for decide interventional methods for chronic pain.

Commentary :

It should be noted that evaluating psychosocial factors of chronic pain is not identifying and/or ruling out psychiatric diseases. In a painful state, such negative emotions develop a vicious cycle, in which the pain persists and worsens. On the other hand, researchers have indicated that the prevalence rate of anxiety disorders and depression is higher among chronic pain patients than the prevalence rate among the general population[72]. There have also been reports on the relationship between strength of anxiety, depression and catastrophizing and response to chronic pain treatment, opioid dependence and treatment prognosis[73-75]. Therefore, psychological assessment plays an important role in predicting prognosis and in deciding on a suitable treatment intervention.

In clinical research on chronic pain patients, scales such as the Hospital Anxiety and Depression Scale (HADS) and State-Trait Anxiety Inventory are widely used as scales for measuring anxiety. An observational study on patients with chronic low back pain (LBP) showed that higher intensity of pain, a higher degree of disability, and a higher risk of opioid analgesic abuse were seen in subjects with high anxiety than in those with low anxiety[73,74]. HADS, the Beck Depression Inventory (BDI), and Profile of Mood States (POMS), are used as scales to measure depression. In addition to evaluating general psychological distress such as anxiety and depression, the evaluation questionnaire has also been developed to assess the thoughts that specifically arise in a state of pain. Of these scales, the Pain Catastrophizing Scale (PCS) and Pain Self-Efficacy Questionnaire have been used in many clinical and research studies on chronic pain to date. A systematic review on chronic musculoskeletal pain indicated that there were a significant relationship between the degree of pain catastrophizing and the severity of pain and physical impairment[76]. Futhermore, a systematic review on chronic musculoskeletal pain showed that there were significant relationships between high self-efficacy and high degree of physical function, QOL, work efficiency, and satisfaction[77]. The fear-avoidance model is a vicious-circle model which explains how pain becomes chronic and intractable ; the cause of their pain being the patient's psychological behavior in which they fall into an avoidance of exercise out of fear of pain. The Fear-Avoid-

PCS : Pain Catastrophizing Scale

ance Beliefs Questionnaire (FABQ) is a questionnaire which evaluates chronic LBP patients' specific fear-avoidance beliefs and the reliability and validity of the Japanese version of the FABQ has been certified. Similarly, the Tampa Scale for Kinesiophobia (TSK), which is a scale evaluating their fear-avoidance thoughts, was initially developed to evaluate their fear of exercise and the validity of this scale for musculoskeletal pain other than LBP has also been certified.

FABQ：Fear-Avoidance Beliefs Questionnaire

LBP：low back pain

TSK：Tampa Scale for Kinesiophobia

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Chapter C. Pharmacotherapy : CQ C-1～CQ C-13

Table C-1 Drugs Used to Manage Chronic Pain

Drug name	Route of administration	Dosage / Usage	Diseases covered under health insurance	Side effects / Precautions
Nonsteroidal Anti-inflammatory Drugs (NSAIDs) (only typical drugs listed) ➡ CQ C-1				
disclofenac	oral / suppository	25～100 mg/day	osteoarthritis/LBP/ cervicobrachial syndrome/ periarthritis of the shoulder / other general pain	gastrointestinal disorders, renal dysfunction, edema, cardiovascular events, asthma
ibuprofen	oral	600 mg/day		
loxoprofen	oral	60～180 mg/day		
celecoxib	oral	200 mg/day		
Acetaminophen ➡ CQ C-2				
acetaminophen	oral	600～4,000 mg/day	general pain	liver dysfunction
Extract from Inflamed Cutaneous Tissue of Rabbits Inoculated with Vaccinia Virus ➡ CQ C-3				
extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus	oral	4 capsules (16 units)/day	postherpetic neuralgia (PHN), LBP, cervicobrachial syndrome, periarthritis of the shoulder, osteoarthritis	nausea, rash
	injected drug	3.6 units intravenous/ intramuscular/ subcutaneous injection	LBP, cervicobrachial syndrome, symptomatic neuralgia, itch accompanying skin disease	drowsiness, rash
Ca^{2+} Channel $\alpha_2\delta$ Ligands (Gaqbapentinoid) ➡ CQ C-4				
pregabalin	oral	starting dosage 50～150 mg/day maintenance dosage 300～600 mg/day	neuropathic pain, fibromyalgia	drowsiness, dizziness, weight gain, edema
gabapentin	oral	starting dosage 400～600 mg/day maintenance dosage 600～1,800 mg/day	refractory epilepsy, neuropathic pain (public application)	drowsiness, dizziness, weight gain
mirogabalin	oral	starting dosage 10 mg/day maintenance dosage 20～30 mg/day	peripheral neuropathic pain	drowsiness, dizziness, weight gain, edema
Antiepileptic Drugs ➡ CQ C-5				
carbamazepine	oral	starting dosage 200～400 mg/day maintenance dosage 600～1,200 mg/day	trigeminal neuralgia, epilepsy, manic depression (bipolar disorder)	drowsiness, dizziness, liver dysfunction, rash, cytopenia
sodium valproate	oral	400～1,200 mg/day	Migraine prevention, epilepsy, manic depression (bipolar disorder)	drowsiness, dizziness, liver dysfunction, pancreatitis
Antidepressants ➡ CQ C-6, 7				
Tricyclic Antidepressants				
amitriptyline	oral	(for peripheral neuropathic pain) initial dosage 10 mg/day increased when necessary, max. dosage 150 mg/day	depression, enuresis, peripheral neuropathic pain	drowsiness, dizziness, sense of fatigue, nausea, dry mouse
impramine	oral	(for depression) starting dosage 25～75 mg/day gradually increased when necessary maintenance dosage up to 200～300 mg/day	depression, bed-wetting	dry mouse, dizziness, drowsiness, constipation
nortriptyline	oral	(for depression) starting dosage 30～75 mg/day gradually increased when necessary maintenance dosage up to 150 mg/day	depression	dry mouse, drowsiness, constipation

Drug name	Route of administration	Dosage / Usage	Diseases covered under health insurance	Side effects / Precautions
Tetracyclic Antidepressants				
maprotiline	oral	starting dosage 10 mg/day maintenance dosage 30～75 mg/day	depression	drowsiness, dizziness, sense of fatigue, nausea
Serotonin-Noradrenaline Reuptake Inhibitors (SNRI)				
duloxetine	oral	starting dosage 20 mg/day maintenance dosage 20～60 mg/day	depression, fibromyalgia, diabetic neuropathy, chronic LBP, knee OA	nausea, drowsiness, dry mouse, headache, sense of fatigue (when used for pain, one should carefully judge whether applicable or not considering the risk of incidence of mental symptoms such as suicidal thoughts, suicidal tendencies, hostility, aggressiveness etc.)
Anxiolytics (benzodiazepine drugs) ➡ CQ C-8				
clonazepam	oral	starting dosage 0.5～1.0 mg/day maintenance dosage 2～6 mg/day	epilepsy (minor motor seizure, psychomotor seizure, autonomic seizure)	drowsiness, dizziness, light headedness, hypotonia, dependence
alprazolam	oral	starting dosage 0.4～1.2 mg/day maintenance dosage 0.4～2.4 mg/day (not to exceed 1.2 mg/day in elderly patients)	anxiety in psychosomatic illness, tension, depression, sleeping disorder	drowsiness, dizziness, light headedness, hypotonia, dependence, withdrawal symptoms
Central Muscle relaxants ➡ CQ C-9				
tizanadine	oral	starting dosage 3 mg/day maintenance dosage 6～9 mg/day	cervicobrachial syndrome, improved muscle tension in LBP, spastic paralysis	drowsiness, dizziness, drop in blood pressure, dry mouse
eperisone	oral	150 mg/day	cervicobrachial syndrome, periarthritis of the shoulder, improved muscle tension in LBP, spastic paralysis	drowsiness, dizziness, light headedness
Opioid analgesics ➡ CQ C-10, 11, 12				
tramadol	oral	starting dosage 50～100mg/day maintenance dosage 50～300mg/day	chronic pain, cancer pain	drowsiness, dizziness, nausea / vomiting, constipation
tramadol / acetaminophen combination tablet	oral	starting dosage 75～150mg/day maintenance dosage 150～300mg/day ※1	chronic pain, post-dental pain	drowsiness, dizziness, nausea / vomiting, constipation
buprenorphine transdermal patch	transdermal patch (for 7 days)	starting dosage 0.12mg/day maintenance dosage 0.12～0.48mg/day	osteoarthritis, chronic LBP	drowsiness, dizziness, nausea / vomiting
morphine	oral (rapid-release agent)	starting dosage 10～30mg/day maintenance dosage 30～90mg/day ※2	chronic pain, cancer pain	nausea / vomiting, constipation, respiratory depression, mental dependence / abuse / misuse
fentanyl transdermal patch	transdermal patch (for 1 or 3 days)	starting dosage 12.5～25 μg/hour maintenance dosage 25～37.5 μg/hour	chronic pain, cancer pain	nausea / vomiting, constipation, respiratory depression, mental dependence / abuse / misuse
oxycodone	oral	(chronic pain) 10～60mg/day (cancer pain) 10～80mg/day	chronic pain (added as eligible for coverage as of October 2020) cancer pain	nausea / vomiting, constipation, respiratory depression, mental dependence / abuse / misuse

※1 Starting dosages and maintenance dosages indicate amount of Tramadol they contain
※2 If we assume that the upper dosage limit is 90 mg/day, then it is recommended that a dosage of 60 mg/day be used

C. Pharmacotherapy

CQ C-1 : Are nonsteroidal anti-inflammatory drugs (NSAIDs) useful for chronic pain ?

NSAIDs : nonsteroidal anti-inflammatory drugs

COX-2 : cyclooxygenase-2

Answer : Nonsteroidal anti-inflammatory drugs (NSAIDs) alleviate chronic low back pain (LBP) and osteoarthritic pain but they have a small effect on chronic LBP. It is not effective in improving fibromyalgia. There is a risk of side effects from selective COX-2 inhibitors on the upper digestive tract and cardiovascular system so long-term use, without any clear purpose in mind, should be avoided.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : Implementation is weakly recommended
〔Consensus 92.9%〕

Summary of overall evidence : B (moderate)

Commentary :

PG : prostaglandins

NSAIDs is a collective name for drugs that provide analgesic effect, reduce fever and act on inflammation, among other effects, by blocking the production of prostaglandins (PG) by blocking cyclooxygenase (COX) in the arachidonic acid cascade. There are 6 systematic reviews and 1 guideline that have been adopted for verifying the efficacy of NSAIDs on chronic pain.

In a systematic review[1] of the efficacy of NSAIDs on chronic low back pain (LBP), researchers found that compared with the placebo, NSAIDs significantly improved pain (MD −6.97, 95%CI −10.74 ～−3.19) according to patients' VAS (visual analogue scale) scores (displaying 0～100 mm) up to the 16th week. NSAIDs overall also significantly improved physical function, compared with the placebo, up to the 12th week (MD −0.85, 95%CI −1.3～−0.4) according to their evaluations on the Roland Morris Disability Questionnaire (RMDQ) (0～24). However, in each case it had a small effect, making it hard to establish if its effects are clinically significant and the reliability of the evidence is low.

OA : osteoarthritis

In a systematic review[2] comparing the effects of each type of NSAID on osteoarthritis (OA) by dosage, the usefulness of NSAIDs was confirmed in 76 placebo-controlled research studies and network meta-analysis is comparing and considering the usefulness of each type of these drugs. NSAIDs that are accessible in Japan and that have indicated a high analgesic effect include diclofenac, naproxen, and ibuprofen. Of these drugs, 150mg of diclofenac/day displayed the largest effect on pain (Effect size : −0.57, 95%CI −0.69 ～−0.45) and physical function (Effect

size：−0.51, 95%CI −0.65～−0.37).

In a systematic review[3] that considered the effects of local administration of NSAIDs on knee OA, they holistically evaluated the effects on pain and improvement of physical function, and found that the difference in the rate of clinical efficacy between weeks 6 and 12 when they were administered, compared with the placebo (adhesive skin patch and drug administered as a base), was 10.2% for diclofenac (RR 1.2, 95%CI 1.12～1.29) and 14.6% for Ketoprofen RR 1.22, 95%CI 1.03～1.45)；a significant improvement in either case. In addition, the difference in the incidence rate of local side effects, such as skin symptoms, compared with the placebo was significantly higher at 6.4% for diclofenac (RR 1.84, 95%CI 1.54～2.21)but a significant difference was not recognized for Ketoprofen with a difference of 2.5% (RR 1.04, 95% CI 0.85～1.27).

Because there was no difference in the frequency of incidence of full-body complications such as gastrointestinal tract disturbance compared with the placebo, local administration of NSAIDs is useful on knee OA pain.

According to the American Academy of Neurology (AAN) and American Headache Society (AHS) guidelines[4] on the prevention of migraine, they recommend fenoprofen (yet to be approved in Japan), ibuprofen, and naproxen as first-line NSAIDs to treat acute-stage migraine. In addition, in a systematic review[5] verifying the effects of aspirin in preventing migraine, based on the results of their analysis of 8 RCTs (dosage of aspirin ranged from 50～650 mg/day), they concluded that oral administration of 325 mg/day of aspirin is required to prevent migraine pain.

AAN：American Academy of Neurology
AHS：the American Headache Society
RCT：randomized controlled trial
FM：fibromyalgia

In a systematic review verifying the effects of NSAIDs on fibromyalgia (FM), the difference compared with the placebo in those who experienced a 30% improvement in pain with NSAIDs was −3.6% (RD −0.04, 95% CI −0.16～0.08) whereas the difference compared with those who experienced a 50% improvement in pain was −6.9% (RD −0.07, 95%CI −0.18～0.04)；a significant difference was not recognized[6].

According to a systematic review[1] of chronic low back pain (LBP), they found that the incidence rate of side effects in all NSAIDs up until the 16th week was 3.4% (RR 1.04, 95% CI 0.92～1.17) compared with the placebo, failing to recognize a significant difference in the frequency of side effects. However, many of these research studies used a small sample size over a short period of time so we need to consider that the only side effects they detected were subjective symptoms.

In a systematic review[7] of the safety of selective COX-2 inhibitors, in a meta-analysis of selective COX-2 inhibitors on OA, researchers found a significantly higher frequency in general side effects from selective COX-2 inhibitors (RR 1.26, 95%CI 1.09～1.46), compared with the placebo. In particular, they found that with the risk of incidence of upper digestive tract symptoms (RR 1.19, 95%CI 1.03～1.38) and cardiovascular system side effects, the risk of high blood pressure (RR

1.45, 95%CI 1.01～2.10), edema and cardiac arrest (RR 1.68, 95%CI 1.22～2.31) were significantly elevated.

When administering NSAIDs, careful attention needs to be paid to the incidence of gastrointestinal mucosal damage, renal dysfunction and cardiovascular events, when using selective COX-2 inhibitors. Therefore it is important to rigorously monitor for side effects and take measures when needed, and avoid any long-term administration without any clear purpose in mind.

Period		2005～2019
Database		PubMed, Cochrane CENTRAL, NPO Japan Medical Abstracts Society
Words searched	P	chronic pain
	I/C	NSAIDs administered group/non-administered group
Limitations		Limited by publication type,PubMed CER randomized controlled trial / systematic review search filter, Cochrane RCT search filter, other (cases of50+) etc
Selection summary		Of the 303 search hits, we narrowed it down to31, and in the end used 7 search hits which matched with the set PICO

CQ C-2 : Is acetaminophen useful for chronic pain ?

Answer : There is a lack of evidence indicating the effects of acetaminophen on musculoskeletal pain (pain due to low back pain or osteoarthritis), so its usefulness remains unclear. On the other hand, it is highly useful in alleviating pain due to tension-type headache (TTH) or migraine. Although severe side effects are rare, one needs to be careful of impaired liver function due to high-dose administration.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : Implementation is weakly recommended
〔Consensus 100%〕

Summary of overall evidence : B (moderate)

Commentary :

The analgesic-acting mechanism of acetaminophen is unclear. It has weak anti-inflammatory effects and is assumed to mainly express its analgesic effects via the central nervous system. Three systematic reviews have been adopted to consider the usefulness of acetaminophen on chronic pain.

According to a systematic review[8] that considered the usefulness of acetaminophen on musculoskeletal pain, even when 4,000 mg of acetaminophen was used in 1 day to treat low back pain (LBP), according to the VAS scores (on a range from 0～10) in which subjects evaluated their pain, researchers did not recognize the effect of acetaminophen compared with the placebo over a short period of time (less than 2 weeks) (MD : −0.5, 95%CI −2.9～1.9) or a medium-length period of time (2 weeks+but less than 3 months) (MD : 1.4, 95%CI −1.3～4.1). Furthermore, on the Short-Form 12-Item Health Survey (SF-12) (0 ～ 100) according to their

SF-12 : Short-Form 12-Item Health Survey

evaluations, there was no recognizable effect on physical function either over the short term (MD：0.4, 95%CI-1.7～2.5) or medium term (MD：-1.9, 95%CI-4.8～1.0) compared with the placebo. Of the 3 randomized controlled trials (RCTs) that were included in this systematic review, only one of them researched chronic low back pain, and apart from this, almost no high-quality RCTs exist that consider the usefulness of acetaminophen on chronic low back pain (LBP).

In the same systematic review, acetaminophen significantly reduced OA pain, compared with the placebo, both over the short term (MD －3.3, 95%CI －5.5～－1.9) and mid-term (MD －3.7, 95%CI －5.8～－0.8). However, they used WOMAC (0～100) for the majority of pain evaluations, which makes it difficult for us to say whether the improvement was clinically significant or not. In addition, there was also a change in physical function over the short term MD －2.9, 95%CI －4.9～－0.9) and mid-term (MD －1.7, 95%CI －6.0 ～ 2.6) but the significant improvement over the short term showed only a slight effect, whereas the improvement over the mid-term was not significant. The usefulness of acetaminophen for OA is negative.

According to a systematic review[9] that considered the usefulness of acetaminophen for tension-type headache (TTH), researchers found that among patients suffering from frequently-recurring tension-type headache (a headache that occurs at a frequency of between 1～15 times a month) in the acute stage, the difference in the number of patients whose pain subsided or disappeared 2 hours later was 9.8% higher for those administered with 1,000 mg of acetaminophen compared with those given a placebo (RR 1.21, 95%CI 1.15～1.28), displaying a significant improvement. On the other hand, the difference between those administered with 560～650 mg of acetaminophen and those given a placebo was 5.8% (RR 1.11, 95% CI 0.90～1.37), failing to yield a significant improvement. The difference in the incidence rate of side effects between those who orally took 1,000 mg of acetaminophen and those given a placebo was 1.4% (RR 1.12, 95%CI 0.94～1.32)；the difference was not significant, meaning its usefulness in actual clinical settings is high.

According to a systematic review[10] that considered the usefulness of acetaminophen on migraine, the difference in the % of patients who experienced an improvement in pain 1 hour later was 19.2% (RR 1.97, 95%CI 1.52 ～ 2.55) comparing those administered with 1,000 mg of acetaminophen with those given a placebo, and the difference in improved physical function 2 hours later was 10.3% (RR 1.76, 95%CI 1.24～2.48) for the acetaminophen group compared with the placebo group, indicating a significant improvement in either case. The difference in the incidence rate of side effects, compared with the placebo, was 4.7% (RR 0.78, 95%CI 0.64～0.95), meaning it is also highly useful in actual clinical settings.

According to a systematic review[8] of side effects related to musculoskeletal pain,

RCT：randomized controlled trial

OA：osteoarthritis

WOMAC：Western Ontario and McMaster University Osteoarthritis Index

the difference in the incidence rate of some form of side effects from acetaminophen was 2% (RR 1.0, 95%CI 0.9–1.1) compared with the placebo, and the percentage of those who discontinued administration due to side effects was 0.9% (RR 1.2, 95%CI 0.9–1.5), showing that the difference was not significant. In addition, the frequency in which severe side effects occur is low and no difference was recognized compared with the placebo (RR 1.2, 95%CI 0.7–2.1), However, in terms of liver function abnormality, it has a high risk compared with the placebo (RR 3.8, 95%CI 1.9–7.4), therefore caution is required.

Impaired liver function due to acetaminophen is caused by the metabolite NAPQI but it carries a high risk when taken in high dosages. According to the Food and Drug Administration (FDA) the daily dosage of acetaminophen is limited to 4,000 mg/day (in Japan as well), and many OTC common-cold medicines contain acetaminophen as well. Therefore, unexpected overdoses can happen meaning doctors need to carefully pay attention to monitoring administration.

FDA : Food and Drug Administration

Moreover, the long-term administration of acetaminophen elevates the risk of gastrointestinal haemorrhage (GIH) and it has become clear that there is a mild increase in systolic blood pressure[11].

Period		2005～2019
Database		PubMed, Cochrane CENTRAL, NPO Japan Medical Abstracts Society
Words searched	P	chronic pain
	I/C	acetaminophen, paracetamol administered group/non-administered group
Limitations		Limited by publication type,PubMed CER randomized controlled trial / systematic review search filter, Cochrane search filter, other (cases of 50+) etc
Selection summary		Of the 375 search hits, we narrowed it down to 21, and in the end used 4 which matched with the set PICO

CQ C-3 : Is extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus useful for chronic pain ?

Answer : Extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus may possibly by useful for low back pain, cervico-omo-brachial syndrome and postherpetic neuralgia. Severe side effects are rare and so because it is highly safe, it is considered for use, in cases where patients fail to respond to standard treatment.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : Implementation is weakly recommended
〔Consensus 84.6%〕

Summary of overall evidence : D (very low)

Commentary :

Extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus

is a type of drug containing non-protein type physiologically-active substances extracted from the inflamed cutaneous tissue of rabbits. Experiments conducted on animals have confirmed that 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[12].

RCT : randomized controlled trial

Three RCTs have been conducted on each type of chronic pain disease to consider the usefulness of extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus on chronic pain.

In a placebo-controlled RCT[13] targeting 120 patients with low back pain (LBP), researchers found that patients experienced a moderate improvement in pain or better while moving, 2 weeks after administration, in 43.6% of patients administered with the drug compared with 24.1% of patients in the placebo group, indicating a significant effect.

More over in a placebo-controlled RCT[14] conducted on 164 patients with cervico-omo-brachial syndrome, researchers reported a moderate improvement or better in spontaneous pain, 3 weeks after administration, in 44.4% of patients administered with the drug compared with 28.4% in the placebo group, indicating a significant effect.

In another placebo-controlled RCT[15] conducted on 238 patients with postherpetic neuralgia (PHN), they reported a moderate improvement in pain or better, 4 weeks after administration, in 34.3% of those who had been administered with the drug compared with 19.6% of those in the placebo group, indicating a significant effect.

PHN : postherpetic neuralgia

In addition, in each of these RCTs, researchers recognized that it was effective in improving patients' ADL and QOL. However, each of these RCTs is old, having been conducted in the 1980s, were small in scope and had a short observation period, and so because their recruitment criteria and the way they evaluated analgesic effects were vague, there is a high risk of bias and the quality of evidence is low.

ADL : activity of daily living
QOL : quality of life

In terms of safety, the incidence rate of side effects in these RCTs was between 5.1～12.1% among patients in the group administered with the drug, failing to indicate a significant difference compared with the placebo group. Specific side effects that were observed include digestive symptoms such as gastric distress, constipation, loss of appetite, diarrhoea, and nausea and drowsiness but in each of these RCTs, symptoms were mild and the drug was discontinued due to side effects in around 0 ～ 4% of cases, indicating a high level of safety. However, there have also been reports of severe side effects such as shock, anaphylactic-like symptoms, impaired liver function and jaundice so caution should be exercised when this drug is being used[16].

According to the Clinical Guidelines of Pharmacotherapy for Neuropathic Pain

(Revised 2nd edition)[17] released by the Japan Society of Pain Clinicians, they highly evaluate the fact that the safety and usability of extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus were assessed in Japan and position this substance as a second-line drug in the pharmacotherapy of neuropathic pain.

The quality of evidence on the efficacy of extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus for treating chronic pain is not high but it is highly safe so in the event where chronic pain disease does not improve under standard treatment, its usage should be considered. In future, in order to confirm the efficacy of extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus, there is a need for researchers to accumulate further evidence through conducting high-quality RCTs.

Period		2005～2019
Database		PubMed, Cochrane CENTRAL, NPO Japan Medical Abstracts Society
Words searched	P	chronic pain
	I/C	Neurotropin (inflamed cutaneous tissue of rabbits inoculated with vaccinia virus, neurotropin) administered group/non-administered group
Limitations		Limited by publication type, PubMed CER randomized controlled trial / systematic review search filter, Cochrane RCT search filter, other (cases of50＋) etc
Selection summary		Of the 227 search hits, we narrowed it down to12, and in the end used 5 which matched with the set PICO, and 1 additional document, brining it to a total of 6 which we used. With the NPO Japan Medical Abstracts Society searches, we expanded our search back to the 1980s

CQ C-4 : Are Ca^{2+} channel $\alpha_2\delta$ ligands useful for chronic pain ?

Answer : Ca^{2+} channel $\alpha_2\delta$ ligands (pregabalin, gabapentin, mirogabalin) are useful on postherpetic neuralgia (PHN) and painful diabetic neuropathy (DN). Pregabalin is effective on fibromyalgia. The main side effects from Ca^{2+} channel $\alpha_2\delta$ ligands are drowsiness, dizziness, edema, increase in weight, and so dosages need to be adjusted for senior patients and those with renal dysfunction.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 1 (strong) : Implementation is strongly recommended〔Consensus 85.0%〕

Summary of overall evidence : B (moderate)

Commentary :

By binding to voltage-dependent Ca^{2+} channel $\alpha_2\delta$ subunits in the central nervous system, Ca^{2+} channel $\alpha_2\delta$ ligands (gabapentinoids) inhibit the release of excitatory neurotransmitters, exhibiting an analgesic effect. Currently, there are three Ca^{2+} channel $\alpha_2\delta$ ligands that can be used in Japan : pregabalin, gabapentin, and mirogabalin.

RCT : randomized controlled trial

There are 4 systematic reviews and 2 RCTs that have considered the usefulness of Ca^{2+} channel $\alpha_2\delta$ ligands on chronic pain.

In systematic reviews[18,19] on the effect of pregabalin and gabapentin on neuropathic pain, they considered their usefulness on postherpetic neuralgia (PHN) and painful diabetic neuropathy (DN).

PHN : postherpetic neuralgia

With PHN, researchers observed that the difference in the % of patients whose pain decreased by 50% or more through pregabalin (300 mg/day) compared with the placebo was 19.5% (RR 2.52, 95%CI 1.86 ～ 3.42) and through gabapentin (1,200～3,600 mg/day) was 14.4% (RR 1.69, 95%CI 1.43～2), compared with the placebo, marking a significant improvement. Evaluations of patients' satisfaction levels using the Patient Global Impression of Change (PGIC) indicated that the % of those showing a large level of improvement over the placebo was 17.1% (RR 2.13, 95%CI 1.54～2.94) for patients administered with pregabalin and 10.3% for those administered with gabapentin (RR 1.32, 95%CI 1.16～1.5), indicating a significant improvement over the placebo.

PGIC : the Patient Global Impression of Change

With painful diabetic neuropathy (DN), the difference in the % of patients whose pain had decreased by 50% or more compared with the placebo was 7.0% (RR 1.3, 95%CI 1.15 ～ 1.46) in patients administered with pregabalin, 15.2% (RR 1.69, 95%CI 1.41～2.02) in patients administered with gabapentin, indicating a significant improvement. According to PGIC, evaluations from patients administered with pregabalin were 20.3% (RR 1.75, 95%CI 1.51～2.03), and 20.3% (RR 1.66, 95% CI 1.36 ～ 2.03) for those administered with gabapentin, indicating significantly higher scores than the placebo.

In addition, in RCTs published since 2017, researchers have considered the usefulness of pregabalin for both post-traumatic neuropathic pain[20] and peripheral neuropathic pain due to oxaliplatin[21], respectively. Both of these placebo-controlled research studies examined over 100 cases but did not recognize a significant improvement in pain or QOL.

In a systematic review[22] that verified the usefulness of antiepileptic agents on chronic low back pain, researchers did not recognize that Ca^{2+} channel $\alpha_2\delta$ ligands were useful in improving pain and physical function, from the 2 months～up to 12 months stage, in chronic low back pain (LBP) and lumbar radiculopathy, compared with the placebo. In standard LBP, researchers did not recognize a significant improvement in pain (evaluations standardized from 0～10), at the 2 week～3 month stage, in patients administered with gabapentin (MD 0.0, 95% CI −0.3 ～ 0.3), compared with the placebo and in patients with lumbar radiculopathy administered with pregabalin (300～600 mg/day), they did not recognize that it was effective in causing a significant improvement in pain MD −0.1, 95%CI −0.3～0.2) or physical function (evaluations standardized from 0～10), compared with the placebo.

In a systematic review[23] of the usefulness of pregabalin on fibromyalgia, researchers considered the usefulness of administering patients with pregabalin in dosages of 150～600 mg/day. In terms of side effects, as the incidence of dosage de-

FM : fibromyalgia

pendence becomes increasingly more frequent, both the rate of improvement of pain at 450 mg/day and patient satisfaction levels have increased and the % of patients who experienced a 50% reduction in pain or higher was 10.4% (RR 1.75, 95%CI 1.44 ～ 2.13) compared with the placebo, indicating a significant improvement. Furthermore, the % of those who indicated a high level of improvement in patient satisfaction through the evaluations of the Patient Global Impression of Change (PGIC) was 8.8% (RR 1.33, 95%CI 1.16～1.52), significantly higher than the placebo.

The main side effects from using Ca^{2+} channel $\alpha_2\delta$ ligands are drowsiness, dizziness, weight gain, and peripheral edema[23]. The difference in the incidence of side effects was 9.4% for pregabalin (300 mg/day) (RR 1.21, 95%CI 1.15～2.28) and 13.2% for gabapentin (1,200～3,600 mg/day) (RR 1.28, 95%CI 1.22～1.36) compared with the placebo, indicating that it was significantly higher. The incidence rate of severe side effects was 3.0% for pregabalin and 3.1% for gabapentin, and there was no significant difference compared with the placebo, but the % of patients for whom oral administration was discontinued due to side effects, was 4.2% for pregabalin (RR 1.86, 95% CI 1.49～2.33) and 3.3% for gabapentin (RR 1.38, 95%CI 1.14～1.67) compared with the placebo ; making it significantly higher[18,19]. For this reason, patients should be rigorously monitored after commencing administration. Of the side effects, drowsiness and dizziness are frequent so during administration, patients should be advised not to drive a car and with elderly patients in particular, one must be careful of bone fractures due to a fall. Moreover, Ca^{2+} channel $\alpha_2\delta$ ligands are excreted by the kidneys as an unmetabolized drug, so it is important to adjust the dosage in accordance with a patient's kidney function[24].

In April 2019, Japan led the world in making mirogabalin available for use. In phase III clinical trials (RCTs), researchers considered the usefulness of mirogabalin on peripheral neuropathic pain (postherpetic neuralgia (PHN), painful diabetic neuropathy), compared with a placebo[25,26]. They examined 671 patients with postherpetic neuralgia (PHN) and at the 14th week stage, they found that 30 mg/day of mirogabalin significantly improved their pain (MD −0.77, 95%CI −1.10 ～−0.44) compared with the placebo. They also examined 834 patients with painful diabetic neuropathy and found that at the 14th week stage, 30 mg/day of mirogabalin significantly improved their pain (MD −0.50, 95%CI −0.82 ～−0.17) compared with the placebo. However, they did not observe a significant improvement in physical function. Side-effects include nasopharyngitis, drowsiness, dizziness, peripheral edema, and weight gain. Around 90% of these participants were able to complete the clinical trial, right through to the end in each case, indicating its tolerability. In future, there is need for further verification in actual clinical settings and a need to accumulate evidence on its usefulness.

According to the Clinical Guidelines of Pharmacotherapy for Neuropathic Pain

(Revised 2nd edition)[17] released by the Japan Society of Pain Clinicians, pregabalin and gabapentin are positioned as first-line drugs in the management of neuropathic pain. However, one comment was added to the revised text : "mirogabalin can be used in the same manner as pregabalin." [27]

Period		2005～2019
Database		PubMed, Cochrane CENTRAL, NPO Japan Medical Abstracts Society
Words searched	P	chronic pain
	I/C	pregabalin, gabapentin, mirogabalin, gabapentinoid administered group / non-administered group
Limitations		Limited by publication type,PubMed CER randomized controlled trial / systematic review search filter, Cochrane RCT search filter, other (cases of50+) etc
Selection summary		Of the 663 search hits, we narrowed it down to 50, and in the end, we used 9 of them which matched with the set PICO as well as 1 additional document and 1 website bringing it to a total of 11 which we used

CQ C-5 : Are antiepileptic drugs (carbamazepine, sodium valproate) useful for chronic pain ?

Answer : Carbamazepine is useful for trigeminal neuralgia, and sodium valproate is useful in preventing migraine attacks. There is no evidence indicating its usefulness on other forms of chronic pain. We need to be careful of its side effects which mainly include drowsiness, dizziness, light-headedness, nausea, and impaired liver function.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : Implementation is weakly recommended
〔Consensus 84.6%〕

Summary of overall evidence : B (moderate)

Commentary :

Carbamazepine exhibits its pharmacological effect by blocking Na^+ channels and sodium valproate by blocking Ca^{2+} channels and inhibiting GABA.

GABA : γ -aminobutyric acid

We have used 3 systematic reviews that consider the usefulness of antiepileptic drugs (carbamazepine, sodium valproate) on chronic pain.

In a systematic review[28] considering the usefulness of carbamazepine on neuropathic pain, researchers found that the % of patients with trigeminal neuralgia administered with carbamazepine (100～2,400 mg/day) who experienced improved symptoms was 60.6% (RR 6.02, 95%CI 2.82～12.85) compared with the placebo, indicating that their pain had significantly improved. The incidence rate of side effects among those administered with carbamazepine compared with the placebo was 38.2% (RR 2.4, 95%CI 1.85～3.12), indicating that the risk of incidence is significantly higher and researchers recognized that they suffer from drowsiness, dizziness, light-headedness, skin rash and impaired liver function but there were no

reports of severe side effects. However, when using carbamazepine, one should also pay attention to severe side effects such as liver dysfunction, granulocytopenia, aplastic anemia, toxic epidermal necrolysis (TEN), and Stevens-Jonson syndrome.

Carbamazepine is the gold standard for pharmacotherapy when treating trigeminal neuralgia[29], and even according to the guidelines on trigeminal neuralgia by the American Academy of Neurology (AAN) and the Federation of European Neuroscience Societies (FENS)[30], it is considered to be the first-line drug based on strong evidence.

AAN : American Academy of Neurology
FENS : Federation of European Neuroscience Societies
RCT : randomized controlled trial

In a systematic review[31] considering the usefulness of sodium valproate on neuropathic pain, researchers mention 2 RCTs that examined painful diabetic neuropathy and 1 RCT that examined postherpetic neuralgia (PHN) but the scope of each of these studies was small and there is a discrepancy in the results so its usefulness has not been validated by meta-analysis. There is insufficient evidence indicating the usefulness of sodium valproate on neuropathic pain and therefore it is not a first-line drug for managing neuropathic pain.

In a systematic review[32] that considered the usefulness of sodium valproate in preventing migraine attacks, oral administration of sodium valproate (800=1,500 mg/day) reduced the frequency of migraines (MD −4.31, 95% CI −8.32～−0.3), compared with the placebo. The same systematic review reported that side effects from taking sodium valproate include, sense of fatigue, nausea, drowsiness, dizziness and impaired liver function. The difference in the incidence rate (of adverse events) compared with the placebo was 6.8% (RR 0.03, 95%CI −0.08−0.13) ; the difference was not significant. Individual side effects were sense of fatigue (RD 0.07, 95% CI −0.03～0.17), dizziness (RD 0.07, 95% CI 0.01～0.13), nausea (RD 0.15, 95% CI 0.04～0.26), and trembling (RD 0.07, 95%CI 0.01～0.13) but severe side effects are rare, meaning that it has high tolerability.

Period		2005～2019
Database		PubMed, Cochrane CENTRAL, NPO Japan Medical Abstracts Society
Words searched	P	chronic pain
	I/C	carbamazepine, valproic acid, valproate administered group/non-administered group
Limitations		Limited by publication type,PubMed CER randomized controlled trial / systematic review search filter, Cochrane RCT search filter, other (cases of50+) etc
Selection summary		Of the 105 search hits, we narrowed it down to 19, of which we ended up using 5 which matched with the set PICO

CQ C-6 : Is duloxetine useful for chronic pain ?

Answer : Duloxetine improves pain and physical function in painful diabetic neuropathy (DN), fibromyalgia, osteoarthritis, and low back pain (LBP) and patient satisfaction is high. There are many types of side effects that arise but severe side effects are rare.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 1 (strong) : Implementation is strongly recommended〔Consensus 80.0%〕

Summary of overall evidence : A (high)

Commentary :

Duloxetine is one of the serotonin-noradrenaline reuptake inhibitors (SNRI), and its analgesic effect is due to an activation of the descending pain inhibitory system. Duloxetine is also used as an antidepressant but its antidepressive effect and its analgesic effect each have their own respective mechanism. The analgesic effects of duloxetine arise faster and in lower dosages than its antidepressive effects[33].

SNRI : serotonin-noradrenaline reuptake inhibitor

There are 2 systematic reviews and 1 (PASS) posthoc analysis that examined the usefulness of duloxetine on chronic pain.

A systematic review[33] on painful diabetic neuropathy and fibromyalgia evaluated the severity of patients' pain, physical function, mental function, and patient satisfaction between weeks 8～12 after being administered with 60 mg/day of duloxetine. The rate of patients whose pain reduced by 50% or more after taking duloxetine was 20.4% (RR 1.73, 95%CI 1.44～2.08) and 13.1% (RR 1.57, 95%CI 1.2～2.06) for painful diabetic neuropathy and fibromyalgia, respectively, compared with the placebo. Their physical function and mental function were evaluated using the Short-Form 36-Item Health Survey (SF-36) and found that the difference in the average change from the baseline compared with the placebo for physical aspects was 2.65 (95%CI 1.38～3.92), and 1.28 (95%CI −0.33～2.89), whereas for mental aspects it was 1.08 (95%CI −0.32～2.48) and 3.11 (95%CI 0.59～6.02), showing that some had significantly improved. Patient satisfaction was evaluated using the Patient Global Improvement-Inventory (PGI-I), and researchers found that the average difference from the control was −0.6 (95% CI −0.07～−0.44), and −0.45 (95% CI : −0.37 ～−0.18), indicating that in either case it had improved significantly.

SF-36 : Short-Form 36-Item Health Survey

PGIC : Patient Global Impression of Change

In a systematic review on OA[34], the rate of patients whose pain reduced by more than 50% between weeks 10～14 after being administered with 60～120 mg/day of duloxetine, was 17.9% (RR 1.62, 95%CI 1.30～2.02) higher than the placebo. Patients' physical function was evaluated using WOMAC, and they found that the difference between the control in average change from the baseline was -5.43 (95%CI -6.87～-3.99), indicating a significant improvement. The average change compared with the control in patient satisfaction according to the Patient Global Impression of Change (PGIC) was -0.48 (95% CI -0.59～-0.37), showing that it had improved significantly.

OA : osteoarthritis

WOMAC : Western Ontario and McMaster University Osteoarthritis Index

A posthoc analysis (PASS)[35] that evaluated its efficacy on low back pain (LBP) evaluated patients' severity of pain and physical function at weeks 12～14, after be-

ing administered with 60～120 mg/day for duloxetine. The relative difference in the average change from the baseline in the severity of pain was −0.29 (95% CI −0.41～−0.16), showing a significant improvement. Their physical function was evaluated using the Roland Morris Disability Questionnaire (RMDQ), and the relative difference in the average change from the baseline was −0.15 (95% CI −0.29～−0.01), indicating that it had significantly improved.

According to a systematic review on the side effects from taking duloxetine for chronic pain, the side effects from this drug include nausea, dry mouth, dizziness, somnolence, fatigue, insomnia, headache, constipation, decreased appetite and hyperhidrosis, although side effects do not occur as frequently as with tricyclic antidepressants[33]. The incidence rate of side effects is related to dosage dependence, with an incidence 8.9% (RR 1.15, 95%CI 1.1～1.2) higher when taking duloxetine than the placebo, and the rate of patients who discontinued taking it orally due to side effects was high at 5.3% (RR 1.95, 95% CI 1.6～2.37). Severe side effects are rare ; there was no significant difference compared with the placebo (RR 0.81, 95% CI 0.53 ～ 1.25). As duloxetine is a serotonin-noradrenaline reuptake inhibitor (SNRI), there is considerable risk of onset of serotonin syndrome. The frequency of onset is low at normal dosages but as there is an elevated risk of serotonin syndrome due to an overdose or when using a serotonin agonist such as tramadol in combination, caution is advised. Drug infomation advises caution ; it mentions paying attention to their mutual effect on pain and when administering this drug for pain, one must consider the risk of mental symptoms arising in patients, such as suicidal thoughts, suicidal tendencies, hostility and aggressiveness, when making a careful judgment whether it is suitable to administer this drug or not.

Period		2005～2019
Database		PubMed, Cochrane CENTRAL, NPO Japan Medical Abstracts Society
Words searched	P	chronic pain*
	I/C	Duloxetine administered group/non-administered group
Limitations		Limited by publication type, PubMed CER randomized controlled trial / systematic review search filter, Cochrane RCT search filter, other (cases of 50+) etc
Selection summary		Of the 137 search hits, we used 11 which matched with the set PICO

CQ C-7 : Are tricyclic antidepressants useful for chronic pain ?

Answer : Tricyclic antidepressants are useful in reducing neuropathic pain and fibromyalgia-related pain. It is not useful in improving low back pain (LBP). Amitriptyline causes a variety of side effects and caution is especially required when treating older patients and those with heart disease.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : Implementation is weakly recommended

〔Consensus 100.0%〕

Summary of overall evidence：C（low）

Commentary：

Analgesic effects of tricyclic antidepressants manifest in a shorter period of time and in lower dosages than antidepressants. Its main analgesic effect mechanism is the activation of the descending pain inhibitory system by blocking re-uptake of serotonin and noradrenaline, but other mechanisms, such as N-methyl-*D*-aspartate（NMDA）receptor antagonism and blockade of sodium channels, and the effect on β_2 adrenergic actions is proposed[36].

We have adopted 5 systematic reviews and 1 meta-analysis on the usefulness of tricyclic antidepressants on chronic pain.

A systematic review[37] has evaluated changes in the intensity of pain in patients with painful diabetic neuropathy, postherpetic neuralgia, and mixed neuropathic pain administered with 10～200 mg of amitriptyline / day over a period of 4～9 weeks. The rate of patients whose pain was reduced by more than 50% was 19.7% higher in amitriptyline patients compared with the placebo（RR 2.0, 95%CI 1.5～2.8）. In a systematic review[38] conducted by the Special Interest Group on Neuropathic Pain（NeuPSIG）of the International Association for the Study of Pain（IASP）, they evaluated the analgesic effects of tricyclic antidepressants（amitriptyline, desipramine, imipramine, nortriptyline）on neuropathic pain, and calculated that the number needed to treat（NNT）to reduce pain by 50% was 3.57（95% CI：3～4.4）. As this value is lower than other drugs, it gives us the impression that tricyclic antidepressants have the strongest effect on neuropathic pain. However, the majority of research on the effects of tricyclic antidepressants on neuropathic pain was conducted prior to the year 2000, and the period of observation was under 1 month, and because indicators such as physical function and mental function and level of patient satisfaction have not been evaluated, in light of the above, careful attention needs to be paid to how the quality of each RCT ranges from low to medium and the level of evidence is not high.

NNT：number needed to treat

In a systematic review[39] that evaluated the usefulness of amitriptyline on fibromyalgia, researchers indicated that the rate of patients administered with 25～50 mg of amitriptyline/day over a period of 8～24 weeks whose pain reduced by more than 50% was 24.6%（RR 2.88, 95%CI 1.69～4.91）higher than the placebo.

FM：fibromyalgia

In a systematic review that evaluated its usefulness on low back pain（LBP）, researchers evaluated changes in the intensity of pain when patients were administered with tricyclic antidepressants（maprotiline, desipramine, imipramine）over a period of 4～12 weeks. The difference in the average change in intensity of pain from the baseline compared with the control was 0.1（95% CI −0.51～0.31）, indicating that there was no significant improvement compared with the placebo[40,41].

According to a meta-analysis evaluating the side effects on patients with chronic pain who were administered with antidepressants, the incidence of side effects from amitriptyline was 43.4% (RR 2.9, 95% CI 0.67～12.58) higher than the placebo. There is a variety of side effects, including dry mouth (RR 18.95, 95% CI 1.19～301.39), weight gain (RR 8.74, 95%CI 1.12～68.32), irritability (RR 8.19, 95% CI 0.45～147.47), blurred vision (RR 6.37, 95% CI 0.34～119.6), headache (RR 3.39, 95% CI 0.92～12.55), dipsia (RR 3.14, 95% CI 1.10～8.94), edema (RR 1.8, 95%CI 0.18 ～ 18.21), constipation (RR 1.60, 95%CI 1.19 ～ 2.15), drowsiness (RR 1.60, 95%CI 0.52～4.91), and palpitations (RR 1.55, 95%CI 0.29～8.24). The incidence rate of patients in which oral administration was discontinued due to side effects was high at 10.8% (RR 4.09, 95% CI 1.31～12.82)[42].

Because tricyclic antidepressants can cause sinus tachycardia through their anticholinergic effects, caution is advised when administering them to patients with ischemic heart disease. It also elevates the risk of sudden cardiac death when 100 mg/day is administered[43]. Therefore, older patients and those in which ischemic heart disease is suspected must be screened with an electrocardiogram (ECG) prior to administration and any medical history of ischemic heart disease needs to be thoroughly taken as well.

Period		2005～2019
Database		PubMed, Cochrane CENTRAL, NPO Japan Medical Abstracts Society
Words searched	P	chronic pain*
	I/C	Tricyclic antidepressants administered group/non-administered group
Limitations		Limited by publication type, PubMed CER randomized controlled trial / systematic review search filter, Cochrane RCT search filter, other (cases of50＋) etc
Selection summary		Of the 246 search hits, we used 21 of them which matched with the set PICO

CQ C-8 : Are anxiolytics (benzodiazepine type drugs) useful for chronic pain ?

Answer : Of the anxiolytics (benzodiazepine type drugs), clonazepam is useful for burning mouth syndrome and alprazolam has a limited usefulness on tension-type headache. There is no evidence on the usefulness of benzodiazepine type drugs on chronic low back pain (LBP), neuropathic pain and fibromyalgia. As benzodiazepine type drugs have a high incidence rate of side effects such as drowsiness and tend to be habit-forming, one should refrain from using them for chronic pain, long-term use or careless concomitant use with opioid analgesics should be avoided.

BMS : burning mouth syndrome

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : Implementation is weakly recommended
〔Consensus 94.1%〕

Summary of overall evidence : C (low)

Commentary：

Benzodiazepine type drugs are mainly used to fight anxiety, as a sedative, and to promote sleep. Furthermore, it is effective as a muscle relaxant, and its expected analgesic effects are used for example on low back pain and stiff shoulders.

We have adopted 4 systematic reviews in order to consider the usefulness of antianxiety drugs (benzodiazepine type drugs) on chronic pain.

According to the pharmacotherapy guidelines[40] by The American College of Physicians (ACP), 2 placebo-controlled RCTs conducted on the usefulness of tetrazepam (yet to be approved in Japan) on chronic low back pain (LBP) as a benzodiazepine type drug, did not recognize a significant improvement when administered for 5～7 days and when administered for 10～14 days (RR 0.71, 95% CI 0.54～0.93) (RR 0.82, 95% CI 0.72～0.94), indicating low evidence of its usefulness.

ACP：The American College of Physicians

In a systematic review[44] on the treatment of burning mouth syndrome (BMS), a meta-analysis was conducted on 22 RCTs to consider the usefulness of various drugs on BMS. As a result, local administration of clonazepam significantly improved pain (on a 0～10 scale) compared with the placebo (MD 1.64, 95%CI 1.23～2.05), and compared with the placebo, the difference in which an improvement of 50% or more occurred was 52.9% (RR 6.92, 95%CI 2.92～16.39), which was significantly higher. Side effects were drowsiness, a burning sensation inside the mouth, and dryness inside the mouth, but there was no difference compared with the placebo. Based on these results, we believed that it is clinically useful.

In a systematic review[45] on the prevention of tension-type headache (TTH), in 1 RCT that was used, there was no recognizable reduction in the frequency of TTH in 62 patients with TTH who were administered with alprazolam compared with the placebo but their overall symptoms tended to improve (evaluated on a headache index from 0～100) (RR 2.0, 95% CI 0.65～6.2) so its effect is limited. Furthermore, the incidence rate of side effects was 16.67%.

In a Cochrane review[46] which considered the usefulness of clonazepam on neuropathic pain and fibromyalgia, 3 research studies were raised as possible candidates but the quality of the research in each case was low, and because they were not eligible for analysis, no evidence on its usefulness was obtained.

There have been many reports of central nervous system type side effects caused by benzodiazepine type drugs, compared with the placebo, such as drowsiness, a feeling of lethargy and lightheadedness. In addition, many patients with chronic pain use benzodiazepine type drugs in combination with opioid analgesics but because they are habit-forming, withdrawal from these drugs is difficult, and there is an elevated risk of drug abuse. Long-term administration of benzodiazepine type drugs, without any specific aim in mind, should be avoided[47].

Period		2005～2019
Database		PubMed, Cochrane CENTRAL, NPO Japan Medical Abstracts Society
Word searched	P	chronic pain
	I/C	benzodiazepine, clonazepam, diazepam administered/not-administered group
Limitations		Limited by publication type, PubMed CER randomized controlled trials / systematic reviews search filter, Cochrane RCT search filter, other（number of cases50＋）etc
Selection summary		Narrowed down from 230 to 21 searches, and ultimately 5 were used that matched with the set PICO

CQ C-9：Are centrally-acting muscle relaxants（tizanidine, eperisone）useful for chronic pain？

Answer： The usefulness of centrally-acting muscle relaxants（tizanidine, eperisone）on chronic low back pain remains unclear. Attention needs to be paid to central nervous system side effects such as drowsiness, dizziness and exhaustion and symptoms of the digestive organs such as dipsia, nausea and vomiting, and pain in the fovea centralis.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade：No recommendation〔Consensus 88.2%〕

Summary of overall evidence：D（very low）

Commentary：

In Japan, the centrally-acting muscle relaxants tizanidine and eperisone are used to improve myotonia in subjects with low back pain（LBP）. Tizanidine displays a muscle-relaxing effect through stimulation of central α_2 adrenergic receptors, whereas eperisone acts by inhibiting reflexes in the spinal cord.

We used 1 systematic review and 2 RCTs that were included under that review in order to consider the usefulness of centrally-acting muscle relaxants（tizanidine, eperisone）on chronic pain.

In a systematic review[48] that considered the usefulness of eperizone on LBP, 7 research studies, that included 5 RCTs, were eligible for analysis but of these, only 2 of the RCTs targeted chronic LBP so here we considered each respective RCT.

In an RCT[49] that investigated how eperizone affects blood flow in the paraspinal muscles, researchers considered the usefulness of oral administration of eperizone in 74 patients with chronic LBP, compared with patients who only received standard physiotherapy as the control group. When they measured the blood flow in the paraspinal muscles at week 4 after administering eperizone, they found that oxyhemoglobin had risen more significantly in the eperizone group than the physiotherapy group. Pain improved by approximately 14 points（VAS：on a scale from 0～100）in both groups；there was no recognizable difference. In addition, there was no recognizable improvement in either group in mental function when evaluat-

ed on the SF-36.

In the other RCT[50], 60 subjects with chronic LBP and with spasticity in their paraspinal muscles were randomly assigned into 2 groups and in addition to the 100 mg/day of tramadol, they were also administered with eperizone and tizanadine, respectively, and researchers investigated improvement in pain. At day 5 and day 30 after administration, at rest, pain had improved in both groups by approximately 40 points on the VAS scale (on a scale from 0～100), but no significant difference in improvement effect was observed between the two groups. (eperizone group：average 63 (SD 12) → 22 (SD 11), tizanadine group：average 69 (SD 11) → 23 (SD 11). As for side effects, drowsiness was significantly higher in the tizanadine group (43.3%) than the eperizone group (16.6%). Administration was discontinued due to side effects in 9 cases due to tizanadine and in 5 cases due to eperizone；it was significantly higher in the tizanadine group.

Based on the above, there is little evidence indicating the usefulness of central-acting muscle relaxants (tizanadine, eperizone) on chronic LBP.

According to a systematic review[48] on LBP mentioned above, researchers reported side effects such as digestive organ symptoms (nausea, vomiting, pain in the fovea centralis), dizziness, and drowsiness, in patients administered with eperizone. However, compared with diazepam and thicolchicoside (yet to be approved in Japan), the difference in the frequency of side effects was significantly lower from eperizone at 25.3% (RR 0.25, 95% CI 0.15～0.41). Common side effects from tizanadine are dipsia, exhaustion and dizziness but in most cases it is mild and if oral administration of tizanadine is discontinued, these symptoms will disappear. Caution is advised with tizanadine because overdoses can cause low blood pressure and bradycardia. Moreover, in some cases researchers have observed elevated liver enzymes and if necessary, monitoring of liver function should be taken into account[51].

There has been much research considering the usefulness of central-acting muscle relaxants on multiple sclerosis (MS) and muscle contracture after spinal cord injury and researchers have evaluated its usefulness. However, there is little high-quality evidence regarding its effect on chronic pain and so in future there is a need to verify its efficacy through RCTs and accumulate evidence.

Period		2005～2019
Database		PubMed, Cochrane CENTRAL, NPO Japan Medical Abstracts Society
Words searched	P	chronic pain
	I/C	central muscle relaxant, Tizanidine, Eperisone administered/non-administered group
Limitations		Limited by publication type,PubMed CER randomized controlled trials, systematic review search filter, Cochrane RCT search filter, other（number of cases50＋）etc
Selection summary		Narrowed down from 190 to 15 searches, and ultimately 4 were used that matched with the set PICO. With NPO Japan Medical Abstracts Society, we expanded our search back to 1990

OA : osteoarthritis
FM : fibromyalgia

CQ C-10 : Is tramadol useful for chronic pain ?

Answer : Tramadol significantly improved pain and physical function in neuropathic pain, low back pain (LBP), and osteoarthritis (OA). There is insufficient evidence of its usefulness on fibromyalgia (FM). In Japan, it is not designated as a narcotic so it is easy to prescribe but considering that it is an opioid, long-term administration of this drug without any clear aim should be avoided.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : Implementation is weakly recommended
〔Consensus 100%〕

Summary of overall evidence : B (moderate)

Commentary :

Tramadol is not designated as a narcotic in Japan. It is a dual drug, which both acts on μ-opioid receptors and inhibits the reuptake of serotonin and noradrenaline. Tramadol is metabolized to O-desmethyltramadol (M1), which has analgesic effects, by CYP2D6. The unchanged compound tramadol and the M1 metabolite bond with the μ-opioid receptor and act as an opioid analgesic but M1 displays a higher analgesic effect than the unchanged compound tramadol. The second metabolite N, O-desmethyltramadol (M5) are also activated and involved in the analgesic effect. In this way, the main analgesic effects of tramadol are M1 and M5 so have been called a prodrug[52].

We have adopted 4 systematic reviews on the usefulness of tramadol on chronic pain.

A Cochrane review[53] evaluated changes in the intensity of pain in patients with neuropathic pain by administering them with 100～400 mg/day of tramadol over 4～6 weeks. The rate of patients who experienced more than 50% reduction in pain was 23% higher (RR 2.16, 95%CI 1.02～4.58) in the tramadol group than in the placebo group.

A Cochrane review[54] which investigated its usefulness on LBP evaluated changes in the intensity of pain and physical function when patients were administered with 150～300 mg/day of tramadol over a 28～90 day period. The difference in the average change in the intensity of pain from the baseline was −0.5 (95%CI −0.66～−0.44) compared with the control ; a significant improvement. Physical function was evaluated on the Roland Morris Disability Questionnaire (RMDQ), and the difference in the average change in the intensity of pain from the baseline was −0.18 (95%CI −0.29～−0.07) compared with the control ; indicating that it had significantly improved.

A Cochrane review[55] on OA evaluated changes in intensity of pain and physical

function when patients were administered with 100～400 mg/day of tramadol over 2 weeks～91 days. The difference in the average change in the intensity of pain from the baseline was −0.25 (95%CI −0.32 ～−0.18) compared with the control ; a significant improvement. Physical function was evaluated by the Western Ontario and McMaster Universities Index (WOMAC) and the difference in the average change from the baseline was −0.20 (95%CI −0.29 ～−0.12) compared with the control ; a significant improvement.

In a systematic review[56] that considered 3 RCTs on subjects with fibromyalgia (FM), researchers evaluated changes in the intensity of pain and quality of life (QOL) in patients who were administered with tramadol only, those administered with tramadol and acetaminophen in combination, and those administered with tramadol and amitriptyline in combination. The average change in intensity of pain from the baseline was −13 (95% CI −25.37～−0.63), −12 (95% CI −18.77～−5.23), and −13 (95% CI −19.08～−6.92) respectively ; pain had improved. QOL was evaluated using the Fibromyalgia Impact Questionnaire (FIQ), and the average change on the FIQ from the baseline for tramadol/acetaminophen was −6.00 (95%CI −9.55 ～−2.45), showing an improvement but no significant effect was seen when tramadol was administered alone at −2.9 (95% CI −10.86 ～ 5.06). Based on the above, tramadol is not sufficiently useful.

QOL : quality of life

Side effects from tramadol include nausea, constipation and drowsiness but the incidence rate for each of these side effects was 9% (RD 0.09, 95%CI 0.05～0.13), 5% (RD 0.05, 95%CI 0.02～0.09), and 6% (RD 0.06, 95%CI −0.01～0.13, higher than the placebo, respectively[54]. In the United States, the number of prescriptions for tramadol has increased more than for any other opioid analgesic. The reason for this is believed to be related to people's awareness that tramadol carries a low risk of drug dependence/abuse[52]. In Japan, tramadol is not designated as a narcotic or psychotropic drug. Furthermore, physician do not have a duty to take an e-learning course upon prescription and it is not essential to obtain a treatment consent form from patients either[57]. However, the risk of dependence/abuse is not nil, so long-term administration without any clear aim in mind must be avoided. Tramadol, which had been an unregulated opioid analgesic up until this point, was designated as a regulated opioid (Schedule IV) by the US Food and Drug Administration (FDA) in 2014.

FDA : Food and Drug Administration

Period		2005～2019
Database		PubMed, Cochrane CENTRAL, NPO Japan Medical Abstracts Society
Words searched	P	chronic pain*
	I/C	Tramadol administered group/non-administered group
Limitations		Limited by publication type, PubMed CER randomized controlled trial / systematic review search filter, Cochrane RCT search filter, other (cases of50+) etc
Selection summary		Of the 322 search hits, we used 12 which matched with the set PICO

CQ C-11 : Are buprenorphine patches useful for chronic pain ?

Answer : Buprenorphine patches are useful in reducing low back pain (LBP) and osteoarthritic pain. On the other hand, there is no evidence indicating their efficacy on neuropathic pain. Compared with other opioid analgesics, they tend to have few side effects and are recommended for older patients with many complications.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : Implementation is weakly recommended 〔Consensus 100%〕

Summary of overall evidence : B (moderate)

Commentary :

Buprenorphine is pharmacologically a partial agonist of μ-opioid receptors but also a complete agonist of μ-opioid receptors in concentrated use in clinical settings, with no noticeable ceiling effects as an analgesic. On the other hand, it does have ceiling effects in respiratory depression[58]. Buprenorphine has low molecular weight just like fentanyl and high liposolubility so it is suited for percutaneous and transmucosal administration[59]. Approximately 2/3 of buprenorphine is not metabolized, the remaining 1/3 is metabolized by CYP3A4 in the liver to norbuprenorphine. It has low pharmacological activity as a metabolite. As an unchanged compound, buprenorphine and 2/3 of its metabolite are excreted in the feces. Because there is very little involvement with the kidneys, when kidney function deteriorates it is possible to use the same dosage as that used in patients with standard kidney function. In the case of impaired liver function, its half-life lingers but it does not really have much impact on patients clinically. Buprenorphine is recommended for older patients because they often have decreased kidney and liver function[60,61].

We have adopted 3 systematic reviews on the usefulness of buprenorphine patches on chronic pain.

In a Cochrane review[54] on low back pain (LBP), researchers evaluated changes in the intensity of pain and physical function in subjects administered with buprenorphine patches containing 5～40 μg/hr over a period of 4～12 weeks. The difference in the average change from the control in intensity of pain from the baseline was −2.47 (95% CI −2.69 ～−2.25) ; a significant improvement. Physical function was evaluated using the SF-36, and the difference in the average change from the baseline was −0.14 (95% CI −0.53～−0.25), indicating that there was no significant improvement compared with the placebo.

OA : osteoarthritis

In a Cochrane review[62] on osteoarthritis (OA), researchers evaluated changes in intensity of pain and physical function in subjects administered with buprenorphine patches containing 5～20 μg/hr over a period of 4～24 weeks. Compared with the

controls, the difference in the average change in pain intensity from the baseline was −0.19 (95% CI −0.30～−0.09) ; a significant improvement. Physical function was evaluated using the Western Ontario and McMaster Universities Index (WOMAC), and compared with the controls, the difference in the average change from the baseline was −0.23 (95% CI −0.40～−0.05) ; a significant improvement.

In a Cochrane review[63] on patients with neuropathic pain, 11 research papers were cited as possible candidates for inclusion but in all papers the quality of the research was low so they were excluded from the eligibility criteria for analysis and there was no discussion on their usefulness.

The incidence rate of side effects from buprenorphine patches was 18.3% (RR 1.25, 95% CI 1.09～1.42) higher than the placebo[62], but compared with other opioid analgesics, there is low risk of side effects such as constipation and nausea and low risk of dependence/abuse or death due to overdose[64,65]. Buprenorphine patches are an opioid analgesic which is not designated as a narcotic in Japan but before prescribing one, a physician are required to take an e-learning course.

Period		2005～2019
Database		PubMed, Cochrane CENTRAL, NPO Japan Medical Abstracts Society
Words searched	P	chronic pain
	I/C	Buprenorphine administered group/non-administered group
Limitations		Limited by publication type, PubMed CER randomized controlled trial / systematic review search filter, Cochrane RCT search filter, other (cases of50+) etc
Selection summary		Of the 380 search hits, we used 12 that matched with the set PICO

CQ C-12 : Are opioid analgesics [strong] useful for chronic pain ?

Answer : Opioid analgesics [strong] improve pain and physical function, for a short period of time, in low back pain (LBP), osteoarthritis (OA), and neuropathic pain. However, there is no evidence indicating their usefulness over a long period of time. Because long-term administration of opioid analgesics [strong] elevates the risk of dependence/abuse and death due to overdose, they become highly disadvantageous to patients. In Japan, there are almost no facilities which can manage patients with opioid dependence abuse. Therefore, before beginning to administer these drugs, rigorous patient screening should be conducted and we do not recommend undergoing treatment by anyone other than a pain management specialist who can conduct rigorous monitoring.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : No recommendation 〔Consensus 100%〕

Summary of overall evidence : B (moderate)

Commentary：

At the current stage, a variety of opioid analgesics [strong] are used in Japan but the only opioid analgesics [strong], which patients with chronic non-cancer pain are able to get a prescription for, are morphine formulations, fentanyl patches and oxycodone extended-release tablets. On the other hand, a large number of formulations can be used overseas and their usefulness has been considered in several RCTs.

We have adopted 3 systematic reviews to consider the usefulness of opioid analgesics [strong] for chronic pain.

In a Cochrane review[54] on low back pain, they evaluated changes in pain intensity and physical function when patients were administered with an opioid analgesics [strong] (tapentadol, oxycodone, morphine, oxymorphone) over a period of 2～12 weeks. Compared with the control, the difference in the average change in pain intensity from the baseline was −0.43 (95% CI −0.52～−0.33)；a significant improvement. Physical function was evaluated using the Roland Morris Disability Questionnaire (RMDQ) and SF-36, and compared with the control, the difference in the average change from the baseline was -0.26 (95% CI −0.37～−0.15), indicating that it had significantly improved.

OA：osteoarthritis

In a Cochrane review[62] on osteoarthritis (OA), researchers evaluated changes in pain intensity and physical function when administered with each type of opioid analgesic [strong] over a period of 1～15 weeks. Compared with the control, the difference in the average change in pain intensity from the baseline was −0.22 (95% CI −0.42～−0.03) for fentanyl, 0.04 (95% CI −0.19～0.28) for hydromorphone, −0.25 (95% CI −0.42～−0.09) for morphine, −0.31 (95% CI −0.47～−0.15) for oxycodone, −0.39 (95%CI −0.58～−0.21) for oxymorphone, and −0.31 (95% CI −0.46 ～−0.16) for tapendatol, indicating a significant improvement except for with hydromorphone. Physical function was evaluated using the Western Ontario and McMaster Universities score (WOMAC), and compared with the control the difference in the average change (in physical function) from the baseline was −0.28 (95% CI −0.48～−0.09) for fentanyl, −0.20 (95% CI −0.38～−0.02) for morphine, −0.30 (95% CI：−0.58～−0.01) for oxycodone, −0.38 (95% CI −0.56 ～−0.19) for oxymorphone, and −0.26 (95%CI −0.35～−0.17) for tapendatol；a significant improvement.

IASP：International Association for the Study of Pain

A systematic review conducted by the Spinal Interest Group on Neuropathic Pain (NeuPSIG) of the International Association for the Study of Pain (IASP)[38], evaluated the analgesic effects of opioid analgesics [strong] on neuropathic pain, and they calculated that the number needed to treat (NNT) to reduce pain by 50% was 4.3 (95% CI 3.4～5.8).

The incidence rate of side effects from opioid analgesics [strong] administered for a short period of time, compared with the placebo, was 27.7% (RR 1.5, 95%CI 1.33 ～1.81) for fentanyl, 4.7% (RR 1.10, 95%CI 0.89～1.35) for morphine, 34.4% (RR

1.69, 95%CI 1.47～1.95) for oxycodone, and 16.3% (RR 1.39, 95%CI 1.17～1.66) higher for tapendatol[62].

There are several research papers indicating the usefulness of opioid analgesics [strong] for chronic pain but most of them are limited to short-term evaluations. Because there are no research papers which have evaluated the usefulness of opioid analgesics used for a period of over 1 year, caution is required for such treatment interventions. Opioid analgesics not only generate an analgesic effect but also euphoria, and dependence/abuse can arise and the risk of death due to overdose increases with dose dependent effects[66]. If the original disease causing chronic pain is low back pain (LBP), osteoarthritis, or neuropathic pain, one can expect these drugs to give a slight improvement in analgesic effect and QOL if limited to a short period of time (within 3 months). However, there is a high possibility that the benefits (analgesic effects) of long-term administration might be outweighed by its disadvantages (dependence/abuse, death). Furthermore, at the current stage in Japan, there are almost no institutions which can manage patients with opioid dependence/abuse. Therefore, rigorous patient screening must be conducted prior to administration and after administration commences, if rigorous monitoring is not conducted, then opioid dependence/abuse may occur. A high level of knowledge about opioid dependence and abuse is required when administering opioid analgesics [strong] for chronic pain. Therefore, we do not recommend that undergoing treatment with opioid analgesics 〔strong〕 by anyone other than a pain management specialist.

Period		2005～2019
Database		PubMed, Cochrane CENTRAL, NPO Japan Medical Abstracts Society
Words searched	P	chronic pain*
	I/C	Strong opioid (opioid strength) administered group/non-administered group
Limitations		Limited by publication type, PubMed CER randomized controlled trial / systematic review search filter, Cochrane RCT search filter, other (cases of 50+) etc
Selection summary		Of the 405 search results, we used 11 which matched with the set PICO

CQ C-13 : Is Kampo medicine (Chinese herbal medicine) useful for chronic pain ?

Answer : As there is insufficient evidence indicating that Kampo medicine (Chinese herbal medicine) is effective on chronic pain, it remains unclear at the current stage. However the fact that in Japan patients can be insured if treated with Kampo medicine is also a factor, so many medical practitioners do positively evaluate its utility to some degree.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : Implementation is weakly recommended

〔Consensus 94.1%〕

Summary of overall evidence : C (low)

Commentary :

In Western medicine, the main purpose is to treat a specific illness and so they mainly use medication that proves to be effective against the sites of lesions or their associated symptoms. On the other hand, in Kampo medicine (Chinese herbal medicine), they understand the whole picture of each individual patient's body and focus on treating patients by fixing the body's overall condition and restoring imbalances and distortions inside the body. This is how Western medicine and Kampo medicine are different in their approach. With pain conditions, in Kampo medicine treatment, they do not directly reduce the pain by ascertaining the organic cause of the patient's pain, but restore the factors which aggravate the pain as "distortions".

There has been much published research which has considered the usefulness of Kampo medicine on chronic pain but the majority of this has been case studies or case series studies and at the current stage there are no RCTs with high-quality research. However it should be noted that, in Japan, Kampo medicine can be used as a form of treatment which is covered by insurance and so many doctors in clinical settings are prescribing them and to a certain degree have positively evaluated their usefulness. In a retrospective research study[67] targeting 221 patients with chronic pain, researchers administered Kampo medicine (such as gosha-jinki-gan, shakuyaku-kanzo-to, yokukan-san) and reported a decrease in pain in 77.9% of the patients (highly effective : 26.3%, moderate improvement : 12.7%, slight improvement : 38.9%).

In a randomized open-label study on 58 spinal canal stenosis patients with painful muscle cramp, the frequency of painful muscle cramps decreased to less than 50% in 81.2% of patients who were administered with 7.5g of shakuyaku-kanzo-to /day (2.5～7.5g/day), indicating that there was no statistically-significant difference in the frequency of occurrence according to the dosage[68]. In a non-randomized comparative trial targeting 83 patients with knee osteoarthritis (OA), compared with the control group, the group who had been administered with shakuyaku-kanzo-to had a lower frequency of painful muscle cramp incidence but statistically speaking, the difference was not significant. However, the rate of change in muscular stiffness in the gastrocnemius muscle did significantly decrease[69].

In a case series study, they have reported on the utility of various Kampo medicines on chronic pain. In 15 patients with postherpetic neuralgia who were administered with 7.5 g of keishi-kajutsu-bu-to/day and 1～5 g of bushimatsu (processed aconite root)/day in combination, 80% of these patients were able to continue taking them internally, and in 91% of these patients, pain intensity decreased by 50%

or more[70]. In a retrospective study considering the usefulness of gosha-jinki-gan on 28 patients with LBP, pain improved in 35% of the patients. The conditions that the researchers cited for improvements were the absence of spinal canal stenosis and regular administration of the Kampo medicine[71]. A retrospective study considering the usefulness of Kampo medicine on 151 patients with pain from spinal canal stenosis and intermittent claudication clearly showed that the the dosage of pregabalin and opioid analgesics had decreased in the group administered with Kampo medicine (for example gosha-jinki-gan, hachimi-jio-gan) compared with non-administration group[72]. In a prospective cohort study that considered the usefulness of hachimi-jio-gan on 14 patients with arteriosclerosis obliterans (ASO), researchers indicated a decrease in pain and patients were able to walk longer distances[73].

Side effects from Kampo medicine (Chinese herbal medicine) include pseudohyperaldosteronism from licorice root, drug-induced interstitial pneumonia from Scutellaria root, excessive β-stimulating effect from the Ephedra herb, and aconite poisoning from aconite tuber. Kampo formulations are composed of various herbal medicines and therefore attention should be paid to the herbal medicines ingredients of which they are composed when administering them to patients.

Period		2005～2019
Database		PubMed, Cochrane CENTRAL, NPO Japan Medical Abstracts Society
Words searched	P	chronic pain*
	I/C	kampo medicine administered group/non-administered group
Limitations		Limited by publication type, PubMed CER randomized controlled group / systematic review search filter, Cochrane RCT search filter, other (cases of50%＋) etc
Selection summary		Of the 170 search hits, we used 18 of them which matched with the set PICO

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Chapter D. Interventional Pain Treatment (Nerve Block) : CQ D-1～CQ D-9

CQ D-1 : Are epidural injections useful for chronic pain ?
CQ D-2 : Are nerve root block/transforaminal epidural injections useful for chronic pain ?
CQ D-3 : Are facet (zygapophyseal) joint injection and medial branch block useful for chronic pain ?
CQ D-4 : Is stellate ganglion block useful for chronic pain ?
CQ D-5 : Is sympathetic ganglion block useful for chronic pain ?
CQ D-6 : Is a trigger point injection useful for chronic pain ?
CQ D-7 : Is a nerve block using radiofrequency thermocoagulation (RF) useful for chronic pain ?
CQ D-8 : Is nerve block using pulsed radiofrequency (PRF) treatment useful for chronic pain ?
CQ D-9 : Are intra-articular injections useful for chronic pain ?

D. Interventional Pain Treatment (Nerve Block)

CQ D-1 : Are epidural injections useful for chronic pain ?

Answer : 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.

Recommendation Grade & Summary of Overall Evidence

1) Lumbar spine disease

- **Epidural steroid injection for radiculopathy due to lumbar disc herniation**
  Recommendation grade : 2 (weak) : Implementation is weakly recommended〔Consensus 83.3%〕
  Summary of overall evidence : B (moderate)
- **Epidural injections for lumbar spinal canal stenosis, discogenic pain**
  Recommendation grade : 2 (weak) : Implementation is weakly recommended〔Consensus 88.2%〕
  Summary of overall evidence : C (low)
- **Caudal block for failed back surgery syndrome**
  Recommendation grade : No recommendation〔Consensus : Implementation is weakly recommended 41.2%, No recommendation 58.8%〕
  Summary of overall evidence : C (low)

2) Cervical diseases

- **Epidural steroid injection for radiculopathy due to cervical disc herniation**
  Recommendation grade : 2 (weak) : Implementation is weakly recommended〔Consensus 100.0%〕
  Summary of overall evidence : B (moderate)
- **Epidural injection for cervical spinal stenosis, axial pain**
  Recommendation grade : 2 (weak) : Implementation is weakly recommended〔Consensus 82.4%〕
  Summary of overall evidence : C (low)

Commentary :

Epidural injections are an interventional therapy frequently used to manage pain. There are 3 pathways in which it is administered : interlaminar epidural, transforaminal epidural (nerve root block) and caudal blocks but here we will discuss epidural injections in general. Transforaminal epidural injection will be described in detail on the following page.

1) Lumbar spine disease

In a meta-analysis of 8 RCTs on the efficacy of epidural steroid injections (interlaminar, transforaminal, caudal) for lumbar disc herniation, researchers found that it indicated significant analgesic effect 1-month and 3-months afterwards compared with those who were only injected with standard saline solution and local anesthetic. In another meta-analysis on 3 RCTs that was conducted one year later, researchers indicated a slight significance but there was no statistical difference in terms of improvement of ADL[1].

In a meta-analysis of 5 RCTs on lumbar radiculopathy including lumbar spinal stenosis, there was no statistical difference in analgesic effect and improvement in ADL compared with the placebo control[2], However, in the RCTs in question, the research did not clearly display a diagnosis of radiculopathy and the method of epidural injection and the site of injection vary greatly from one research study to the next and because they included research in which only the placebo group was prescribed an analgesic and research in which an epidural standard saline solution injection was used as the placebo, we have some doubts whether this meta-analysis is able to evaluate the usefulness of epidural injection or not.

There is a large number of RCTs that have considered the usefulness of epidural steroid injections on lumbar spine diseases but the control used in the majority of them is a local anesthetic and injection of standard saline solution or a different approach method. There are mixed results, some showing a significant difference, others not but in both the control group and steroid injection group, they showed analgesic effect over a short period of time. A systematic review of 52 research papers[3], contains an RCT on caudal blocks for patients with lumbar spinal canal stenosis (steroid injection) over a short period of time (12 weeks) and the usefulness of interlaminar epidural injection over a 2-year period, and both indicating analgesic effect and an improvement in ADL. Similarly, there exist respective RCTs on the 2-year usefulness of a caudal block and interlaminar epidural injection for discogenic pain as well as caudal block for failed back surgery syndrome (FBSS). Based on the above, the evidence is limited but we believe that epidural injections are useful on lumbar spine diseases. Some cases of FBSS include strong psychosocial factors and therefore as careful judgment is required when applying a caudal block, we decided on assigning a 'no recommendation' grade.

RCT : randomized controlled trial

FBSS : failed back surgery syndrome

2) Cervical spine disease

As there have been reports of lethal complications from cervical transforaminal epidural injection (nerve root block), only the interlaminar approach is subject to these guidelines. There are several RCTs but the conditions vary so no meta-analysis has been conducted. According to a systematic review[4], 4 RCTs have shown strong evidence of its usefulness in providing analgesic effect and improving ADL over the long term (1～2 years) in cases of cervical disc herniation. There are also respective RCTs, displaying the same level of usefulness, on cases of axial pain, and

spinal canal stenosis.

3) Regarding steroid injections

One of the causes of spinal disease pain is inflammation surrounding the epidural space. Theoretically, it is believed that steroid injections are useful. There have been attempts to investigate the superiority of steroid injections but apart from lumbar disc herniation, its usefulness has not been proven compared with local anesthetic injections used alone[5]. The reason for this is believed to be, for example how the saline solution is useful by washing away the inflammatory substances. As for lower back and leg pain, a meta-analysis that considered whether lumbar spine surgery could be avoided or not by comparing an epidural steroid injection with only a local anesthetic injection, 5 RCTS showed that it did have the effect of slightly reducing the risk of surgery within 1 year but 16 of the RCTS indicated that it did not have an effect for over 1 year[6]. Considering side effects such as impaired glucose tolerance, frequent injections of steroid should be avoided.

Furthermore, in a systematic review on the difference in the effects of steroid injections according to particulate or non-particulate steroids, there was no superiority with particulate steroids[7]. When we consider the dangers of spinal cord infarction and cerebral infarction due to intravascular administration, non-particulate steroids should be used, unless there is some specific reason.

4) Adverse effects

With reports of fatal complications such as spinal cord infarction due to intravascular injection of particulate steroids in cervical transforaminal approach, intravascular injections in interlaminar approach should be avoided as well. There are reports recommending that real-time contrasts be conducted under fluoroscopic control at all sites, as well as prohibiting injections at postoperative wounds[8]. Considering the situation with pain clinic treatment in Japan, injections at lumbar sites should be conducted, as much as possible, under fluoroscopic control and at cervical sites, it is essential that epidural injections be conducted under fluoroscope.

Considering fluoroscope control, it is believed that intravascular injections occur 0.5% at lumbar sites, 4.1% occurring at cervical sites, and dural punctures occurring 0.5% of the time[9]. In a retrospective look at cervical epidural injections under fluoroscope in 4,396 patients, research reported that the incidence rate of dural puncture was 1.3% but there was no incidence of spinal cord injury or postdural puncture headache (PDPH)[10]. There were almost no reports of severe side effects, and as long as the injection is made under fluoroscopic control caudally from $C_{6/7}$, and as long as a nonparticulate steroid injection is used, it is a relatively safe procedure.

It is believed that there is no difference in efficacy between a lumbar injection performed under ultrasound guidance and one performed under fluoroscope. Furthermore, the operation can be shortened with a caudal injection. However, consid-

ering the inability to check intravascular injections and the lack of visibility in deep lumbar sites when performed under ultrasound, lumbar epidural injections (interlaminar/transforaminal) conducted under fluoroscope should be prioritized[11].

Period		2005～2019
Database		PubMed, Cochrane CENTRAL, NPO Japan Medical Abstracts Society
Words searched	P	chronic pain,neck pain, Complex Regional Pain Syndromes, Phantom Limb, Neuralgia, zoster associated pain, Peripheral Vascular Diseases, back pain, low back pain, postherpetic neuralgia
	I/C	Epidural Injections, caudal block
Limitations		Limited by publication type,PubMed CER randomized controlled trials / systematic review search filter, Cochrane RCT search filter, other (cases of50+) etc
Selection overview		Of the 523 searches, we used 18 that matched with the set PICO

CQ D-2 : Are nerve root block/transforaminal epidural injections useful for chronic pain ?

Answer : Nerve root blocks are useful on lumbar spine diseases, and in particular steroid injections are useful on radiculopathy due to disc herniation. There have been severe complications with cervical sites so its use is limited.

Recommendation Grade & Summary of Overall Evidence

1) Lumbar spine disease

- Transforaminal epidural steroid injection for lumbar disc herniation

  Recommendation grade : 2 (weak) : Implementation is weakly recommended〔Consensus 82.4%〕

  Summary of overall evidence : B (moderate)

- Transforaminal epidural injection for lumbar spinal canal stenosis

  Recommendation grade : 2 (weak) : Implementation is weakly recommended〔Consensus 88.9%〕

  Summary of overall evidence : C (low)

2) Cervical diseases

- Nerve root block under limited conditions such as ultrasound guidance

  Recommendation grade : 2 (weak) : Implementation is weakly recommended〔Consensus 83.3%〕

  Summary of overall evidence : C (low)

Commentary :

In Japan, nerve root block is a technique of injecting into the nerve sheath and some think that it is different from transforaminal epidural injection but this concept is not consistently agreed upon. Based on the extent of our search, most research has reported on using transforaminal epidural injections for the purpose of treatment, but as they have been unable to clearly distinguish between the two, we will treat them as one and the same technique.

RCT : randomized controlled trial

1) Lumbar spine diseases

In a systematic review of 18 RCTs on transforaminal epidural injection[3], most of the research that was utilized did not show any difference between the groups in terms of the drug that was administered or the pathway via which it was administered, and researchers showed significant analgesic effect for lumbar spine diseases and improvement in ADL in the control group and the group administered with the steroid. In 4 RCTs on radiculopathy due to lumbar disc herniation, researchers showed long-term efficacy (1 ～ 2 years). In 3 of the RCTs, researchers showed short-term effects on lumbar spinal canal stenosis but the evidence was limited and no high-quality RCTs exist on discogenic low back pain (LBP) or failed back surgery syndrome (FBSS). In another RCT that was published after that on unilateral leg pain due to lumbar disc herniation, in which physiotherapy and pharmacology were used as the controls, researchers found that when transforaminal epidural injection (steroid injection) was added, there was a significant improvement in pain and ADL 1 month later[12].

Theoretically, we expect transforaminal epidural injections to be more effective than interlaminar epidural injections and caudal blocks because the advantage is the steroid can be directly injected into the inflamed area around the nerve root. In a systematic review of 12 research studies on lumbar disc herniation, in comparison with interlaminar epidural injection, several reports clearly indicated that transforaminal epidural injection were more highly effective but the results of a meta-analysis of 5 RCTs, which were uniform, did not show any significant difference in analgesic effect or improved ADL[13]. Similarly, in a meta-analysis of 3 RCTs, it was not found to be superior when compared with a caudal block[14]. In conclusion, there is limited evidence indicating that transforaminal epidural injection is more useful than interlaminar epidural injection and caudal block for treating lumbar disc herniation but considering things like the possibility of root arterial injury during a transforaminal epidural injection and a feeling of discomfort at the time of the steroid injection, we need to judge which form of treatment to choose.

We would like to refer you to the epidural injection (**CQ D-1**) for deciding whether to add a steroid injection or not. Researchers have demonstrated the statistical superiority of a steroid injection over just a local anesthetic injection for lumbar disc herniation[1], but there is another RCT that failed to show the statistical difference for other types of lumbar spine diseases[5]. Furthermore, in a meta-analysis of 4 RCTs comparing injections of particulate and non-particulate steroids for lumbar transforaminal epidural injection, researchers did not find any difference in analgesic effect nor any difference based on the type of steroid used[15]. When it comes to actually using non-particulate steroid, we should limit the frequency of its usage.

2) Cervical spine diseases

There have been reports that cervical transforaminal epidural injection may result in rare, but severe complications, What researchers have thought could be possible mechanisms causing this include brainstem/spinal cord infarction mainly due to an intravenous particulate steroid injection and also vascular spasm due to the puncture needle. Therefore, in recent years there have been few high-quality reports. In a systematic review of transforaminal epidural injections conducted under fluoroscope to treat radiculopathy, 16 research papers indicated that it was effective (provides analgesic effect, and avoidance of surgery) but the evidence was limited. In addition, there is a case report of 23 severe complications, including 13 cases of death, so we recommend conducting the interlaminar approach[16].

In a retrospective consideration of nerve root block conducted under ultrasound guidance and epidural injection (interlaminar) conducted under fluoroscope control[17], a nerve root block conducted under ultrasound guidance was a shorter procedure but there was no difference in analgesic effect or improved ADL. In an epidural injection, there was some blood reflex in 8% of cases at the time of absorption but this phenomenon did not occur in a nerve root block conducted under ultrasound guidance. An angiography detected 11% during epidural injection. A nerve root block conducted under ultrasound guidance offered superior visibility of the blood vessels in the area surrounding the puncture site and therefore may possibly be safer but we should also keep in mind the danger of being unable to confirm an intravascular injection. There have been no reports of severe complications from nerve root block under ultrasound guidance but it is recommended to have some safety measures in place when using non-particular steroids such as using real time fluoroscopy concomitantly as much as possible.

Period		2005～2019
Database		PubMed, Cochrane CENTRAL, NPO Japan Medical Abstracts Society
Words searched	P	chronic pain,neck pain, Complex Regional Pain Syndromes, Phantom Limb, Neuralgia, zoster associated pain, Peripheral Vascular Diseases, back pain, low back pain, postherpetic neuralgia
	I/C	Epidural Injections
Limitations		Limited by publication type,PubMed CER randomized controlled trials / systematic review search filter, Cochrane RCT search filter,other (case number of50+) etc
Selection outline		Of the 523 search hits, we utilized 9 that matched with the set PICO

CQ D-3 : Are facet (zygapophyseal) joint injection and medial branch block useful for chronic pain ?

Answer : We can expect medial branch block to provide analgesic effect and improved QOL for facet joint-derived chronic low back pain (LBP), cervical pain, and thoracic back pain. There is a possibility that giving or not giving patients a steroid injection may not even have an influence. Facet (zygapophyseal) joint injection is widely used to treat facet joint-derived chronic low back pain (LBP), cervical pain, and thoracic back pain but evidence indicating its usefulness is limited.

Recommendation Grade & Summary of Overall Evidence

1) Medial branch block

Recommendation grade : 2 (weak) : Implementation is weakly recommended [Consensus 94.1%]

Summary of overall evidence : C (low)

2) Facet (zygapophyseal) joint injection

Recommendation grade : 2 (weak) : Implementation is weakly recommended [Consensus 83.3%]

Summary of overall evidence : C (low)

Commentary :

1) Medial branch block

When one suspects facet joint-derived chronic low back pain (LBP), cervical pain, or thoracic back pain, a nerve root block is conducted on the posterior rami of the spinal nerves, which are the sensory nerves of the facet joints, for the purposes of diagnosis and treatment. Research on medial branch block is conducted on the premise of evaluating research being carried out for a rigorous diagnosis of facet joint-derived pain. A systematic review[22] has been conducted, and there are 4 RCTs that investigated the usefulness of medial branch block on chronic LBP, cervical pain, and thoracic back pain[18-21]. There is no research comparing it against sham treatments. In all 3 RCTs (lumbar[18], cervical[19], thoracic[20]) comparing the difference in effect of a medial branch block by the drug used (local anesthetic vs. local anesthetic + steroid), each displayed analgesic effect and improved QOL over the short-term and long-term, irrespective of the type of steroid used. The results of a follow-up study conducted over 2 years were that pain had improved at 14～19 weeks after the 1 medical branch block, and after conducting 5～6 blocks over a 2-year period, it maintained a reduction in pain over the long term. In another RCT[21] on LBP, compared with radiofrequency thermocoagulation of the medial branch of posterior ramus of which there is much evidence of its efficacy, lumbar medial branch block provides inferior analgesic effect over the short and long term, and there was no difference in improved QOL. Also in these RCTs, there was not 1 report of any severe complications.

RCT : randomized controlled trial

Based on the above, we do recommend medial branch block as a form of treatment which we expect can provide analgesic effect and improved QOL for facet joint-derived chronic LBP, cervical pain, and thoracic back pain. However, as there is no high-quality research comparing it against sham treatments, the certainty of its evidence is low.

2) Facet (zygapophyseal) joint injection

Facet (zygapophyseal) joint block is a widely-used form of treatment with the same purpose as the medial branch block mentioned above. Research on facet (zy-

gapophyseal) joint injection is conducted under the premise of evaluating research being carried out for a rigorous diagnosis of facet joint-derived pain. There are 5 RCTs (4 lumbar, 1 cervical)[23-27] on the usefulness of facet (zygapophyseal) joint injection on chronic low back pain (LBP), cervical pain, and thoracic back pain, and a systematic review has been conducted[22]. When we evaluate a quantitative synthesis of 2 RCTs[23,24] that compare a facet (zygapophyseal) joint injection for LBP with a sham treatment (saline solution, hyaluronic acid), there was found to be no difference in analgesic effect over the short term, and over the long term, analgesic effect was slightly superior from the facet (zygapophyseal) joint injection and no difference in improved QOL. In a research study[25] on long-term analgesic effect and improved QOL comparing a facet (zygapophyseal) joint injection with radiofrequency thermocoagulation of the medial branch of posterior ramus (for which a large number of evidence its efficacy exists), researchers did not find any difference in efficacy or degree of effect. In another research study[26] comparing short-term analgesic effect and improved QOL in a facet (zygapophyseal) joint injection group with a NSAIDs (only) group and a NSAIDs + facet (zygapophyseal) joint injection group, the results showed that analgesic effect and improved QOL were significantly higher in the NSAIDs + facet (zygapophyseal) joint injection group (1^{st}) > the facet (zygapophyseal) joint block group (2^{nd}) > the NSAIDs group (3^{rd}), in that order. Furthermore, in another research study[27] comparing analgesic effect on patients with cervical pain across 2 groups : one group receiving analgesic + home exercise management and an additional facet (zygapophyseal) joint injection and one group without the injection, researchers found that only those in the group to which a facet (zygapophyseal) joint injection was added experienced a significant reduction in pain over the short and long term, compared with prior to treatment. These RCTs did not report any cases of severe complications.

Based on the above, facet (zygapophyseal) joint injection is a widely-used form of treatment for facet joint-derived chronic low back pain (LBP), cervical pain, and thoracic back pain but there have been reports of results that contradict these effects, meaning there is poor grounds on which we are able to strongly recommend it as a form of treatment from which one can expect analgesic effect and improved QOL, and the certainty of its evidence remains low.

Period		2005～2019
Database		PubMed, Cochrane CENTRAL, NPO Japan Medical Abstracts Society
Words searched	P	chronic pain, low back pain, neck pain, back pain
	I/C	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/no particular specifications
Limitations		Limited by publication type,PubMed CER randomized controlled trials,/systematic reviews/meta-analysis search filter,Cochrane RCT search filter, other (English, Japanese) etc
Selection summary		Of the 169 search hits, we utilized 10 searches that matched with the set PICO

CQ D-4 : Is stellate ganglion block useful for chronic pain ?

SGB : stellate ganglion block

Answer : Apart from its effects in preventing postherpetic neuralgia (PHN) from herpes zoster, there is no high-quality evidence on stellate ganglion block (SGB). However, it is widely used to alleviate head and neck pain and sympathetic nerve-dependent pain, and there are reports indicating its efficacy. One needs to give each case plenty of consideration about its applicability and when performing this block, one needs safety measures such as performing it under ultrasound guidance.

Recommendation Grade & Summary of Overall Evidence

CRPS : complex regional pain syndrome

1) CRPS in the upper limbs

Recommendation grade : No recommendation〔Consensus 81.3%〕

Summary of overall evidence : C (low)

2) Prevention of postherpetic neuralgia (PHN) for herpes zoster

Recommendation grade : 2 (weak) : Implementation is weakly recommended〔Consensus 86.7%〕

Summary of overall evidence : C (low)

3) Orofacial pain

Recommendation grade : No recommendation〔Consensus : 47.1% implementation is weakly recommended : 52.9% no recommendation〕

Summary of overall evidence : D (very low)

Commentary :

PHN : postherpetic neuralgia

PTSD : post-traumatic stress disorder

Stellate ganglion block (SGB) is used for various types of chronic pain such as complex regional pain syndrome (CRPS), postherpetic neuralgia (PHN), headache, and orofacial pain, and also for disease other than pain such as blood circulation disorder in the upper limbs, facial (nerve) paralysis, drug-refractory ventricular arrhythmia, hot flashes which is a symptom of menopause in women, and post-traumatic stress disorder (PTSD). In recent year, researchers have reported on using guides, such as X-ray fluoroscopy and ultrasound, in order to increase the efficacy and safety of this procedure.

1) CRPS in the upper limbs

In a Cochrane review[28] on sympathetic nerve block using local anesthetic for CRPS, researchers claimed they were unable to reach a conclusion on the efficacy and safety of this intervention due to insufficient evidence. In a CRPS review published in 2011[29], they gave SGB a weak recommendation for CRPS in the upper limbs. In addition, other researchers reported on an observational research study on the efficacy of early-stage SGB in treating CRPS in the upper limbs, recognizing a significant improvement in pain and range of motion (ROM) in the hand joints through SGB and also reported a more significant improvement in pain in the

group with a shorter interval between onset of the condition and when they began the SGB compared with the other group with a longer interval between onset and SGB[30]. Furthermore, in another study[31] researchers reported that the effect of SGB was weak either when 16 weeks or more had passed since the time of onset or in cases where skin blood flow had decreased by more than 22% compared with the normal side. They reported a correlation between how early treatment began using SGB and the effects of the treatment and also that the effects of SGB were high if treatment began by the 12th week after onset[31].

Some cases of CPRS include strong psychosocial factors and therefore careful judgment is required when applying SGB and we recommend performing it at an early stage after onset.

2) Prevention of postherpetic neuralgia (PHN) for patients with herpes zoster

According to a double-blind RCT on the possibility of preventing the transition from acute-stage herpes zoster of the head to postherpetic neuralgia (PHN)[32], researchers reported that the frequency of transitions to PHN had significantly decreased. We recommend performing SGB at an early stage after onset. Similarly, SGB is considered to be useful for herpes zoster at an early stage, but there is not high-quality evidence.

3) Orofacial pain

No high-quality RCTs or observational studies exist on the effects of SGB on orofacial pain. There are reviews[33] and case series[34] indicating the efficacy of SGB on orofacial pain, and case reports[35] for example that SGB was effective on atypical facial pain. Performing SGB should be considered when the effects from other forms of treatment have proven to be insufficient.

4) Using guides

There is no high-quality evidence verifying the superiority of one guide, by comparing the landmark method, X-ray fluoroscopy, and ultrasound guidance. In a review[36] on SGB-related complications, researchers reported that the method used for performing SGB in cases where complications arose were the landmark method at 48.5%, X-ray fluoroscopy at 26.9%, and ultrasound guidance at 24.6%. Under ultrasound guidance, the blood vessels and other tissue can be visualized, and therefore this may improve its safety. There is 1 RCT[37] indicating the usefulness of ultrasound guidance compared with the landmark method, for treating CRPS in the upper limbs. In addition to this, there are also some observational research studies indicating the usefulness of ultrasound guidance compared with X-ray fluoroscopy.[38,39]

Period		2005～2019
Database		PubMed, Cochrane CENTRAL, NPO Japan Medical Abstracts Society
Words searched	P	chronic pain, neck pain, complex regional pain syndromes, zoster associated pain, herpetic pain, atypical facial pain, phantom limb
	I/C	stellate ganglion block, cervical sympathetic ganglion block
Limitations		Limited by publication type, PubMed CER randomized comparative trials,/systematic review search filter, Cochrane RCT search filter, etc.
Selection summary		Of the 192 search hits, 13 were utilized that matched with the set PICO

CQ D-5 : Is sympathetic ganglion block useful for chronic pain ?

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

CRPS : complex regional pain syndrome

Recommendation Grade & Summary of Overall Evidence

1) Thoracic sympathetic ganglion block

- **CRPS in the upper limbs**
  Recommendation grade : No recommendation 〔Consensus 84.6%〕
  Summary of overall evidence : C (low)
- **Pain due to vascular disorders in the upper limbs**
  Recommendation grade : 2 (weak) : Implementation is weakly recommended 〔Consensus 92.3%〕
  Summary of overall evidence : D (very low)

PHN : postherpetic neuralgia

- **Post-traumatic syndrome, PHN, brachial plexus syndrome**
  Recommendation grade : No recommendation : 〔Consensus : Implementation is weakly recommended 33.3% No recommendation 66.7%〕
  Summary of overall evidence : D (very low)

2) Lumbar sympathetic ganglion block

- **Pain due to vascular disorders in the lower limbs**
  Recommendation grade : 2 (weak) : Implementation is strongly recommended 〔Consensus 92.3%〕
  Summary of overall evidence : C (low)
- **CRPS in the lower limbs**
  Recommendation grade : No recommendation 〔Consensus 91.7%〕
  Summary of overall evidence : D (very low)

FBSS : failed back surgery syndrome

- **Lumbar spinal canal stenosis**
  Recommendation grade : 2 (weak) : Implementation is weakly recommended 〔Consensus 83.3%〕
  Summary of overall evidence : D (very low)

Commentary :

In the management of chronic pain, sympathetic ganglion block is often used in clinical settings for the purpose of alleviating ischemic pain in peripheral vessel disease. We have already talked about stellate ganglion block (SGB) at **CQ D-4** so here we will discuss thoracic sympathetic ganglion block and lumbar sympathetic ganglion block.

1) Thoracic sympathetic ganglion block

There are few reports about its effects on pain-related diseases and the evidence is limited.

In an RCT[40] that investigated the effects of thoracic sympathetic ganglion block on 36 cases of CRPS type I of the upper limbs, researchers found that intensity of pain displayed significantly lower scores in the thoracic sympathetic ganglion block group 12 months later according to their McGill Pain Questionnaire Scores, the Neuropathic Pain Symptom Inventory, and Hospital Anxiety and Depression Scale. In a crossover test on 15 patients with CRPS in the upper limbs, which included SGB and thoracic sympathetic ganglion block at a high position of T_2, patients had a more definite effect (rise in upper limb temperature, reduced pain) with the T_2 block[41]. Furthermore, in a retrospective study[42] focusing on 51 patients and investigating the usefulness of thoracic sympathetic ganglion block (at the high position of T_3 using 5 m*l* of 0.25% [w / v] levobupivacaine) on chronic upper-limb pain (CRPS, post-traumatic syndrome, PHN, brachial plexus disorder), researchers found it to be effective when assessed 2-weeks later in 52.9% of patients. When it was performed within 1 year after onset it was found to more effective than cases that had occurred over 1 year ago. In a 2016 Cochrane review[28], there was a lack of high-quality reports on thoracic sympathetic ganglion block using local anesthetic for CRPS patients and therefore they were unable to conclude that it was effective. Intervention treatment for CRPS requires caution because CRPS patients have possibility to have strong association with psychosocial factors. Thus, we decided to assign a "no recommendation" grade.

In a comparative research study[43] on thoracic sympathetic ganglion block radiofrequency thermocoagulation for treating vascular disorders in the upper limbs, researchers divided and compared 50 patients with Raynaud's disease into a group that underwent radiofrequency coagulation at T_2 and T_3 and a group in which coagulation was only performed at T_2, receiving an injection of 6% [v/v] phenol and 0.5 m*l* of water. In both groups, researchers acknowledged a significant reduction in pain and a rise in skin temperature in the upper limbs, as well as improved QOL but there was no recognizable significant difference between the groups apart from the time required to perform the procedure. Just like above, the evidence was insufficient and in a 2011 systematic review[41], they were unable to come to a clear conclusion about its usefulness. As there are few severe side effects, physicians

should consider performing this when the effects of other forms of conservative treatment prove to be insufficient.

2) Lumbar sympathetic ganglion block

Lumbar sympathetic ganglion block is applied to pain caused by vascular disorders of the lower limbs. There is 1 RCT[45] on blocks using a neurolytic agent to treat vascular disorders of the lower limbs. Researchers targeted 41 limbs in 37 patient with chronic ischemic limbs and when comparing a phenol group with a local anesthetic group, researchers found that pain had significantly reduced in the phenol group after 6 months. In addition to this, there are also some reports[46,47] indicating the efficacy of lumbar sympathetic ganglion block using a neurolytic agent on ischemic diseases of the lower limbs. In a neurolytic agent-type block, although there are complications such as inflammation of the genitofemoral nerve, the frequency of severe complications is low, and if other forms of conservative treatment are insufficiently effective, it is useful in terms of alleviating pain and preventing amputation of the diseased limb.

There is an extremely small number of high-quality research reports indicating the usefulness of lumbar sympathetic ganglion block using local anesthetic, and in a 2016 Cochrane review[28], due to a lack of high-quality reports on lumbar sympathetic ganglion block using a local anesthetic for patients with CRPS, researchers were unable to conclude whether it was useful or not.

When expecting long-term effects, apart from a neurolytic agent-based block, another choice is to use the method of physical destruction of nerves using radiofrequency thermocoagulation (RF). There is a report[48] indicating that the usefulness of lumbar sympathetic ganglion block using RF was inferior to neurolytic agents and also a report[49] indicating that both treatment had the same usefulness. In a comparison of the effect of using radiofrequency thermocoagulation (RF) and phenol in a lumbar sympathetic ganglion block (temperature rise, and prevention of sweating), on patients with CRPS type I, caused for example by injuries to the knee, shin, and leg joints, they found that it had 89% efficacy at 8 weeks after the block had been conducted on the phenol group, whereas it was only 12% for the RF group[48]. On the other hand, in a comparative research study conducted on 20 patients with CRPS type I, allocating 10 patients into each group, researchers reported a significant reduction in pain from the baseline in all patients in both groups when evaluated 4 months later. Lumbar sympathetic ganglion block using RF and phenol had an equal efficacy[49]. For the reasons mentioned above, we also decided to assign a "no recommendation" grade for CRPS of the lower limbs.

RF : radiofrequency thermocoagulation

There are no RCTs which have considered the effect of lumbar sympathetic ganglion block on lumbar spinal canal stenosis. In terms of reports indicating its usefulness, there is a report[50] indicating that it might possibly be effective on patients who have been suffering from cauda equina syndrome for a short period of time,

and its efficacy rate on 62 patients with lumbar spinal canal stenosis was 48.4% and had a high efficacy rate on patients with coldness in the lower limbs[51], and there are also reports in which there was a recognizable improvement in intermittent claudication[51,52,].

Period		2005～2020
Database		PubMed, Cochrane CENTRAL, NPO Japan Medical Abstracts Society
Words searched	P	chronic pain
	I/C	Sympathetic ganglion block chemical (alcohol), physical (RF) blockage / local anesthetic, chemical (alcohol)
Limitations		Limited by publication type,PubMed CER randomized comparative trial / systematic review search filter,Cochrane RCT search filter, limited number of RCTs,important observational research, cases series included
Selection summary		Of the 37 PubMed search hits, 126 Cochrane CENTRAL search hits, from 42 NPO Japan Medical Abstracts Society search hits, we utilized 14 search hits that matched with the set PICO

CQ D-6 : Is a trigger point injection useful for chronic pain ?

Answer : Although evidence indicating the usefulness of a trigger point injection (local anesthetic) for myofascial pain syndrome (MPS) has been accumulating, it still remains insufficient. As long as it is performed by an experienced pain management specialist, then it is a relatively safe and easy procedure and can help treat pain. Attention should be paid to complications during the procedure and we must consider how frequently to make the procedure and type of the drug should be administered.

MPS : myofascial pain syndrome

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : Implementation is weakly recommended 〔Consensus 94.1%〕

Summary of overall evidence : B (moderate)

Commentary :

There is a systematic review[53] which conducted a meta-analysis of the analgesic effects of a trigger point injection (TPI) on myofascial pain syndrome (MPS) including tension-type headache (TTH). They divided patients into a local anesthetic injection group and an 'other intervention' group (saline solution, topical local anesthetic, dry needling, acupuncture and moxibustion, stabilization sprint, and stretches, etc). They found that the local anesthetic group experienced significant pain relief 16 weeks after the procedure compared with the other intervention group. Furthermore, in the meta-analysis from the same systematic review, botulinum toxin injection had an inferior analgesic effect than the local anesthetic injection. However, due to a high lack of uniformity among the research studies, in order to draw conclusions, there is need for further research in future, taking into account the research design, type of drug used and its concentration, whether there was an addi-

TPI : trigger point injection

tional steroid drug or not, the site of injection, and any concomitant treatments (stretches, muscle strengthening exercises, stabilization spring, manipulation, etc). At the current stage, there is no strong evidence[54] supporting the usefulness of botulinum toxin and steroid drugs, and there is a need to consider side effects and the problem of treatments which are ineligible to be covered under health insurance.

There are a few reports on complications, for example subcutaneous bleeding, dizziness and injection site pain, but the majority of them are local and temporary so TPI is considered to be a relatively safe procedure.

If performed by a highly-experienced physician, the procedure is highly safe and is widely used in clinical settings. However, when performing this procedure, its effects must constantly be evaluated and should not be performed over a long period of time without some clear aim in mind. In addition, for TPI's effects on stiff shoulders in particular, we wish to refer you to **CQ L-4**.

Period		2005～2019
Database		PubMed,Cochrane CENTRAL, NPO Japan Medical Abstracts Society
Words searched	P	tension type headache, Temporomandibular Joint Disorders, Musculoskeletal Pain, neck pain, back pain, myofascial pain syndrome, chronic pain
	I/C	Trigger point injection
Limitations		Limited by publication type,PubMed CER randomized controlled trials / systematic review search filter, Cochrane RCT search filter, other (cases of50+) etc
Selection overview		Of the 138,215 search hits, we utilized 21 of them which matched with PICO

CQ D-7 : Is a nerve block using radiofrequency thermocoagulation (RF) useful for chronic pain ?

RF : radiofrequency thermocoagulation

Answer : We expect that nerve block using radiofrequency thermocoagulation (RF), provides short- and long-term pain relief and short-term improved QOL for patients suffering from chronic low back pain (LBP) originating in the facet and sacroiliac joints. Furthermore, we expect it to provide short- and long-term pain relief for patients with trigeminal neuralgia but we recommend that the form of treatment be selected keeping in mind that there is a risk of complications in patients who are resistant to drug therapy. It also has the possibility of being useful over the short-and long-term for chronic pain in patients with knee osteoarthritis (OA).

Recommendation Grade & Summary of Overall Evidence

1) Chronic low back pain originating in the facet and sacroiliac joints

Recommendation grade : 1 (strong) : Implementation is strongly recommended〔Consensus 83.3%〕

Summary of overall evidence : A (high)

2) Trigeminal neuralgia

Recommendation grade : 2 (weak) : Implementation is strongly recommended [Consensus 100.0%]

Summary of overall evidence : C (low)

3) Chronic pain in knee OA

Recommendation grade : 2 (weak) : Implementation is weakly recommended [Consensus 90.5%]

Summary of overall evidence : B (moderate)

Commentary :

1) Chronic low back pain (LBP) originating in facet and sacroiliac joints

Radiofrequency thermocoagulation (RF) is performed on the dorsal rami of the spinal nerve, which is a sensory nerve of the facet joints, for patients with chronic low back pain (LBP) originating in the facet joints and sacroiliac joints, as well as the L_5 ($+L_4$) dorsal ramus and S_{1-3} dorsal rami of the sacral nerve. In addition to evaluating their symptoms, it is also important to assess whether it is suitable to perform treatment or not through a rigorous diagnostic nerve block[23].

There are many RCTs that have investigated the usefulness of RF for treating chronic low back pain originating in the lumbar facet joints and sacroiliac joints and in 2019, researchers reported a meta-analysis[55]. We conducted a new meta-analysis on 16 RCTs including the paper in the previous meta-analysis and new research papers that were found by our search for these guidelines[56] (short-term pain relief : 13 RCTs, long-term pain relief : 7 RCTs, short-term improvement in QOL : 5 RCTs, long-term improvement in QOL : 3 RCTs, incidence rate of severe complications : 14 RCTs). Although we saw a wide dispersion between the results of each research study, a quantitative synthesis, indicated that short- and long-term pain relief and improved QOL could be expected. The incidence rate of severe complications was low at 0.92% (injection, mild burns, vagal reflex), with no complications that leave patients with long-term impairments. In addition, because there was no difference in the incidence rate as compared with the control treatment, we strongly recommend it as being a highly safe, form of treatment, which we can expect to be useful.

2) Trigeminal neuralgia

With trigeminal neuralgia patients who are resistant to drug therapy, radiofrequency thermocoagulation (RF) is conducted on trigeminal ganglion (Gasserian ganglion or semilunar ganglion) and the peripheral branches of the trigeminal nerve (supraorbital nerve, supratrochlear nerve, maxillary nerve, infraorbital nerve, mandibular nerve, mental nerve).

There are 2 systematic reviews[57,58] on interventional treatments of trigeminal neuralgia. They used RCTs that were subject to this research, and including new research papers[59,60] that were found while searching for references for these guide-

lines, 5 RCTs in total were applicable. There is no research which compares it against sham treatments or other forms of treatment apart from nerve block. There have been comparisons based on the target of treatment (trigeminal ganglion vs. peripheral branch), a comparison with pulsed radiofrequency (PRF) and a comparison with RF + PRF and in terms of outcomes, they were only able to evaluate pain relief. In a research study comparing trigeminal ganglion RF with RF of the peripheral branches of the trigeminal nerve, in both instances, they reported a high pain relief rate over the short and long term. In a research study comparing RF and PRF of the trigeminal ganglion, RF showed a marked decrease in trigeminal neuralgia pain over the short term but there was no effect from PRF. In another research study that compared RF of the trigeminal ganglion against RF + PRF of the trigeminal ganglion, both reduced trigeminal neuralgia pain over the short and long term but researchers indicated the possibility that the effect was slightly superior in the RF + PRF group. There is need to conduct further research into the concomitant use of RF and PRF.

PRF : pulsed radiofrequency

In a large-scale case series study[61] on the incidence rate of severe complications on 1,600 patients, researchers reported an incidence rate of 0.6～5.7%, including complications such as anesthesia dolorosa, dysesthesia, loss of corneal reflex, keratitis, masseter muscle weakness, and diplopia (double vision). As the data were old, it is possible that the incidence rate would be even lower using current procedures but before conducting the procedure, it is necessary for doctors and patients to sufficiently discuss (informed consent) the risks of complications first.

In light of the above, for severe cases of patients resistant to drug therapy, after sufficiently considering the risks of complications, we believe that RF for trigeminal neuralgia would prove to be highly effective.

3) Chronic knee pain in knee osteoarthritis (knee OA)

There are some RCTs comparing RF treatment of the genicular nerve with other forms of treatment (sham treatments, knee joint injection, taking NSAIDs internally) to treat chronic knee pain in patients with knee OA, and in 2019, researchers reported a meta-analysis[62]. Along with the research papers that were subject to this meta-analysis, we also found and included new research papers[63] when searching for references for these guidelines, and when we conducted a new meta-analysis on 4 RCTs in total (short-term pain relief : 4 RCTs, long-term pain relief : 2 RCTs, short-term improvement in QOL : 4 RCTs, long-term improvement in QOL : N/A, incidence rates of severe complications : 4 RCTs), it indicated that we can expect short- and long-term pain relief. There was a dispersion in QOL depending on the evaluation method used (2 research papers used WOMAC to evaluate, 2 used OKS) but it is possible that it improves QOL over the short term. Not even 1 severe complication arose in these RCTs so it has been evaluated as a safe form of treatment.

WOMAC : Western Ontario and Mcaster Universities Oateioarthritis Index

In light of the above, RF on the knee joint nerve in patients with chronic knee pain from knee OA is a form of treatment which we can expect to be effective but the number of cases in this research remains small, and as this has not yet been positioned as a standard form of treatment in Japan, we weakly recommend it.

Period		2005～2019
Database		PubMed,Cochrane CENTRAL, NPO Japan Medical Abstracts Society
Words searched	P	chronic pain, low back pain, neck pain, back pain, trigeminal neuralgia, osteoarthritis, CRPS, sympathetically, sympathetic, ischemic
	I/C	radiofrequency/no specifications
Limitations		Limited by publication type, PubMed CER randomized controlled trials/systematic review/meta-analysis search filter, Cochrane RCT search filter, other (English, Japanese) etc
Selection Summary		Of the 502 search hits, we utilized 10 searches that matched with PICO

CQ D-8 : Is nerve block using pulsed radiofrequency (PRF) treatment useful for chronic pain ?

Answer : Of the diseases that may give rise to chronic pain, nerve block using pulsed radiofrequency (PRF) is believed to be a form of treatment that can be selected for treating postherpetic neuralgia (PHN) and chronic shoulder joint pain and researchers have shown its short-term and long-term efficacy (for at least 3 months) and its high level of safety. In some cases, it may also be applicable for treating radiculopathy, lumbar facet joint-derived pain, knee OA, and idiopathic trigeminal neuralgia.

PRF : pulsed radiofrequency
PHN : postherpetic neuralgia

Recommendation Grade & Summary of Overall Evidence

1) Postherpetic neuralgia (PHN)

Recommendation grade : 2 (weak) : Implementation is weakly recommended〔Consensus 85.7%〕

Summary of overall evidence : B (moderate)

2) Chronic joint pain

・Chronic shoulder joint pain

Recommendation grade : 2 (weak) : Implementation is weakly recommended〔Consensus 95.2%〕

Summary of overall evidence : B (moderate)

・Chronic knee joint pain

Recommendation grade : 2 (weak) : Implementation is weakly recommended〔Consensus 85.0%〕

Summary of overall evidence : C (low)

3) Radiculopathy

Recommendation grade : 2 (weak) : Implementation is weakly recommended〔Consensus 81.0%〕

Summary of overall evidence : B (moderate)

4) Lumbar facet joint-derived pain

Recommendation grade : 2 (weak) : Implementation is weakly recommended〔Consensus 90.0%〕

Summary of overall evidence : C (low)

5) Idiopathic trigeminal neuralgia

Recommendation grade : 2 (weak) : Implementation is weakly recommended〔Consensus 100.0%〕

Summary of overall evidence : C (low)

Commentary :

RCT : randomized controlled trial

There are many RCTs and prospective controlled trials and in a meta-analysis and systematic review researchers indicated its safety and that just from one procedure, patients experienced analgesic effect persisting for at least 12 weeks, particularly for PHN and chronic shoulder joint pain. Therefore, nerve block using PRF is a form of treatment that should be chosen to treat chronic pain, mainly the pathologies mentioned above. Furthermore, the temperature of the needle tip is maintained at 42℃ and below in PRF so there is a low possibility that it will destroy nerves, and because there have been no reports of complications to date, it can be called a highly-safe form of treatment[64-68]. Therefore, performing PRF in clinical settings on pathologies other than those mentioned above (radiculopathy, lumbar facet joint-derived pain, chronic knee joint pain, idiopathic trigeminal neuralgia) will not be hampered ; we expect further research to be conducted in future. However, there is little evidence available on the optimal amount of time for the procedure, the site of treatment, and parameters, and there for it requires further consideration.

1) Postherpetic neuralgia (PHN)

In a double-blind placebo-controlled RCT on PHN[69], researchers compared and considered patients with chest PHN ; 48 cases underwent peripheral nerve (intercostal nerve) PRF while another 48 cases underwent a sham stimulation over a period of 6 months. Researchers reported a significant decline in VAS scores and significant improvement in QOL (SF-36) in the PRF group. In a meta-analysis[67] on the efficacy of PRF targeting patients with neuropathic pain, researchers compared patients who underwent a nerve block using local anesthetic as well as drug therapy such as pregabalin for PHN, and results indicated that PRF was highly useful. Furthermore, there is another report[70] that showed that we can expect even better analgesic effects for patients when PRF is used in combination with pregabalin. Based on the above, we can say that PRF can be selected to treat PHN. However, regarding the site for performing PRF, we wish to refer you to CQ O-7.

2) Chronic joint pain

In a double-blind RCT[71] conducted over 3 months on patients with frozen shoul-

der, they compared a group (68 cases) that underwent PRF of the suprascapular nerve with a sham stimulation group (68 cases), and reported a significantly higher improvement in pain and shoulder joint disorders. Moreover, there is a systematic review[66] that discussed 5 RCTs on the effects of PRF on chronic shoulder joint pain, and researchers found that PRF on the suprascapular nerve was effective for at least 12 weeks or more on chronic shoulder joint pain and with no reports of complications, indicating that it is highly safe. Therefore, we recommend PRF on the suprascapular nerve for treating patients with chronic shoulder joint pain. However, it is not clear whether PRF is superior over conventional forms of treatment such as intra-articular steroid injection, physiotherapy, and nerve block using a local anesthetic and therefore further consideration is required. Although there is a report[72] indicating the efficacy of PRF on chronic knee joint pain, there are no high-quality retrospective-looking studies that we can cite as references and so because the evidence is not clear, we only give it a weak recommendation.

3) Radiculopathy

In a 2015 meta-analysis[67] on the efficacy of PRF on patients with neuropathic pain, they were unable to indicate its efficacy on radiculopathy. However, according to a recent meta-analysis on cervical radiculopathy[65], performing a single dorsal root ganglion (DRG) PRF may possibly mitigate pain from the short term to the long term (6 months). Furthermore, in a double-blind RCT[73] on lumbar radiculopathy, researchers indicated that compared with an epidural injection using a local anesthetic, the analgesic effect and functional improvement effects from DRG PRF lasted for a longer period of time. Therefore, although the evidence on the efficacy of DRG PRF on radiculopathy is limited, it could be considered as an option for patients who show resistance to treatments such as epidural injection.

DRG : dorsal root ganglion

4) Lumbar facet joint-derived pain

In a systematic review[64] of 3 RCTs comparing the effects of PRF and radiofrequency thermocoagulation (RF) on lumbar facet joint-derived pain, the results indicated that the effects of a medial branch of the posterior ramus PRF persisted for a shorter duration than a conventional medial branch of the posterior ramus block using RF did. However, there is another report[74] indicating that a medial branch of the posterior ramus PRF provided longer analgesic effects than the medial branch of the posterior ramus block using a local anesthetic (and steroid drug), and therefore it might be applicable for certain cases.

RF : radiofrequency thermocoagulation

5) Idiopathic trigeminal neuralgia

According to a meta-analysis[68] that compared and considered the efficacy and safety of PRF, RF and a nerve block, used concomitantly to treat trigeminal neuralgia, there was no recognizable difference in analgesic effect between PRF and RF but PRF had a higher level of safer. Researchers also indicated that rather than using RF alone, it was more effective and safe when RF was used in combination

with PRF. Therefore, if PRF is to be utilized as an analgesic method for trigeminal neuralgia, then we recommend performing it in combination with RF.

Period		2004～2019
Database		PubMed,Cochrane CENTRAL,NPO Japan Medical Abstracts Society
Words searched	P	pain, chronic pain, frozen shoulder, adhesive capsulitis,shoulder peroarthritis, radiculopathy, osteoarthritis, postherpetic neuralgia
	I/C	pulsed radiofrequency treatment, pulse-dose radiofrequency, pulsed radiofrequency / nothing specified
Limitations		Limited by publication type,PubMed CER randomized controlled trial / systematic review search filter, Cochrane RCT search filter, other (number of cases50+) etc.
Selection summary		Of the 294 search hits, 11 were utilized that matched with PICO

CQ : D-9 : Are intra-articular injections useful for chronic pain ?

Answer : Intra-articular steroid injections are useful over the short-and mid-term for adhesive shoulder capsulitis and hip osteoarthritis (hip OA) and their usefulness might increase when used concomitantly with physiotherapy. There is low evidence regarding the possibility that hyaluronic acid injection might be effective on adhesive shoulder capsulitis and hip OA. Its usefulness might possibly improve when using an ultrasound device.

Recommendation Grade & Summary of Overall Evidence

1) Adhesive shoulder capsulitis

- Intra-articular steroid injection

  Recommendation grade : 2 (weak) : Implementation is weakly recommended〔Consensus 85.7%〕

  Summary of overall evidence : C (low)

- Intra-articular hyaluronic acid injection

  Recommendation grade : 2 (weak) : Implementation is weakly recommended〔Consensus 100.0%〕

  Summary of overall evidence : C (low)

2) Hip osteoarthritis (OA)

- Intra-articular steroid injection

  Recommendation grade : 2 (weak) : Implementation is weakly recommended〔Consensus 85.0%〕

  Summary of overall evidence : C (low)

- Intra-articular hyaluronic acid injection

  Recommendation grade : 2 (weak) : Implementation is weakly recommended〔Consensus 95.2%〕

  Summary of overall evidence : C (low)

Commentary：

This CQ will describe intra-articular injections on adhesive shoulder capsulitis and hip osteoarthritis (hip OA), and we will discuss knee osteoarthritis (knee OA) at CQ K-3. There are many RCTs and systematic reviews on the efficacy of intra-articular injections on adhesive capsulitis and OA.

hip OA：hip osteoarthritis

1) Adhesive shoulder capsulitis

According to the clinical guidelines of the American Physical Therapy Association, using intra-articular steroid injection in combination with range of motion (ROM) exercises and stretching is more effective over the short term (4～6 weeks) on pain and functional improvement in adhesive shoulder capsulitis than performing ROM exercises or stretching alone[75].

In a systematic review of 9 RCTs regarding the efficacy of intra-articular steroid injection on adhesive shoulder capsulitis and also the efficacy of a steroid injection into the subacromial bursa, over the short-term, the group who were administered with an intra-articular steroid injection displayed significant improvement in pain relief and improved ROM, compared with the group who were administered a steroid injection into the subacromial bursa. However, at 12 weeks, researchers claimed there was no significant difference between the 2 groups[76].

There is a systematic review of 5 RCTs that reported a comparison between an intra-articular shoulder steroid injection with an intra-articular shoulder injection of saline solution on adhesive shoulder capsulitis. 4 of these RCTs reported a single injection, while in the other RCT, a total of 3 injections were administered at 1-week intervals. Over the short term (0～8 weeks), the intra-articular shoulder steroid injection showed to be significantly more effective in providing pain relief but between 9～24 weeks after the procedure, there was no significant difference between the groups. Furthermore, over the short term, passive shoulder joint ROM significantly improved in the intra-articular shoulder steroid injection group but this significant difference was only temporary[77]. In addition, in a systematic review of 8 research papers comparing the effects of intra-articular shoulder injection of saline solution on frozen shoulder with the effects of an intra-articular shoulder steroid injection, researchers indicated the possibility that intra-articular shoulder steroid injection was more effective over the short and mid term[78]. Because of small sample size and methodological heterogeneity of the studies, the evidence on intra-articular shoulder steroid injections is low.

In a systematic review of 3 RCTs examining intra-articular shoulder injections of hyaluronic acid, researchers claimed that there was insufficient evidence due to a lack of uniformity among the research reports.[79]

In a systematic review of 7 RCTs comparing the efficacy of an intra-articular shoulder steroid injection under ultrasound guidance with one performed under the landmark method, efficacy and accuracy improved under the ultrasound guidance

method[80].

The effects of both an intra-articular shoulder steroid injection and an intra-articular shoulder hyaluronic acid injection on adhesive shoulder capsulitis are limited in either case and when performing these injections, their effects must be constantly evaluated and they should not be performed over the long term without a clear aim in mind.

2) Hip OA

According to the guidelines of the Osteo Arthritis Research Society International (OARSI), they compared the effects of an intra-articular hip steroid injection with those of an intra-articular hip hyaluronic acid injection on hip OA and found that the intra-articular hip steroid injection had higher pain-relief effects and functional improvement over the short-term compared with intra-articular hip hyaluronic acid injection.

We need to consider the intra-articular hip steroid injection in cases where inflammation and severity of pain are strong. There is an RCT that claims that using intra-articular hip steroid injection in combination with ROM exercises and stretching is more effective in improving pain and function than using ROM exercises and stretching alone[81].

In a systematic review of 9 RCTs on the usefulness of intra-articular steroid injections on hip OA prior to total hip replacement,2 of these RCTs recommend an intra-articular steroid injection before the replacement procedure while the other 7 RCTs claimed that they do not have an effect on post-surgical injections. On the other hand, in a research study comparing the frequency of incidence complications on 40 patients who were administered an intra-articular hip steroid injection prior to total hip replacement with 40 patients who did not under the operation, there were injections in 3 of the joints (7.5%) among the group of subjects who did not undergo the procedure but there were 12 injections (30%) among the group who were administered an intra-articular hip steroid injection, reporting a higher risk of post-surgical injection. Therefore, the procedure should not be performed over the long-term without any clear aim in mind[82].

We can expect short-term pain relief and functional improvement in subjects with hip OA when administered with an intra-articular hip hyaluronic acid injection. In an RCT that considered the efficacy of intra-articular hip hyaluronic acid compared with a placebo, when the injection was given 3 times under ultrasound guidance fortnightly, researchers found that on the 14th day, the intra-articular hip hyaluronic acid injection had significantly improved pain at time of walking but after the 14th day, they claimed that there was no difference between the treatment groups[83].

On the other hand, in an RCT that compared the usefulness of an intra-articular hip hyaluronic acid injection on hip OA with an intra-articular hip local anesthetic

injection, both administered once a month, twice in total, researchers evaluated the intensity of pain after 3 months and after 6 months and reported that intensity of pain had significantly improved in the intra-articular hip hyaluronic acid injection group and that adverse events were insignificant at 6～23%[84].

There are various RCTs on the usefulness of intra-articular hyaluronic acid injection but due to a lack of uniformity between the research studies, there is no high-quality evidence indicating its efficacy and level of safety. What is more, it is not eligible to be covered under the Japanese health insurance system so caution is required when performing this procedure.

In a systematic review of intra-articular hip injections, researchers reported increased accuracy and efficacy if conducted under ultrasound guidance, just like with intra-articular hip injections[85].

Period		2005～2019
Database		PubMed, Cochrane CENTRAL, NPO Japan Medical Abstracts Society
Words searched	P	chronic pain, frozen shoulder Adhesive Capsulitis Hip Osteoarthritis
	I/C	intra-articular injections
Limitations		Limited by publication type,PubMed CER randomized controlled trial / systematic review search filter,Cochrane RCT search filter, other (number of cases of50+etc)
Selection summary		Of the 1,016 search hits, we utilized 27 of them that matched with the set PICO

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Chapter E. Interventional Pain Treatment (Low-Invasive Surgery/Orthopedic Treatments) : CQ E-1～CQ E-5

CQ E-1 : Is spinal cord stimulation (SCS) useful for intractable chronic pain ?
CQ E-2 : Are intradiscal therapies useful for chronic pain ?
CQ E-3 : Are spring-guide catheters and epiduroscopy useful for chronic low back and leg pain ?
CQ E-4 : Is spinal fusion useful for chronic pain associated with spinal diseases ?
CQ E-5 : Is surgical therapy useful for chronic pain associated with strangulated peripheral neuropathy ?

E. Interventional Pain Treatment (Low-Invasive Surgery/Orthopedic Treatments)

CQ E-1 : Is spinal cord stimulation (SCS) useful for intractable chronic pain ?

Answer : SCS is something worth trying on chronic pain patients who did not obtain sufficient analgesic effects from other forms of treatment. Its usefulness has been indicated especially for failed back surgery syndrome (FBSS), peripheral vascular disease (PVD), and painful diabetic peripheral neuropathy (PDPN). Apart from this, there are reports of its efficacy on central post-stroke pain, pain following spinal cord injury, complex regional pain syndrome (CRPS), phantom limb pain, and postherpetic neuralgia (PHN) but there are no reports with high evidence.

FBSS : failed back surgery syndrome
PVD : peripheral vascular disease
PDPN : painful diabetic peripheral neuropathy
PHN : postherpetic neuralgia
CRPS : complex regional pain syndrome

Recommendation Grade & Summary of Overall Evidence

1) Lower limb pain of failed back surgery syndrome (FBSS)
   Recommendation grade : 2 (weak) : Implementation is weakly recommended [Consensus 90.5%]
   Summary of overall evidence : B (moderate)
2) Peripheral vascular disease (PVD) in the lower limbs
   Recommendation grade : 2 (weak) : Implementation is weakly recommended [Consensus 81.0%]
   Summary of overall evidence : C (low)
3) Painful diabetic peripheral neuropathy (PDPN) in the lower limbs
   Recommendation grade : 2 (weak) : Implementation is weakly recommended [Consensus 95.2%]
   Summary of overall evidence : B (moderate)
4) Central post-stroke pain, pain following spinal cord injury, phantom limb pain, PHN
   Recommendation grade : 2 (weak) : Implementation is weakly recommended [Consensus 90.5%]
   Summary of overall evidence : D (very low)
5) Complex regional pain syndrome (CRPS)
   Recommendation grade : No recommendation [Consensus 94.7%]
   Summary of overall evidence : C (low)

Commentary :

1) Failed back surgery syndrome (FBSS)

In an RCT[1] on lower limb pain in patients with FBSS, researchers compared an

SCS group with a group that underwent conservative treatment. There is also an RCT[2] that compared an SCS group with a group that underwent surgery again. There was a significantly larger number of patients who experienced a reduction in lower limb pain by 50% or more in the SCS group. In an RCT on low back pain (LBP)[3], that compared SCS using a paddle lead with SCS using cylindrical-type leads, and an RCT[4] that compared an optimal treatment group with a group that had optimal treatment in addition to SCS, they found that SCS using the paddle leads was more effective on LBP. In an RCT comparing an SCS group with a conservative treatment group[1], researchers indicated that QOL and ADL had improved. In cost-benefit analysis[1,2,5], researchers reported that SCS was superior to conservative forms of treatment and patients undergoing surgery for a second time.

In a systematic review[6] that considered the differences in effect according to method of stimulation, such as high-frequency stimulation (10kHz), burst stimulation, sub-perception simulation (1～5 kHz), researchers found these forms of stimulation superior in terms of absence of paresthesia, but they were unable to conclude whether the analgesic effects were high or not.

In a systematic review that investigated adverse events[7], researchers found 184 complications out of 542 cases studied but it was possible to cope with the majority of the complications and reported that the number of life-threatening events or severe adverse events that could cause dysfunction were extremely rare. FBSS has a complex pathology, and there are patients with strong psychosocial factors. When performing SCS, one needs to judge whether it is indicated for each individual patient or not so we assign it a weak recommendation for lower-limb pain. Researchers have indicated the utility of paddle-type leads for LBP but an even more cautious procedure is required.

2) Peripheral vascular disease (PVD) in the lower limbs

Several reviews of its efficacy on peripheral vascular disease (PVD) have been reported[8-10]. Researchers have not yet established its efficacy in alleviating pain[9,10], but they indicated a rise in the limb salvage rate (decline in the amputation rate). However, they also indicated that it did not have an effect on the mortality rate or ulcer healing rate[8]. In terms of its analgesic effect and limb salvage rate, researchers indicated increased efficacy with suitable patient selection, such as evaluating percutaneous oxygen partial pressure[8].

3) Painful diabetic peripheral neuropathy (PDPN) in the lower limbs

There are 2 RCTs on PDPN, which indicated not only an improvement 6 months later in daytime pain, night-time pain and sleeping disorders, researchers also indicated that it was effective in improving ADL and QOL[11,12]. Furthermore, in terms of its long-term results, 55% of patients experienced reduced pain for a 5-year period[13].

4) Other refractory pain diseases (central post-stroke pain, pain following spinal cord injury, phantom limb pain, PHN)

There have been reports of the efficacy of SCS on various forms of refractory pain, such as central post-stroke pain[14], pain following spinal cord injury[15], phantom limb pain[16], and postherpetic neuralgia (PHN)[17]. However, the number of reports is low and the level of evidence is not high. Its applicability should be considered for each respective patient, in cases where there are no other means of effective treatment.

5) Complex regional pain syndrome (CRPS)

There have also been reports that SCS is effective on CRPS[18], but there are some patients with strong psychosocial factors, so one needs to make a cautious judgment regarding their indication.

Period		2005～2019
Database		MEDLINE, Cochrane CENTRAL,NPO Japan Medical Abstracts Society
Words searched	P	mainly chronic pain,words similar to this
	I/C	spinal cord stimulation
Limitations		Limited by publication type,PubMed CER randomized controlled trial / systematic review search filter, Cochrane RCT search filter, etc
Selection summary		Of the 59 search hits, we utilized 18 that matched with the set PICO

CQ E-2 : Are intradiscal therapies useful for chronic pain?

Answer : Researchers have indicated that intradiscal steroid injections have a limited effect on intradiscal low back pain (LBP) and that several intradiscal therapies are effective as a form of intradiscal treatment but their efficacy is limited.

Recommendation Grade & Summary of Overall Evidence

1) Intradiscal steroid injection :

Recommendation grade : 2 (weak) : Implementation is weakly recommended〔Consensus 80.0%〕

Summary of overall evidence : C (low)

2) Intradiscal treatment

Recommendation grade : 2 (weak) : Implementation is weakly recommended〔Consensus 80.0%〕

Summary of overall evidence : C (low)

3) Intradiscal condoliase injection for lumbar disc herniation

Recommendation grade : 2 (weak) : No recommendation〔Consensus 89.5%〕

Summary of overall evidence : C (low)

Commentary :

1) Lumbar intradiscal steroid injection

There is 1 RCT[19] indicating its short term efficacy on intradiscal low back pain (LBP) with Modic changes in the vertebral body on MRI and there is 1 RCT[20] that showed no effect 3 months after the injection was performed. Administering this injection should be limited to intradiscal LBP with an active period of inflammation in the endplate.

RCT : randomized controlled trial

2) Intradiscal therapy

Intradiscal therapy is an intervention in which a percutaneous intra-discal puncture is performed using a cannula under X-ray fluoroscopy but there are few high-quality RCTs, and so its usefulness is limited.

① Percutaneous nucleotomy

A percutaneous nucleotomy is when the nucleus pulposus is excised, reducing the intradiscal pressure, and its efficacy as a treatment has been indicated for the contained type (swelling, protrusion, and subligamental prolapse) of intradiscal lumbar hernia. Percutaneous disc decompression (PDD : Dekompressor®), is a system of excising the nucleus pulposus using an Archimedes' screw , and the procedure is simple using a cannula with an external diameter of 15 mm, compared with conventional types. In a review of 3 observational research studies, researchers recognized its short-term and long-term effects but evidence was limited[21].

② Percutaneous laser disc decompression (PLDD)

PLDD is a procedure which reduces intradiscal pressure by decreasing its volume by evaporating the water content of the nucleus pulposus using a laser. In an RCT that used a discectomy to treat sciatica as a control, researchers reported an equivalent short-term and long-term improvement in pain and QOL[22].

PLDD : percutaneous laser disc decompression

③ Intradiscal electrothermal treatment (IDET)

IDET is performed on intradiscal LBP. A catheter is inserted cylindrically via a cannula intradiscally, along the annulus fibrosus, and the coil part of the catheter is placed dorsally to the site of lesion for the annulus fibrosus. Radiofrequency thermocoagulation (RF) is conducted on the coil, brining about a degeneration in the annulus fibrosus nerve and thereby reducing pain. In a recent review, there were 4 RCTs, 3 of them reporting its efficacy on pain, 1 reporting its efficacy on ADL, and 1 of them reported no significant difference in effect[23]. Overall, they confirmed its efficacy with a high level of evidence.

IDET : intradiscal electrothermal treatment

④ Intradiscal pulsed radiofrequency (PRF)

Intradiscal PRF is a procedure in which the active tip is placed in the center of the disc, and creates an analgesic effect by adding a pulse radiofrequency. Its analgesic mechanism remains unclear but is believed to be highly safe as there is no tissue damage or injury through heat, and a report has recognized that it provides equivalent analgesic effect through an RCT on IDET[24]. Fukui et al.[25] conducted the procedure over 15 minutes on intradiscal LBP using intradiscal contrast and reported analgesic effect even 12 months after the procedure.

PRF : pulsed radiofrequency

⑤ Percutaneous radiofrequency intradiscal ablation/excision (Disc-Fx®)

Disc-Fx® treatment uses 1 cannula to excise the nucleus pulposus uses forceps, RF uses a probe with a bended tip and modulation of the annulus fibrosus. In addition to the contained type (swelling, protrusion, and subligamentous extrusion) of intradiscal hernia, it is believed to also be effective on LBP due to degenerative disc, and there are observational research studies that have demonstrated its efficacy[26,27] We recommend accumulating (more) evidence in future.

3) Intradiscal condoliase injection for lumbar disc hernia

There have been trials of new interventions as well. Condoliase that went on the market in August 2018, is the first lumbar disc hernia drug to be used in Japan that can be directly injected intradiscally. Condoliase specifically breaks down chondroitin sulfate and hyaluronic acid which are components of proteoglycan which is found in the intradiscal nucleus pulposus, and reduces the intradiscal pressure by water retention capacity in the marrow. As a result, it reduces the pressure in the nerve root that leads to a hernia in the parent nucleus pulposus, improving low back and leg pain. It is believed to be effective on lumbar intra-discal hernia such as bulging, protrusion and subligamentous extrusion, and there is 1 RCT that demonstrated its efficacy in a dosage-controlled trial[28] Furthermore, researchers conducted condoliase treatment for lumbar intradiscal hernia on 47 patients and analyzed the background details by dividing them into the 33 cases where it was effective and 14 cases where it was not effective. There is also an observational research study[29] on cases where it was ineffective, in which there were many complications such as discectomy, lumbar spondylolisthesis and a narrowing in the posterior intravertebral width (posterior intervertebral angle ≧ 5 degrees). In both research studies, there were no adverse events that became clinical problems. In future, we recommend accumulating evidence on its long-term efficacy and safety.

Period		2005～2019
Database		PubMed, Cochrane CENTRAL, NPO Japan Medical Abstracts Society
Words searched	P	chronic pain,lumbago, low back pain, disc hernia, discogenic pain, disc degeneration etc.
	I/C	Intradiscal treatments such as intradiscal steroid injection, percutaneous disc decompression/ conservative treatment/analgesic effect, QOL indicators, complications
Limitations		Limited by publication type, PubMed CER randomized controlled trial / systematic review search filter, Cochrane RCT search filter, etc
Selection summary		From the searches of the above database, we utilized 9 search hits that matched with the set PICO, as well as 2 important references which we found through manual search, for a total of 11 references

CQ E-3 : Are spring-guide catheters and epiduroscopy useful for chronic low back and leg pain ?

Answer : Treatment using a spring-guide catheter is effective on chronic low-back and leg pain. Epiduroscopy is effective for treating chronic lower back and leg pain but there is insufficient evidence.

Recommendation Grade & Summary of Overall Evidence

1) Spring-guide catheter :

Recommendation grade : 2 (weak) : Implementation is strongly recommended [Consensus 85.0%]

Summary of overall evidence : B (moderate)

2) Epiduroscopy

Recommendation grade : 2 (weak) : Implementation is weakly recommended [Consensus 80.0%]

Summary of overall evidence : C (low)

Commentary :

1) Spring-guide catheter

Epidural adhesiolysis is also called epidural neuroplasty and epidural nerve ablation using a spring-guide catheter is one type of intervention for treating refractory pain such as failed back surgery syndrome (FBSS) and spinal canal stenosis. In 2016, Helm et al.[30] reported the results of a systematic review and meta-analysis of treatments using spring-guide catheters. Patients' pain status (level of improvement of pain was evaluated on a 5-point scale from 0～4, the higher the score the greater the improvement) and functional improvement scores (evaluated in the same way as pain status) improved significantly both 3 months later and 6 months later in the group that underwent an epidural nerve ablation using a spring-guide catheter, compared with groups that underwent other forms of treatment (mainly epidural block). In terms of pain that had improved by 50% or more, it was 55% higher in the group that underwent the spring-guide catheter both 3 months later and 6 months later. In a report by Manchikanti et al.[31], researchers found that up to 24 months later, the dosage of opioid analgesic had significantly decreased through a spring-guide catheter treatment, compared with a caudal epidural block. When performing percutaneous epidural adhesiolysis, in many cases hypertonic saline solution (10% [w/v] NaCl solution) is used. When using either 10% or 5% [w/v] NaCl solution, there was no difference in analgesic effect and researchers reported there was less pain in the group that was injected with 5% [w/v] NaCl solution[32]. However, there have only been observational research studies and no RCTs so we are waiting for research to be conducted on this in future. With complications resulting from spring-guide catheters, there was a report of 47 cases, which included dural puncture and arachnoid inflammation[30]. As of April 2018, epidural adhesiolysis using a spring-guide catheter became eligible to be covered under the health insurance system.

FBSS : failed back surgery syndrome

2) Epiduroscopy

Epiduroscopy is a procedure in which an endoscope is inserted into the lumbar and sacral epidural space to observe the situation inside the epidural space and a

VAS : visual analogue scale

catheter is used for example with adhesions, and the procedure either separates or cleans it by injecting a saline solution. In 2005, Manchikanti et al.[33] reported an RCT in which they compared an epidural adhesiolysis using an epiduroscopy and a caudal epidural block. Patients' pain (VAS) and scores on the Oswestry Disability Index had significantly improved in the group that underwent treatment using an epiduroscopy at 3 months, 6 months, and 12 months following the procedure. Epiduroscopy is a relatively safe form of surgery but in terms of severe complications, there have been cases of loss of eyesight due to excessive epidural hypostatic pressure, and Helm et al.[30], reported 12 cases of this occurring. Other complications include dural puncture, epidural hematoma, and infection. There are no reports of RCTs conducted on each type of illness such as failed back surgery syndrome (FBSS) and spinal canal stenosis and according to a systematic review and meta-analysis that was published in 2016[30], they stated that at the current stage, the evidence supporting epidural adhesiolysis using epiduroscopy is limited. In Japan, treatment using epiduroscopy had been recognized as a form of 'advanced medical treatment' since 2004 but as of FY2015, it was withdrawn from this designation (as an 'advanced medical treatment') and can no longer be performed as such or as a form of treatment covered under insurance.

Period		2005～2019
Database		PubMed, Cochrane CENTRAL, NPO Japan Medical Abstracts Society
Words searched	P	Mainly chronic pain*, spinal stenosis, failed back surgery syndrome,low back pain etc.
	I/C	epidural neuroplasty, epidural adhesiolysis, Racz catheter etc./no limitations
Limitations		Limited by publication type. Systematic reviews, Randomized controlled trial,Meta-analysis etc
Selection Summary		Of the 81 PubMed search hits, 35 Cochrane CENTRAL search hits, 3 search hits from NPO Japan Medical Abstracts Society, we used 2 search hits that matched with the set PICO as well as 2 important references we had found through a manual search for a total of 4 references

CQ E-4 : Is spinal fusion useful for chronic pain associated with spinal diseases ?

Answer : There are no high-level reports on the effects of spinal fusion for treating neck pain and back pain. The effects of spinal fusion on chronic low back pain (LBP) without neuropathy are limited.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : Implementation is weakly recommended
〔Consensus 100.0%〕

Summary of overall evidence : C (low)

Commentary :

There are no high-level reports on the effects of spinal fusion for treating neck

pain and back pain. Therefore, in these guidelines we considered spinal fusion for chronic LBP. For LBP accompanied with neurological symptoms, generally decompression, fusion or corrective fusion is performed. Other forms of treatment are necessary for these conditions and therefore we have excluded them from the purposes of this CQ. As a result, we considered the results of spinal fusion for treating chronic LBP without any clear accompanying presence of stenosis or spondylolisthesis.

We utilized 3 recent systematic reviews[34-36] which included spinal fusion and nonsurgical forms of treatment for chronic LBP.

Results did not show any difference in a decrease in low back pain VAS scores or decrease in ODI over the short term (1～2 years) among patients undergoing spinal fusion compared with nonsurgical treatments. These 3 reviews included 6 low～moderate level RCTs[37-42]. These reviews had different inclusion criteria and used different nonsurgical treatments as the control, and there is a diverse number of fusion methods ; ALIF, PLF, and PLIF among others.

VAS : visual analogue scale
ODI : Oswestry Disability Index

In terms of nonsurgical forms of treatment that were used as a control, 4 of the studies used a combination of physical therapy (PT) methods such as CBT, muscle-strengthening exercises and stretches, whereas the other 2 studies conducted PT alone so we divided them according to the control treatment used and conducted a new meta-analysis. Furthermore, using the same references, we also considered the incidence of complications and frequency of patients undergoing surgery a second time, following spinal fusion.

ALIF : anterior intervertebral fusion
PLIF : posterior lumbar intervertebral fusion
CBT : cognitive-behavioral therapy
PT : physical therapy

There are 4 RCTs that compared spinal fusion with CBT＋PT[38-41], in which researchers compared the decrease in ODI one year later. Two of these studies[39,41] compared a decrease in VAS scores for LBP. In each respective meta-analysis, researchers did not recognize a significant difference in decline in LBP among each of the treatment methods, and there was no difference in treatment effect between spinal fusion and CBT＋PT one year later. Furthermore, in a follow-up report on these RCTs, researchers reported that there was no difference between the 2 types of treatment in terms of decline in LBP 9 years later[43], or on average 11 years later[44].

There are 2 RCTs that compared spinal fusion with physical therapy (PT) alone[37,42], and they found that ODI and VAS scores for LBP had significantly decreased 2 years later following spinal fusion, compared with the group that underwent PT alone. However, in 1 of these RCTs[42], one of their inclusion criteria was "pain was triggered through an intradiscal contrast but reduced afterwards through a block", and so because they had rigorously conducted a diagnosis of intradiscal LBP, it is possible that the effects of spinal fusion were larger than other reports.

In terms of complications resulting from treatment[37,39-41], researchers reported

0% in the non-surgical treatment group, and an incidence of 19.0% complications arising in the spinal fusion group, on average[45]. Furthermore, the % of those in the surgical intervention group who underwent surgery a second time[37,40] was 7.7%, on average.

All things considered, there are no RCTs with a high level of evidence and so in future we expect researchers to report on RCTs containing little bias, and uniformity in terms of enrolled patients, surgical methods and non-surgical methods. However, at the current stage, there is no difference in the effects of treatment between spinal fusion and CBT+PT for patients with chronic LBP without any clear signs of stenosis or spondylolisthesis. As there is a risk that complications may arise after undergoing surgery or patients may need to undergo surgery a second time, we believe it should only be conducted within the parameters of a well-thought-out treatment plan.

Period		2005～2019
Database		PubMed, Cochrane CENTRAL, NPO Japan Medical Abstracts Society
Words searched	P	Mostly chronic pain and low back pain,similar words (back pain,neck pain etc.)
	I/C	Spinal fusion, intervertebral fusion etc./nothing specified
Limitations		Limited by publication type, with PubMed we limited it to clinical trials, guidelines, meta-analysis etc., no limitations with Cochrane, with NPO Japan Medical Abstracts Society, we used original research papers, excluded meeting minutes
Selection summary		Of the 624 PubMed search hits, 139 Cochrane CENTRAL search hits, and 29 NPO Japan Medical Abstracts Society search hits, we utilized 8 search hits that matched with the set PICO, and used 4 important references that were outside of the period through manual search to give us a total of 12 references in total that we utilized

CQ E-5 : Is surgical therapy useful for chronic pain associated with strangulated peripheral neuropathy ?

Answer : Surgical treatment is more effective than conservative forms of treatment in achieving mid- to long-term results with chronic pain due to carpal tunnel syndrome. There is no evidence comparing its effect on pain related to cubital tunnel syndrome and tarsal tunnel syndrome with conservative methods of treating pain and other surgical treatments.

Recommendation Grade & Summary of Overall Evidence

1) Surgical therapy for carpal tunnel syndrome :

Recommendation grade : 2 (weak) : Implementation is weakly recommended〔Consensus 100.0%〕

Summary of overall evidence : B (moderate)

2) Surgical therapy for cubital tunnel syndrome

Recommendation grade : 2 (weak) : Implementation is weakly recommended〔Consensus 85.0%〕

Summary of overall evidence : D (very low)

3) Surgical therapy for tarsal tunnel syndrome :

Recommendation grade : No recommendation 〔Consensus 95.0%〕

Summary of overall evidence : D (very low)

Commentary :

With strangulated peripheral neuropathies, carpal tunnel syndrome and cubital tunnel syndrome are cited for the upper limbs as arising frequently and tarsal tunnel syndrome for the lower limbs. Conservative forms of treatment include drug therapy, steroid injection, and orthotic treatment, and surgical procedures such as decompression surgery and neurolysis are performed.

1) Carpal tunnel syndrome

There are 2 systematic reviews[46,47] that compared the effect of conservative forms of treatment (steroid injection, night orthosis) on carpal tunnel syndrome, with surgical forms of treatment, and there have been reports in 2 RCTs,[48,49] as well. Both conservative forms of treatment and surgical procedures were useful in mitigating pain ; conservative forms of treatment were effective in reducing pain over the short term, 3 months, whereas surgery was effective over the mid and long term, from 6～12 months. Conservative forms of treatment were particularly effective on mild to medium level pathologies, whereas on the other hand, there is the risk of complications arising, such as postoperative wound pain and hematoma with surgical treatments. However, researchers recognized an improvement in symptoms over the long term and improved nerve conduction studies.

Researchers recognized that conservative treatments were effective in mitigating pain, and also reported cases in which a steroid injection was highly effective, cases where the symptoms persisted for a short period of time, and cases of patients who had been administered their initial steroid injection[50]. Researchers also reported that 56 out of 68 patients, who had undergone conservative treatment for 6 months since their initial consultation, either displayed no change in their condition and symptoms or a deterioration so they ended up undergoing surgery and also there were reports of inferior outcomes in patients who had undergone surgery without undergoing any conservative form of treatment since their initial consultation[51]. Therefore, around the time of choosing the form of surgical treatment, one needs to keep in mind the degree of neuropathy, how long the symptoms have persisted and the severity of the condition.

2) Cubital tunnel syndrome

There are reports of both conservative forms of treatment (drug therapy, orthotic treatment, steroid injections etc.) and surgical procedures (simple decompression, upper medial resection, forward transfers/translocations etc.) to treat cubital tunnel syndrome. In our study, there were no research papers that compared the pain-mitigating effects from conservative forms of treatment and surgical proce-

dures. In a review, conservative forms of treatment were effective on mild～moderate-level cases, and there were cases in which symptoms were aggravated, but in some cases, there was dysfunction such as impaired perception and decline in muscle strength, so timely surgical treatment is recommended[52-54].

3) Tarsal tunnel syndrome

There were no research papers comparing the pain-mitigating effects of conservative forms of treatment with surgical procedures to treat tarsal tunnel syndrome. Prior to treatment, an accurate diagnosis is required, and along with making a rigorous evaluation of the related clinical symptoms, neurological and neurophysiological findings, it is also important to carefully consider other possible differential diagnoses. Surgery is considered to be useful in cases where tumor mass lesions or pressure factors have been clearly identified[55,56].

Period		2005～2019
Database		PubMed, Cochrane CENTRAL, NPO Japan Medical Abstracts Society
Words searched	P	Mainly chronic pain*, similar terms (pain etc.)
	I/C	carpal tunnel syndrome, cubital tunnel syndrome, tarsal tunnel syndrome, surgical treatment, conservative treatment etc,/nothing specified
Limitations		Limited by publication type, with PubMed, we searched for clinical trials, guidelines, meta-analysis etc., no limitations with Cochrane, original research papers searched for on NPO Japan Medical Abstracts society, excluding meeting minutes
Selection summary		Of the 638 PubMed search hits, 389 Cochrane CENTRAL search hits, and 206 NPO Japan Medical Abstracts Society search hits, we utilized 5 search hits that matched with the set PICO, and also 6 important references outside of the period obtained by manual search to give us a total of 11 search hits

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Chapter F. Psychological Approach

: CQ F-1～CQ F-8

CQ F-1 : Is psychoeducation useful for chronic pain ?
CQ F-2 : Is behavioral therapy (BT) useful for chronic pain ?
CQ F-3 : Is cognitive-behavioral therapy (CBT) useful for chronic pain ?
CQ F-4 : Is mindfulness useful for chronic pain ?
CQ F-5 : Is acceptance and commitment therapy (ACT) useful for chronic pain ?
CQ F-6 : Is hypnotherapy useful for chronic pain ?
CQ F-7 : Is autogenic training useful for chronic pain ?
CQ F-8 : Is progressive muscle relaxation useful for chronic pain ?

F. Psychological Approach

CQ F-1 : Is psychoeducation useful for chronic pain ?

Answer : We are unable to acknowledge that psychoeducation (sharing information) alone is useful. However, it is a necessary part of a variety of psychological interventions to be introduced and so we recommend implementing it in combination with other interventions.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : Implementation is weakly recommended under certain conditions 〔Consensus 88.2%〕

Summary of overall evidence : C (low)

Commentary :

This is 1 systematic review[1] that investigated whether psychoeducation (sharing information), the use of which is limited to promoting the knowledge of chronic pain, was effective or not when used alone. The review targeted patients suffering from chronic pain aged 18 years or older, compared the target group with a waiting list or a treatment as usual, and they considered its effects on 4 outcomes (pain, disability, depression, and catastrophizing) at 2 stages ; post-treatment and 3-month follow-up. There is a large variety of formats for implementing psychoeducation, including individual and group discussion, distributing paper materials, interacting with patients online and ways of implementing it without any direct interaction between the practitioner and patient. Because the number of research studies and sample sizes have been small, the quality of evidence is weak and therefore there was no recognizable beneficial or harmful effect from it, irrespective of the stage or outcome. Therefore, we believe that psychoeducation alone is not effective.

However, some researchers[1,2] have indicated the efficacy of psychoeducation when it is used in combination with other interventions. By fostering an understanding among patients, through psychoeducation, of the psychosocial factors that relate to the onset, maintenance and deterioration of chronic pain, as well as how the mechanism of their psychological intervention works, an intervention they will soon undergo, as well as the procedures for implementing them, psychoeducation may possibly have encouraging effects on the treatments that follow. Thus, we recommend implementing psychoeducation in combination with other interventions.

Period		2005～2019
Database		MEDLINE, Cochrane CENTRAL, NPO Japan Medical Abstracts Society
Words searched	P	Mainly chronic pain*, words regarded as synonyms (intractable pain, resistant pain, etc.), names of separate pathologies of which chronic pain is the main symptom (complex regional pain syndromes, fibromyalgia, etc.), etc
	I/C	psychoeducat*, pain educat* (education), etc./nothing specified
Limitations		Limited by publication type (we targeted RCTs, systematic reviews, meta-analysis), Limited by target (on humans), etc
Selection summary		Of the 796 MEDLINE search hits, 256 Cochrane CENTRAL search hits, and 59 NPO Japan Medical Abstracts Society search hits, we utilized 1 systematic review that matched with PICO and 1 other systematic review as a supplement

CQ F-2：Is behavioral therapy (BT) useful for chronic pain ?

Answer： Behavioral therapy (BT) alone (graded behavioral activation, operant (conditioning) therapy) is only partially effective and so we recommend that it be implemented as part of multidisciplinary treatment and cognitive behavioral therapy (CBT), as well as acceptance & commitment therapy (ACT).

CBT： cognitive behavioral therapy
ACT： acceptance and commitment therapy

Recommendation Grade & Summary of Overall Evidence

Recommendation grade：2 (weak)： Implementation is weakly recommended under certain conditions〔Consensus 100.0%〕

Summary of overall evidence：C (low)

Commentary：

In a systematic review of psychological interventions on adult patients with chronic pain, excluding those with headache, researchers considered the effects of behavioral therapy (BT)[3]. We excluded an RCT related to relaxation from the systematic review (because in this guideline, new pages were created on autogenic training and progressive muscle training), and conducted a meta-analysis of the remaining 3 RCTs. As a result, there was a visible moderate effect on catastrophizing in the intervention group. A statistically-significant effect on intensity of pain and disability was not observed. There was only 1 RCT which considered the effects on mood, which showed a high effect. However, overall we cannot say that the quality of the evidence is high and as there have been no RCTs since then which meet the systematic review criteria (mention of 'chronic', 20 patients＋in a group), there has been insufficient consideration of the effects of behavioral therapy alone.

However, BT is often utilized as part of a multidisciplinary treatment, CBT or ACT. For example, graded behavioral activation (a method in which activity is increased in stages) is often incorporated under occupational therapy (OT) or physical therapy (PT)[4], whereas behavioral activation is often incorporated under CBT and ACT[5]. Therefore, we recommend implementing BT for the purpose of improv-

ing catastrophizing and mood and also as part of a combined form of treatment for the purposes of improving pain and disability.

Period		2005～2020
Database		MEDLINE, Cochrane CENTRAL, NPO Japan Medical Abstracts Society, PubMed
Words searched	P	Mainly chronic pain*, words considered to be synonyms (intractable pain, resistant pain, etc.), names of separate pathologies of which chronic pain is the main symptom (complex regional pain syndromes, fibromyalgia, etc.), etc.
	I/C	behavior therapy, behavior medicine, etc./nothing specified
I/C		behavior therapy, behavior medicine, etc./nothing specified
Limitations		Limited by publication type (we targeted RCTs, systematic review, meta-analysis), Limited by target (on humans), other (20 cases + in one single group), etc
Selection Summary		Of the 104 MEDLINE search hits, 459 Cochrane CENTRAL search hits, 1,445 NPO Japan Medical Abstracts Society 1,445 search hits, we utilized 1 systematic review that matched with PICO, and 2 systematic reviews (PubMed, Cochrane CENTRAL) that were found by hand search, as supplements

CQ F-3 : Is cognitive-behavioral therapy (CBT) useful for chronic pain?

CBT : cognitive behavioral therapy

Answer : Cognitive-behavioral therapy (CBT) has been recognized to be useful for chronic pain in multiple aspects, and is recommended as a psychological intervention for chronic pain. However, as the system in place of implementing CBT in Japan is insufficient, we are hoping that it will undergo further development in the immediate future.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : Implementation is weakly recommended
〔Consensus 93.8%〕

Summary of overall evidence : B (moderate)

Commentary :

There is 1 systematic review investigating the effects of CBT on chronic pain excluding headache[3]. They targeted adults aged 18 years and over with chronic pain and conducted CBT face-to-face either in an individual or group format, assigning a waiting list or a treatment as usual as the control, and considered the effects of CBT on 4 outcomes (pain, disability, mood, catastrophizing) at 2 stages, short-term effects (post-treatment) and long-term effects (follow-up). In terms of the short-term effects of CBT, it displayed a small effect on pain and disability and moderate-level effects on mood and catastrophizing. On the other hand, in terms of its long-term effects, researchers recognized only a small effect on mood. Considering the insufficient number of research studies on this area and that the risk of bias is not necessarily low, the strength of evidence was moderate but both in terms of its short-term and long-term effects, we believe CBT is effective on chronic pain overall.

RCT : randomized controlled trial

There are many systematic reviews and RCTs that have investigated its effects

according to the site of treatment, and they have reported its effects on chronic low-back pain[6], and fibromyalgia[7] among others. However, there was a recognizable difference in the size of the effect, how long the effects persist, and whether CBT was effective or not, depending on the research study. As for the format under which it is implemented, researchers recognized that CBT was effective when conducted online[8,9]. Furthermore, there are some research papers[10] indicating the effectiveness of CBT when it was incorporated under a form of multidisciplinary treatment, and we expect CBT to also be useful when not implemented alone (but in combination).

However, the system in place in Japan for implementing CBT has not yet been sufficiently developed. In the field of chronic pain, in many cases there are no practitioners in medical departments who are able to implement CBT and there are issues about it being ineligible for health insurance coverage. In light of the above, we recommend implementing CBT but on the premise that we expect that a system will quickly be put in place for its implementation.

Period		2005～2020
Database		MEDLINE, Cochrane CENTRAL, NPO Japan Medical Abstracts Society, PubMed
Words searched	P	Mainly chronic pain*, words regarded as synonyms (intractable pain, resistant pain, etc.), names of separate pathologies of which chronic pain is the main symptom (complex regional pain syndromes, fibromyalgia, etc.), etc
	I/C	cognitive behavior therapy, cognitive therapy, behavior medicine, etc./nothing specified
Limitations		Limited by publication type (we targeted RCTs, systematic reviews, meta-analysis), Limited by target (on humans), other (20 cases + in one single group), etc
Selection Summary		Of the 2,389 MEDLINE search hits, 1,993 Cochrane CENTRAL search hits, 1,004 NPO Japan Medical Abstracts Society search hits, we utilized 1 systematic review that matched with PICO, 3 systematic reviews as supplements, and 2 RCTs that were found by hand search (PubMed, Cochrane CENTRAL)

CQ F-4 : Is mindfulness useful for chronic pain ?

Answer : Mindfulness-based intervention has been recognized to be useful for chronic pain in multiple aspects, and is recommended as a form of psychological intervention for chronic pain. However, the system in Japan for implementing mindfulness-based intervention is insufficient, so we expect that it will be quickly developed.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : Implementation is weakly recommended
〔Consensus 100.0%〕

Summary of overall evidence : B (moderate)

Commentary :

Researchers reported on a systematic review comparing a group of patients who

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

underwent mindfulness-based intervention for managing chronic pain (mindfulness-based stress reduction (MBSR), mindfulness-based cognitive therapy (MBCT), and other types of mindfulness training) with a control group of patients (treatment as usual, waiting list, or patient education/support group)[11]. Based on the synthesized results of the longest follow-up data in each RCT, it showed that mindfulness-based intervention has a significant small effect on pain intensity, depression, physical domains of QOL, and mental domains of QOL. There tended to be an improvement in disability as well but a significant difference was not obtained. Subgroup analyses by the type of intervention, medical condition, or treatment duration showed that efficacy of mindfulness-based intervention on pain did not differ.

There is also some research which has compared mindfulness with other forms of psychotherapy. Compared against mindfulness-based stress reduction (MBSR) and group-based cognitive-behavioral therapy (CBT), it showed that there was no significant difference in improvement for pain intensity, physical function, and depression at post-treatment[12]. A systematic review comparing mindfulness-based intervention to acceptance & commitment therapy (ACT) showed that ACT has significantly greater effects on depression and anxiety than mindfulness-based intervention[5]. However, there is still only a small number of RCTs that have directly compared mindfulness with CBT and ACT so we need to be cautious when interpreting the results. In recent years, they have been conducting mindfulness-based interventions online. In an RCT comparing the effects of an online MBCT on patients with chronic pain against the effects of online psychoeducation, researchers observed a moderate-level improvement in both groups in disability, at post-treatment and 6-month follow-up[13]. As interventions that are conducted online are highly convenient, we expect them to be further developed in future.

However, in Japan there is no sufficient system in place for implementing mindfulness-based intervention. In the field of chronic pain, there are many cases in which there are no practitioners belonging to a medical department who are able to implement mindfulness-based intervention, and there are issues with its health insurance coverage. In light of the above, we recommend implementing mindfulness-based intervention but under the premise that we soon expect that a system will be put in place in Japan for its implementation.

Period		2005～2019
Database		MEDLINE, Cochrane CENTRAL, NPO Japan Medical Abstracts Society, PubMed
Words searched	P	Mainly chronic pain*, words considered as synonyms (intractable pain, resistant pain, etc.), names of separate pathologies of which chronic pain is the main symptom (complex regional pain syndromes, fibromyalgia, etc.), etc
	I/C	mindful*, etc./nothing specified
Limitations		Limited by publication type (we targeted RCTs, systematic reviews, meta-analysis), Limited by target (on humans), other (50 cases+ in one single group), etc
Selection Summary		Of the 546 MEDLINE search hits, 480 Cochrane CENTRAL search hits, 100 NPO Japan Medical Abstracts Society search hits, we utilized 1 systematic review that matched with PICO, 2 systematic reviews as supplements, and 1 RCT that was found by hand search (PubMed, Cochrane CENTRAL)

CQ F-5 : Is acceptance and commitment therapy (ACT) useful for chronic pain ?

Answer : Acceptance and commitment therapy (ACT) has been recognized to be effective on chronic pain in multiple aspects and is recommended as a form of psychological intervention for chronic pain. However, there is an insufficient system in place in Japan for implementing ACT and so we expect that this will be established soon.

ACT : acceptance and commitment therapy

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : Implementation is weakly recommended 〔Consensus 100.0%〕

Summary of overall evidence : B (moderate)

Commentary :

Researchers have reported on a systematic review[14] that compared a group of patients with chronic pain (excluding pain due to headache or malignant diseases) who underwent an ACT intervention with control groups (waiting list or treatment as usual). At post-treatment, researchers found that compared with the control groups, there had been a small effect on disability and pain intensity, a moderate-level effect on anxiety, and a large effect on depression, pain acceptance and psychological flexibility in the group that underwent ACT intervention. At 3-month follow-up, researchers indicated a small effect on disability and a moderate-level effect on depression and psychological flexibility. There was a large variety in the formats in which the RCTs included in this review were conducted, including face-to-face, self-help, online, individually and as a group.

RCT : randomized controlled trial

In reports after this, researchers have proceeded to consider its effects on chronic headache (including migraine)[15], as well as consider the moderators and predictable variables of the effects during web-based interventions[16]. Furthermore, researchers have focused on differences in the format of treatment ; when they compared the effects of ACT conducted under interdisciplinary treatment with ACT conducted under unidisciplinary treatment, they found that interdisciplinary ACT had a larger effect on physical disabilities, psychosocial impacts and depression, whereas there was no difference between the groups in terms of intensity of pain, anxiety, and pain acceptance[17].

Some have also compared ACT with other psychotherapy. Research has indicated[5] that compared with mindfulness-based psychological interventions, ACT had a larger effect on anxiety and depression at post-treatment. In addition, other research has indicated that when comparing ACT and cognitive-behavioral therapy (CBT), the response rate to each respective treatment varies according to the age group of the patients[18]. In recent years, some research[19] has considered the effects

of ACT when a single session was conducted on breast-cancer patients in the early postoperative stages, in terms of its effects in preventing persistent postoperative pain. Other research[20] has considered the effects of a 1-day workshop conducted prior to surgery on veterans for the purposes of preventing persistent postoperative pain and long-term usage of opioid analgesics.

However, there is an insufficient system in place in Japan for implementing ACT. In the field of chronic pain, in many cases there are no practitioners in medical departments who are able to implement ACT and there are issues with health insurance coverage as well. In light of the above, we recommend implementing ACT but on the premise that hopefully a system will soon be established for its implementation.

Period		2005～2020
Database		MEDLINE, Cochrane CENTRAL, NPO Japan Medical Abstracts Society, PubMed
Words searched	P	Mainly chronic pain*, words considered to be synonyms (intractable pain, resistant pain, etc.), names of separate pathologies of which chronic pain is the main symptom (complex regional pain syndromes, fibromyalgia, etc.), etc
	I/C	acceptance and commitment therapy, acceptan*, commit*, etc./nothing specified
Limitations		Limited by publication type (we targeted RCTs, systematic review, meta-analysis), Limited by target (on humans), etc
Selection Summary		Of the 205 MEDLINE search hits, 151 Cochrane CENTRAL search hits, 43 NPO Japan Medical Abstracts Society search hits, we utilized 1 systematic review that matched with PICO, 1 systematic review as a supplement, 4 RCTs, 1 systematic review and 1 RCT that we found by hand search (PubMed, Cochrane CENTRAL)

CQ F-6 : Is hypnotherapy useful for chronic pain ?

Answer : It is difficult to judge the effectiveness of hypnotherapy and therefore we are unable to recommend its implementation apparently.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : No recommendation 〔Consensus 100.0%〕

Summary of overall evidence : C (low)

Commentary :

Two systematic reviews[21,22] have reported the effectiveness of hypnosis for managing chronic pain overall. We excluded 5 clinical trials that had been used in these systematic reviews (two studies with pre-post comparison design, one study that tested the effect of hypnosis in combination with another psychotherapy, and two studies that did not report the values required for conducting the meta-analysis), and then re-conducted a meta-analysis using 3 RCTs and 1 quasi-RCT. One newly added RCT was identified by a hand search. Targeting chronic pain in general, we used a waiting list or a treatment as usual as the control, to investigate the effectiveness of hypnosis on the outcomes including pain, disability, health-related quali-

HRQL : health-related quality of life

ty of life, depression, and anxiety. While a statistical significance was not observed, we found pain reduction with large effect size in the hypnosis intervention group. Concerning the other outcomes, we were unable to obtain sufficient evidence to discuss the effectiveness of hypnosis. There was only 1 RCT that investigated the effectiveness of hypnosis in outcomes other than pain. Also, the sample size of that RCT was very small (only 18 participants).

Hypnosis may have a large effect on reducing pain. Also, as another advantage, hypnosis can be covered as a psychosomatic treatment within the current health care insurance in Japan. RCTs conducted abroad report that a short-term intervention[23] consisting of 2 hypnosis sessions may be effective and that combining hypnosis with CBT and psychoeducation enhances its effectiveness[24,25]. However, evidence reported in the current stage is weak, and reporting on the effectiveness of hypnosis on outcomes other than pain is lacking. In addition to them, there are several barriers to introduce hypnosis in Japanese medical settings. For example, in Japan, the training system for hypnosis is not well prepared. As a result, patients' accessibility to hypnosis is poor. Also, the misunderstanding that patients would be manipulated by a hypnotist and forced to act against their will is prevailing.

In light of the above, we are unable to indicate a apparent recommendation for implementing hypnosis.

Period		2005～2020
Database		MEDLINE, Cochrane CENTRAL, NPO Japan Medical Abstracts Society, PubMed
Words searched	P	Mainly chronic pain*, words considered as synonyms (intractable pain, resistant pain, etc.), names of separate pathologies of which chronic pain is the main symptom (complex regional pain syndromes, fibromyalgia, etc.), etc
	I/C	hypnosis, hypnotherapy, etc./nothing specified
Limitations		Limited by publication type (we targeted RCTs, systematic reviews, meta-analysis), Limited by target (on humans), etc
Selection summary		Of the 600 MEDLINE search hits, 227 Cochrane CENTRAL search hits, 171 NPO Japan Medical Abstracts Society search hits, we utilized 2 systematic reviews that matched with PICO, and 1 RCT that we found after conducting a hand search (PubMed, Cochrane CENTRAL)

CQ F-7：Is autogenic training useful for chronic pain ?

Answer： It is difficult to judge the usefulness of autogenic training alone so we are unable to recommend its implementation apparently.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade：No recommendation〔Consensus 94.4%〕

Summary of overall evidence：Nothing

Commentary：

As there is only 1 small-scale randomized controlled trial (RCT) that has report-

RCT：randomized controlled trial

ed on the effects of autogenic training on chronic pain in general[26], it is difficult to evaluate on the evidence level so we decided on a 'no recommendation' grade.

In the 1 RCT reported, there were 35 targeted adult patients with chronic pain aged 20 years and over, researchers used a treatment as usual as a control, and considered its effects on pain, disability, depression and anxiety after the intervention. In this research study, patients undergoing treatment received individual guidance for 20 minutes per session, fortnightly, for a total of 3 sessions, received guidance from a recorded voice and pamphlet 3 times a day, as part of autogenic training, and also some self-learning once for several minutes. Outcomes were measured 4 weeks later. As a result, researchers failed to recognize the effects of autogenic training alone in any of the 4 outcomes (pain, disability, depression, and anxiety). However, in terms of heart rate variability which indicates autonomic nerve activity, researchers did recognize a trend ; high frequency components, which are an indicator of parasympathetic activity, increased significantly in the intervention group, compared with the control group. Some researchers reported[27] that autogenic training was effective not on chronic pain in general but on specified pain syndromes (migraine and somatoform disorders [somatic symptom disorder : DSM-5]).

With autogenic training, although the person in charge needs to have special expertise and skills (for example a certified public psychologist), its medical fee points have been specified as a form of psychosomatic medicine, and therefore the fact that it can be implemented within the framework of medical treatments covered under health insurance is considered to be one of its benefits. As for contraindications for autogenic training, researchers have cited that at the time of implementation, caution needs to be exercised : 1) when the practitioner suspects myocardial infarction, or immediately after myocardial infarction has occurred ; 2) with patients with diabetes who would have trouble with glycemic control and those for whom it is impossible to observe over the long term ; 3) with patients who experience hypoglycemia or patients with hypoglycemic-like symptoms ; 4) in cases of acute psychosis and those with severe schizophrenic reactions ; 5) patients displaying degenerative psychosis, delusions of persecution, and delusions of grandeur ; 6) in cases of extreme anxiety and exacerbated feelings of frustration ; and 7) active periods for peptic ulcers[28].

Period		2005～2019
Database		MEDLINE, Cochrane CENTRAL, NPO Japan Medical Abstracts Society
Words searched	P	Mainly chronic pain*, words regarded as synonyms (intractable pain, resistant pain, etc.), names of separate pathologies of which chronic pain is the main symptom (complex regional pain syndromes, fibromyalgia, etc.), etc
	I/C	autogenic training, progressive muscle relaxat*, etc./nothing specified
Limitations		Limited by publication type (we targeted RCTs, systematic reviews, meta-analysis), Limited by target (on humans), etc
Selection summary		Of the 187 MEDLINE search hits, 151 Cochrane CENTRAL search hits, and 151 NPO Japan Medical Abstracts Society search hits, we utilized 1 RCT that matched with PICO

CQ F-8 : Is progressive muscle relaxation useful for chronic pain ?

Answer : It is difficult to judge the usefulness of progressive muscle relaxation alone and so we are unable to recommend its implementation apparently.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : No recommendation 〔Consensus 100.0%〕

Summary of overall evidence : Nothing

Commentary :

There have been reports of 2 RCTs that have investigated the effects of progressive muscle relaxation alone on chronic pain in general and for 1 research study, we were unable to obtain the research data[29] while for the other 1, we assessed the quality of evidence as extremely low so we judge that it was difficult to assess its evidence level, and decided on a 'no recommendation' grade.

For the 1 RCT study for which we were able to obtain the data[30], researchers targeted 89 patients with chronic pain, aged from 11～77 years, in which a treatment as usual was used as the control, and researchers considered the effects on pain, disability and depression at 2 stages ; post-treatment and 3-month follow-up. With the progressive muscle relaxation used in this research study, patients followed the progressive muscle relaxation instructions which patients heard twice a week and then measured the outcomes 5 weeks later. As a result, they were unable to recognize the efficacy of progressive muscle relaxation on all outcomes (pain, disability, depression) both at post-treatment and 3-month follow-up. Also, massage, which was implemented as a treatment as usual, was significantly more effective than progressive muscle relaxation for all outcomes (pain, disability, depression) at post-treatment but at 3-month follow-up, all outcomes deteriorated significantly and were on par with those at the start of the treatment. On the other hand, there was neither a significant improvement nor aggravation due to progressive muscle relaxation ; the outcomes were around the same as those at the start of the treatment as compared with both post-treatment and 3-month follow-up.

Although progressive muscle relaxation requires that the person implementing it has special expertise and skills (for example a certified public psychologist), it is widely used as a form of psychosomatic medicine for psychosomatic disorders and neurosis.

Period		2005～2019
Database		MEDLINE, Cochrane CENTRAL, NPO Japan Medical Abstracts Society
Words searched	P	Mainly chronic pain*, words considered as synonyms (intractable pain, resistant pain, etc.), names of separate pathologies of which chronic pain is the main symptom (complex regional pain syndromes, fibromyalgia, etc). etc
	I/C	autogenic training, progressive muscle relaxat*, etc./nothing specified
Limitations		Limitations by publication type/(we targeted RCTs, systematic reviews, meta-analysis), Limited by target (on humans), etc
Selection summary		Of the 187 MEDLINE search hits, 151 Cochrane CENTRAL search hits, 151 NPO Japan Medical Abstracts Society search hits, we utilized 2 RCTs that matched with PICO

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Chapter G. Rehabilitation: CQ G-1-1～CQ G-5-3

G. Rehabilitation

CQ G-1-1 : Is general exercise therapy useful for chronic pain ?

Answer : Exercise therapy is useful for improving pain and dysfunction in patients with chronic pain. However, there was not a large difference between disease-specific and general exercises in its effects. Furthermore, researchers did not recognize that exercise therapy alone improved comprehensive quality of life (QOL), and therefore it needs to be used in combination with other forms of treatment.

QOL : quality of life

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 1 (strong) : Implementation is strongly recommended〔Consensus 87.5%〕

Summary of overall evidence : B (moderate)

Commentary :

We conducted a meta-analysis of 24 RCTs that investigated the effects of exercise therapy, such as aerobic exercise and muscle-strengthening exercises. The target was adults aged 18 years and over with chronic low back pain (LBP), chronic neck pain, and knee osteoarthritis (OA), who were compared against a group without exercise therapy (including waiting list group, and usual care group), physical therapy group, and other exercise therapy groups, as the control groups. As a result, researchers acknowledge that compared with the group without exercise therapy, the exercise therapy group had analgesic effects and was effective in improving dysfunction. However, there was not a large difference between like disease-specific exercise and general exercise therapies in terms of its effectiveness to improve their condition. Neither did they recognize an improvement in comprehensive QOL due to exercise therapy. We did not include stiff shoulders[Note G1], or fibromyalgia[Note G2] on this CQ.

Note G1 : Please refer to CQ L-5

Note G2 : Please refer to CQ Q-5

In terms of non-pharmacological forms of treating patients with chronic pain, we recommend incorporating exercise therapy under a treatment with the aim of improving lifestyle habits, such as obesity, and improving and maintaining physical activity[1-3]. Furthermore, researchers also claim it is advisable to utilize exercise therapy in combination with pharmacotherapy and approaches to behavioral medicine[1-3]. Based on this, although the effects from exercise therapy are not that high, it is useful for managing chronic pain.

Period		2010～2019
Database		MEDLINE, Cochrane Library, NPO Japan Medical Abstracts Society
Words searched	P	chronic pain, chronic pain［mesh］, low back pain［TI］, neck pain［TI］, Osteoarthritis［TI］
	I/C	exercise, aerobic exercise, Muscle Stretching Exercises, Resistance Training, walking, Exercise Therapy
Limitations		Review ; Systematic Reviews ; Meta-Analysis ; Randomized Controlled Trial ; published in the last10 years ; English
Selection summary		Based on the search results of the database, we extracted 1,179 MEDLINE search hits, 1,167 Cochrane Library search hits, and 36 NPO Japan Medical Abstract Society search hits, collated the searches with PICO and confirmed the data etc., and conducted a meta-analysis using 24 RCTs. Furthermore, these did not apply to our search method but we utilized 3 reviews（References1）～3）, which we had found through a manual search, which we deemed to be useful in providing supplementary information

CQ G-1-2：Is motor control exercise useful for chronic pain ?

Answer： Compared with a group without exercise therapy and exercise therapy group, motor control exercise（MCE）is useful in improving chronic pain and dysfunction. Furthermore, compared with a group without exercise therapy, it is useful in improving comprehensive quality of life（QOL）, but it is believed that there is not a big difference when compared with exercise therapy.

MCE：motor control exercise

QOL：quality of life

Recommendation Grade & Summary of Overall Evidence

Recommendation grade：2（weak）： Implementation is weakly recommended

〔Consensus 94.1%〕

Summary of overall evidence：C（weak）

Commentary：

Broadly speaking, MCE is training conducted with the aim of improving posture and motor control but generally speaking, its objective is to improve spinal stability and control and frequently refers to training that fosters cooperative and efficient activity of the superficial layer of muscles of the trunk such as the erector spinae muscles and rectus abdominus muscle as well as the deep trunk muscles such as the transverse abdominal muscles and the multifidus muscle. We conducted a meta-analysis of 16 RCTs which investigated the effects of MCE. The target was adults aged 18 years and over with chronic low back pain（LBP）and chronic neck pain. A group without exercise therapy（including a waiting list group and standard-treatment group）, a exercise therapy group, and manual-therapy group were used as the control groups. As a result, researchers recognized that MCE was effective in its analgesic effects and was effective in improving dysfunction compared with non-treatment, exercise therapy and manual therapy. However, only 1 RCT was utilized to compare it against manual therapy and so due to the low certainty of evidence, careful attention is required. In addition, MCE is effective in improving comprehensive QOL compared with non-treatment, but there was not a big differ-

ence compared with exercise therapy.

The majority of RCTs on MCE targeted chronic LBP ; there are few RCTs on chronic neck pain. Therefore, careful attention is required to the fact that compared with chronic LBP, the certainty of evidence on the effects of MCE for chronic neck pain is low. Moreover, the analgesic effects and the effectiveness of MCE in improving dysfunction are higher than those of exercise therapy, but there is a low certainty of evidence. Therefore, when selecting and deciding on a type of exercise for managing chronic pain, we recommend making a global judgment, considering factors such as patient preferences, costs and safety[4,5].

Period		2015～2020
Database		MEDLINE, Cochrane Library, NPO Japan Medical Abstracts Society
Words searched	P	chronic pain, chronic pain［mesh］, low back pain［TI］, neck pain［TI］, osteoarthritis［TI］
	I/C	motor control exercise, core stabilization exercise, stabilization exercises, motor control
Limitations		Review ; Systematic Reviews ; Meta-Analysis ; Randomized Controlled Trial ; published in the last5 years ; English
Selection summary		Based on the search results of the database, we extracted 462 MEDLINE search hits, 590 Cochrane Library search hits, collated the searches with PICO and confirmed the data etc., and conducted a meta-analysis using 16 RCTs. Furthermore, we utilized 2 systematic reviews (References 4) 5), which we deemed to be useful in providing supplementary information.

CQ G-1-3 : Is neuroscience-based rehabilitation (neurorehabilitation) useful for chronic pain ?

Answer : Using neurorehabilitation in combination with standard rehabilitation on the motor system is useful on patients with chronic pain but its effect in improving dysfunction has not been recognized. However, there is not a large difference in the effects obtained from using neurorehabilitation in combination with standard rehabilitation on the somatosensory system compared with when using standard rehabilitation alone. Its effects on comprehensive QOL and work remain unclear.

Recommendation Grade & Summary of Overall Evidence

1) Neurorehabilitation of the motor system

Recommendation Grade : 2 (weak) : Implementation is weakly recommended〔Consensus 100.0%〕

Summary of overall evidence : B (moderate)

2) Neurorehabilitation of the somatosensory system :

Recommendation Grade : No recommendation〔Consensus 100.0%〕

Summary of overall evidence : B (moderate)

Commentary :

Neurorehabilitation is rehabilitation based on the knowledge of neuroscience. It can be broadly divided into neurorehabilitation (such as exercise images, motor illusion) for processes related to motor expression (motor system), from motor pro-

grams to motor output, and neurorehabilitation (such as identification of tactile sites) for processes for somatosensory processing. In the former, visual feedback such as using mirrors or the evocation of images that the affected painful limb is moving even though it is not actually moving are used, which corresponds to mirror therapy which creates the illusion in the patient's mind that the affected limb is actually moving. On the other hand, in the case of the latter, it corresponds to sensation identification tasks for identifying the site on the affected left which is touched, without using any visual information. As the mechanisms that cause chronic pain and make it persist are implicated in modulations occurring in the central nervous system[6], neurorehabilitation has come to be implemented as one form of rehabilitation treatment for chronic pain.

We conducted a meta-analysis using 12 RCTs that investigated the concomitant effects when neurorehabilitation was used in combination with standard rehabilitation on the motor system. We targeted patients aged 18 years and over with chronic pain, excluding patients with cancer pain and visceral pain (such as phantom limb pain, complex regional pain syndrome (CRPS), pain after spinal cord injury (SCI), post-stroke pain, low back pain (LBP), and motor system pain), and compared it with a standard rehabilitation group as the control. As a result, using neurorehabilitation in combination with standard rehabilitation on the motor system displayed high analgesic effects. However, there was no difference between the 2 groups in terms of its effects on improving dysfunction and in the RCT that was used, comprehensive QOL was not used as an outcome, and therefore its effects on comprehensive QOL are not clear. In terms of adverse events, there have been reports[7] of aggravated pain or nausea arising when patients imagined exercising the affected limb, and therefore one should advise a specialist (physical therapist, etc.) at the time of implementation.

QOL : quality of life

Furthermore, we conducted a meta-analysis using 4 RCTs that investigated the effects of using neurorehabilitation and standard rehabilitation in combination on the somatosensory system. The subjects and control group used for comparison were the same as the above-mentioned neurorehabilitation analysis conducted on the motor system. As a result, there was no difference in analgesic effect or its efficacy in improving dysfunction on the somatosensory system when neurorehabilitation was used in combination with standard rehabilitation. Once again, comprehensive QOL was not an outcome of the RCT we used, and so its effects were not clear. Based on this, we can say that at the current stage, neurorehabilitation is not useful in managing chronic pain in the somatosensory system, when used in combination with standard rehabilitation.

Period		2005～2019
Database		PubMed, Cochrane Library
Words searched	P	phantom limb pain, CRPS, low back pain, spinal cord injury, stroke, neuropathic pain, limb pain, Musculoskeletal pain, Musculoskeletal disorders
	I/C	motor imagery, graded motor imagery, movement representation, kinesthetic imagery techniques, illusion, virtual visual feedback, mirror visual feedback, mirror box, MVF, mirror therapy, sensory discrimination, tactile discrimination, sensory discrimination retraining, tactile sensory discriminatory training, perceptive rehabilitation
Limitations		Review ; Systematic Reviews ; Meta-Analysis ; Randomized Controlled Trial ; published in the last 15 years ; English
Selection summary		Based on the search results of the database, we extracted 1,217 searches, collated the search hits with PICO and confirmed the data etc, and conducted a meta-analysis using 16 RCTs

CQ G1-4 : Is exercise therapy used in combination with cognitive-behavioral therapy (CBT), patient education, and occupational therapy (OT) useful for chronic pain ?

CBT : cognitive behavioral therapy
OT : occupational therapy

Answer : Exercise therapy used in combination with social approaches, cognitive-behavioral therapy (CBT), patient education, and occupational therapy (OT) is useful for improving pain and dysfunction in patients with chronic pain as well as comprehensive quality of life, and useful for social involvement and patients returning to work. However, the specific protocols for obtaining high effects remain unclear.

Recommendation Grade & Summary of Overall Evidence

1) Exercise therapy using a combination of CBT and patient education

Recommendation grade : 1 (strong) : Implementation is strongly recommended〔Consensus 94.4%〕

Summary of total evidence : B (moderate)

2) Occupational therapy, social approaches

Recommendation grade : 2 (weak) : Implementation is weakly recommended〔Consensus 89.5%〕

Summary of total evidence : C (low)

Commentary :

We conducted a meta-analysis using 26 RCTs that investigated the effects of exercise therapy in combination with CBT and patient education. The subjects were adults aged 18 years and over with chronic pain (chronic low back pain (LBP), chronic neck pain, knee osteoarthritis (knee OA), and other forms of chronic musculoskeletal pain) and the control groups were single interventions (CBT, patient education, exercise therapy), and standard rehabilitation. As a result, exercise therapy used in combination with CBT and patient education was recognized to have higher analgesic effects, was more effective in improving dysfunction, and improved comprehensive QOL over the mid- to long-term, compared with single in-

terventions. Furthermore, it was also recognized to provide analgesic effects over the mid- to long-term, was effective in improving dysfunction, and improved comprehensive QOL for patients with chronic neck pain and chronic pain, compared with standard rehabilitation.

In Europe and America, they recommend introducing CBT and patient education for chronic pain management. Through these treatment methods, patients with chronic pain understand their pain and are encouraged to change their behaviors, thereby contributing towards an improvement of and reduced risk of aggravating various symptoms[8-10]. There is a large variety of protocols such as the contents of a CBT and patient education program, the period of implementation, how frequently it is implemented, and the format (individual, group) and at the current stage, it remains unclear what kind of protocol yields high effects. In addition, we have not included fibromyalgia in this CQ.[Note G3]

Note G3 : refer to CQ Q-3

Next, we conducted a meta-analysis, just like the one above, using 11 RCTs which investigated the effects of exercise therapy when used in combination with occupational therapy (OT) and social approaches. As a result, exercise therapy used in combination with OT and social approaches proved to be effective in improving dysfunction over the short to long term, comprehensive QOL as well as social participation and a return-to-work, compared with standard rehabilitation.

OT not only targets physical dysfunction but also mental dysfunction such as depression, focusing on lifestyle actions (=occupation) with objectives and values, for example daily lifestyles, work and hobbies, and uses these as a mean for treatment and guidance. To be more specific, it aims to improve activity, physical and psychological function through occupational activities such as self care and housework. Therefore, OT has a wide target, and one of its treatment goals is securing social roles beginning with a return-to-work. In addition, coordinating on the personal level with people such as managers at the workplace or the patient's family, towards the achievement of this aim, requires a social approach which is adjusting to the environment at home and at work and in Japan ; an occupational therapist will often attend to these matters as well.

Many patients with chronic pain have trouble participating in society and this leads to the social problem of massive economic loss due to reduced productivity, absence from work and taking time off work. By introducing for example activity pacing and occupational counselling by an occupational therapist, and work-based rehabilitation to tackle this problem, it is recognized to be effective in ways such as reducing the number of days people are absent from work and encouraging people to participate in society[11,12]. Therefore, there are still few RCTs at the current stage, and the contents of an effective program, the period to implement it, and how frequently it should be implemented remain unclear. In future, researchers are required to accumulate much more evidence.

Cognitive-behavioral therapy (CBT), patient education

Period		2015～2019
Database		PubMed, Cochrane Library, NPO Japan Medical Abstracts Society
Words searched	P	chronic pain, chronic pain [mesh], chronic low back pain, chronic neck pain, knee osteoarthritis, chronic musculoskeletal pain
	I/C	cognitive behavioral therapy", education, self-management, back school, pacing, pain coping skills, brief education, behavioral approach, neuroscience education, neurophysiology education, cognitive behavioral treatment, general exercise, exercise, physical therapy, aerobic exercise, stretching exercise, resistance training, walking, physiotherapy
Limitations		Review ; Systematic Reviews ; Meta-Analysis ; Randomized Controlled Trial ; published in the last5 years ; English
Selection summary		Based on the search results of the database, we extracted 488 PubMed search hits, 67 Cochrane Library search hits, and 7 NPO Japan Medical Abstract Society search hits, collated the searches with PICO and confirmed the data etc, and conducted a meta-analysis of 26 RCTs. We also used 3 systematic reviews (References 8)～10) that were deemed useful as supplementary information

Occupational therapy (OT)

Period		2005～2019
Database		Cochrane Library, PubMed, NPO Japan Medical Abstracts Society
Words searched	P	chronic pain, chronic pain [mesh], upper limb conditions, chronic conditions, low back pain, neck pain
	I/C	occupational therapy, pacing, chronic pain management, work strategies, counseling, work focused rehabilitation, workplace-based rehabilitation/nothing specified
Limitations		Meta-Analysis, Randomized Controlled Trial, Systematic Reviews, Reviews, guideline
Selection summary		Based on the search results of the database, we extract 94 Cochrane Library search hits, 748 PubMed search hits, 0 NPO Japan Medical Abstract searches, collated the search hits with PICO and confirmed the data etc, and conducted a meta-analysis using 11 RCTs

CQ G-2 : Is mind-body exercise (yoga, pilates, Tai chi etc.) useful for chronic pain ?

Answer : Mind-body exercise is useful for improving pain and dysfunction in patients with chronic pain. On the other hand, researchers have not recognized that mind-body exercise improves comprehensive quality of life (QOL).

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : Implementation is weakly recommended [Consensus 94.7%]

Summary of overall evidence : B (moderate)

Commentary :

Mind-body exercise is a form of exercise that incorporates elements from meditation, such as deep rhythmical abdominal breathing, and making slow movements and being conscious of the body's movements and muscles. It includes yoga, pilates, Tai Chi, and Qigong. Yoga and pilates cooperatively contract the superficial-layer muscles and deep-layer muscles of the trunk and they have the same exercise components in common with motor control exercise. Furthermore, mind-body exercise, which will be discussed here, is an exercise performed under medical management by a specialist such as a mind-body exercise therapist.

We conducted a meta-analysis using 26 RCTs that investigated the effects of mind-body exercise. The subjects were adults aged 18 years and over with chronic low back pain (LBP), chronic neck pain, and knee osteoarthritis (knee OA) and the control groups were groups without exercise therapy (including a waiting-list group, standard-treatment group), a exercise therapy group, a manual therapy group, and patient-education group. As a result, mind-body exercise displayed higher analgesic effects and effect on improving dysfunction than the waiting-list groups, exercise therapy group and patient-education group. On the other hand, analgesic effects were higher in the manual therapy group but there was only 1 RCT so the certainty of evidence was low. As for improvement in comprehensive QOL, there was no difference between mind-body exercise and the exercise therapy group and no-treatment groups. In addition, we did not include stiff shoulders[Note 4], or fibromyalgia[Note 5] on this page.

There have been few reports of adverse events but some reports[13-15] that there is a higher risk of mild aggravated pain compared with non-treatment and patient education. However, compared with exercise therapy, the risk of aggravated pain is about the same and so mind-body exercise could be considered as an option for exercise therapy.

Period		2015～2020
Database		MEDLINE,Cochrane Library,NPO Japan Medical Abstracts Society
Words searched	P	chronic pain, chronic pain［mesh］, low back pain［TI］, neck pain［TI］, osteoarthritis［TI］
	I/C	mindful exercises, Tai Chi, yoga, pilates, Qigong
Limitations		Review ; Systematic Reviews ; Meta-Analysis ; Randomized Controlled Trial ; published in the last5 years ; English
Selection summary		Based on the search results of the database,we extracted 463 MEDLINE search hits, 895 Cochrane Library search hits, collated the searches with PICO and confirmed the data etc, and conducted a meta-analysis using 26 RCTs

CQ G-3 : Is physical therapy useful for chronic pain ?

Answer : Physical therapy has been recognized to be effective in improving short-term pain and dysfunction compared with non-treatment but researchers have not recognized that it improves QOL. Furthermore, the quality of evidence indicating its effects is low so caution is required. Furthermore, the long-term effects under physical therapy are still unclear. Furthermore, adverse events have been reported such as strain and a feeling of tension at the site of treatment and exacerbated pain. Therefore, when introducing physical therapy to manage chronic, it is important to sufficiently weigh up the pros and cons.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : No recommendation 〔Consensus 89.5%〕

Summary of overall evidence : C (low)

RCT：randomized controlled trial

LLLT：Low level laser treatment

QOL：quality of life

Commentary：

We conducted a meta-analysis using 26 RCTs that investigated the effects of physical therapy (including therapeutic ultrasound, transcutaneous electrical nerve stimulation (TENS), interferential current stimulation (IFC), microwave therapy, low level laser treatment (LLLT), cryotherapy, balneotherapy, indirect traction therapy). Subjects were patients aged 18 years or older with chronic low back pain (LBP), chronic neck pain, and knee osteoarthritis (OA). Control groups underwent sham treatments, other forms of physical therapy, pharmacotherapy, and exercise therapy. As a result, researchers found that while therapeutic ultrasound, TENS, LLLT had greater short-term analgesic effects and an effect on improving dysfunction than non-treatments (including sham treatments), researchers did not recognize that it had an effect in improving comprehensive QOL. Furthermore, compared with other treatments such as exercise therapy, there was no difference in its effects. When we look at its concomitant effects when used together with another form of treatment, researchers recognized that therapeutic ultrasound used in combination with exercise therapy had a greater effect in improving short-term dysfunction than when exercise therapy alone was used. However, the sample used in many of the RCTs for analysis was small and so the results of the meta-analysis showed high heterogeneity and imprecision；meaning the certainty of the evidence is low. Furthermore, its mid-to long-term effects have not been considered. Therefore, caution needs to be exercised when interpreting the above results. Also, we have not included in this CQ stiff shoulders, painful diabetic neuropathy, and fibromyalgia.

In terms of RCTs that have investigated the effects of physical therapy on chronic pain, it has been pointed out that there has been an inadequate blinding and small sample sizes[3], therefore the quality of the evidence is low, and we do not recommend it as a form of non-pharmacological therapy for chronic pain[1,3]. In addition, as physical therapy is a passive (inactive / hands-on) form of treatment, researchers fear that it may encourage inactivity in patients with chronic pain or their (over)dependence upon treatment[1]. Therefore, if introducing physical therapy as a treatment for chronic pain, it is advisable to implement it as an auxiliary form of treatment alongside exercise therapy.

Period		1999～2020
Database		MEDLINE, Cochrane Library
Words searched	P	chronic pain, chronic pain [mesh], low back pain [TI], neck pain [TI], osteoarthritis [TI]
	I/C	physical modalities, therapeutic ultrasound, transcutaneous electrical nerve stimulation, TENS, low level laser therapy, LLLT, interferential therapy, superficial heat, thermotherapy, balneotherapy, diathermy, superficial cold, cryotherapy, cold therapy, electro-muscular stimulation, traction
Limitations		Review ; Systematic Reviews ; Meta-Analysis ; Randomized Controlled Trial ; published in the last 22 years ; English
Selection summary		Based on the search results of the database, we extracted 401 MEDLINE search hits, and 348 Cochrane Library search hits, collated the searches with PICO and confirmed the data etc, and conducted a meta-analysis using 26 RCTs. Furthermore, we used 2 reviews (References 1) 3)) that did not apply to our search method but through a manual search were deemed useful as supplementary information

CQ G-4 : Is manual therapy useful for chronic pain ?

Answer : Compared with non-treatment, it is believed that manual therapy is useful for improving pain and dysfunction. However, there is no difference in its effects compared with exercise therapy. Furthermore, researchers have not recognized that manual therapy alone leads to a comprehensive improvement in quality of life (QOL).

QOL : quality of life

The certainty of the evidence indicating these effects is low and so when introducing manual therapy alone for managing chronic pain, one needs to sufficiently weigh up the pros and cons.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : No recommendation 〔Consensus 100.0%〕

Summary of overall evidence : C (low)

Commentary :

We conducted a meta-analysis of 18 RCTs that investigated the effect of manual therapy. Subjects were adults aged 18 years and over with chronic low back pain (LBP), chronic neck pain, and knee osteoarthritis (OA). The control groups were groups without exercise therapy (waiting-list group, and standard-treatment group), a physical therapy group, and an exercise therapy group. As a result, there was low analgesic effect and an improvement in dysfunction in the manual therapy group, compared with the waiting-list groups and physical therapy group. On the other hand, compared with the exercise therapy group, there was not a big difference in its improvement effect. Furthermore, researchers did not recognize a comprehensive improvement in QOL through using manual therapy alone, in patients with chronic LBP and chronic neck pain. Of the research papers that were used for analysis, many of them did not handle data sufficiently and there was a lack of blind studies, so caution needs to be exercised when interpreting these results. In

Note 6 : Refer to CQ L-5
Note 7 : Refer to CQ Q-6

addition, we have not included stiff shoulders[Note 6], and fibromyalgia[Note 7] in this CQ.

Researchers[3] have pointed out the high bias risk and low-quality evidence of RCTs to date that have investigated the effects of manual therapy on chronic pain. Furthermore, as manual therapy is a passive (inactive / hands-on) form of treatment, there are fears that it may encourage inactivity in patients with chronic pain and (over) dependence on treatment (medicalizing)[1]. Therefore, we do not recommend implementing manual therapy alone as a form of non-pharmacological therapy for chronic pain[1,3]. However, recently, some have asserted that manual therapy is useful in improving pain when it is used in combination with exercise therapy for a short period of time, rather than when exercise therapy alone is implemented[16]. Therefore, if introducing manual therapy for managing chronic pain, it is important to first have a clear purpose and timeframe and implement it in combination with exercise therapy.

Period		2010～2019
Database		MEDLINE, Cochrane Library, NPO Japan Medical Abstracts Society
Words searched	P	chronic pain, chronic pain [mesh], low back pain [TI], neck pain [TI], osteoarthritis [TI]
	I/C	manual therapy, massage [Mesh], muscle energy techniques, shiatsu, Acupressure, Musculoskeletal Manipulations [Mesh], myofascial release
Limitations		Review ; Systematic Reviews ; Meta-Analysis ; Randomized Controlled Trial ; published in the last 10 years ; English
Selection summary		Based on the search results of the database, we extracted 278 MEDLINE search hits, 290 Cochrane Library search hits, and 11 NPO Japan Medical Abstract Society searches, collated the search hits with PICO and confirmed the data etc,and conducted a meta-analysis using 18 RCTs. Furthermore, we used 3 reviews (References 1) 3), 16)) that did not apply to our search method but through a manual search were deemed useful as supplementary information

CQ G-5-1 : Is cervical collars useful for chronic pain ?

Ans : Irrespective of whether neurological symptoms of chronic neck pain or a related disease are present or not, we do not recommend cervical collar, more from the perspective of its harmful effects rather than in terms of its benefits.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) No implementation is weakly recommended〔Consensus 100.0%〕

Summary of overall evidence : C (low)

Commentary :

According to the 'Guidelines for Neck Pain and Related Diseases (2016),' in the absence of neurological symptoms within 3 months of onset, and furthermore, even if neurological symptoms are present, in addition to within 3 months, we did not recommend cervical collar even for follow-up cases beyond 3 months. This is due to an ethical viewpoint that rather than its benefits, it has high harmful effects,

such as inactivity, poor physical condition, and a decline in self-efficacy[17]. Furthermore, even though the amount of research and sample sizes were insufficient upon meta-analysis, in terms of its response rate to cervical radiculopathy pain, as an outcome, there was no difference between the group which used a cervical collar, and the waiting list group, physical therapy group, and traction group[18]. According to the guidelines on non-invasive treatment for non-specific low back pain (LBP) and neck pain for low- to medium-income families in Germany, researchers concluded that a cervical collar should not be used in the acute stage to treat non-specific neck pain or neck pain accompanying radiculopathy. However, they do not mention anything about its use for chronic-stage patients[19]. In an RCT conducted on patients with cervical radiculopathy, researchers compared 3 groups : a cervical collar group, a physical therapy group, and a control group ; and reported that that there was no significant difference for the cervical collar group compared with the other groups, in terms of alleviation of neck pain at 6 months, nor at 6 weeks was there any significant difference in level of satisfaction, the dosage of NSAIDs and opioid analgesics administered, or amount of sick leave taken[20].

RCT : randomized controlled trial

Period		2005～2019
Database		MEDLINE, Cochrane CENTRAL, NPO Japan Medical Abstracts Society
Words searched	P	chronic neck pain, cervical radiculopathy
	I/C	neck collar/nothing fixed (stand-by control group, physical therapy, traction etc.)
Limitations		Limited by publication type. PubMed CER randomized controlled trial/systematic review search filter, Cochrane RCT search filter, etc
Selection summary		Of the 198 MEDLINE 198 search hits, we used 4 which matched with the set PICO

CQ G-5-2 : Are lumbar corsets (lumbar fixation belts) useful for chronic low back pain ?

Answer : There is no significant difference in using a lumbar corset compared with other active treatment methods for LBP and functional improvement. Furthermore, lumbar corsets, used as an apparatus to prevent LBP among laborers and at the workplace, are not effective compared to for example training, and also in terms of LBP episodes (short-term and long-term) and short-term prevention of sick leave, researchers did not observe that a lumbar corset was effective compared with controls.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : No recommendation [Consensus 82.4%]

Summary of overall evidence : C (low)

Commentary :

According to the US guidelines (2017), although evidence is low, at 8 weeks or 6

months, comparing a lumbar corset＋exercise group with an exercise only group (muscle strengthening exercises), researchers reported that there was no difference in pain or function and compared with other active treatment therapies (traction, spinal manipulation, exercise, physical therapy or TENS), there was no clear difference in pain or function from the use of a lumbar corset[21]. They did not report on ADL or QOL. As an apparatus for preventing LBP among laborers and at the workplace, compared with training, the lumbar corset was not effective and so we do not recommend its use as a form of protective equipment[22]. In a systematic review on preventing LBP, researchers reported moderate-level evidence that it does not reduce LBP episodes over the long-term and low-level evidence in which they did not observe any effects in preventing short-term absence from work due to sick leave[23]. In a report on the dosage of analgesics used, the pharmacological consumption amount decreased in patients with sub-acute LBP but there were no long-term reports on chronic LBP[24]. In a single report from Japan that a lumbar corset was effective, LBP improved over the short term, increasing muscular endurance, and they reported that they did not observe a decrease in paraspinal muscular fatigue or reduced muscular strength through wearing the lumbar corset for a long period of 6 months[24]. Researchers suggested that wearing a lumbar corset might possibly be useful for elderly patients with complications and as a form of adjuvant therapy or alternative therapy to pharmacotherapy. However, there are issues such as the small total number of cases examined：40 patients[24].

Period		2005～2019
Database		MEDLINE, Cochrane CENTRAL, NPO Japan Medical Abstracts Society
Words searched	P	chronic low back pain
	I/C	lumbar corset/not fixed (exercise therapy and surgery etc.)
Limitations		Limited by publication type. PubMed CER randomized controlled trial/systematic review search filter, Cochrane RCT search filter, etc
Selection summary		Of the 78 MEDLINE search hits, we used 4 which matched with the set PICO

CQ G-5-3：Are knee braces (knee corsets) useful for chronic knee joint pain due to knee osteoarthritis (OA)？

Ans： When pain, knee joint function, walking distance and QOL were assessed after 12 months in a knee brace group, there was no significant difference compared with patients without a knee brace and therefore we are unable to judge whether it is recommendable.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade：No recommendation 〔Consensus 94.4%〕

Summary of overall evidence：C (low)

Commentary：

In a 2015 Cochrane review, at 12 months follow-up, through using VAS pain scores, researchers did not recognize a statistically significant difference in analgesic effect in the knee brace group compared with a group that did not undergo the treatment. At 12 months follow-up, there was no statistically significant difference in knee joint function between the knee brace group and the group which did not use a knee brace. Furthermore, researchers reported that there was no evidence of its effect on HSS knee function[25]. As for QOL, at 12 months follow-up, irrespective of whether patients were wearing a knee brace or not, researchers did not observe a statistically significant difference in the EuroQol Scores among participants. There is a low-level evidence report indicating the possibility that wearing a knee brace might reduce the prevalence rate through prevention[26]. There were no reports of complications either in a group that wore a knee brace or in the non-treatment group but due to skin irritation and ill-fitting braces, a very small number of patients enrolled in the study discontinued wearing it[25]. There are no reports on the effects of a knee brace on absence from work due to knee joint pain, workers going back to work, dosage of analgesic administered or pain relapse. On the other hand, according to guidelines published by the American College of Rheumatology/Arthritis Foundation (2020), pain experienced by patients when walking up and down stairs and during the 6-minute walk test (6MWT) significantly improved in the knee brace group compared with the standard-treatment group, and therefore they recommend wearing a knee brace[27].

HSS：Hospital for Special Surgery
QOL：quality of life

Period		2005～2020
Database		MEDLINE, Cochrane CENTRAL, NPO Japan Medical Abstracts Society
Words searched	P	Osteoarthritis of the knee, chronic knee pain
	I/C	knee brace/no equipment (non-treatment, footplate etc.)
Limitations		Limited by publication type. PubMed CER randomized controlled trial/systematic review search filter, Cochrane RCT search filter, etc
Selection summary		Of the 53 MEDLINE search hits, collating the searches with PICO, we used 2 reviews

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Chapter H. Integrative Medicine : CQ H-1～CQ H-2

CQ H-1 : Are acupuncture and moxibustion useful for chronic pain ?
CQ H-2 : Is massage useful for chronic pain ?

H. Integrative Medicine

CQ H-1 : Are acupuncture and moxibustion useful for chronic pain ?

Answer : We believe that acupuncture and moxibustion are useful on patients with chronic pain but when selecting a form of treatment, we recommend prioritizing the values of the patient after taking into consideration the effects and costs. An important element when opting for acupuncture and moxibustion treatment is having acupuncture and moxibustion practitioners who have an appropriate knowledge of chronic pain.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : Implementation is weakly recommended 〔Consensus 84.2%〕

Summary of overall evidence : C (low)

Commentary :

We investigated the efficacy of acupuncture and moxibustion treatment on patients with chronic pain but definitions of chronic pain vary widely depending on the research paper so this time we targeted "patients with pain persisting for 3 months or more" and investigated without narrowing it down by specific disease. Furthermore, there are many research studies that have used sham acupuncture treatment as the control when investigating the efficacy of acupuncture and moxibustion. However, considering the definition of sham acupuncture and also the fact that there are reports for example which have recognized bioactivity due to sham acupuncture, we considered its efficacy by using pharmacotherapy or pharmacotherapy + regular care as the control groups, in accordance with actual clinical settings.

RCT : randomized controlled trial

As a result, in the end we found 4 RCTs on chronic neck pain[1], chronic migraine[2], fibromyalgia[3], and chronic pelvic pain syndrome[4]. With pain, the mean difference between the indicators (the pain-related scores of VAS, SF-36, FIQU, NIH-CPSI, respectively) of each research paper were −0.8 [−2.4～0.77] (no significant difference), −5.6 [−8.7～−2.5] (significant in the intervention group), 0.5 [−1.6～2.6] (no significant difference)[3], and −2.8 [−4.6～−1] (significant in the intervention group)[4]. Two of these research papers mentioned QOL[1,4], and the results were−3.7 [−5.4～−2.0] (significant in the intervention group)[1], and −1.2 [−2.5～0.2] (no significant difference)[4]. There was 1 research paper that clearly mentioned adverse events[2] ; there were side effects among 6% of the patients in the intervention group, and 66% in the control group. Additionally, there were 2 research pa-

pers that mentioned there were no adverse events in either of the groups[1,4].

For our meta-analysis, we integrated 2 research studies on pain[1,3]. Essentially, these conditions were not suitable for conducting a meta-analysis so we deliberately chose the large category of what patients encounter in actual clinical settings at an acupuncture and moxibustion clinic in order to understand what kind of results we would get, using "subjects whose pain has persisted for 3 months or more, internal medicine as the control group, and pain as the outcome." As a result, we did not recognize a significant difference ; SMD −0.24 [−0.75 ～ 0.27] ($P=0.35$). In terms of a balance of benefits and harmful effects, we believe it was more effective in the intervention group but we believe the control group was useful when considering costs.

SMD : standardized mean difference

In this systematic review, diseases were limited and therefore as it does not represent chronic pain overall, we ended up investigating the efficacy of acupuncture and moxibustion only on specific diseases and symptoms. As diseases and symptoms vary and there are few research studies on it, the quality of evidence is low so we are unable to reach a fixed conclusion. However, depending on the relative importance of values, such as treatment effects, costs and side effects, we believe that for patients it is an effective option for both groups.

Based on the results above, when the "patient has a chronic illness (disease in which the main symptom is chronic pain) and there are no means for them to undergo suitable treatment by a health insurance doctor," which is the condition for patients to be eligible for medical expenses from acupuncture and moxibustion, this might be regarded as the ideal option for patients, both in terms of effects and costs. However, in this case, this is provided that the acupuncturist performing the treatment has adequate knowledge of chronic pain.

Moreover, this time pharmacotherapy was set as the control group, so there were few research papers but we saw many papers which had used a sham treatment for the control and also had compared acupuncture combined with pharmacotherapy against pharmacotherapy.

In a meta-analysis of chronic pain patients overseas, researchers reported highly reliable evidence that moxibustion therapy was effective in managing chronic pain[5]. In overseas clinical guidelines, The National Institute for Health and Care Excellence (NICE) recommends acupuncture treatment in comparison to sham treatments or standard care for reducing pain and improving QOL over a short period of time (3 months)[6]. Furthermore, the American College of Physicians (ACP) recommends acupuncture treatment for chronic LBP.[7]

Period		2005～2019
Database		MEDLINE, Cochrane CENTRAL, NPO Japan Medical Abstracts Society
Words searched	P	Mainly chronic pain*, similar words to this (intractable pain,complex regional pain syndromes etc.)
	I/C	acupuncture, moxibust,moxa,needl etc./nothing specified
Limitations		Limited by publication type, PubMed CER randomized controlled trials / systematic review search filter,Cochrane RCT search filter
Selection summary		Of the 502 MEDLINE search hits, 1,102 Cochrane CENTRAL search hits, and 53 NPO Japan Medical Abstracts Society search hits, we utilized 4 that matched with the set PICO

CQ H-2 : Is massage useful for chronic pain ?

Answer : We believe that massage is useful for chronic pain but from our results this time, we were unable to recommended it with certainty. When choosing a form of treatment, it is recommended that one prioritize the patient's values after taking into consideration its costs and effects. Furthermore, an important element of choosing massage is the purpose for performing a massage and the credentials of the masseur or masseuse and whether they have adequate knowledge of chronic pain or not.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : No recommendation 〔Consensus 85.0%〕

Summary of overall evidence : C (weak)

Commentary :

We investigated the usefulness of massage on patients with chronic pain but definitions of chronic pain vary widely depending on the research paper so this time we targeted "patients with pain persisting for 3 months or more" and investigated without narrowing it down particularly by disease.

To define 'massage,' we referred to the "traditional Japanese massage (anma), massage and shiatsu evidence report 2011-18 : RCT-(EAMS 2011)"[8] in our search method and Cochrane systematic review search[9] and used general manual therapy search hits. Therefore, in addition to "massage" and "shiatsu" we also included "Thai-style massage."

RCT : randomized controlled trial

Researchers have thought of a variety of forms of treatment as the control groups when considering the efficacy of massage, but this time we considered pharmacotherapy or pharmacotherapy + regular care as the control groups, in accordance with actual clinical settings. As a result, in the end we found 4 RCTs that had targeted primary headache[10], chronic headache[11], chronic tension-type headache (TTH)[12], and chronic musculoskeletal pain[13]. Not only does each disease vary, there is no uniformity to the treatment methods used in the intervention groups, and so because there were various control groups as well, we did not con-

duct a meta-analysis. In each respective research paper, pain was −0.5 [−2.8～1.78] (no significant difference)[10], −23.1 [−41～−5] (significant in the intervention group)[11], 0.44 [0.11～0.76] (significant in the intervention group)[12], and 2.77 [0.22～5.32] (significant in the intervention group)[13].

There were 2 papers that mentioned QOL, and in each respective one it was −1.07 (SD not mentioned, $P=0.02$) (significant in the intervention group)[10], 9.7 [−9.54～28.9] (no significant difference)[13].

QOL：quality of life

There was 1 paper that clearly specified adverse events；0 out of 13 patients had adverse events in the intervention group, 4 out of 13 patients had adverse events (3 cases of drowsiness, 1 case of tachycardia) in the control group[8] .

As for a balance of benefits and harmful effects, we believe that it is useful in intervention groups but the control groups are thought to be useful when thinking about costs.

Diseases were limited in this systematic review, and therefore as it does not represent chronic pain as a whole, we ended up considering the efficacy of massage on specific diseases and symptoms. As the diseases and symptoms vary and there is a small number of research studies, the quality of the evidence is low so we are unable to reach a fixed conclusion. However, depending on the relative importance of values such as treatment effects, costs and side effects, we believe that massage is a useful option for patients in both groups.

However, even if we use the single expression of “massage,” it is necessary to choose this option after distinguishing whether practitioners have or do not have a national licence to practice anma massage and shiatsu, and also for practitioners and patients to distinguish the purposes for conducting massage. In addition, this is also provided that the anma massage and shiatsu practitioner has adequate knowledge of chronic pain for treating patients.

We came up with these results but as there were few patients in each of the research studies, there were many parts in each research design which lacked transparency, so as it was difficult to obtain reliable results, we were not able to recommend it this time.

Period		2005～2019
Database		MEDLINE, Cochrane CENTRAL, NPO Japan Medical Abstracts Society
Words searched	P	Mainly chronic pain, words similar to this (intractable pain,complex regional pain syndromes etc.)
	I/C	Massage (massage, anma), shiatsu,acupressure etc./nothing specified
Limitations		Limited by publication type, PubMed CER randomized controlled trials / systematic review search filter, Cochrane RCT search filter
Selection summary		Of the 180 MEDLINE search hits, 326 Cochrane CENTRAL search hits, and 13 NPO Japan Medical Abstracts Society search hits, we utilized 3 that matched with the set PICO

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Chapter I. Multidisciplinary Treatment

: CQ I-1～CQ I-5

CQ I-1 : What is the definition of multidisciplinary treatment ?
CQ I-2 : What are the individual approaches (therapeutic interventions) included under multidisciplinary treatment ?
CQ I-3 : What kind of staff make up the multidisciplinary treatment team for managing chronic pain ? And what roles do the staff play ?
CQ I-4 : Is multidisciplinary treatment useful for chronic pain?
CQ I-5 : What is the cost-effectiveness of multidisciplinary treatment for chronic pain ?

I. Multidisciplinary Treatment

CQ I-1 : What is the definition of multidisciplinary treatment ?

Answer : Multidisciplinary treatment is a form of treatment for patients with chronic pain in which they are treated not by a single medical practitioner but by medical experts from a variety of professionals. There is no established differentiation between this term and the term 'interdisciplinary treatment' in Japan, which is used with the same meaning. According to the definition by the International Association for the Study of Pain (IASP), in both cases, specialists from various fields and occupations are engaged in treatment but with 'interdisciplinary treatment,' specialists from diverse fields and occupations work in close co-operation with each other in the decision-making process regarding the treatment policies (goals), differentiating it from multidisciplinary treatment.

IASP : International Association for the Study of Pain

Commentary :

In patients with chronic pain, as the cause of the pain and the regions it affects are diverse, having not only a physical, but also a psychological and social aspect, it is recommended that the medical practitioners' areas of specialty and what they treat in terms of chronic pain should be diverse, taking into consideration these elements (physical, psychological, social) and their interrelations[1-3]. Multidisciplinary treatment refers to a treatment intervention conducted by professionals from diverse fields and occupations.

The term 'interdisciplinary treatment' is used with the same meaning as multidisciplinary treatment. In both cases, a diverse range of specialists from various fields and occupations coordinate their efforts to treat and there is no clear line drawn between them. They are often confused in both clinical and academic settings but according to the IASP's definition, the words are differentiated according to whether the decision-making process for treatment policies (goals) is conducted by a single specialist or through shared communication[2] with other health care professionals.

To be more specific, in both instances, experts from a diverse range of fields and occupations treat patients. However, in multidisciplinary treatment, each respective specialist has his/her own treatment policies (goals) and it is not necessarily the case that each specialist directly consults other specialists face-to-face (or for example online)[2]. On the other hand, in interdisciplinary treatment, the experts from various fields and occupations together form a treatment team, communicate frequently with each other, for example face-to-face or online, and then coordinate their decision-making process regarding treatment policies (goals) and diagnosis

based on the test results[2]. Within this clinical team, they share their concepts and treatment goals based on a biopsychosocial model for pain[1,2].

With the items of multidisciplinary treatment in these guidelines, we will handle both multidisciplinary and interdisciplinary treatment, taking into consideration the differences between them. For the sake of convenience, when there is no particular explanation, we will use the term 'multidisciplinary treatment' meaning that it includes the definition of interdisciplinary treatment.

With the multidisciplinary approaches to patients with pain, we also use names that use the term 'rehabilitation' (such as multidisciplinary rehabilitation). According to the structure of an approach based on various professionals, it is the same as the definition for multidisciplinary treatment but it can be thought of as a name from the viewpoint of something that places more emphasis upon for example the recovery of disability[4].

In multidisciplinary treatment, reducing symptoms including pain is not the main objective ; it is encouraging social activity and improving quality of life (QOL). Therefore, what is important is not leaving it up to the physician to control the patient's pain, but things like encouraging patients' self-management of pain by skillfully making the most of the effects of physical activity for example, policies to encourage social activity including work, and also reducing dependence on healthcare, including pharmaceuticals[5].

QOL : quality of life

CQ I-2 : What are the individual approaches (therapeutic interventions) included under multidisciplinary treatment ?

Answer : Multidisciplinary treatment for patients with chronic pain comprises individual approaches that make the most of the respective expertise of specialists, each from a diverse range of fields and occupations, based upon a biopsychosocial model. The individual approaches implemented by each specialist vary widely such as exercise therapy, psychotherapy and pharmacotherapy.

Commentary :

As mentioned above in the definition of multidisciplinary treatment, when managing chronic pain through multidisciplinary treatment, in order to address the diverse number of causes of pain and their effects that cover physical, and psychosocial aspects, it is recommended to implement treatment while making the most of the expertise of the respective experts who hail from various professions[1-3]. Several therapeutic approaches are described below, which may be included within a multidisciplinary treatment to manage chronic pain[5-7].

1) Physical approach

QOL : quality of life

TENS : transcutaneous electrical nerve stimulation

CBT : cognitive-behavioral therapy

ACT : acceptance and commitment therapy

Multidisciplinary treatment is suited for goal-oriented treatment plans. The objectives are to improve physical capacity, lifestyle habits, quality of life (QOL) and overall health. Negative behavioral patterns accompanying pain should be changed. For example, these include advice recommending patients to be active, pacing, and various physical exercises. In addition, manual therapy, transcutaneous electrical nerve stimulation (TENS), and low-level laser therapy are sometimes used concomitantly[5-7].

2) Psychological approach

After identifying the psychological aspects that the patient has including undesirable thoughts and behaviors, a suitable intervention such as corrections targeting these thoughts and behaviors is conducted. For example, this includes education to develop a deeper understanding of the mechanisms giving rise to pain and various patterns that accompany pain, cognitive-behavioral therapy (CBT), gradual relaxation, electromyographic (EMG) feedback, graded exposure, and also mindfulness and acceptance and commitment therapy (ACT), which are called third-generation forms of CBT. With CBT in particular, specialists identify and correct non-adaptive reactions in for example cognition and behavior among chronic pain patients, and foster adaptive reactions for raising lifestyle functions including physical function. CBT is frequently used in multidisciplinary treatment for the action of maximizing the effects of the pain management[5-7].

3) Pharmacotherapy

We will leave it for another chapter to detail the drugs used in pharmacotherapy. Doctors not only select the pharmaceuticals that should be newly prescribed to patients but also evaluate, from a biopsychosocial aspect, the proper use of OTC drugs and pharmaceuticals that have already been prescribed. It is especially important to provide guidance on the suitable use of opioid analgesics. In addition, if polypharmacy (the harm of taking multiple medications at once) is an issue, the possibility of curtailing the drugs will be considered[6,7].

In addition to what has been mentioned above, after close scrutiny of its indication, various nerve blocks, acupuncture and moxibustion therapy and surgical treatment may also be introduced[6,7].

CQ I-3 : What kind of staff make up the multidisciplinary treatment team for managing chronic pain ? And what roles do the staff play ?

Answer : As mentioned above, multidisciplinary treatment involves specialists from a wide variety of fields and professionals, and assumes a variety of styles, such as a style in which specialists make treatment strategies (goals) together for the same patient, a style in which each independent specialist has his/her own re-

spective treatment strategy (goal), and also a style in which specialists coordinate their efforts through providing intrahospital referrals for the patient or referring them to other facilities.

The following outlines the general members of a multidisciplinary treatment team. However, you can make the team flexibly, according to the circumstances in each respective facility.

1) The professionals that make up the team

A multidisciplinary team for managing chronic pain is comprised of various professionals, such as medical doctors, nurses, physical therapists, occupational therapists, certified public psychologists (clinical psychologists), pharmacists, registered dietitians, and social workers (social welfare workers / psychiatric social workers)[8-11].

With the current situation in Japan, there are few facilities in which all of the above-mentioned professionals can be found in the one location ; in many cases the team is comprised of medical doctors, nurses, physical therapists and psychologists.

2) The roles of the staff

In the multidisciplinary treatment of pain, specialized staff evaluate patients with pain from the interactional physical, psychological and social aspects, consider treatment strategies, and need to conduct a multidisciplinary and comprehensive approach in coordination with each of the specialty disciplines. The multidisciplinary approach is based on the biopsychosocial model, listed in the commentary column, and the professionals who comprise the multidisciplinary treatment team first need to understand the biopsychosocial factors in each respective patient with chronic pain before attending to treatment. In indicating the roles of the staff, for the sake of convenience, it is easier to understand if we broadly divide them into a 'physical approach' and 'psychosocial approach.'

The specialties who are mainly in charge of the physical approach include doctors, physical therapists and occupational therapists. We recommend including doctors from as diverse a range of departments as possible, such as orthopedic surgeons, anesthesiologists, neurosurgeons, neurologists, physicians, rehabilitation doctors, and dentists. The specialties who are mainly in charge of the psychosocial approach include psychiatrists, psychosomatic physicians, nurses, and certified public psychologists (clinical psychologists). When necessary, staff members, especially doctors, may also have the role of coordinating with other medical members, for example doctors such as a patient's family doctor and occupational physicians, as well as public health nurses, in cases where it is difficult to attend to the patient within the same facility.

① The roles of doctors mainly in charge of the physical approach

As a specialist, they diagnose whether biological factors contribute to pain symptoms based on physical findings, neurological examination and imaging. They con-

duct swift management, conducting necessary tests to discern diseases requiring urgent attention, such as fractures and undiagnosed cancer i.e. 'red flag signs'. Based on their evaluations of the pathologies, they perform treatments such as patient education, pharmacotherapy, and nerve blocks. When conducting pharmacotherapy, careful attention needs to be given to improper use of drugs, such as polypharmacy (harm caused by taking multiple medications), keeping in mind the peculiar pain behaviors of patients with chronic pain. Furthermore, surgical therapy may be selected in some cases, after first carefully considering its applicability[9].

② The roles of psychiatrists and psychosomatic physicians mainly in charge of the psychosocial approach

They diagnose psychiatric diseases as a specialist and they implement for example a suitable pharmacotherapy to treat mental diseases that coexist with chronic pain. Furthermore, they cooperate with a psychologist to evaluate the psychosocial problems of patients with chronic pain, manage the approach and conduct treatments.

③ Nurses

Nurses manage patients for example by taking patient history and conducting self-reported questionnaires. When taking history, nurses inquire about patient's clinical history, past history of illnesses, family history and general lifestyle information, as well as information that patients are convinced is unrelated to their pain. They also collect information on basic physical findings such as patient height, weight and vital signs. When a patient receives a treatment intervention, they also provide medical assistance, such as help with examination and treatment.

They carefully observe patient behavior, consult them on the various pain-related anxieties, concerns and worries that patients have, and while listening attentively to patients' complaints, they also provide the necessary support at the same time. They also serve as a bridge or channel between the multidisciplinary team members. When necessary, they may also be in charge of educating, not only the actual patient, but also educating people accompanying the patient, such as family, on things like lifestyle habits.

④ Physical therapists/Occupational therapists

They conduct evaluations of things like physical function, and in particular musculoskeletal flexibility, muscle endurance, muscular strength and physical capacity. Subsequently, they provide guidance on stretching and muscular strengthening exercises, for the purposes of improving blood flow and muscular tone. They implement aerobic exercise such as walking and aquatic exercises, and provide guidance on how patients can practice on their own. It is important to assign the pace of activity, in other words, understand the proper amount of physical activity for each individual patient, ensuring that it does not result in strong pain and an accompanying cessation of activity for a long period of time, and provide guidance so that

the patient can continue to be active within the range for which it is comfortable for that patient and gradually increase the amount of activity. Physical therapists and occupational therapists analyze the patients' actual activities of daily living (ADL) and contents of their activities, and conduct pragmatic training with the aim of improving their social adaptability.

⑤ Certified public psychologist/Clinical psychologist

After evaluating patients' psychosocial problems through an intake interview, they share information with members of the multidisciplinary team. Furthermore, they select the suitable form of psychotherapy, such as from various forms of CBT and psychoeducation, including suitable knowledge about pain and coping methods, and they provide support to the patient and their family.

⑥ Pharmacists

They collect comprehensive information on pharmacotherapy, not just information related to pharmaceuticals, but information based on assessments by nurses, and treatment strategies by doctors, as well as the patient's physical and mental condition. And through liaising with the actual patient and people accompanying the patient, such as family, they manage the proper use of pharmaceuticals in the pharmacotherapy used for each individual patient. To be more specific, they explain the importance of maintaining strict adherence based on the prescription intentions of the physician and a correct knowledge of analgesics and occasionally may also for example assist in explanations of the time of onset for the pharmaceutical product and any pharmacological actions of the drug.

As for matters that specifically apply to patients with chronic pain, they focus on explaining the types of analgesics, especially the side effects of opioid analgesics, to ensure they are used safely. Furthermore, in cases where their pain is not eligible for pharmacotherapy, the explanations for this will be properly given, and they will avoid any unnecessary oral administration of drugs. In addition, regarding the polypharmacy problem (harm caused by taking multiple medications), information will be provided to the prescribing physician. Pharmacists listen carefully to patients' complaints, and especially in terms of pharmaceuticals, in cases where patients have not successfully conveyed information to their doctors, they will provide them with the adequate information.

⑦ Registered dietitians

In addition to support on nutrients and calories to consume, they take into consideration their circadian rhythms (chrono nutrition), provide nutritional support and basic meals for their lifestyle, and nutritional guidance for chronic pain comorbidity, such as obesity, diabetes, osteoporosis and sarcopenia. Also in cases of loss of appetite and oral hypofunction, they provide guidance to the actual patient and to family members accompanying them. Through coordinating with physical therapists, they can also calculate the necessary amount of energy the patients need to

perform exercises (physical activity).

⑧ Social worker (certified social worker/psychiatric social workers)

In cases where patients with chronic pain either are suspended from their job or lose their job and in cases where they do not receive any lifestyle support, they provide or coordinate information on the social security system. For example, they consult patients about matters relating to the social security system that they are currently receiving, including whether intractable diseases or physical/mental disabilities apply, towards assisting a transition to work (return to work), and they provide comprehensive support towards helping them return to society.

Commentary :

When managing patients with chronic pain, a 'biological model' that understands their pain as an organic disease is insufficient ; it will be difficult to achieve an improvement in the patient's pathological condition and quality of life (QOL). In other words, it is difficult to improve the pain by an etiology that simply believes it is a (single) cause for pain and just by getting rid of that (single) cause. In the multidisciplinary treatment of chronic pain, what is needed is comprehensive care, using a 'biopsychosocial model' as its foundation, which includes psychosocial factors along with organic abnormalities in the patient (biological factors). This is not about one single specialist managing the pain but specialists from various fields and members cooperating and if possible, what is needed is to regularly hold joint conferences and coordinate their efforts with treatment.[8,10,11]

QOL : quality of life

What is important is to make the most of the expertise, that is the knowledge and skills for example of each individual specialist and also launch a cooperative approach.[8–11]

When discussing the recommendations at I–4 and I–5, as a definition for 'multidisciplinary treatment' for these CQs, we assume in principle at least 2 or more different specialists performing the treatment. Moreover, we have targeted research that has investigated the treatment effects of combining at least 2 or more types of treatment (for example CBT and exercise therapy). In other words, this means we have excluded research which has investigated the effects of single treatments, such as CBT (alone) or exercise therapy (alone). Furthermore, in cases where it is unclear to mention who is performing the treatment, we have included under the multidisciplinary treatments in I–4 and I–5, the pain programs, back schools, and multidisciplinary / interdisciplinary rehabilitation, which were planned to provide multidimentional and comprehensive pain treatment, in which generally speaking several medical practitioners are involved in performing the treatment.

CQ I-4 : Is multidisciplinary treatment useful for chronic pain ?

Answer : The effects of multidisciplinary treatment on chronic pain in general and its adherence (the patients' active stance of positively undergoing treatment) depend upon their pain-related beliefs, such as catastrophizing, fear-avoidance beliefs, and self-efficacy. And there is a lack of consistency regarding the treatment effects as an outcome, such as improvement in pain intensity and improvements in disability. In other words, there is room to give further consideration regarding pathologies, within chronic pain overall, which are applicable for undergoing multidisciplinary treatment. Therefore, we will limit ourselves to making weak recommendations regarding the implementation of multidisciplinary treatment for chronic pain overall.

On the other hand, some evidence has been accumulated on some of the diseases within chronic pain. In particular, much evidence has been gathered on chronic low back pain (LBP) so we strongly recommend implementation. In addition, if further research is conducted in future on osteoarthritis, fibromyalgia, and chronic pelvic pain including chronic prostatitis, although it is possible that the certainty of the estimated effects might change, we weakly recommend conducting multidisciplinary treatment based on the grounds of the evidence available at the current stage. However, this does not mean, in the case of these diseases, that multidisciplinary treatment applies across the board for all pathologies. As the symptoms and pathologies of patients with chronic pain vary, it is essential to conduct a biopsychosocial evaluation prior to introducing treatment.

Recommendation Grade & Summary of Overall Evidence

(However, it is essential to conduct a biopsychosocial evaluation and consider whether treatment applies, before introducing treatment)

1) Chronic pain overall

Recommendation grade : 2 (weak) : Implementation is weakly recommended [Consensus 81.3%]

Summary of overall evidence : B (moderate)

2) Chronic low back pain

Recommendation grade : 1 (strong) : Implementation is strongly recommended [Consensus 100.0%]

Summary of total evidence : A (high)

3) Osteoarthritis

Recommendation grade : 2 (weak) : Implementation is weakly recommended [Consensus 88.2%]

Summary of overall evidence : B (moderate)

4) Fibromyalgia

Recommendation grade : 2 (weak) : Implementation is weakly recommended〔Consensus 100.0%〕

Summary of overall evidence : B (moderate)

5) Chronic pelvic pain including chronic prostatitis

Recommendation grade : 2 (weak) : Implementation is weakly recommended〔Consensus 94.1%〕

Summary of overall evidence : B (moderate)

Commentary :

This is something we can say about research in general which has investigated the effects of non-pharmacological treatments on chronic pain but when planning research to consider the effects of multidisciplinary treatment on chronic pain, in some cases researchers set respondent criteria for the individual disease category for those displaying chronic low back pain (LBP) and fibromyalgia. And in many cases research has elected to target 'chronic pain' comprehensively defined as pain persisting for 3 months or longer or a recurrent pain. According to a systematic review by Thompson et al. based on 10 RCTs, the adherence to multidisciplinary rehabilitation for general chronic pain (the patients' active stance of positively undergoing treatment) and the effects of the treatment depended upon their pain-related beliefs such as catastrophizing, fear-avoidance beliefs, and self-efficacy, affecting our ability to recommend the treatment[12].

RCT : randomized controlled trial

There are many reports of multidisciplinary treatment of chronic LBP, from the perspective of not only patients' subjective symptoms, such as pain, but also rehabilitation which placed emphasis on an improvement in functional aspects. According to a systematic review[13] conducted in 2018, based on 13 RCTs, where the outcomes were an improvement in the intensity of pain and degree of daily lifestyle dysfunction 1 year after intervention, the effects of a multidisciplinary rehabilitation effect on chronic LBP were significant, along with having a moderate level of effect. When the outcome was return to work, 3 of the reports indicated that 1 year after multidisciplinary rehabilitation, there was a significant positive correlation with return to work as an outcome. When sick leave due to pain was the outcome, the results were the same, and in terms of the number of days absent due to sickness during the follow-up period, 3 reports[13] gave a moderate to high amount of effect due to multidisciplinary rehabilitation. Furthermore, according to a 2014 Cochrane review, multidisciplinary rehabilitation was found to be superior in terms of improvement in analgesic effect and daily life dysfunction for patients with chronic LBP, as compared to standard treatment. However, as the size of the effect was small, researchers stated that a balance should be obtained between the amount of time required for conducting the treatment and the costs of the equipment and facilities. Furthermore, the researchers were unable to assertively conclude how ef-

fective it will be in improving symptoms but at the same time, concluded that multidisciplinary treatment is recommended for patients with chronic LBP exhibiting psychosocial factors[14]. Furthermore, in terms of exercise-related fear, which can become a problem when conducting exercise, a systematic review conducted in 2019[15] reported a significant improvement in patient's fear of falling over (compared with a group who underwent physical therapy alone) and patient kinesiophobia (compared with a group of patients undergoing regular treatment or exercise), through multidisciplinary intervention.

In a systematic review conducted in 2016 regarding the effects of multidisciplinary treatment on osteoarthritis, RCTs on osteoarthritis in a large number of joints were considered, and although they concluded that multidisciplinary treatment was suitable for primary care, only 4 RCTs were eligible for consideration[16]. In the recommendations for treating hip and knee osteoarthritis (OA) through non-pharmacological treatment, published in 2013 by the European League against Rheumatism (EULAR), they recommended a multidisciplinary biopsychosocial approach from the initial stage evaluation, and recommended providing individualized medical treatment after taking into consideration the risk factors of OA. They recommended providing education on OA, pacing for the amount of activity, providing a daily exercise program tailored to the individual patient and a multidisciplinary treatment with weight control[17].

OA : osteoarthritis

EULAR : European League against Rheumatic Diseases

In the 2016 EULAR recommendations for fibromyalgia treatment, they described the recommendation grades based on a detailed review they undertook on 107 citations that were selected from a total of 2,979 references[18]. In the recommendations, they concluded that exercise therapy is the only treatment they can strongly recommend on the grounds of their meta-analysis as a guideline. Furthermore, in the same recommendations, Häuser et al. determined the recommendation grades based on a meta-analysis conducted on 9 RCTs and including a total of 1,119 patients[19]. The results of the meta-analysis showed that compared with a waiting list group, multidisciplinary treatment had a mild effect on pain and fatigue and compared with regular treatment and education, multidisciplinary treatment also showed to have a relaxation effect. However, these effects were limited to short periods of time and because they were not effective over the long term, they gave a weak recommendation to multidisciplinary treatment used alone. On top of this, in the same recommendations, as an expert opinion, they stated that focus should be put on education, exercise, and other non-pharmacological treatments (CBT, mindfulness, acupuncture and moxibustion therapy, manual therapy etc.) for the initial stages of treatment. In addition, if there is no improvement through these forms of treatment and individualized treatment is considered as the next stage, they mention psychotherapy for cases of mood disorder or cases for whom training about coping proved to be ineffective, and pharmacotherapy for strong pain or sleep dis-

order. Moreover, they mention considering the implementation of a multimodal rehabilitation program alone or in combination "for severe disability." [18] Regarding fibromyalgia, we also wish to refer you to CQ Q-7.

According to a meta-analysis of the effects of treatment for chronic pelvic pain including chronic prostatitis without any accompanying bacterial infection, sample size was small in individual research studies and treatment protocols varied but researchers found that exercise therapy in the pelvic floor muscles alone or used in combination with CBT was significantly effective[20]. In this meta-analysis, the National Institutes of Health Chronic Prostatitis Symptom Index (CPSI) score, which is an international evaluation scale for chronic prostatitis/chronic pelvic pain syndrome, was used and improvement by 6 points was regarded as a clinically-significant improvement. After an analysis based on the data from 8 reports, including a total number of 280 patients who met the eligibility criteria, the CPSI score had improved by 8.8 points (95% CI 7.5-10.1, $p<0.001$)[20]. There has been little research conducted for the purpose of investigating the effects of multidisciplinary treatment on chronic pain patients in Japan. Therefore, in summarizing the recommendation grades and total evidence for these current guidelines, as mentioned above, we have no choice but to make a judgment based on the research results that have been mainly conducted in foreign countries. If additional further research is conducted in future on Japanese patients, there is a possibility that our degree of certainty regarding its estimated effect may also change.

CPSI : the National Institutes of Health Chronic Prostatitis Symptom Index

CQ I-5 : What is the cost-effectiveness of multidisciplinary treatment for chronic pain ?

Answer : As mentioned above in CQ I-4, we recommend conducting multidisciplinary treatment for chronic pain but as of 2020, it is not covered under the health insurance system in Japan. There is increasing interest in its cost-effectiveness and the costs of implementation when treatment is introduced. In terms of the cost-effectiveness of multidisciplinary treatment for chronic pain, there are few disease categories of chronic pain that are being considered for research. There is a certain level of evidence that has been accumulated on the cost-effectiveness of multidisciplinary treatment for chronic low back pain (LBP), traumatic cervical syndrome and non-specific neck pain, but it is still insufficient.

Commentary :

From an analysis of cost-effectiveness, in cases where the costs of a new treatment increase compared with a conventional treatment, an incremental cost-effectiveness ratio (ICER) is used to evaluate whether the effect is worthwhile or not.

To be more specific, ICER is additional costs required to extend 1QALY, and if this is below the ceiling value (willingness-to-pay), it is concluded to be cost-effective. The ICER ceiling value varies from one country and study to the next ; in the US, a figure of USD50,000～USD10,000 can be used, in the UK, it is £20,000～£30,000 and in Japan, is 5～6 million yen. For more details, we wish to refer you to the explanation of the terms later on.

In a systematic review that considered multidisciplinary treatment for chronic LBP, they included 3 RCTs with cost-effectiveness as an outcome, and although the cost-effectiveness of multidisciplinary treatment for chronic LBP was superior, they claimed that evidence was insufficient[13]. In a systematic review[21] that targeted 26 RCTs on the cost-effectiveness of LBP that complied with US LBP guidelines, they considered the individual effects of treatments such as multidisciplinary rehabilitation, exercise therapy, and cognitive-behavioral therapy, and when used in combination, on acute or chronic LBP. These 26 RCTs included 3 RCTs from the UK which compared treatments provided by general practitioners (GPs) and treatments that conformed with the definition of multidisciplinary treatment in the above-mentioned **CQ I-5**. Compared with the single treatments performed by GPs over a period of 18 months, the ICER when exercise therapy and behavior therapy (BT) counselling were added to the treatments provided by GPs came to £2,847 per 1 QALY[22]. Compared with the GP treatments conducted over 15 months, the ICER for education using CBT and exercise therapy came to £5,000 per 1 QALY[23]. Furthermore, in an RCT conducted in the Netherlands, compared with physical therapy conducted alone, the ICER for a back school combination based on exercise therapy and CBT principles came to £5,141 per 1 QALY[24].

In a systematic review conducted by a research team from Ontario, Canada, considering the cost-effectiveness of a treatment intervention method for traumatic cervical syndrome and cervical pain disorder, they considered 6 research papers that matched the eligibility criteria. They claimed that for the grades I-III 'whiplash-associated disorder', categories for the severity of traumatic cervical syndrome, education was more cost-effective, and for cervical pain disorder, multidisciplinary treatment that included a combination of advice and exercise therapy as well as manual therapy was superior in terms of their cost-effectiveness[25]. In this systematic review, interventions conducted solely by a physical therapist, which included advice, exercise therapy and manual therapy, were called 'multimodal care.' In these research studies, there is a possibility that treatment was not conducted by 2 or more people from 2 or more different occupations, which is our definition of multidisciplinary treatment in these guidelines, but in Japan, interventions by a physical therapist are conventionally conducted according to a physician's guidance so these research papers were also included as ones relating to multidisciplinary treatment in Japan.

In an RCT on traumatic cervical syndrome in an emergency department in the UK, the results did not support the cost-effectiveness of multidisciplinary treatment ; they implemented a 2-stage intervention targeting patients with acute pain within 6 weeks of injury, and of these patients who displayed symptoms 3 weeks or more after receiving treatment. Standard advice given orally by expert practitioners, such as emergency department physicians, and also advice based on pamphlets for the acute stage was found to have superior cost-effectiveness than guidance on activating their behaviors (a special textbook was used, they were encouraged to lead a regular life and exercise, and take analgesics not only when needed but regularly, and they were advised not to use a neck / cervical collar). After 3 weeks, single evaluation and advice given by a physical therapist was found to be more cost-effective than multidisciplinary treatment that introduced physical therapy for 8 weeks, but they did not calculate its ICER[26]. However, in Japan, in the case of patients with traumatic cervical syndrome who are being treated in the acute state by a physician from an emergency department, assuming that it is not common to provide advice using pamphlets and consulting them on how to prevent protracted pain, we cannot say that the results of this RCT negate the cost-effectiveness of multidisciplinary treatment for cases of traumatic cervical syndrome in Japan.

In a 2006 RCT conducted in Germany on patients with chronic neck pain, adding acupuncture to a standard treatment was found to be more cost-effective, and compared with a standard treatment, the ICER was CAD 23,443 per 1QALY[27]. In a 2007 RCT conducted in the UK, targeting patients aged 18 years and over with non-specific neck pain (pain duration was not defined), multidisciplinary treatments (combination of advice and exercise therapy) was found to be more cost-effective from the healthcare beneficiary's point of view than the one in which passive hyperthermic treatment or manual therapy was added to the above[28].

＊Explanation of Terminology

QALY : quality-adjusted life year

This is a common method for measuring disease burden ; a method in which the 2 aspects of survival, quantity and quality, are evaluated. It is used as a method for economically evaluating the cost-effectiveness of a medical practice. It is an indicator that considers the number of years of survival and the quality of life (QOL). It represents one's QOL with the pathology as a 'utility value,' in which a perfectly healthy condition is represented as '1', and death as '0' and then it is calculated by multiplying this figure by the number of years of survival. The higher the value, the more effective it is considered to be.

ICER : incremental cost-effectiveness ratio

For the treatment in question, this is the additional cost required in order to extend it by 1 QALY through introducing the treatment. It is calculated by dividing the increase in cost by the amount of improvement (increase in effect) as an outcome. The lower the ICER figure, the 'more cost-effective' the treatment is deemed to be.

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Chapter J. Chronic Low Back Pain

: CQ J-1～CQ J-9

CQ J-1 : How to define low back pain (LBP) ?
CQ J-2 : What is the pathology of low back pain (LBP) ?
CQ J-3 : Is chronic low back pain (LBP) related to lifestyle habits ?
CQ J-4 : Is there any relation between chronic low back pain (LBP) and one's occupation ?
CQ J-5 : Are psychosocial factors related to chronic low back pain (LBP) ?
CQ J-6 : Which elements are important when evaluating chronic low back pain (LBP) ?
CQ J-7-1 : Are serotonin-noradrenaline reuptake inhibitors (SNRI) useful for chronic low back pain (LBP) ?
CQ J-7-2 : Is tramadol useful for chronic low back pain (LBP) ?
CQ J-7-3 : Are nonsteroidal anti-inflammatory drugs (NSAIDs) useful for chronic low back pain (LBP) ?
CQ J-8 : Is exercise therapy useful for chronic low back pain (LBP) ?
CQ J-9 : Are patient education and behavioral psychology approaches useful for chronic low back pain (LBP) ?

J. Chronic Low Back Pain

CQ J-1 : How to define low back pain (LBP) ?

Answer : The site of the low back is defined as 'located on the rear side of the trunk, situated between the 12th rib and the lower end of the gluteal sulcus, and pain must persist for at least 1 day or more. This pain may or may not entail pain diffusing to either one or both of the lower limbs.'

Commentary :

The term 'low back pain' is a medical term represent the 'symptoms', and so because it does not refer to 'the name of the disease', there are many vague parts to this definition. It is difficult to define unambiguously, so the definition describes the 3 viewpoints of site of pain, period of illness and pathology according to the 'Guidelines for Managing Low Back Pain (2019)'[1].

1) Site of pain

It is located on the rear side of the trunk, is situated between the 12th rib and the lower end of the gluteal sulcus, and pain must persist for at least 1 day or more. This pain may or may not entail pain diffusing to either one or both of the lower limbs[2]. What is called 'buttock pain' may possibly include pain derived from the nerve root. Low-back pain sometimes entails nerve root or cauda equina type lower-limb symptoms (pain and numbness), and lower-limb pain which is called 'referred pain.'

2) Period of illness from onset

There is a respective definition for each period from time of onset : acute LBP, subacute LBP, and chronic LBP. The definition that chronic LBP is 'LBP that persists for 3 months or longer' has basically been established[3]. On the other hand, LBP less than 1 month old since time of onset should be classified as acute or subacute but there is no consistent viewpoint on this. However, acute LBP is generally defined as pain less than 4 weeks old since onset[4]. Between acute LBP and chronic LBP we have what is called subacute pain. This corresponds to LBP persisting for some where between 4 weeks and less than 3 months since onset.

3) Pathology

LBP is caused by an impairment of anatomical tissue, which mostly makes up the spine. In other words, this includes intervertebral discs, the facet joints, the nerve root, muscles, fascia and ligaments. These kinds of tissue are impaired by various disorders and trauma, leading to the onset of LBP. To be more specific, it can be classified into spinal-derived, neuropathic, viscerogenic, angiogenic, psychosocial, and other classifications.

The following four differentiations regarding the origin of LBP are especially necessary : 1) tumor (primary, metastatic spinal/spinal cord tumor etc.) ; 2) infection (pyogenic spondylodiscitis, spinal caries etc.) ; 3) fracture (vertebral fracture etc.) ; 4) lumbar disease with severe neurological symptoms (lower-limb paralysis, lumbar disc herniation and lumbar spinal stenosis with neurogenic bladder and rectal dysfunction).

When differentiating the underlying cause, it is also important to consider whether the LPB arises from one of these tissues that make up the spine. In other words, this includes LBP derived from the intervertebral discs, the facet joints, muscles, fascia, nerve root or ligaments. Many of them are affected by regressive changes caused by aging.

CQ J-2 : What is the pathology of low back pain (LBP) ?

Answer : There are various causes of LBP : spinal-derived, neuropathic, viscerogenic, angiogenic, psychosocial, and other classifications. In terms of the anatomical origins of the pain, LBP originates from for example the facet joints, muscles, fascia, intervertebral discs, sacroiliac joints, hip joints, and spinal alignment.

Commentary :

The origins of low back pain (LBP) can be classified into spinal-derived, neuropathic, viscerogenic, angiogenic, deriving from psychosocial factors and other causes. LBP derived from the spine includes spinal tumor, spinal infection, spinal trauma, lumbar disc herniation, lumbar spinal stenosis, lumbar spondylolysis/isthmic spondylolisthesis, lumbar degenerative spondylolisthesis, osteoporosis, ankylosing spondylitis, among others. The origin of the anatomical pain includes the facet joints, muscle, fascia, intervertebral discs, sacroiliac joints, and hip joints. Furthermore, there is LBP caused by spinal alignment such as adult spinal deformities (kyphosis, scoliosis) with a large variety of pathologies. In particular, LBP that accompanies regressive changes is not limited to one single origin of pain ; it is not infrequent for several causes to be present. These diverse causes can be broadly categorized into two groups from a different perspective. One group consists of pathologies for which diagnostic methods and treatment have already been established and this applies to for example spinal tumor, spinal infection, spinal trauma, lumbar disc herniation, and urinary tract stones. The other group consists of pathologies for which diagnostic methods and treatment have not yet been sufficiently established. This applies to LBP caused by muscles, fascia, intervertebral discs and psychosocial factors. In order to further clarify the pathology, in addition to approaches to the lumbar spine, extensive research is also required on other surrounding tissue

and upper tissue, or in other words pain from the lumbar spine to the brain. With the lumbar spine, the search for the mechanisms that develop pain is underway, as well as evaluations of motor system function such as the intervertebral discs, the vertebrae, and trunk muscles. As for the pain itself, research is being conducted on the posterior horn of the spinal cord, dorsal root ganglion, nociceptors and pain fibers. In addition, in the brain researchers are also analyzing cerebral functions in relation to pain.

CQ J-3 : Is chronic low back pain (LBP) related to lifestyle habits ?

Answer : Researchers have observed that low weight and obesity are related to the risk of onset of LBP. Maintaining a healthy weight is recommended. Researchers have indicated a relationship between smoking and drinking alcohol and the risk of LBP onset and its prevalence rate. In order to prevent LBP, we recommend leading a healthy lifestyle which incorporate a moderate amount of exercise.

Commentary :

There is little research with high-level evidence on the relationship between lifestyle habits and LBP. In a meta-analysis on weight control, they observed a low relationship between low weight and the prevalence rate of LBP, compared with standard weight. As for being overweight or obese, researchers also recognized a low relationship between being overweight and the prevalence rate of LBP (OR1.37 [95%CI 1.09～1.71]). In addition, they recognized a low relationship between a BMI of 30 or above and the prevalence rate of LBP, compared with those with a BMI under 30. There is also a meta-analysis on being overweight and obese as a risk factor for LBP. That is to say, maintaining a regular weight is related to the prevention of LBP and its prevalence rate[5-10]. Researchers recognized a low risk of onset of LBP if either the patient has a lower weight than standard (BMI 18.5 ～ 25.0) or is not obese. Therefore, we recommend maintaining a healthy weight.

We identified 6 research studies related to the prevalence rate of LBP and smoking. Researchers considered and compared categories by classifying subjects based on the number of days smoked / week, targeting non-smokers, smokers, and ex-smokers. In a meta-analysis of smokers and non-smokers, few non-smokers tended to have LBP (OR1.10 [95%CI 0.78～1.57]), and they did not notice a relationship between whether patients had a history of smoking or not. Moreover, they showed that there was a relatively higher complaint rate of LBP among smokers, than among non-smokers and they indicated that this trend was strong among young people[5,8,9,11,12].

Researchers also indicated a relationship between alcohol intake and LBP. They observed a weak relationship between the frequency of alcohol intake and the prevalence rate of LBP (OR2.62 [95%CI 1.65～4.16])[5,13,14]. However, to date there is a limit to the number of research studies reported and the number of patients targeted (in each study), and therefore one must be careful when interpreting the results.

Researchers have also demonstrated a weak relationship between the effects of daily exercise and LBP. In a research study comparing a group of patients who do not exercise with an exercise group, there was an elevated risk of LBP in the group who did not do exercise[5] but as it was a small-size research study, they did not find a relationship between the two[15]. In all this research, there is a limit to the number of research studies included and the quality of the research so one should consider them carefully. In terms of improving LBP and physical dysfunctions related to LBP, there is a connection between exercise and prevention and improvement of LBP. Therefore, we recommend healthy lifestyle habits which incorporate a moderate amount of exercise in order to prevent LBP[5,7,15].

CQ J-4：Is there any relationship between chronic low back pain (LBP) and one's occupation ?

Answer： Although there is moderate-level evidence suggesting a relation between occupations with a high physical burden (physically-demanding jobs) and LBP, we cannot necessarily identify any poor posture or jobs while working as independent factors for LBP. Work and psychosocial factors at the workplace are related to the onset and prevention of LBP.

Commentary：

Regarding LBP and occupation, there are many reports about the burden on the lower back from specific occupations and its relationship to the onset of LBP. According to epidemiological surveys in Japan on LBP and occupation, researchers reported for example 71～74% in the transport industry,69% in cleaning, 46～65% in nursing, and 63% in aged care[16-18], therefore heavy labor which has a high physical burden is a risk factor in the onset of LBP. Furthermore, in a report on the prevalence rate of LBP in 4 types of industry in the Tokyo Metropolitan Area (deskwork, nursing, sales, transportation), the prevalence rate (of LBP) was higher in nursing and transportation, occupations with a higher workload, compared with deskwork and sales.

In a systematic review of LBP and occupation in relation to physical activity, there was a recognizable correlation between labor involving carrying heavy items

and lifting and the onset of LBP. Researchers observed a strong correlation between movements involving lumbar flexion, rotation, and forward movements and the onset of LBP[19]. In a meta-analysis on LBP and occupation, researchers also observed a correlation between farm work and nurses lifting patients and LBP[20,21]. In a longitudinal research meta-analysis study on work involving the lifting of heavy objects and LBP, they reported that the weight of the heavy objects and the frequency of lifting significantly increased the onset of LBP[22]. As seen above, although we recognize a medium-level of evidence, there are many reports where researchers were not necessarily able to identify poor posture or labor while working as an independent factor of LBP[23-29]. Some papers have also reported on the difficulty of evaluating the relationship between physical burden due to occupation and LBP[30].

There have been reports on the psychosocial factors in the workplace relating to the onset of LBP. Level of satisfaction with work, the monotony of work, relationships with others at work, size of workload, mental stress, self-evaluations of one's ability at work, each of them has a strong relationship to the future onset of LBP[31]. Poor levels of satisfaction with work, a depressive state, low sociability, fear-avoidance beliefs (a destructive mindset in which the person is convinced the situation will get worse and worse without any particular reason) have been cited as psychosocial poor prognostic factors for LBP[32].

In research that has focused on "non-specific LBP that is an impediment to work," risk factors for new incidences of LBP are a history of LBP, and lifting heavy objects with a weight of 25 kg or more, frequent lifting (more than half of one's daily work), and additionally, working for more than 60 hours/week and high stress from human relationships in the workplace[33,34]. Furthermore, researchers have cited that risk factors for prolonged or chronic LBP are dissatisfaction with work or lifestyle, low social support, depression, anxiety the psychosocial factors of somatization, low expectations that LBP will improve and working for more than 60 hours/week[35,37].

In a Cochrane review, only about half the research papers in question had investigated in detail the prognostic factors for LBP. As information about patient's overall health, social support, and work-related conditions were often lacking, accurate and forward-looking RCTs will need to be conducted in future[38].

CQ J-5：Are psychosocial factors related to chronic low back pain (LBP)？

Answer： Psychosocial factors are related to the intensity of pain, dysfunction and prognosis.

Commentary：

In the field of primary care, there is a systematic review which has analyzed the psychosocial factors related to the transition from acute LBP to chronic pain from the 3 domains of social/occupational factors, psychological factors and cognitive/behavioral factors. Researchers cited that risk factors included the existence of compensation issues, depression, psychological distress, passive coping and fear-avoidance beliefs as individual factors. On the other hand, occupation, education level, social status, level of job satisfaction, and social/occupational factors did not show an effect on the prognosis of LBP[39].

In a systematic review on the effects of catastrophizing on the treatment of non-specific LBP, catastrophizing did have an effect on treatment, on the intensity of LBP, its persistence, and dysfunction[40]. In each of the respective stages, the acute stage, the subacute stage and chronic stage, catastrophizing affected intensity of LBP and dysfunction[41].

In a systematic review on how fear-avoidance beliefs affect the prognosis of non-specific LBP, fear-avoidance beliefs elevated the risk of people taking sick leave or people being unable to return to work in the subacute stage (4 weeks ～ 3 months after onset), and was a prognostic factor in poor clinical outcomes. Therefore, early-stage treatment interventions to reduce fear-avoidance beliefs prevent delays to improvements in LBP and prevent it from becoming chronic. However, in chronic LBP, we cannot say that it is a prognostic factor that regulates the outcome of LBP[42].

In a systematic review of forward-looking cohort research studies on the psychological predictive factors on the transition from acute or subacute LPB to chronic LBP, distress, depression and somatization were found to be involved in the transition to chronic LBP[42]. In addition, there have been reports that depression is a risk factor for LBP[43-45].

There is a wide variety of psychosocial factors：there are social factors such as work, education level, and social status, social factors such as compensation issues, psychological factors of which depression is a typical example and also distinctive thoughts on pain such as catastrophizing and fear-avoidance beliefs and factors related to cognition and behavior such as passive coping. It is believed that these factors act either independently or mutually. We must also bear in mind how psychosocial factors may vary depending on patients' outcomes such as intensity of LBP, period of illness, history of surgery, dysfunction due to LBP, quality of life (QOL) and activities of daily living (ADL), among others.

CQ J-6：Which factors are important when evaluating chronic low back pain (LBP)？

Answer： We need to be careful of red flags, in which severe spinal diseases (tumors, infections, fractures etc.) are also suspected to be present. When red flags and neurological symptoms are present, physicians actively conduct imaging studies such as X-ray photography and MRI, and blood biochemistry, striving to identify the underlying disease. Evaluations are made from a variety of aspects such as intensity of pain, quality of pain, QOL, ADL and psychosocial factors. Images are looked at from the point of view of whether they can address the functional abnormality that can explain the patient's complaint.

Commentary：

1) LBP triage[1)]

What is necessary during the first consultation with an LBP patient is that by carefully taking patient history and conducting a physical examination, the following 3 diagnostic triage can be performed accurately.

① LBP with red flags (Table J-1) present, severe spinal diseases (tumors, inflammation, fractures etc.) are suspected to be also present；

② LBP with neurological symptoms；

③ LBP other than 1 or 2 above.

2) Confirmation of neurological symptoms[1)]

When patients do not have a clear awareness of their lower-limb symptoms, it is important to conduct tests of their lower limb deep tendon reflexes, perceptions and muscular strength to prevent any pathologies from being overlooked. In terms of neurological symptoms, physicians should evaluate the presence or absence of severe nerve deficiency symptoms accompanied by rapidly progressive or a clear weakness in muscular strength, and bladder and rectal dysfunction. Researchers have indicated that urinary retention in particular accompanies cauda equina syndrome. Symptoms of radiculopathy complications are indicated if the following points are present：

- Single lower-limb pain is stronger than LBP
- Pain diffusing to the feet and toes
- Numbness at the same site and sensory paralysis
- When they test positive to a straight leg raising (SLR) test

When the above-mentioned red flags or neurological symptoms are present, physicians actively conduct imaging studies such as X-ray photography or MRI and blood biochemistry, striving to identify the underlying disease.

3) Evaluation methods of specific QOL for LBP [Note J1]

The RDQ (Roland-Morris Disability Questionnaire)[47)], the ODI (Oswestry Low

Note J1：Refer to Chapter B Table B-3

Back Pain Disability Questionnaire)[48], and JOABPEQ (JOA Back Pain Evaluation Questionnaire)[49] are used as specific QOL scales for LBP diseases.

4) Evaluation of psychosocial factors

Chronic pain and psychosocial factors are closely related, and so when evaluating the pathology, physicians needs to evaluate the psychological factors and social (environmental) factors at the same time. As for social factors related to LBP, researchers have cited culture, family and social support, social status, education, employment management and labor relations, the unemployment situation, early retirement, and lawsuits/litigation. One needs to be careful in cases of LBP involving compensation issues such as traffic accidents and work-related injuries.

When evaluating psychosocial factors, one must not depend upon the subjective evaluations of a medical practitioner but must evaluate them objectively. Useful tools for evaluating include the Hospital Anxiety and Depression Scale (HADS)[50,51] and the Pain Catastrophizing Scale (PCS)[52,53], the Fear-Avoidance Beliefs Questionnaire (FABQ)[54,55] Subgrouping for Targeted Treatment Screening Tool (STarT Back)[56,57]and the Brief Scale for Psychiatric Problems in Orthopedic Patients (BS-POP)[58,59].

5) Physical findings

On a physical examination, physicians can further differentiate pathologies assumed from taking patient history ; it is a means of confirmation. In order to avoid anything being overlooked on the examination, it is important to make standard protocols.

a. Palpation

Physicians check the presence or absence of knock pain on spinous process and tenderness on paraspinal muscles. If there is knock pain on spinous processes, one must bear in mind the possibility of inflammation such as infection or vertebral fracture at this level.

b. Spinal findings

Physicians also check motion limitations such as when the lumbar spine is bending forward or backwards. They confirm what kinds of symptoms manifest with what particular postures or actions. When patients are restricted in bending forward, and the posterior or lateral side of the lower leg induces radiating pain, then a herniated disc of the lower lumbar spine is suspected. If a patient has restrictions in bending backwards with reappearing lower-limb pain and numbness, then one suspects spinal stenosis and a herniated disc of the upper lumbar spine due to spondylosis and spondylolisthesis. When patients test positive to the Kemp test, then one suspects radiculopathy due to lateral recess stenosis of the spinal canal. In other words, researchers often observe positive findings with nerve root type lumbar spinal stenosis and lumbar disc herniation.

c. Differentiating between the pelvic region and hip joint disorders

ADL : activity of daily living

psychosocial factor

MMPI : Minnesota Multiphasic Personality Inventory

HADS : Hospital Anxiety and Depression Scale

PCS : Pain Catastrophizing Scale

SDS : Self-rating Depression Scale

BS-POP : Brief Scale for Psychiatric Problems in Orthopaedic Patients

When pain is evoked on the Patrick test, then one suspects hip joint disease. In addition, when pain is evoked on the Newton test, and Gaenslen test, then one suspects sacroiliac joint-derived LBP. In the one-finger test, the patient him/herself points to the site exhibiting the strongest pain and when they point to the posterior superior iliac spine and in the vicinity of the ilium side, one suspects pain derived from the sacroiliac joints.

d. Evaluating motor function

For conducting a global evaluation of motor function such as walking ability and balance, useful tests are the Timed-Up-and-Go test (TUG)[60], and for evaluating exercise tolerance, there is the 6-minute walking test (6MWT)[61]. Furthermore, as there is the risk of overlooking the pathology just from examining a patient at rest for LBP which mainly occurs while moving, the tester should walk together with the person taking the test, the walking load test is useful for evaluating subjective symptoms when they manifest and neurological findings[62].

6) Diagnostic imaging

Diagnostic imaging such as X-ray imaging, myelography, MRI, CT, CT myelography, discography, CT discography, radiculography and facetgraphy are conducted to clarify the morphological causes. According to the Guidelines for Managing Low Back Pain (2019), X-ray image is claimed to be meaningful for the initial diagnosis of LBP in patients with this condition[1]. However, imaging is not essential during the first consultation for non-specific LBP patients without radiculopathy. With patients with red flags and neurological symptoms, after X-ray imaging, we recommend conducting an MRI. The images are needed just from the viewpoint of deciding whether they are attending to the functional abnormality which can explain the patient's complaint. And where necessary, we recommend using several diagnostic imaging in combination.

CQ J-7-1 : Are serotonin-noradrenaline reuptake inhibitors (SNRI) useful for chronic low back pain (LBP) ?

SNRI : serotonin-noradrenaline reuptake inhibitor

Answer : SNRI is effective on pain, QOL and dysfunction in patients with chronic LBP. On the other hand, there tend to be many adverse events.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : Implementation is weakly recommended 〔Consensus 81.0%〕

Summary of overall evidence : B (moderate)

Commentary：

The results of a systematic review found 9 references that met the eligibility criteria, and 4 of them were used for meta-analysis[63-66]. The indicators used for the meta-analysis include the Roland-Morris Disability Questionnaire (RMDQ) [lumbar function], EQ-5D [QOL], Brief Pain Inventory (BPI-S) [degree of severity of pain], BPI-I [degree of impairment due to pain]. In each of the outcomes, SNRI showed a significant improvement in these outcomes, as compared with the placebo. However, even though it was statistically significant, degree of improvement was small, so we are unable to say that the effect exceeded a difference that was clinically important difference and the certainty of the synthesized evidence is weak.

QOL：quality of life

Adverse events include nausea, dipsia, and loss of appetite and the degree of these adverse events ranged from mild to medium. In a meta-analysis in the 'Guidelines for Managing Low Back Pain (2019)' on the adverse events due to SNRI compared with a placebo, researchers did not observe a significant difference between the two gorups but adverse events were frequent in the SNRI group[1].

In a calculation of the quality-adjusted life year (QALY), which included the side effects and cost of treatment, and incremental cost-effectiveness ratio (ICER), comparing duloxetine and an existing drug, researchers reported that duloxetine was more cost-effective[67,68].

QALY：quality-adjusted life year

ICER：Incremental cost-effectiveness ratio

SNRI received a recommendation grade of 1 for chronic pain in general but (refer to **Chapter C**), as it has a small effect only on chronic LBP, its recommendation grade only came to a 2. However, in research that is used for analysis, we must pay attention to the fact that there are diverse pathologies for chronic LBP which are targeted. For local primary chronic pain according to the chronic pain categories of the International Association for the Study of Pain (IASP), there is a possibility of getting a stronger effect so physicians should consider actively using SNRI according to the patient's condition.

Period		2005～2019
Database		MEDLINE, Cochrane CENTRAL,NPO Japan Medical Abstracts Society
Words searched	P	Mainly chronic low back pain, similar words to this (back pain, not acute, refractor, intractable, resistan, etc.)
	I/C	SNRI, serotonin, duloxetine, milnacipran, venlafaxine etc./nothing specified
Limitations		We limited the test design to randomized controlled trial, meta-analysis, systematic review including chronic low back pain, and SNRI in the title
Selection summary		Of the 11 MEDLINE search hits, and 34 Cochrane CENTRAL search hits, we used 4 of them that matched with the set PICO.

CQ J-7-2：Is tramadol useful for chronic low back pain (LBP)？

Answer： Tramadol is effective for the pain and dysfunction due to chronic LBP. On the hand, there are many adverse events.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : Implementation is weakly recommended 〔Consensus 100.0%〕

Summary of overall evidence : B (moderate)

Commentary :

The results of a systematic review were 6 references met the eligibility criteria and 4 of the references were used for meta-analysis[69-72]. The items used for the meta-analysis were the Roland-Morris Disability Questionnaire (RMDQ)〔lumbar function〕, and the Short-Form McGill Pain Questionnaire (SF-MPQ)〔pain evaluation scale 〕, and in each of the outcomes, researchers indicated that tramadol used alone (or tramadol / acetaminophen used in combination) significantly improved these outcomes compared with the placebo. On the other hand, the degree of improvement was small so we are unable to say whether the effect exceeded clinically important difference and judged that the certainty of the synthesized evidence was low.

Adverse events included nausea, vomiting, dizziness, drowsiness, constipation, headache and insomnia, with adverse events significantly more frequent when tramadol was used alone (or tramadol/acetaminophen were used in combination). In a meta-analysis from the 'Guidelines for Managing Low Back Pain (2019)' on adverse events from tramadol, they found that the frequency of adverse events was significantly more frequent from tramadol as compared with the placebo[1].

Period		2005～2019
Database		MEDLINE, Cochrane CENTRAL,NPO Japan Medical Abstracts Society
Words searched	P	Mainly chronic low back pain, similar words to this (back pain, not acute, refractor, intractable, resistan, etc.)
	I/C	Tramadol etc./nothing specified
Limitations		We limited the test design to randomized controlled trial, meta-analysis, systematic review including chronic low back pain, and tramadol in the title
Selection summary		Of the 5 MEDLINE search hits, and 24 Cochrane CENTRAL 24 search hits, we used 4 of them that matched with the set PICO.

CQ J-7-3 : Are nonsteroidal anti-inflammatory drugs (NSAIDs) useful for chronic low back pain (LBP) ?

NSAIDs : nonsteroidal anti-inflammatory drugs

Answer : NSAIDs are effective on the pain intensity of chronic LBP and also dysfunction due to chronic LBP. However, they have a small effect.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : Implementation is weakly recommended 〔Consensus 95.0%〕

Summary of overall evidence : B (moderate)

Commentary：

In the results of a 2016 Cochrane systematic review[73], researchers found 6 placebo-controlled study references (1,354 patients) that met the eligibility criteria and used them for a meta-analysis. The items used in the meta-analysis were VAS [pain indicator], RMDQ [function indicator], and adverse events. Research indicated that NSAIDs significantly improved the outcomes of pain and function as compared with the placebo, but the degree of improvement was small so we are unable to say whether the effects exceeded a difference that was statistically significant and assessed that the certainty of the evidence was low. According to the IASP's classifications of chronic pain, they do not recommend the use of NSAIDs for localized chronic primary pain Note J2.

Note J2：refer to Chapter A. table A-1

With adverse events, there was no statistical difference in the incidence rate of events as compared with the placebo.

In the 'Guidelines for Managing Low Back Pain (2019)'[1], they utilized 4 references[74-77]. In terms of improved pain, they observed a tendency for reduced pain according to the meta-analysis of 2 research studies[76,77], and in the other 2 research studies[74,75]pain had significantly improved. There were 3 research studies which considered its efficacy in improving function but as their evaluations methods were different, it was not possible to perform a meta-analysis. In 2 of these research studies,[75,76] researchers observed that it was effective in improving function but in 1 of the research studies they did not observe that it was effective.[77]. In a meta-analysis on adverse events, they did not recognize a significant difference from NSAIDs as compared with the placebo. However, we need to consider how only subjective symptoms are detected when it comes to adverse events. With selective COX-2 inhibitors, as there is the risk of side effects such as the upper gastrointestinal tract, and the cardiovascular system, one must pay attention to avoid any long-term administration without any clear aim in mind Note J3

Note J3：refer to Chapter C

Period		2005～2019
Database		MEDLINE, Cochrane CENTRAL,NPO Japan Medical Abstracts Society
Search words	P	Mainly chronic low back pain, similar words (back pain, not acute, refractor, intractable, resistan, etc.)
	I/C	NSAIDs, non-steroid etc./placebo
Limitations		We limited our test design to randomized controlled trial, meta-analysis, systematic review, including chronic low back pain, tramadol in the title.
Selection summary		Of the 18 MEDLINE search hits, and 87 Cochrane CENTRAL search hits, we used 3 that matched with the set PICO but they were not suitable for meta-analysis. Therefore, we used the 2016 Cochrane systematic review.

CQ J-8：Is exercise therapy useful for chronic low back pain (LBP)？

Answer： Exercise therapy for chronic LBP is effective in improving pain, function and LBP-related QOL.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade：1（strong）：Implementation is strongly recommended〔Consensus 95.0%〕

Summary of total evidence：B（moderate）

Commentary：

There are many reports on the efficacy of exercise therapy on chronic LBP. In a 2017 systematic review of non-drug therapies for treating chronic LBP by the American College of Physicians（ACP）, researchers found that in addition to being effective on chronic LBP, exercise therapy was also effective in improving dysfunction[78]. In particular, they found that in terms of reducing pain and physical disability in patients with chronic CBP, multidisciplinary biopsychosocial rehabilitation（MBR）was more effective on pain and dysfunction than regular treatment or non-multidisciplinary biopsychosocial rehabilitation[78]. In a Cochrane systematic review as well, researchers claimed that MBR was effective in reducing pain and dysfunction in patients with chronic LBP[79]. In RCTs conducted in Japan, although researchers did not observe a difference in intensity of LBP when they compared an exercise group（strengthening of trunk muscles and stretching conducted 10 times, with at least 2 sets/day）with a control group（NSAIDs taken orally）, LBP-related QOL improved significantly in the exercise group[80]. However, at the current stage, the types of effective therapeutic exercise and their long-term effects remain unclear[1].

MBR：multidisciplinary biopsychosocial rehabilitation

RCT：randomized controlled trial

There has not been a rigorous investigation into the adverse events from exercise therapy but there have been many reports that adverse events are rare[1].

In terms of cost-effectiveness, in an RCT on 3 different types of exercise therapy, the research described their effects in improving QOL and their QALY. However, there were no high-quality reports about the cost-effectiveness of these exercise therapies[1].

Period		2005～2019
Database		MEDLINE, Cochrane CENTRAL,NPO Japan Medical Abstracts Society
Words searched	P	Mainly chronic low back pain, similar words to this（back pain, not acute, refractor, intractable, resistan, etc.）
	I/C	exercise, rehabil, physiotherp etc./nothing specified
Limitations		We limited our test design to randomized controlled trial, meta-analysis, systematic review including either chronic low back pain, exercise, rehabil, physiotherp in the title.
Selection summary		Of the 120 MEDLINE search hits, 139 Cochrane CENTRAL search hits, and 15 NPO Japan Medical Abstracts Society search hits, we used 7 key papers that matched with the set PICO.

CQ J-9：Are patient education and behavioral psychological approaches useful for chronic low back pain（LBP）？

Answer：Patient education and behavioral psychological approaches are effective

in improving pain cognition in patients with chronic LBP.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : Implementation is weakly recommended 〔Consensus 95.2%〕

Summary of overall evidence : B (moderate)

Commentary :

The results of a systematic review found that 11 references met the eligibility criteria, and were used for a meta-analysis[81-91]. As the contents of many of the research studies on patient education and behavioral psychological approaches were different and also as there was a large number of research studies that used different interventions as the control for comparison, we were unable to secure a sufficient number of patients and research studies. The items used for the meta-analysis were the Roland-Morris Disability Questionnaire (RMDQ) [lumbar function][81,82], and NRS [intensity of pain][82-84], and because the evaluation scales used for each outcome, QOL, pain cognition and medical costs varied from one reference to the next, we decided on a qualitative systematic review[85-90].

For the 3 outcomes of function, intensity of pain and QOL, we did not observe a desirable affect from the intervention used. On the other hand, it indicated that it might possibly improve pain cognition. The intervention group was on pair with the control group for medical costs. In each of the outcomes, there was a high risk of performance bias and detection bias related to making the study blind, and inconsistencies were also found, therefore we assessed that the certainty of the synthesized evidence was low.

There were no reports of adverse events.

In terms of the cost-effectiveness of patient education and behavioral psychological approaches, there are RCTs that have reported on the cost-effectiveness of group cognitive-behavioral therapy (GCBT) and face-to-face patient education but, some opinions were positive whereas others were not, so it was not uniform.[82,91]. In patient education, with treatment that is included in the category of informed consent for example, we believe the costs are at a level where they can be basically ignored. On the other hand, in implementing a more specialized behavioral psychological approach, what is necessary are the costs to cover the human resources who possess a set level of knowledge and the time required for the person in charge to implement patient education. In particular, we also assume that new persons in charge must be obtained for general hospitals. Another problem is that in Japan, behavioral psychological approaches for chronic LBP are not covered under the health insurance system at the moment.

Period		2005～2019
Database		MEDLINE, Cochrane CENTRAL,NPO Japan Medical Abstracts Society
Words searched	P	Mainly chronic low back pain, words similar to this（back pain, not acute, refractor, intractable, resistan, etc.）
	I/C	patient education, behavior therapy, psycho therapy etc./nothing specified
Limitations		We limited our test design to randomized controlled trial, meta-analysis, systematic review, including either chronic low back pain, patient education, behavior therapy, or psychotherapy in the title.
Selection summary		Of the 38 MEDLINE search hits, 78 Cochrane CENTRAL search hits, and 9 NPO Japan Medical Abstracts Society search hits, we used 11 that matched with the set PICO.

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Chapter K.　Knee Osteoarthritis（Knee OA）

：CQ K-1～CQ K-4

CQ K-1：What kind of illness is knee osteoarthritis（knee OA）?
CQ K-2：Are chondroitin and glucosamine useful for knee osteoarthritis（knee OA）?
CQ K-3：Is an intra-articular injection of hyaluronic acid useful for knee osteoarthritis（knee OA）?
CQ K-4：Is total knee arthroplasty（TKA）useful for knee osteoarthritis（knee OA）when conservative therapies are ineffective at a progressed stage of the illness ?

K. Knee Osteoarthritis (Knee OA)

CQ K-1 : What kind of illness is knee osteoarthritis (knee OA) ?

Answer : Knee osteoarthritis (knee OA) is a regressive degenerative disease of the knee joints causing pain restricting activities of daily living (ADL). It has an extremely high prevalence rate and is a severe illness that threatens the quality of life (QOL) of middle-aged and senior citizens. The goals of treatment are to improve physical function and alleviate the symptoms such as pain and stiffness.

ADL : activities of daily living

QOL : quality of life

OA : osteoarthritis

Commentary :

Osteoarthritis (OA) is a regressive degenerative disease which typically causes proliferative changes that frequently occur in the joint structures such as bones and synovium membrane, as well as changes and wear to articular cartilage. There is a high incidence of OA for example in the hands, hip and knees and the prevalence rate is especially high in knee OA. It inhibits ADL in middle-aged and senior citizens and causes a remarkable deterioration in the QOL. The number of people suffering from knee OA in Japan is estimated to be approximately 25 million people according to X-ray, of which 8 million people are estimated to have symptomatic knee OA, displaying pain symptoms[1].

Diagnosis is made according to clinical symptoms and simple X-ray findings. Typical symptoms include pain, stiffness, swelling, and restricted movement. Pain mainly occurs while moving and as the condition progresses, it may also be accompanied by for example pain at rest and pain during the night. Symptoms are often aggravated when going upstairs, rather than walking on level ground, and in Japanese lifestyles rather than Western ones. In a plain X-ray test, images are taken from 3 directions : standing anteroposterior, lateral and an axial images. With the stage classifications that are used for X-rays of knee OA, the Kellgren-Lawrence classifications is widely used ; it is graded on a 5-point scale from Grade 0～4, focusing on things like osteophyte formation, joint space narrowing (JSN), and subchondral bone sclerosis.

As no clear disease-modifying anti-OA drugs currently exist, the goal of treatment is to improve physical function and alleviate symptoms such as pain and stiffness. At the X-ray stage, many things are not related to the symptoms so it is recommended to assess, in addition to the imaging findings, the symptoms and degree of dysfunction, the age and level of activity of the patient and also consider the patient's lifestyle and values when making an overall assessment.

Treatment of knee OA can be broadly divided into conservative treatment and surgical treatment and no matter what stage it is, we recommend conducting con-

servative treatment first. Within conservative treatment, what should be conducted first is patient education, exercise therapy and reducing the weight for patients who are overweight. Its usefulness is evaluated both from the aspects of efficacy and safety, and has high cost-effectiveness and so it should be the first line of treatment for knee OA[2]. Exercise therapy not only alleviates symptoms but also has the effect of improving physical function and so it should be the central form of treatment, and for the contents of the exercise therapy, researchers recommend muscle training, aerobic exercise, and range of motion (ROM) training. For further details about exercise therapy, we would like to refer you to the chapter G on 'rehabilitation.'

In pharmacotherapy, oral and topical nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, tramadol, opioid analgesics, and duloxetine for example are used to treat OA. Furthermore, in terms of injection therapy, hyaluronic acid and steroids are injected into the joint. The recommendation grades for each drug vary slightly depending on the guidelines. For more details, we wish to refer you to the latest international guidelines[2,3] that were published in 2019 by the Osteoarthritis Research Society International and American College of Rheumatology.

If conservative treatments are unsuccessful and pain and dysfunction persist, then surgical treatments should be considered. Surgery can be broadly divided into joint-sparing surgery, which is typically represented by a high tibial osteotomy (HTO) and joint replacement. Generally, joint-sparing surgery applies in cases of unicompartmental OA in relatively young patients who are highly active and with mild deformations, whereas joint replacement applies in elderly patients with a higher degree of deformations. Knee OA is a disease that progresses into the chronic stage and therefore specialists should carefully consider the patient's lifestyle and their values throughout their career and consider the applicability of the surgical method and the best timing.

CQ K-2 : Are chondroitin and glucosamine useful for knee osteoarthritis (knee OA) ?

Answer : We are unable to say with clinical significance that chondroitin and glucosamine are effective in improving ADL and as an analgesic. The chondroitin and glucosamine that are used in high-quality clinical trials are not the same formulation as those commonly used in Japan.

Recommendation Grade & Summary of Overall Evidence

1) Chondroitin

Recommendation grade : No recommendation 〔Consensus 94.4%〕

Summary of overall evidence : B (moderate)

2) Glucosamine

Recommendation grade : No recommendation [Consensus 94.7%]

Summary of overall evidence : B (moderate)

Commentary :

1) Chondroitin

We used 5 randomized controlled trials (RCTs) which had investigated the effects of chondroitin on patients with pain due to knee OA[4-8]. The dosage of chondroitin used ranged from between 400～1,500mg, the period of administration was wide and varied with chondroitin administered over a period of 6 months in 2 of the RCTs, and 2 years in 3 RCTs, with a high risk of indirectness we conducted a qualitative review instead of a meta-analysis. In 2 of the reports[4,7] researchers observed a significant difference in analgesic effect between chondroitin and the placebo but the improvement was not recognized to be clinically significant. In 1 report,[7] researchers observed a significant difference in the effects of improved ADL from chondroitin as compared with the placebo but the difference in the effect was small. Limited to reports without conflict of interest (COI)[8], researchers did not observe that chondroitin was effective. Researchers observed mild side effects (gastrointestinal disorders, stomachache, nausea) in 4.0～8.5% of the patients but did not observe any severe side effects and the there was no significant difference compared with the placebo. Based on the above, chondroitin may be slightly effective on knee OA but its efficacy was not indicated in reports without COI, meaning that chondroitin has low usefulness.

2) Glucosamine

We used 2 randomized controlled trials (RCTs) which had investigated the effects of glucosamine on patients with pain due to knee OA[7,8]. The dosages of glucosamine administered were 1,500 mg and 753 mg, and the administration periods were not consistent either with 6 months and 2 years, with a high indirect risk, and no meta-analysis, we conducted a qualitative review. Neither report recognized a significant difference in analgesic effect and improved ADL between the glucosamine group and placebo group. They observed mild side effects (gastrointestinal disorders, rash) in 1.3～2.8% of the patients but did not observe any severe side effects and there was no significant difference when compared with the placebo. Based on the above, glucosamine is not useful on knee OA.

If chondroitin and glucosamine are taken appropriately, they are probably safe but there have been some case reports of side effects so some matters remain unclear. Furthermore, one also needs to consider the aspect of how it might encourage polypharmacy, which has become a problem among the elderly, as well as the burden of costs for the patient.

Period		2005～2019
Database		PubMed, Cochrane CENTRAL, NPO Japan Medical Abstracts Society
Words searched	P	knee osteoarthritis
	I/C	chondroitin, glucosamine, placebo
Limitations		Randomized controlled trials (RCTs)
Selection Summary		Of the 35 Pubmed search hits and 7 Cochrane CENTRAL search hits, we used 5 that matched with the set PICO

CQ K-3 : Is an intra-articular injection of hyaluronic acid useful for knee osteoarthritis (knee OA) ?

Answer : An intra-articular injection of hyaluronic acid may possibly have a slightly effect on improving pain and ADL.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : Implementation is weakly recommended 〔Consensus 100.0%〕

Summary of overall evidence : B (moderate)

Commentary :

Intra-articular hyaluronic acid (IAHA) is covered under the Japanese health insurance system as a treatment for knee OA and so it is a widely used form of treatment. However, according to the international guidelines reported by the American College of Rheumatology (2019) and Osteoarthritis Research Society International (2019), there is not a consistent viewpoint regarding its usefulness. This time we did a systematic review of an RCT on IAHA, in which an intra-articular injection of saline solution was used as the control.

After the results of our citation search, we considered 5 RCTs that were applicable. We were unable to do a meta-analysis as the outcomes set varied from one research paper to the next so we conducted a qualitative systematic review. In 2 papers[9,10] researchers recognized a statistically-significant difference in efficacy (analgesic effect, effect on improving ADL) in the IAHA group, compared with the control group, whereas in the other 3 papers[11-13], they did not recognize a difference and there was no consistency among the papers. Furthermore, in 1 of the 2 research studies that recognized that IAHA was effective, they acknowledged a conflict of interest (COI)[9]. We were unable to conduct a meta-analysis on the 5 research papers we considered and the amount of research and sample size in each one was small and as there were strong inconsistencies in the results, we cannot say that the evidence is sufficiently strong. There were no severe side effects recognized from IAHA and therefore we can say that there are no major problems in terms of its safety. Mild side effects were observed in both the IAHA group and

control group, such as pain at the site of puncture from the injection, bleeding, stiffness, joint pain, and allergic-type reactions[9].

Considering the above results and the current situation with this form of treatment in Japan, there are no severe side effects from IAHA, it is a form of treatment which may have a slight effect and so we decided that "implementation is weakly recommended." However, there are many unclear aspects on the usefulness of continuing to administer IAHA and so if it has a poor effect, then care should be taken to ensure that it is not administered for a long period of time without a clear and specific aim in mind.

Period		January 2005-December 2019
Database		PubMed, Cochrane CENTRAL, NPO Japan Medical Abstracts Society
Words searched	P	chronic pain, knee osteoarthritis
	I/C	hyaluronic acid/placebo
Limitations		Randomized controlled trial
Selection summary		Of the 11 PubMed search hits, 40 Cochrane CENTRAL search hits, and 1 NPO Japan Medical Abstracts Society search, we used 5 search hits that matched with the set PICO

CQ K-4 : Is total knee arthroplasty (TKA) useful for knee osteoarthritis (knee OA) when conservative therapies are ineffective at a progressed stage of the illness ?

TKA : total knee arthroplasty

Answer : Total knee arthroplasty (TKA) for patients with knee OA at a progressed stage of the illness, and who have been resistant to conservative forms of treatments and with deteriorated joint function, is useful for its effects in improving pain and ADL over the mid and long term.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 1 (strong) : Implementation is strongly recommended〔Consensus 100.0%〕

Summary of overall evidence : C (low)

Commentary :

As total knee arthroplasty (TKA) is used as a final treatment for patients where conservative treatments have proved to be ineffective, there are extremely few clinical trials which have been conducted with the purpose of comparing it with other treatment methods. On this systematic review, we only targeted RCTs that compared TKA with conservative treatment and ran a search for citations. We selected 3 research papers but although what they had in common was the original clinical trials[Note K1], they differed in their follow-up periods, what they compared TKA against, and which items they evaluated. In 2 research papers that evaluated it 1 year after surgery and 2 years after surgery, researchers found that analgesic pain and improved ADL were significantly superior in the group where TKA had

Note K1 : ClinicalTrials.gov NCT01410409

been performed rather than in the conservative treatment group[14,15]. In 1 research paper which evaluated pain at 3 months after surgery, researchers did not observe a significant difference between the two groups in their analgesic effects[16]. However, 3 months later, there was lingering wound pain is commonly observed 3 months after the procedure, and this may have affected the results. In 1 research study which evaluated complications, they reported that in the group which had undergone TKA, there were complications such as stiffness that required joint mobilization, deep vein thrombosis that required anticoagulant therapy, periarticular infection, and supracondylar fracture of the femur[16].

There was only 1 RCT and the group that underwent TKA was small at just 50 patients so the evidence was insufficient. However, in a report on the mid-and long-term effects that TKA had in analgesic effect and improving ADL, there is an incredibly large number of research papers in the past, which are observational studies and so there is almost no scope for discussion on its efficacy, we believe. On the other hand, surgery may possibly cause severe complications and so in principle it should be applied when conservative treatments have proven ineffective and there is end-stage knee OA with deterioration of joint function. In addition, even though knee pain may clearly decrease and ADL improve prior to the operation, it is recommended that physicians explain to the patients before surgery that one sees persistent postoperative pain (PPP) in around 20% of the cases. The eligibility criteria for surgery, which we wish to refer you to, are "an Oxford knee score of 26 or below or a varus or valgus deformity" according to the UK's NHS (National Health Service) and "when there are moderate-level or high-level osteoarthritic changes according to the X-ray", when complications have been adequately controlled and these have continued for 18 weeks or longer[17]. Finally, it is necessary to take into consideration aspects such as the individual patient's age, level of activity, illness complications as well as his/her values and lifestyle when considering TKA.

Period		2005～2019
Database		PubMed, Cochrane CENTRAL, NPO Japan Medical Abstracts Society
Words searched	P	knee osteoarthritis
	I/C	TKA/non-surgical
Limitations		Randomized controlled trial, other (guidelines, notifications) etc.
Selection summary		Of the 7 PubMed 7 search hits, 35 Cochrane CENTRAL search hits, we used 4 search hits that matched with the set PICO

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Chapter L. Chronic Neck and Shoulder Pain (Katakori) : CQ L-1～CQ L-6

CQ L-1 : What is the pathology of chronic neck and shoulder pain (Katakori) ?

CQ L-2 : Which elements are useful for diagnosing and evaluating chronic neck and shoulder pain (Katakori) ?

CQ L-3 : Is pharmacotherapy useful for chronic neck and shoulder pain (Katakori) ?

CQ L-4 : Are interventional treatments useful for chronic neck and shoulder pain (Katakori) ?

CQ L-5 : Which elements of non-drug and non-invasive therapy are useful for treating chronic neck and shoulder pain (Katakori) ?

CQ L-6 : Is there a useful way to prevent chronic neck and shoulder pain (Katakori) ?

L. Chronic Neck and Shoulder Pain (Katakori)

CQ L-1 : What is the pathology of chronic neck and shoulder pain (Katakori) ?

Answer : Chronic neck and shoulder pain (called "Katakori" in Japanese) is generally considered to be dull pain, discomfort, and muscle tension from the posterior region of the neck spreading to the shoulders and researchers have indicated that many women have it, and is associated with sleep, build, work content, and psychological condition. However, this does not necessarily mean that we have clarified everything on the pathology of chronic neck and shoulder pain (Katakori) .

Commentary :

The expression 'chronic neck and shoulder pain (Katakori)' is unique to Japan ; and is generally believed to be discomfort, dull pain, and a feeling of heaviness from the posterior neck region to the scapula and surrounding regions[1]. However, it is mainly assessed on subjective symptoms alone ; there is no consensus on standardized diagnostic criteria or its symptom recognition site[1]. Chronic neck and shoulder pain (Katakori) can be divided into one with an unclear underlying (primary) condition and a symptomatic type with a clear primary disease (secondary : orthopedic disease, a surgical disease, an internal medicine disease, otorhinolaryngological disease, ophthalmic disease, psychiatric disorder, dental disease). The category of symptomatic chronic neck and shoulder pain (Katakori) can also include severe illnesses such as tumor, infection and neurological disorders[2]. The complaint rate for chronic neck and shoulder pain (Katakori) is incredibly high, with approximately 6% of males, and 13% of females reported to suffer from this condition[3], and the incidence rate of new cases of severe chronic neck and shoulder pain (Katakori) among workers over 1 year was claimed to be approximately 3%[2]. Furthermore, the amount of work estimated to be lost due to chronic neck and shoulder pain (Katakori) is so large that it is regarded as a problem[4]. Furthermore, researchers have cited that the risk factors for onset including being a woman, lack of sleep (sleeping for less than 5 hours a night), work-related depressive mood, loss of trunk muscle mass, and deskwork[2,5]. On the other hand, regarding morphological changes to muscle tissue, with trapezius (muscle) myalgia, which displays similar symptoms to chronic neck and shoulder pain (Katakori) , some researchers have reported that the trapezius muscle fibers change exclusively in women[6]. However, as the research study did not target Japanese patients, the evidence on this is limited.

CQ L-2 : Which elements are useful for diagnosing and evaluating chronic neck and shoulder pain (Katakori) ?

Answer : Although researchers have indicated that the elements for diagnosing and evaluating chronic neck and shoulder pain (Katakori) might possibly relate to upper-back pain and a reduction in the size of the cervical muscles, as well as a decline in blood flow and oxygen saturation in the trapezius muscles, there is limited evidence to conclude that this is useful. Furthermore, level of satisfaction with one's workplace environment, position of the keyboard, repeating the same type of work, and subjective muscle tone are the elements related to the onset of work-related neck pain.

Commentary :

Researchers have indicated a decrease in the volume of multifidus muscle, longus colli muscle and the semispinalis capitis muscle in people with neck pain[7]. Furthermore, there have been reports that compared with healthy subjects, researchers observed a decrease in blood flow in the trapezius muscle and a decrease in oxygenated hemoglobin in people with upper-back muscular pain when at rest, when performing work involving the upper limbs (typing, hand grip), and during cold pressor stimulation[4].

The risk factors related to the onset of non-specific chronic neck pain from office work that were extracted were : low level of satisfaction with one's workplace environment (RR 1.28 ; CI 1.07～1.55), the keyboard is positioned too close to the trunk (RR 1.46 ; CI 1.07～1.99), having monotonous work tasks (RR 1.27 ; CI 1.08～1.50), and high subjective muscle tension (RR 2.75/1.82 ; CI 1.60/1.14～4.72/2.90[5].

These results are based on research studies conducted outside of Japan and therefore they act as limited evidence on their usefulness in diagnosing and evaluating 'chronic neck and shoulder pain (Katakori)'.

CQ L-3 : Is pharmacotherapy useful for chronic neck and shoulder pain (Katakori) ?

Answer : Non-steroidal anti-inflammatory drugs (NSAIDs) may possibly improve cervical dysfunction due to chronic neck and shoulder pain (Katakori) in the short term and in terms of its analgesic effect, it is believed to be more effective when used in combination with other treatments, rather than when used alone. However, the certainty of the evidence on its effects is very low and on top of this, researchers have not recognized the usefulness of pharmacotherapy using for ex-

NSAIDs : nonsteroidal anti-inflammatory drugs

ample capsaicin.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : Implementation is weakly recommended under certain conditions (limited to NSAIDs only) [Consensus 100.0%]

Summary of overall evidence : C (low)

Commentary :

We conducted a meta-analysis using 8 RCTs that investigated the effects of pharmacotherapy on chronic neck and shoulder pain (Katakori). The only drugs we extracted were NSAIDs, local anesthetics, and capsaicin ; no other RCTs investigating the effects of other drugs on chronic neck and shoulder pain (Katakori) exist.

As a result, researchers observed that patch NSAIDs may possibly improve cervical dysfunction due to chronic neck and shoulder pain (Katakori) over the short term, more than menthol patches[9]. Furthermore, other researchers indicated that NSAIDs may possibly have a higher immediate analgesic effect when used in combination with physical therapy (hot packs and transcutaneous electrical nerve stimulation (TENS)) or acupuncture, rather than when used alone[10,11]. However, in each case, the amount of research conducted and sample size were very small and therefore we need to take plenty of care when interpreting these results. In addition, there are no reports which have investigated its mid-to long-term effects and therefore we do not recommend using NSAIDs without some clear purpose in mind. What is more, the effects of using a local anesthetic or capsaicin compared with a placebo were unclear[12,13]. In addition, the effects of these drugs on neck mobility, the pressure pain threshold and QOL were around the same as those of other treatments and the placebo and therefore researchers did not acknowledge the usefulness of pharmacotherapy.

QOL : quality of life

Furthermore, as there are no high-quality research papers targeting Japanese patients, there is no conclusive evidence which can allow us to conclude that the target of these research studies was chronic neck and shoulder pain (Katakori) and therefore we believe the certainty of the evidence is very low[Note L1].

Note L1 : Please refer to Chapter C for pharmacotherapy on diseases and symptoms other than chronic neck and shoulder pain (Katakori).

Period		2010～2019
Database		PubMed, Cochrane Library, NPO Japan Medical Abstracts Society
Words searched	P	neck shoulder pain, neck and shoulder pain, trapezius myalgia, work related neck shoulder pain, work related trapezius myalgia, chronic neck pain, myofascial pain, neck pain
	I/C	pharmacological, medication, NSAIDs, acetaminophen, kampo, muscle relaxant, antianxiety, benzodiazepine, eperisone, myonal, telnelin, baclofen, indometacin, patch, poultice, compress, ointment, cream, liniment/nothing specified
Limitations		Review ; Systematic Reviews ; Meta-Analysis ; Randomized Controlled Trial ; published in the last10 years ; English
Selection summary		We extracted 501 PubMed search hits, 32 Cochrane Library search hits, and 11 NPO Japan Medical Abstracts Society search hits, and compared them alongside PICO and confirmed the data etc., and ultimately conducted a meta-analysis using 8 RCTs

CQ L-4 : Are interventional treatments useful for chronic neck and shoulder pain (Katakori) ?

Answer : Trigger-point injections (TPI) might possibly be effective on chronic neck and shoulder pain (Katakori) which have trigger point and muscle stiffness. However, one must be careful about continuing to perform them without any clear aim in mind and one must consider the period of treatment as well. There is a lack of evidence regarding other forms of interventional treatment and therefore its usefulness is unclear.

Recommendation Grade & Summary of Overall Evidence
Recommendation grade : No recommendation 〔Consensus 100.0%〕
Summary of overall evidence : C (low)

Commentary :

We performed a meta-analysis using 14 RCTs which investigated the effects of interventional treatments on chronic neck and shoulder pain (Katakori). The interventional treatments that we extracted were mainly TPI. TPI can be divided into the procedures of dry needling[Note L2] (a procedure in which only a puncture is made without injecting a liquid medicine) and a drug injection (local anesthetic, botulinum toxin). TPI used for chronic neck and shoulder pain (Katakori) which have trigger point and muscle stiffness

Researchers have observed that dry needling could possibly improve pain, dysfunction, neck mobility, muscle conditions (pressure pain threshold), and QOL both over the short-and mid-term, compared with other treatments (trigger-point manual pressure, stretching)[14-16]. Local anesthetic may possibly have a higher analgesic effect over the short-term than dry needling and placebo injections but its effects on dysfunction, muscle condition and QOL was unclear[17]. On the other hand, a botulinum toxin injection had no significant difference[18] when compared with a placebo injection and on top of this, one needs to consider its side-effects and the problem with it being ineligible to be covered under the health insurance system so we do not recommend it.

Pain at the injection site and bleeding for example have been reported as adverse events from TPI but there have been few reports of severe adverse events. However, as there have been a poor number of reports which have investigated its long-term effects, one needs to be careful about continuing to perform TPI without any clear aim in mind. As for other interventional treatments, there is a lack of high-quality evidence and so we were unable to confirm their usefulness. Furthermore, there are no high-quality research studies which have targeted Japanese subjects and we have no conclusive evidence which allow us to say with certainty

Note L2 : Technique is different from acupuncture

that these reports targeted chronic neck and shoulder pain (Katakori) so we believe the certainty of the evidence is low.

Period		2010～2019
Database		PubMed, Cochrane Library, NPO Japan Medical Abstracts Society
Words searched	P	neck shoulder pain, neck and shoulder pain, trapezius myalgia, work related neck shoulder pain, work related trapezius myalgia, chronic neck pain, myofascial pain, neck pain
	I/C	trigger points, myofascial trigger points, injections, needlesdry needling, hydrodissection, hydrorelease, myofacial release, nerve root block, stellate ganglion block, botulinum type A toxin, invasive techniques, saline, ozone, lidocaine, hyaluronidase, steroid, corticosteroid, wet needling, local anesthetic/Nothing specified
Limitations		meta-analysis, randomized controlled trial, systematic review, review, guideline filters : published in the last10 years
Selection summary		We extracted 1,038 PubMed search hits, 8 Cochrane Library search hits, and 37 NPO Japan Medical Abstracts Society search hits, compared them with PICO and confirmed the data etc., and ultimately performed a meta-analysis using 14 RCTs. We also used 2 systematic reviews that we had deemed useful as supplementary information

CQ L-5 : Which elements of non-drug and non-invasive therapy are useful for treating chronic neck and shoulder pain (Katakori) ?

Answer : With non-drug and non-invasive treatments for chronic neck and shoulder pain (Katakori) (exercise therapy, physical therapy, patient education/behavioral psychology approaches, manual therapy, and complementary and alternative medicine), researchers have indicated that exercise therapy (using several exercise programs in combination), physical therapy (low-level laser therapy) and complementary and alternative medicine (acupuncture) are effective in improving pain and dysfunction over the short-term. However, it remains unclear what the mid-term～long-term effects are for each of these interventional methods.

Commentary :

In a systematic review[19] which investigated the efficacy of non-drug and non-invasive treatments for chronic neck and shoulder pain (Katakori) (exercise therapy, physical therapy, patient education / behavioral psychology approaches, manual therapy, and complementary and alternative medicine), researchers reported that although each respective exercise therapy (such as muscle-strengthening exercises, flexibility / stretching exercises, aerobic exercise, yoga and pilates) performed alone, had a poor effect on improving pain and dysfunction and although there was no difference between the exercise programs[20] , when used in combination, they reported that it showed an improvement in dysfunction and reduced pain over the short-term. With dysfunction, researchers observed a short-term improvement in pain and physical function through low-level laser therapy but did not acknowledge the usefulness of other forms of physical therapy such as transcutaneous electrical nerve stimulation (TENS) and cervical traction[Note L3]. Furthermore, in terms of complementary and alternative medicine, researchers recognized that acupunc-

Note L3 : Refer to CQ G-1 for exercise therapy and CQ G-3 for physical therapy on diseases and symptoms other than chronic neck and shoulder pain (Katakori) .

ture was effective in improving dysfunction over the short term but its effects in reducing pain were unclear. With behavioral psychology approaches such as cognitive-behavioral therapy (CBT) and (patient) education, although they had poor efficacy when used alone, when used in combination with for example exercise therapy, researchers reported that it was effective in improving physical function and reducing pain over the short-term[21]. However, none of these interventional methods were recognized to be useful on pain and physical function over the mid-to long-term.

As the conditions such as control group settings and interventional amount and period were not consistent in these reports, it was difficult for use to compare the usefulness of each interventional method and therefore the certainty of the evidence is low.

CQ L-6：Is there a useful way to prevent chronic neck and shoulder pain (Katakori)？

Answer： Although exercise intervention may possibly be useful in preventing chronic neck and shoulder pain (Katakori), there is insufficient evidence on this.

Commentary：

In a systematic review which targeted office workers and investigated the methods of preventing the onset of "neck pain", researchers reported a moderate level of evidence indicating that an exercise program was useful[22]. To be more specific, through exercise intervention, the risk of incidence of "neck pain" declined by 53% (RR 0.47, 95%CI 0.32～0.68)[22]. However, there were only 2 RCTs relating to the exercise that were used in the meta-analysis and the contents of these interventions varied so it did not lead to a standard conclusion.

On the other hand, researchers did not recognize that ergonomic interventions (work environment guidance, posture guidance, and the use of arm supports etc.) were effective in preventing chronic neck and shoulder pain (Katakori) [22]. Furthermore, in a Cochrane systematic review, even though the results of a meta-analysis partially acknowledged the preventive effects of using arm supports, researchers were able to conclude that the effects were unclear[23].

What is more, these research results were based on studies conducted outside of Japan and therefore, strictly speaking, we think we are unable to interpret them as targeting 'chronic neck and shoulder pain (Katakori)'.

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Chapter M. Orofacial Pain : CQ M-1～CQ M-4-4

CQ M-1 : How is chronic orofacial pain classified ?
CQ M-2-1 : What is the pathology of trigeminal neuralgia ?
CQ M-2-2 : What is the algorithm for diagnosing trigeminal neuralgia ?
CQ M-2-3 : What kind of pharmacotherapy is useful for trigeminal neuralgia ?
CQ M-2-4 : What other treatments, apart from pharmacotherapy, are useful for treating trigeminal neuralgia ?
CQ M-3-1 : What kind of disease is burning mouth syndrome (BMS) ?
CQ M-3-2 : What is the algorithm for diagnosing burning mouth syndrome (BMS) ?
CQ M-3-3 : What kinds of pharmacotherapy are useful for burning mouth syndrome (BMS) ?
CQ M-3-4 : What other forms of treatment, apart from pharmacotherapy, are useful for treating burning mouth syndrome (BMS) ?
CQ M-4-1 : What is the pathology of persistent idiopathic dentoalveolar pain ?
CQ M-4-2 : What is the algorithm for diagnosing persistent idiopathic dentoalveolar pain ?
CQ M-4-3 : What kinds of treatment are there for burning mouth syndrome (BMS) apart from pharmacotherapy ?
CQ M-4-4 : What are other ways to treat persistent idiopathic dentoalveolar pain, apart from pharmacotherapy ?

M. Orofacial Pain

CQ M-1 : How is chronic orofacial pain classified ?

Answer : It is classified into primary chronic orofacial pain when the cause of the pain is unknown, and secondary chronic orofacial pain when it involves dental disease-derived chronic pain and when the disease causing the pain is clearly known. Chronic primary orofacial pain is characterized as persistent spontaneous pain, that appears to be from the mucous membrane of the oral cavity (burning mouth syndrome), the teeth and alveolar part (persistent idiopathic dentoalveolar pain), and the face (persistent idiopathic facial pain). It cannot be explained by known diseases of the orofacial area ; it is indicated by modulations to the central pain control mechanism. On the other hand, what is included under chronic secondary orofacial pain is chronic pain derived from dental diseases, temporomandibular disorders of which the origin is clearly known, trigeminal neuralgia, neuropathic pain derived from trigeminal neuralgia/the glossopharyngeal nerve and orofacial pain with accompanying functional headache.

Commentary :

Orofacial function is controlled by several sensation-related and exercise-related cranial nerves, and the pain is involved with several cranial nerves and these symptoms are incredibly complex and diverse[1].

The prevalence rate of orofacial pain, which includes toothache such as pulpitis and periodontitis and the prevalence rate of chronic orofacial pain is reported to be approximately 10%[1]. Furthermore, 5% of adults have jaw/facial pain persisting for 3 months or longer, and it is relatively high among women, and tends to increase with age.

Orofacial pain is classified as a secondary headache in Part Two of the International Classification of Headache Disorders (ICHD-3), and in Part Three, among painful cranial nerve neuropathy, other orofacial pain and other types of headache[2]. In the International Classification of Orofacial Pain (ICOP), 1st edition, it was re-

ICHD : International Classification of Headache Disorders

ICOP : The international classification of orofacial pain

Table M-1 International Classifications of Orofacial Pain

1. Orofacial pain attributed to disorders of dentoalveolar and anatomically related structures
2. Myofascial orofacial pain
3. Temporomandibular joint (TMJ) pain
4. Orofacial pain attributed to lesion or disease of the cranial nerves
5. Orofacial pains resembling presentations of primary headaches
6. Idiopathic orofacial pain

classified by following the international chronic pain categories, with orofacial pain being classified into 6 categories (Table M-1)[3].

CQ M-2-1 : What is the pathology of trigeminal neuralgia ?

Answer : Trigeminal neuralgia is pain from the trigeminal nerve affected unilaterally, or paroxysmal sudden shooting unilateral pain, restricted to the adjacent regions dominated by several branches. In particular, a recognizable constriction and exclusion of the blood vessels of the trigeminal nerve root is called typical trigeminal neuralgia.

Commentary :

Trigeminal neuralgia is strong pain in the orofacial region. It is sharp paroxysmal pain appearing in regions dominated by 1 or several branches of the trigeminal nerve root, and is stabbing pain which recurs in a short period of time. This pain is characteristically triggered when for example washing one's face, shaving, brushing one's teeth, chewing or engaging in conversation. As an intense pain arises in the teeth and periodondal tissue when moving the mouth, such as for brushing the teeth, chewing or engaging in conversation, on many occasions people suffering from it visit a dentist. It is also not rare for people to undergo tooth extraction, an irreversible and invasive treatment. It becomes necessary for departments involved in the treatment of dentistry, oral surgery, pain clinics, neurosurgery, neurology, radiology and diagnostic imaging to coordinate their efforts[4].

In the past, trigeminal neuralgia was classified into idiopathic trigeminal neuralgia (ITN) and symptomatic trigeminal neuralgia (STN) but now the International Classification of Headache Disorders, 3rd Edition (ICHD-3)[2], and the International Classification of Orofacial Pain (ICOP) 1st Edition[3], have organized the pathologies in a clearer manner.

ICOP : The international classification of orofacial pain

REZ : root entry zone

When the cause is pressure on root entry zone (REZ) of the trigeminal nerve due to microvessels, frequently occurring in the superior cerebellar artery, this is currently classified as typical trigeminal neuralgia and through improvements made to diagnostic imaging technology, it has become possible to evaluate this by performing an MRI test. Pathologies that had been previously summarized under symptomatic trigeminal neuralgia, have been classified into 2 different diseases : secondary trigeminal neuralgia not derived from the microvessels, such as cerebellopontine angle lesion and multiple sclerosis (MS), and trigeminal neuropathic pain arising due to damage to the peripheral trigeminal nerve. The nature of the pain is different for secondary trigeminal neuralgia and trigeminal neuropathic pain. While there is paroxysmal pain with typical trigeminal neuralgia and secondary trigemi-

nal neuralgia, trigeminal neuropathic pain is generally persistent, deriving from impaired tissue/nerves. Therefore, as a result, it is accompanied by for example hypoesthesia in the trigeminal nerve region (negative symptoms), as well as allodynia and hyperalgesia (positive symptoms). This meets the IASP's diagnostic criteria for neuropathic pain.

On the other hand, with pressure on the root entry zone of the trigeminal nerve due to microvessels and when physicians are unable to acknowledge that the pain might be caused by another disease, it is diagnosed as idiopathic trigeminal neuralgia. The majority of 'idiopathic trigeminal neuralgia' that was formerly used currently refers to typical trigeminal neuralgia, and therefore one must be careful because pathologies that are shown to be idiopathic are different. Trigeminal neuralgia has been clearly categorized in this way according to the IASP algorithm, ICHD-3, and ICOP categories.

CQ M-2-2 : What is the algorithm for diagnosing trigeminal neuralgia ?

Answer : The algorithm for diagnosing trigeminal neuralgia is thought out over the two stages of a medical interview and a test. In the medical interview, physicians need to confirm through taking patient history whether the patient has a current history of paroxysmal pain occurring on one side of the face due to exercise of the face or when lightly stimulated through touch. In the physical examination, physicians test to see whether there are any sensation abnormalities, whether the paroxysmal pain recurs on one side of the face when touched with something like a cotton swab. Diagnostic imaging by MRI is an essential test to perform in order to differentiate between typical trigeminal neuralgia and secondary trigeminal neuralgia.

Commentary :

When diagnosing trigeminal neuralgia, physicians first confirm whether paroxysmal pain is recurring unilaterally in the region dominated by the trigeminal nerve, whether it is sharp pain that disappears within 2 minutes from the onset of the attack, and whether it is like an electric shock, with a shooting, stabbing, or sharp pain. If these criteria are met, then through taking patient history and actual medical tests, if the physician can confirm through a brushing test using a cotton swab or a non-invasive form of stimulation of their daily activities such as washing the face, shaving and brushing the teeth, or that an attack of pain is triggered through stimulation when exercising or moving such as chewing or engaging in conversation, then the condition is clinically diagnosed as trigeminal neuralgia. In addition, an MRI and electrophysiological examination are performed if the MRI confirms

Table M-2 Differentiating Trigeminal Neuralgia

ICHD-3 (2018) ICOP (2010)	Classical trigeminal neuralgia	Secondary trigeminal neuralgia	Trigeminal neuropathic pain
Cause	Constriction of the blood vessels (mainly the superior cerebellar artery (SCA))	Tumor, multiple sclerosis (MS), arteriovenous malformation	Trauma, Herpes zoster etc.
Former disease name	Idiopathic trigeminal neuralgia Primary trigeminal neuralgia	Symptomatic trigeminal neuralgia (STN)	
Symptoms	Paroxysmal pain (several seconds ~ 2 mins.)		Persistent pain, Induced pain, Allodynia, Hyperalgesia
Refractory period	Yes		No
Sensation	Normal	Hypoesthesia (+/−)	Hypoesthesia (+)
	Diagnosed through QST		

compression and exclusion of the blood vessels of the root entry zone (REZ) of the trigeminal nerve, then the condition is diagnosed as typical trigeminal neuralgia. On the other hand, if the physician confirms the characteristic findings of a neurological disorder such as multiple sclerosis (MS) or brain tumor on the MRI test or an electrophysiological test, then the condition is diagnosed as secondary trigeminal neuralgia. Finally, if there is no clear abnormality observed on the MRI or electrophysiological test, then it is diagnosed as idiopathic trigeminal neuralgia[5].

Furthermore, when abnormal findings are confirmed on an MRI or electrophysiological test, trigeminal neuropathic pain is the disease required in order for it to be differentiated from secondary trigeminal neuralgia. Quantitative sensory testing (QST) is useful for a differential diagnosis. With differentiating between secondary trigeminal neuralgia and trigeminal neuropathic pain, they are differentiated by paroxysmal pain, which is mainly for trigeminal neuralgia, whereas persistent pain is mainly for trigeminal neuropathic pain[2,3,6] (Table M-2).

QST : quantitative sensory testing

CQ M-2-3 : What kind of pharmacotherapy is useful for trigeminal neuralgia ?

Answer : In terms of pharmacotherapy for trigeminal neuralgia, carbamazepine, an antiepileptic drug, is recommended as a first-line drug. However, when continuing a patient on carbamazepine becomes difficult, researchers have cited gabapen-

tin and pregabalin as alternatives. In addition, researchers have recognized the effects of oxycarbazepine, baclofen and lamotrigine, which are not covered under the health insurance system in Japan. However, there is scant medical grounds that using these second-line drugs either alone or in combination with carbamazepine provide satisfying analgesic effect and therefore often non-drug therapy is necessary.

Recommendation Grade & Summary of Overall Evidence

1) Carbamazepine

Recommendation grade : 1 (strong) : Implementation is strongly recommended〔Consensus 100.0%〕

Summary of overall evidence : A (high)

2) Gabapentin

Recommendation grade : 2 (weak) : Implementation is weakly recommended〔Consensus 94.4%〕

Summary of overall evidence : B (moderate)

3) Pregabalin

Recommendation grade : 2 (weak) : Implementation is weakly recommended〔Consensus 94.4%〕

Summary of overall evidence : B (moderate)

4) Oxcarbazepine

Recommendation grade : 2 (weak) : Implementation is weakly recommended〔Consensus 84.2%〕

Summary of overall evidence : B (moderate)

5) Baclofen

Recommendation grade : 2 (weak) : Implementation is weakly recommended〔Consensus 84.2%〕

Summary of overall evidence : B (moderate)

6) Lamotrigine

Recommendation grade : No recommendation〔Consensus 89.5%〕

Summary of overall evidence : B (moderate)

Commentary :

In terms of pharmacotherapy for trigeminal neuralgia, the antiepileptic drug, carbamazepine, is recommended as a first-line drug by western guidelines in the American Academy of Neurology (AAN) and the European Federation of Neurological Societies (EFN)[7,8]. The 'Pharmacotherapy Guidelines for Neuropathic Pain, Revised 2nd Edition' by the Japan Society of Pain Clinicians (JSPC) is used as the existing guidelines for Japan, and they recommend carbamazepine as a first-line drug[9]. The number needed to treat (NNT) trigeminal neuralgia with carbamazepine is between 1.7～1.8 (95%CI 1.3～2.2), indicating that it is highly effective.

AAN : American Academy of Neurology
EFN : The European Federation of Neurological Societies
NNT : number needed to treat

However, in a report on the long-term efficacy of Carbamazepine, although the initial response rate was 60%, this dropped to 22% 5-16 years later, 44% of patients needed additional or alternative treatment[10]. In a systematic review by Zakrzewska et al.[11], they reported that the response rate had fallen by over 50% over a long-term observation of 5～10 years.

Along with its declining effect, side effects also made it difficult for patients to continue on carbamazepine. A wide variety of side effects manifest, from mild side effects such as drowsiness and lightheadedness to more severe ones such as immunoreactions like drug rash, bone marrow suppression, and liver disorder. In a Cochrane review by Wiffen et al.[12], 66% of patients who had used carbamazepine had experienced some form of side effects (27% for the placebo group), and the number needed to harm (NNH) was 2.6 (95% CI 2.1～3.5). In most cases, their condition improves if administration is discontinued but in the event of severe cases such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug-induced hypersensitivity syndrome (DIHS), treatment interventions by an expert are required. With DIHS in particular, it may manifest after several months ～several years have passed and therefore caution is required. As it is difficult to foresee these side effects, it is important to start patients on a small dosage and not neglect monitoring and observing their condition.

NNH：number needed to harm

SJS：Stevens-Johnson syndrome

TEN：toxic epidermal necrosis

DIHS：drug-induced hypersensitivity syndrome

NMA：network meta-analysis

When it is difficult for patients to continue taking carbamazepine, then alternative drugs researchers cite for example gabapentin, pregabalin, baclofen, and lamotrigine. In addition, the effects of oxcarbazepine and type-A botulinum toxin have been recognized, although they are not covered under the Japanese health insurance system.

In a systematic review of gabapentin on trigeminal neuralgia[13], researchers reported its effects on the disease. In a meta-analysis on the use of gabapentin to manage trigeminal neuralgia14), gabapentin's OR＝1.6 (95%CI 1.185 ～ 2.161), was not inferior to that of carbamazepine, and the results for its side effects were low at OR＝0.312 (95%CI 0.240～0.407). According to the guidelines for the European Headache Federation, both Gabapentin and Pregabalin are second-line drugs for managing trigeminal neuralgia[15]. In the European Federation Headache Congress guidelines, it was a second-line drug, along with gabapentin, for treating trigeminal neuralgia.

In a network meta-analysis of the effects and tolerance of antiepileptic drugs for trigeminal neuralgia, what researchers recommended first and foremost as an alternative for carbamazepine was oxcarbazepine[16]. There was no significant difference from its effects and those of carbamazepine[17], and researchers also confirmed its high tolerance[9], and therefore in western guidelines, they strongly recommend long-term administration of oxcarbazepine for treating trigeminal neuralgia[18]. However, in Japan, its use has been approved only as a limited epileptic drug and its

use in treating trigeminal neuralgia is not covered under the health insurance system. We expect that its use will be expanded to be covered under health insurance for trigeminal neuralgia.

RCT : randomized controlled trial

Baclofen can be an alternative drug for carbamazepine but in a 4-armed RCT (carbamazepine, baclofen, phenytoin, and a placebo) conducted on 10 patients with trigeminal neuralgia, researchers observed that it was effective in alleviating pain over a 2-week treatment period. In addition, in a 3-armed RCT (carbamazepine, baclofen + carbamazepine, baclofen) RCT on 30 patients with trigeminal neuralgia, researchers found good outcomes in the group that had been administered a mix of baclofen and carbamazepine but due to a dropout rate of over 30% and its unclear randomization, it had a low level of evidence. In Japan, baclofen is evaluated as 2 C (implementation is weakly recommended) and in overseas guidelines, it has received a Level C evaluation[19].

Compared with a placebo, lamotrigine had a significantly high combined effectiveness score ($p<0.01$), and its NNT was 2.1[19]. When administering lamotrigine, one must be careful of side effects such as lightheadedness, constipation, nausea and drowsiness. Furthermore, one must be careful of increasing the dosage all of a sudden as it might cause allergic reactions or severe skin redness.

One can say that type-A botulinum toxin is superior in terms of side effects but its coverage under the Japanese health insurance system is strictly determined so it is difficult to use.

Period		2005～2019
Database		MEDLINE, Cochrane CENTRAL,NPO Japan Medical Abstracts Society
Search word	P	(Trigeminal neuralgia) AND (randomized controlled trial OR controlled clinical trial OR random allocation OR double-blind method OR single-blind method OR clinical trial OR placebo OR random OR evaluation studies OR follow-up studies OR prospective studies OR crossover studies OR control OR prospective OR systematic review OR meta analysis)
	I/C	carbamazepine, gabapentine,pregabaline, oxcarbazepine,baclofen, lamotrigine, type-A botulinum toxin
Limitations		Limited by publication type, PubMed CER randomized controlled trials / systematic review search filter, Cochrane RCT search filter, the conditions of an RCT with SR, N = 100 +, and observational research studies with N = 500 +. etc.
Selection Summary		We extracted 1,343 references from PubMed, Cochrane, and NPO Japan Medical Abstracts Society, we used 7 searches that matched with the set PICO

CQ M-2-4 : What other treatments, apart from pharmacotherapy, are useful for treating trigeminal neuralgia ?

MVD : microvascular decompression
RF : radiofrequency thermocoagulation
LLLT : low level laser therapy
PRF : pulsed radiofrequency
GKS : gamma knife surgery
Note 14 : Please refer to CQ D-7, CQ D-8

Answer : Forms of treatment other than pharmacotherapy can be divided into surgical treatment and non-invasive treatment. In terms of surgical treatment, there is microvascular decompression (MVD), percutaneous radiofrequency rhizotomy of the trigeminal nerve [radiofrequency thermocoagulation (RF)[Note 14], pulsed radiofrequency[Note 14], trigeminal ganglion balloon compression, glycerol rhizotomy], radiation stereotactic surgery [gamma knife surgery (GKS), cyber knife, linac].

Moxibustion, low-level laser therapy (LLLT) are examples of non-invasive treatment methods that are performed. The level of evidence for each treatment method is low but there are almost no reports of adverse events.

Recommendation Grade & Summary of Overall Evidence

1) Surgical treatment

a. Microvascular decompression (MVD)

Recommendation grade : 1 (strong) : Implementation is strongly recommended〔Consensus 95.0%〕

Summary of overall evidence : B (moderate)

b. Radiation stereotactic surgery (gamma knife surgery, cyber knife, linac)

Recommendation grade : 2 (weak) : Implementation is weakly recommended〔Consensus 100.0%〕

Summary of overall evidence : B (moderate)

c. Radiofrequency thermocoagulation (RF)

Recommendation grade : 1 (strong) : Implementation is strongly recommended〔Consensus 95.0%〕

Summary of overall evidence : C (low)

d. Pulsed radiofrequency (PRF)

Recommendation grade : 2 (weak) : Implementation is weakly recommended〔Consensus 100.0%〕

Summary of overall evidence : C (low)

2) Non-invasive treatments

a. Low-level laser therapy (LLLT)

Recommendation grade : No recommendation〔Consensus 85.0%〕

Summary of overall evidence : C (low)

b. Moxibustion

Recommendation grade : No recommendation〔Consensus 100.0%〕

Summary of overall evidence : C (low)

Commentary :

Forms of treatment other than pharmacotherapy can be divided into surgical treatment and non-invasive treatment, and according to overseas guidelines, when pharmacotherapy cannot be used or when it fails to provide insufficient effect, then surgical treatment is recommended as a second-stage treatment[7]. There have been no reports of RCTs conducted on each type of surgical treatment using a sham treatment as the control and therefore the level of evidence is low for each treatment. At the current stage, our considerations are based upon case control research and research which has evaluated treatment effect and complications by comparing the forms of surgical treatment with each other.

SR : stereotactic radiosurgery

Surgical treatments such as percutaneous trigeminal nerve surgery, typically represented by microvascular decompression (MVD) and radiofrequency thermocoagulation (RF), and stereotactic radiosurgery (SR) typically represented by gamma knife surgery (GKS), were all shown to be effective in improving intractable trigeminal neuralgia in patients resistant to carbamazepine[21-25]. In terms of their analgesic effects right after surgery was performed, the % of patients who did not need to be administered with medicine post-operatively was about the same for MVD and RF[21], while MVD was superior to SR[23]. Compared with SR, MVD has a higher pain removal rate 5 years later[23]. In addition, MVD led to a higher QOL than SR[24]. The pain recurrence rate post-surgery was 11% for MVD, and 25% for SR, but there was no difference in the amount of time up to recurrence[25]. There were more cases of secondary procedure required due to a recurrence of pain post-surgery in RF patients than MVD patients[21]. An issue with these RCTs is that MVD targeted young patients while RF and RS targeted elderly patients. Gamma knife surgery is problematic in terms of immediate analgesic effect and recurrence rate but it is a first-line surgical treatment that should be performed on patients who receive anticoagulation therapy. With RF, there is sustained method and intermittent method but if patients are treated through the sustained method at a high temperature, patients have strong post-operative sensory impairment but if they are treated at a low temperature, then the analgesic effects are weakened. There are accidental symptoms post-surgery such as facial sensory disorders and decline in muscular strength such as the muscles of mastication. There are almost no reports of severe complications.

Non-invasive therapy on the other hand, is often used as an alternative treatment method instead of pharmacotherapy or as a supplementary treatment method in addition to pharmacotherapy. There are reports which have compared it with carbamazepine but the level of evidence is low[26]. However, compared with carbamazepine, there are almost no adverse events so it may be okay to try using it in combination with carbamazepine. There exists 1 systematic review on the use of lower-level laser therapy (LLLT) to treat trigeminal neuralgia but in each of the RCTs used, there are major problems with the control group settings, the level of evidence is low and therefore, it does not help us reach a fixed conclusion[27].

Period		2005～2019
Database		MEDLINE, Cochrane CENTRAL,NPO Japan Medical Abstracts Society
Search word	P	(Trigeminal neuralgia) AND (randomized controlled trial OR controlled clinical trial OR random allocation OR double-blind method OR single-blind method OR clinical trial OR placebo OR random OR evaluation studies OR follow-up studies OR prospective studies OR cross-over studies OR control OR prospective OR systematic review OR meta-analysis)
	I/C	microvascular decompression, radiofrequency thermocoagulation, puled radiofrequency, gamma knife surgery, CyberKnife, LINAC, lower-level laser therapy, acupuncture
Limitations		Limited by publication type, PubMed CER randomized controlled trial / systematic review search filter,, Cochrane RCT search filter, the conditions of an RCT with SR, N＝100＋, and observational research studies with N＝500＋, etc.
Selection Summary		We extracted 1,343 references from PubMed, Cochrane, and NPO Japan Medical Abstracts Society, we used 7 searches that matched with the set PICO

CQ M-3-1 : What kind of disease is burning mouth syndrome (BMS) ?

Answer : Burning mouth syndrome (BMS) is a typical disease causing chronic primary pain in the oral region and a characteristic of this syndrome is persistent pain of the oral mucosa. The pain is bilateral and it frequently occurs on the edge of the tongue, with glossitis, and on the palate. There have been reports on its relationship to mood disorder and menopause, but it is unclear which mechanism causes it. Physicians diagnose BMS only after they have excluded all local and systemic causes.

BMS : burning mouth syndrome (also known as glossodynia, glossopyrosis, oral dysesyhesia, stomatodynia)

Commentary :

As global diagnostic criteria have not yet been established regarding whether to include secondary BMS symptoms as BMS or not, there is a lack of uniformity from one research study to the next regarding how rigorously each study has excluded secondary BMS from the target of its research. Therefore, there is a risk that past research studies may have included patients exhibiting various BMS symptoms and therefore it is difficult to collect accurate epidemiological data from these research studies. In fact, we observed a large variance in the prevalence rate among the whole population, depending on the report, from 0.7～15%. On the other hand, BMS occurs more frequently in women than in men, and in particular, many researchers have reported that cases perimenopause or post-menopause are frequent[28], and as this is a widely shared finding, the tendency of this condition to appear frequently in post-menopausal women we believe reflects the pathology of the disease.

Many of the causes of BMS have not been explained but with many BMS patients, we believe that it involves the mutual interaction of local, systemic and mental factors. Much recent research has indicated grounds that it derives from neuropathies involving central and peripheral nerves. According to the 2020 'International Classification of Orofacial Pain 1st, edition'[3] (ICOP), when conducting a quantitative sensory test (QST), we recommend classifying it into one of 2 sub-categories : the '6.1.1 BMS without somatosensory changes' or '6.1.2 BMS with somatosensory changes'.

BMS is a pain which usually occurs bilaterally ; it is rarely seen to be unilateral. The severity of pain fluctuates. The most frequently occurring site is the tip of the tongue. There have been reports that in 2/3 of the cases, there was subjective dry mouth (xerostomia), dysesthesia and an alteration to taste. We could say that persistent BMS is a symptom which causes a severe impediment to one's daily lifestyle. Furthermore, just like with other chronic pain illnesses such as anxiety, hypersensitivity, depression and reduced sociability, there are findings that are often observed among BMS patients. However, it still remains unclear what kind of sig-

nificance these factors play in the underlying cause of BMS. Furthermore, it is characteristic to often see BMS patients' fear of oral cancer[29].

CQ M-3-2 : What is the algorithm for diagnosing burning mouth syndrome (BMS) ?

Answer : When patients complain of persistent pain on both sides of the oral mucosa, first of all, the physician will examine and test whether there are local lesions exhibiting a burning sensation inside the mouth, which will be touched upon later, and a systemic disease present or not. When some type of underlying disease is suspected, the necessary treatment is conducted and in cases where both local and systemic involvement have been negated, then the physician will pronounce a diagnosis of burning mouth syndrome (BMS) if the following diagnostic criteria are met.

BMS : burning mouth syndrome

Commentary :

The International Classification of Orofacial Pain (ICOP)[3] define this disease as, "a burning sensation inside of the mouth or dysesthesia, which recurs repetitively for over 2 hours a day, and persisting for more than 3 months, and for which the physician fails to identify a clear underlying disease after conducting clinical examinations and tests". What is very important when diagnosing BMS is differentiating between cases in which there is an underlying cause of the disease where the burning sensation arises secondarily, or in which cases it is BMS. When the burning sensation arises secondarily, researchers believe it is due to one of the local causes (oral candidiasis, oral lichen planus, decreased saliva volume, metal allergy) or systemic causes (drug-induced, anemia, vitamin B_{12} and folic acid deficiency, zinc deficiency, Sjogren's syndrome, diabetes, hypothyroidism) (in such cases, the disease is identified and the burning sensation must disappear through the treatment)[29]. A diagnosis by exclusion is made by considering these factors.

According to the ICOP, after a diagnosis of BMS is pronounced, we recommend conducting a sensory test of the affected site using a quantitative sensory test (QST) and in the event that neither positive nor negative symptoms can be seen, it is sub-classified as BMS without accompanying somatosensory changes, and if either positive symptoms or negative symptoms are recognized, then it is sub-classified into BMS with accompanying somatosensory changes.

CQ M-3-3 : What kinds of pharmacotherapy are useful for burning mouth syndrome (BMS) ?

Answer : The only RCT reports on BMS have been on clonazepam, capsaicin, and α-lipoic acid (ALA). Like with other forms of chronic pain, antidepressants are used experimentally but there are not reports which have considered the evidence. Research has recognized the analgesic effects of local administration of clonazepam, on BMS over the short-term (3 months) and over the long-term (6 months+). Administering clonazepam orally may possibly be useful but we recommend avoiding long-term administration from the perspective of side effects and dependence. Researchers have confirmed the efficacy of administering capsaicin locally but there are few high-quality RCTs and its usefulness when administering over the long-term remains unclear.

ALA : α-lipoic acid

Recommendation Grade & Summary of Overall Evidence

1) Local administration of clonazepam

Recommendation grade : 2 (weak) : Implementation is weakly recommended 〔Consensus 95.0%〕

Summary of overall evidence : C (low)

2) Local administration of capsaicin

Recommendation grade : 2 (weak) : Implementation is weakly recommended 〔Consensus 100.0%〕

Summary of overall evidence : C (low)

Commentary :

Methods for treating BMS have not yet been established. The first line for treating BMS is pharmacotherapy. In a recent meta-analysis, in accordance with the treatment for neuropathic pain, local and oral administration of clonazepam is the first line that is used clinically to treat BMS[30]. Local administration of clonazepam (1.0 mg) inside the mouth (clonazepam is placed on the top of the tongue and dissolved in the saliva, and placed near the site of pain inside the mouth for 3 minutes, and after that, spat out with the saliva ; this action is conducted 3 times a day) had a reduced (intensity of pain) outcome, compared with the placebo and displayed analgesic effects both over the short-term (3 months) and the long-term (6 months+). After administering clonazepam (1.0mg) both over the short-term and long-term, there are no side effects (dysgeusia, dryness in the mouth), and therefore we think clonazepam is useful but it has a weak recommendation grade[31].

In a research study which considered the usefulness of ALA[32], a publication bias has been pointed out as a problem so it is not listed in these guidelines.

There are few research studies which have investigated the effects of adminis-

tering capsaicin locally and the sample sizes of the studies are small as well. Capsaicin for gargling (0.02%[w/v]) or 0.01% [w/v] of capsaicin or 0.025% [w/v] of a gel application, showed beneficial effects on improving pain over the short-term, after intervention[31].

Other drugs that have been reported on include drugs that act on the serotonin nervous system, such as amitriptyline, nortriptyline, duloxetine, paroxetine, but although their analgesic effects on BMS were reported, there were no high-quality research reports and therefore its evaluation in a Cochrane systematic review was low[31].

Period		2005～2019
Database		MEDLINE, Cochrane CENTRAL,NPO Japan Medical Abstracts Society
Search word	P	(Burning mouth syndrome) AND (randomized controlled trial OR controlled clinical trial OR random allocation OR double-blind method OR single-blind method OR clinical trial OR placebo OR random OR evaluation studies OR follow-up studies OR prospective studies OR cross-over studies OR control OR prospective OR systematic review OR meta-analysis)
	I/C	Clonazepam, capsaicin,
Limitations		Limited by publication type, PubMed CER randomized controlled trial / systematic review search filter, Cochrane RCT search filter, the conditions of an RCT with SR, N＝100＋, and observational research studies with N＝500＋, etc.
Selection summary		We extracted 1,343 searches from PubMed, Cochrane, and NPO Japan Medical Abstracts Society, we used 3 searches that matched with the set PICO

CQ M-3-4：What other forms of treatment, apart from pharmacotherapy, are useful for treating burning mouth syndrome (BMS)？

CBT：cognitive behavioral therapy
PCS：pain catastrophizing scale
HRQL：health-ralated quality of life

Answer： Researchers have confirmed that cognitive-behavioral therapy (CBT) intervention, improves the pain catastrophizing scale, which is related to pain and analgesic effect for BMS, as well as facial health-related quality of life (QOL). Researchers observed that a long-term CBT intervention was effective over the short-to mid-term. However, its effects after 6 months remain unclear. They have confirmed the efficacy of other forms of psychotherapy but there are no RCTs on BMS, and therefore no high-quality research reports exist. There is little research that has been conducted on low level laser therapy (LLLT), and transcranial magnetic stimulation (TMS) but these treatments were not recognized as providing sufficient effect.

LLLT：low level laser therapy
TMS：transcranial magnetic stimulation

Recommendation Grade & Summary of Overall Evidence

1) Cognitive-behavioral therapy (CBT)

Recommendation grade：2 (weak)： Implementation is weakly recommended〔Consensus 100.0%〕

Summary of overall evidence：C (low)

2) Low level laser therapy

Recommendation grade：No recommendation〔Consensus 100.0%〕

Summary of overall evidence : D (very low)

3) Transcranial magnetic stimulation (TMS)

Recommendation grade : No recommendation〔Consensus 100.0%〕

Summary of overall evidence : D (very low)

Commentary :

There are few research reports on CBT for treating BMS ; there is 1 Cochrane systematic review that has been reported[31]. The outcomes (VAS) of a CBT intervention (once / week) were evaluated after 6 months, and researchers observed that it was effective with a reduction in long-term pain (after 6 months).

VAS : visual analogue scale

As for other forms of non-pharmacological treatment, there have been 4 RCTs which have reported on LLLT but 2 of these RCTs showed the same level of analgesic effect as that from the pseudo-irradiation ; in the other 2 RCTs, there was a large indirect bias. In 1 RCT, researchers conducted transcutaneous electrical nerve stimulation (TENS), running a current of 10 Hz on the left temporo-frontal area of patients with BMS, and reported that pain had significantly reduced as compared with the control group. However, in each of these reports, the number of cases was small, and therefore we need to wait for further research to be conducted in future in order to discuss its efficacy.

Period		2005～2019
Database		MEDLINE, Cochrane CENTRAL, NPO Japan Medical Abstracts Society
Search word	P	(Burning mouth syndrome) AND (randomized controlled trial OR controlled clinical trial OR random allocation OR double-blind method OR single-blind method OR clinical trial OR placebo OR random OR evaluation studies OR follow-up studies OR prospective studies OR cross-over studies OR control OR prospective OR systematic review OR meta-analysis)
	I/C	cognitive behavior therapy, low reactive-level laser therapy, transcranial magnetic stimulation
Limitations		Limited by publication type, PubMed CER randomized controlled trial / systematic review search filter, Cochrane RCT search filter, the conditions of an RCT with SR, N＝100＋, and observational research studies with N＝500＋, etc.
Selection summary		We extracted 1,343 searches from PubMed, Cochrane, and NPO Japan Medical Abstracts Society, we used 2 searches that matched with the set PICO

CQ M-4-1 : What is the pathology of persistent idiopathic dentoalveolar pain ?

Answer : Persistent idiopathic dentoalveolar pain (PIDAP) is a chronic primary pain which along with burning mouth syndrome (BMS) is characteristic of the orofacial region. While BMS is superficial pain of the oral mucosa, PIDAP is pain of the tooth and alveolar part, equivalent to deep pain. It tends to be understood as a type of neuropathic pain, as pain after tooth extraction, after a root canal treatment. However, the International Classification of Orofacial Pain (ICOP), recommends diagnosing it as post-traumatic trigeminal neuropathic pain if it is clearly related to trauma, whereas PIDAP is considered to be an idiopathic form of pain with an unclear cause.

PIDAP : persistent idiopathic dentoalveolar pain

Commentary：

The term 'persistent idiopathic dentoalveolar pain' (PIDAP), is a persistent pain arising in the (alveolar) site in 1 tooth or after the loss of a tooth and is used when no dental cause for the pain exists whatsoever[4,34].

It was first reported in 1778, and the pathologies of idiopathic periodontalgia were named in 1974, phantom tooth pain was named in 1978, and atypical odontalgia (AO) was named in 1979, and it has been called 'AO' for the past 40 years up until the present. Because they have not clarified its pathophysiology, various names have been used for this disease, and in 1992 they proposed idiopathic toothache, in 2012 painful post-traumatic trigeminal neuropathy (PTTN), and persistent dentoalveolar pain disorder[3,34].

AO：atypical odontalgia

In the 2018 International Classification of Headache Disorders 3rd Edition (ICHD-3[2]), in classification 13.12 for persistent idiopathic facial pain (PIFP), the viewpoint they indicate is that "AO is a sub-type of PIPF." Experts define PIPF as a persistent pain of the face or mouth (or both) with various accompanying symptoms. And they indicated that its characteristics are that it is not clearly localized and the majority of the patients are women, whereas with AO, the localization is clear, the age of onset is relatively young/low, and there is little difference in gender (of the patients).

PIFP：persistent idiopathic facial pain

On the other hand, in the 2020 International Classification of Orofacial Pain 1st Edition (ICOP)[3], they bring up PIFP in category 6.2 but they list PIDAP in category 6.3, which had up until then been called AO, and so both have been classified as a separate disease.

There have been 2 mainstream theories regarding the pathophysiology of PIDAP：it has been conventionally considered to be a form of neuropathic pain or assumed to arise due to mental and psychological factors. However, recently, some researchers have also proposed the theory that it arises due to central sensitization and modulations to the pain processing process in the brain.

In 70～83% of PIDAP cases, it is triggered by dental treatment, and as many of the patients who have this disease are seen to have for example a peculiar feeling of distrust in healthcare, anger and anxiety, an existing history of mental diseases such as anxiety disorder, stress-related disorder, and somatoform disorders (somatic symptom disorder：DSM-5), or several of these coexist, one needs to evaluate patients both on their mental state and on their psychosocial condition. In other words, the key to obtaining an accurate diagnosis of PIDAP is to exclude organic diseases including of the brain, and the physician needs to try diverse approaches, such as confirm that it is not some other non-odontogenic disease and conduct a psychosocial evaluation[4].

CQ M-4-2 : What is the algorithm for diagnosing persistent idiopathic dentoalveolar pain ?

Answer : Diagnosing persistent idiopathic dentoalveolar pain (PIDAP) is basically a diagnosis by exclusion, and so it is necessary to confirm that diseases or lesions that could be the cause of the pain at the site in question (the tooth or alveolar part) are not present. When physicians are unable to find any abnormalities to the tooth or surrounding tissue (periodontal membrane, the jawbone), then they search for pathologies which may give rise to referred pain at the same site. With the results of a diagnosis by exclusion, if one cannot see a pathology which could be thought of as another cause of the pain, then it is compared against the diagnostic criteria of PIDAP, and if it meets those diagnostic criteria, then a diagnosis of PIDAP is pronounced.

PIDAP : persistent idiopathic dentoalveolar pain

Commentary :

In the International Classification of Headache Disorders 3rd Edition (ICHD-3)[2] it is assumed to be PIFP, and in the International Classifications of Orofacial Pain (ICOP)[3], they classify PIDAP as pain of the tooth and alveolar part whereas pain of the face is classified as PIFP. In these guidelines we will follow the classifications of the ICOP.

In the ICOP, when there is no event that could be thought of as a preceding cause, and the pain has persisted for more than 2 hours a day and for more than 3 months, and recurs every day, it is considered to be a persistent pain of the mouth with various accompanying symptoms. It is rare for it to manifest in several places ; in many cases it manifests unilaterally[3]. It is rare for the pain to appear at several sites and over time, it might possibly spread to a wider region of the head and neck.

Several words are used to explain the characteristics and nature of this pain. It is sometimes expressed as a pain in a deep part of the face, and is sometimes expressed as being on the surface. In order to explain the sensations and complexities of this disorder, sometimes one opts to explain the supplementary symptoms. It displays relatively stable symptoms but sometimes the pain worsens and may possibly be exacerbated due to stress.

In a clinical somatosensory evaluation such as pinprick or light exposure to the touch, it is almost never the case that paresthesia becomes apparent. A nociceptive pain which reflects the processes of a changed somatosensory system is present and this may possibly be related to changes in a descending pain inhibitory system. On the other hand, in cases of an existing history of clear trauma to the trigeminal nerve (disorders which are mechanical, chemical, temperature-based or due to radiation), and when it has been less than 6 months since receiving the trauma, dis-

playing either negative symptoms indicating dysfunction in the area served by the nerve that has received trauma (hypaesthesia/hypoesthesia, hypoalgesia) or positive symptoms (hyperalgesia, allodynia), or when both symptom types are present, then according to the ICOP classification, it is classified as '4.1.2.3 post-traumatic trigeminal neuropathic pain.

Furthermore, in the ICOP classification, they define '6.2 persistent idiopathic facial pain' (PIFP)[3], as "symptoms of neurological deficit are absent, pain persists for more than 2 hours a day and for more than 3 months, recurs every day, and is persistent pain in the face with various accompanying symptoms." Patients suffering from PIFP sometimes also suffer from other pain diseases such as chronic widespread pain and irritable bowel syndrome (IBS), and mental illness or psychosocial problems are frequently concomitant. PIFP is sometimes triggered by minor operations or trauma to the face, maxillary sinus, teeth or periodontal tissue, and after the wounds have healed, the situation might be prolonged without a clear identification of the local cause. However, a psychophysical and a neurophysiological examination may sometimes indicate a sensory disorder.

CQ M-4-3 : What kinds of treatment are there for burning mouth syndrome (BMS) apart from pharmacotherapy ?

Answer : Amitriptyline, gabapentin, pregabalin, venlafaxine, duloxetine are used experimentally, but at the present stage, there is no scientifically-proven pharmacological method.

Commentary :

In 2020, primary chronic orofacial pain of the orofacial region was sorted and classified by the ICOP, and this led to the establishment of the disease concept, PIDAP. As mentioned previously, with chronic pain which does not clearly originate from the orofacial region, just like with chronic pain in other regions, antidepressants have come to be used experimentally. There are some research studies which have considered the effects of antidepressants, including its effects on chronic pain of the orofacial region of which the cause is unknown, but with this, it is difficult to evaluate their effects in treating PIDAP. At the current stage. no high-quality evidence reports exist which could allow us to judge the efficacy of specific drugs on PIDAP. As for case reports and case control studies on pathologies which apply to PIDAP, there are scattered research papers here and there which have reported on the utility of TCA, SNRI and Gabapentinoid. Therefore, using analgesics and antidepressants for treating PIDAP is not at this stage supported by evidence[35], and therefore there will be a need for materials allowing us to judge its effects based

on the ICOP[3] in an objective manner through future RCT studies.

CQ M-4-4 : What are other ways to treat persistent idiopathic dentoalveolar pain, apart from pharmacotherapy ?

Answer : Researchers have considered cognitive-behavioral therapy (CBT), transcranial magnetic stimulation (TMS), and lower-level laser therapy (LLLT) for treating primary chronic pain of the orofacial region. However, just like with pharmacotherapy, they have yet to establish a specific form of treatment for PIDAP.

TMS : transcranial magnetic stimulation

Commentary :

PIDAP was established as a disease concept by the ICOP in 2020[3], and its neuropathic mechanism is not required as part of its diagnostic criteria. Pathologies that had traditionally been covered and treated as orofacial pain without a known cause, no longer need to have elements of neuropathic pain. Regarding the effects of the methods to treat primary chronic orofacial pain mentioned above, revision is now required on which pathology was targeted. As for non-pharmacological ways of treating primary chronic orofacial pain, including PIDAP, there are reports which have considered the effects for example from CBT, hypnotherapy, TMS, and LLLT but nothing has yet been reported on research specifically on the effects of treating PIDAP. We hope researchers will consider the effects of treatments targeting patients with PIDAP based on the ICOP diagnostic criteria[3].

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Chapter N. Headache : CQ N-1～CQ N-5-3

CQ N-1 : How is headache classified ?
CQ N-2 : How do we differentiate dangerous headaches ?
CQ N-3 : How can we treat medication-overuse headache ?
CQ N-4-1 : Are anti-CGRP antibodies and anti-CGRP receptor antibodies useful for preventing chronic migraine ?
CQ N-4-2 : Are oral drugs useful for preventing chronic migraine ?
CQ N-5-1 : Is non-invasive (percutaneous) vagus nerve stimulation useful for chronic cluster headache ?
CQ N-5-2 : Is transcranial magnetic stimulation (TMS) useful for chronic migraine and chronic tensions-type headache ?
CQ N-5-3 : Is acupuncture useful for chronic migraine/chronic tension-type headache ?

N. Headache

CQ N-1 : How is headache classified ?

ICHD : International Classification of Headache Disorders

Answer : We recommend using the 'International Classification of Headache Disorders 3rd Edition' (ICHD-3) published by the International Headache Society for classification and diagnosis, in order to advance headache treatment based upon scientific research.

Commentary :

Epidemiological research into headaches is lagging behind other fields. The reason for this is, although there were no problems with diagnosis secondary headache, diagnosis of primary headache, which accounts for the majority of headache disorders, is not consistent among reports and investigators. Therefore, one is unable to compare findings with other reports and it has been difficult to conduct epidemiological research. In this context, in 1988, the International Headache Society announced the classification of headaches according to clinical findings as well as diagnostic criteria in its 'International Classification of Headache Disorders' (ICHD), thereby swiftly bringing about a worldwide standardization to the treatment of headaches. Upon this occasion, there was the first consensus regarding migraine as a disease concept. A 2nd Edition was published in 2004, and then in agreement with formulation ICD-11 by the World Health Organization (WHO), they published the 3rd Edition (beta edition) in 2013. They published the Official 3rd Edition (ICHD-3) in January 2018, and a Japanese version was published in November of the same year[1-3].

In ICHD-3, they have made significant changes mainly to migraine and what had been previously categorized as a complication of migraine. 'Chronic migraine' was classified in the same level headache category as "migraine without aura" and "migraine with aura", making it even more important to differentiate it from 'tension-type headache (TTH)'. Furthermore, 'basilar migraine' was reclassified under "migraine with aura" as "migraine with brainstem aura". As mentioned above, researchers have pointed out the relationship between dizziness and migraine, but they have added the new category of "vestibular migraine" to the Appendix.

The current ICHD-3 is comprised of Part 1 : The primary headache, Part 2 : The secondary headache, and Part 3 : Painful cranial neuropathies, other facial pain and other headaches. It has classified over 300 types of headache categories and each one is diagnosed in stages according to first to fifth-digit levels. In cases where patients exhibit several headache diagnoses, they will be enumerated in the order of importance to the patient (Table N-1).

Table N-1 Headache Classifications according to the International Classification of Headache Disorders 3rd Ed (Cited from References #3)

Part 1 : The primary headache
1. Migraine
2. Tension-type headache (TTH)
3. Trigeminal/autonomic cephalalgias (TACs)
4. Other primary headache disorders

Part 2 : The secondary headache
5. Headache attributed to trauma or injury to the head and/or neck
6. Headache attributed to cranial and/or cervical vascular disorder
7. Headache attributed to non-vascular intracranial disorder
8. Headache attributed to a substance or withdrawal disorder
9. Headache attributed to infection
10. Headache attributed to disorder of homeostasis disorder
11. Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cervical structure
12. Headache attributed to psychiatric disorder

Part 3 : Painful cranial neuropathies, other facial and other headaches
13. Painful lesions in the cranial nerves and other facial pain
14. Other headache disorders

Appendix

CQ N-2 : How do we differentiate dangerous headaches ?

Answer : There is an overwhelmingly high percentage of people with primary headache in which no abnormalities can be found on tests, and if it progresses to chronic headache and new symptoms arise, it is important to discern dangerous secondary headache at an early stage, especially possibility of subarachnoid haemorrhage. In the following cases, the physicians actively investigates when secondary headache is suspected. ① Systemic symptoms including fever ; ② Neoplasm in history ; ③ Neurologic deficit or dysfunction (including decreased consciousness) ; ④ Onset of headache is sudden or abrupt ; ⑤ Older age (after 50 years) ; ⑥ Pattern change or recent onset of headache ; ⑦ Positional headache ; ⑧ Precipitated by sneezing, coughing, or exercise ; ⑨ papilledema ; ⑩ Progressive headache and atypical presentations ; ⑪ Pregnancy or puerperium ; ⑫ Painful eye with autonomic features ; ⑬ Posttraumatic onset of headache ; ⑭ Pathology of the immune system such as HIV ; ⑮ Painkiller overuse or new drug at onset of headache.

Commentary :

Headache is divided into two types : primary headache where the headache itself is a disease and secondary headache which manifests due to some underlying cause. The 'SNNOOP10 List' introduces the red-flag symptoms of secondary head-

ache as clinical clues allowing us to differentiating between the two (primary and secondary) (Table N-2).[4] . It is hard to diagnose secondary headache in patients who complain just of a mild headache and who are able to walk without assistance to the hospital, in particular even upon their first consultation or if they are a patient with a previous history of chronic pain, if patients are aware that their headache is different from usual, such as the site of pain and how long it persists, then it is important to make a differential diagnosis of secondary headache.

Dangerous secondary headache is one that occurs frequently and unexpectedly and which within 1 minute the intensity of the pain reaches a peak and becomes a thunderclap headache. With this kind of sudden headache, it is difficult to differentiate it as primary headache just on consultation alone, especially in cases where there are no other symptoms other than headache., In the 'Clinical Practice Guidelines for Chronic Headache 2013' they recommend actively conducting imaging tests[5]. The cause of a thunderclap headache is often due to cerebrovascular diseases such as subarachnoid haemorrhage, reversible cerebral vasoconstriction syndrome (RCVS), cerebral artery dissection, cerebral venous sinus thrombosis, and pituitary apoplexy. Other causes of sudden headache include hydrocephalus, meningitis, encephalitis, glaucoma, acute sinusitis, systemic infection, brain tumor, drug-induced headache, and trauma. One should proceed with treatment after under-

RCVS : reversible cerebral vasoconstriction syndrome

Table N-2 Secondary headache warning signs (red flags) : SNNOOP 10 List
(Cited from Reference #1)

	Signs & Symptoms	Flag color
1	Systemic symptoms including fever	Red (orange if only fever is present)
2	Neoplasm in history	Red
3	Neurologic deficit or dysfunction (including decreased consciousness)	Red
4	Onset of headache is sudden or abrupt	Red
5	Older age (after 50 years)	Red
6	Pattern change or recent onset of headache	Red
7	Positional headache	Red
8	Precipitated by sneezing, coughing, or exercise	Red
9	Papilledema	Red
10	Progressive headache and atypical presentations	Red
11	Pregnancy or puerperium	Red
12	Painful eye with autonomic features	Red
13	Posttraumatic onset of headache	Red
14	Pathology of the immune system such as HIV	Red
15	Painkiller overuse or new drug at onset of headache	Red

Table N-3 Ottawa Subarachnoid Haemorrhage Rule (Ottawa SAH Rule)
(based on Reference #5)

Headache in which pain reaches its peak within 1 hour, in adult patients without any recognizable neuropathy, and when the following items do not apply, then generally subarachnoid haemorrhage (SAH) can be ruled out. If one of them is present, sensitivity 100% (97.2～100.00) ; specificity 15.3% (13.8～16.9) , then one needs to consider the possibility of subarachnoid haemorrhage.

- Age ≥ 40 years old
- Neck pain or stiffness
- Witnessed loss of consciousness
- Onset during exertion
- Thunderclap headache (instantly peaking pain)
- Limited neck flexion on examination

standing the characteristics of each respective disease, such as the mode of onset and physical findings of the headache and if necessary, conduct additional tests such as on imaging test findings.

With subarachnoid haemorrhage (SAH), the most important disease to differentiate is thunderclap headache but in cases were only mild pain manifests and a diagnosis is delayed and the condition is not properly attended to, then it can lead to medical litigation[6]. A frequent characteristic of this pain is thunderclap headache in 80% of the cases, and symptoms are throbbing pain and stabbing pain[7]. According to a report which considered whether subarachnoid haemorrhage (SAH) could be diagnosed or not on clinical characteristics alone, the Ottawa SAH rule says that it is not subarachnoid haemorrhage when none of these 6 items apply : patient aged ≥ 40 years old, neck pain or stiffness, witnessed loss of consciousness, onset during exertion, thunderclap headache (instantly peaking pain), limited neck flexion on examination (Table N-3)[8]. However, in actual clinical settings, it is difficult to give a definitive diagnosis of subarachnoid haemorrhage (SAH) just on headache symptoms and taking patient history alone, and therefore imaging test is essential. CT and MRI are the typical imaging tests but sometimes a CT is unable to detect small amounts of bleeding or a hematoma at the posterior fossa or vertex side and the rate of diagnosis declines over time : 98% within the first 12 hours ; 86～93% within the first 24 hours, 76% within the first 48 hours, 50% within the first week, and 30% within two weeks[9]. On the other hand, with Fluid Attenuated Inversion Recovery (FLAIR) images on MRI, the false negative rate within 24 hours of onset is 2%, which is relatively low at 14% on CT. In cases where a subarachnoid haemorrhage (SAH) cannot be ruled out, an MRI including FLAIR images and T2* weighted images (T2*WI) can be useful[10]. When doing this, an MR angiography (MRA) should be performed at the same time, and it is important to confirm the presence or absence of cerebrovascular lesions, which are often a cause of thunder-

clap headache, such as cerebral aneurysm and arterial dissection and reversible cerebral vasoconstriction syndrome (RCVS).

CQ N-3 : How can we treat medication-overuse headache ?

MOH : medication-overuse headache

Answer : Patients who have had recurrent headache before and whose condition has deteriorated due to an excessive amount of analgesics and for example triptan, experience medication-overuse headache (MOH). This condition is diagnosed based on the International Classifications of Headache Disorders 3rd Edition (ICHD-3) and the basic principles of treatment are ① discontinue the overused medication ; ② treatment of headache after discontinuation of the overused medication ; and ③ administer preventive medicine.

Commentary :

1) Diagnosis

MOH is a condition in which patients with a previous history of primary headache overuse in the acute phase symptomatic headache medicine or a new type of headache manifests. Alternatively the primary headache that was already present becomes markedly worse and the person suffers from the headaches for more than 15 days a month in total (Table N-4)[3]. In the International Classification of Headache Disorders 3rd Edition (ICHD-3), it is classified as a sub-type 8.2 under "medication-overuse headache (MOH)" (Table N-5) which is then sub-divided into each respective sub-category depending on the underlying drug that the patient was overusing. Overuse is defined as taking medication for more than 15 days in a month in total for over 3 months for non-opioid analgesics, and for other types of medication, it refers to taking medication for more than 10 days a month.

The prevalence rate has been reported to be about 1～2% of the entire population, chronic pain is 25～50%, and 30～50% of headache outpatients and headache center patients[11-13]. Often the original headache is a migraine[14]. It tends to occur

Table N-4 Diagnostic criteria for headaches due to medication-overuse headache (MOH) (Cited from Reference #1)

A. Headache occurring on 15 days/month in a patient with a pre-existing headache disorder
B. Regular overuse* for > 3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache
C. Not better accounted for by another ICHD-3 diagnosis
Abuse / overuse* is defined as taking non-opioid analgesics for 15 days or more per month and for other medication, 10 days or more per month

Table N-5 Classifications of headache due to medication-overuse headache (MOH) (Cited from Reference #1)

8.2 Medication-overuse headache (MOH)
8.2.1 Ergotamine-overuse headache
8.2.2 Triptan-overuse headache
8.2.3 Non-opioid analgesic overuse headache
8.2.3.1 Paracetamol (Acetaminophen) overuse headache
8.2.3.2 Non-steroidal anti-inflammatory drugs (NSAIDs) overuse headache
8.2.3.2.1 Acetylsalicylic acid overuse headache
8.2.3.3 Other non-opioid analgesic overuse headache
8.2.4 Opioid overuse headache
8.2.5 Combination-analgesic overuse headache
8.2.6 Medication-overuse headache attributed to multiple drug classes not individually overused
8.2.7 Medication-overuse headache attributed to unspecified or unverified overuse of multiple drug classes
8.2.8 Medication-overuse headache attributed to other medication

often in women, and if the person is a habitual smoker and lacks exercise, the prevalence rate of MOH doubles and low-income families and those with a poor educational background are at risk of MOH[15-17]. Researchers claims that compared with triptan and ergotamine, there is a higher risk from combined analgesics as they are a medication that causes MOH[18].

2) Treatment

When treatment begins, the most important thing is to provide advice and education on MOH to patients and then discontinue the medicine causing the problem and provide preventive treatment[19]. It is also important to encourage patients that there is a reasonable possibility for their condition to improve through a treatment intervention, explain to them that overusing analgesics can in fact make their headache worse and first make them withdraw through the thought that, "the headache they are aware of = taking analgesics orally." In some cases, their condition improved just through advice on how to use analgesics. Many cases do not improve immediately after commencing treatment and one should explain to patients a long-term treatment plan, such as how treatment will last for more than several months, including how the effects of headache preventive medicine would be expressed. In particular, physicians should explain properly the rebound symptoms once the medicine causing the headache has been discontinued, and by making them aware beforehand of the treatment process, in which temporarily the symptoms may worsen but after that, before a steady improvement in symptoms, one may continue the treatment smoothly without terminating it. Furthermore, one should let patients know beforehand of the high possibility that treatment might be prolonged, that in terms of intractable cases, there are intractable complications, mental disease complications such as mood disorder and eating disorder, and cases

of patients using several symptomatic drugs, and relapse cases of MOH[20].

The basic principles for treatment according to the 'Clinical Practice Guideline for Chronic Headache 2013' are : ① discontinuing the overused medication ; ② attend to headaches that occur after medication has been discontinued ; and ③ administer preventive medicine[5]. During treatment, a 'headache diary' is used, and it is important to proceed by objectively evaluating the frequency and intensity of headache, and how frequently medication is being used.

① Discontinuing the overused medication

There is no evidence on methods for discontinuing the drug of cause but some researchers have claimed there is a higher relapse rate when dosage is gradually decreased compared with when suddenly stopped[21]. Furthermore, as there was no difference in the prevalence rate when the drug was discontinued during hospitalization or for outpatients, one should first of all consider immediately discontinuing the drug for outpatients[22]. However, withdrawal is recommended during hospitalization for overuse of more complex analgesics (barbiturates, benzodiazepines, and opioid analgesics etc.), long-term overuse of acute-stage treatment drugs, for patients with a failed history of withdrawal as outpatients, and for patients with coexisting mental disease[2].

② Treatment of the headache after discontinuing the overused medication

Between 24～72 hours after discontinuing the drug of cause, withdrawal symptoms occur such as aggravated headache, nausea, vomiting, low blood pressure, tachycardia, and sleeping disorders[23]. These typically continue for 2～10 days but vary depending on the drug of cause ; researchers claim an average of 4.1 days with triptan, an average of 6.7 days with ergotamine, and an average of 9.5 days with NSAIDs[24].

What is used as a rescue for post-withdrawal headache is long-lasting naproxen and COX-2 inhibitors for example used in combination with tizanadine. In patients where there is a strong migraine attack, one could consider using triptan but it is necessary to limit the number of days they can use it[25]. Furthermore, for withdrawal symptoms other than headache, physicians should provide symptomatic treatment such as through rehydration, antiemetics, sedatives and steroid drugs[26].

③ Administering preventive medicine

It is recommended to start patients on preventive medicine either while the overuse medication has been discontinued or before it is discontinued[27]. The choice of preventive medicine varies depending on what triggered the onset of MOH but often it is migraine so for example sodium valproate, lomeridine, proplanol, and amitriptyline are frequently used. Although they are not eligible to be covered under the Japanese health insurance system, there are many overseas reports that topiramate and botulinum toxin are effective too[19]. Furthermore, in cases where mood disorder is also present, one can proceed with a more efficient treatment by choos-

ing a drug taking into consideration any coexisting conditions. In future, one of these possible choices is a new type of drug for treating migraine which is already on the market overseas (anti-CGRP antibodies and anti-CGRP receptor antibodies)[28].

3) Prognosis

Many cases respond well to treatment, with an improvement in episodic migraine in 57% in the 1st year, and 66% in the 2nd year. On the other hand, researchers have reported a recurrence of episodic migraine in 28-31% of cases at 6 months, in 41% of cases at 1 year, and 45% of cases at 4 years[29]. Reports of poor prognosis factors include a long period of duration for migraine, frequent migraine attacks after withdrawal, frequent taking of combination medicine, or frequent intake of medication after withdrawal, alcohol, smoking, or taking previous drugs once again[11,30].

The most important thing with MOH is to take precautions and even after remission due to treatment, it is important to prevent a relapse by providing patient education while confirming at the same time the frequency of headaches and frequency with which medication is taken through using a headache diary.

CQ N-4-1 : Are anti-CGRP antibodies and anti-CGRP receptor antibodies useful for preventing chronic migraine ?

Answer : Anti-CGRP antibodies and anti-CGRP receptor antibodies are useful for preventing chronic migraine.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 1 (strong) : Implementation is strongly recommended〔Consensus 95.0%〕

Summary of overall evidence : B (moderate)

Commentary :

Anti-CGRP receptor antibodies are useful for preventing chronic migraine but considering their cost-effectiveness, one must consider administering them or not in cases where for example 2 types of oral medications can either be ineffective or produce side-effects.

There have been 6 RCT reports which considered and compared the usefulness of anti-CGRP antibodies on chronic migraine (eptinezumab : not approved in Japan, galcanezub : approved in Japan, fremanezumab : currently under application for approval) and anti-CGRP receptor antibodies (erenumab : currently under application for approval). These studies targeted adult patients aged 18 years old +

RCT：randomized controlled trial

with chronic migraine, and researchers investigated whether there was an improvement in chronic migraine or not, and whether it was safe or not, in a placebo-controlled RCT in which patients were administered the treatment drug once a month through a subcutaneous injection. In all of the research studies, the results consistently showed that the antibody medicine for CGRP or CGRP receptors was effective in reducing symptoms of chronic migraine and also that there were few adverse events. However, in some parts of the research, they identified some slight risk of bias, for example the reporting of selected outcomes and therefore the strength of the evidence was around the medium level.

Period		2001～2019
Database		Cochrane Library, PubMed, NPO Japan Medical Abstracts Society
Words searched	P	chronic migraine
	I/C	eptinezumab, galcanezumab, fremanezumab, erenumab,preventive therapy, prevention,cgrp
Limitations		Limited by publication type, PubMed CER randomized controlled trial / systematic review search filter, Cochrane RCT search filter, other（cases of50＋）etc
Selection Summary		Of the 142 MEDLINE 142 search hits, 237 Cochrane search hits, a NPO Japan Medical Abstracts Society search hits, we used 9 of them which matched with the set PICO

CQ N-4-2：Are oral drugs useful for preventing chronic migraine？

Answer： Oral drugs are useful for preventing chronic migraine.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade：2（weak）： Implementation is weakly recommended〔Consensus 94.7 %〕

Summary of overall evidence：B（moderate）

Commentary：

There have been reports from 3 placebo-controlled RCTs which investigated and compared the efficacy of oral drugs on chronic migraine；2 of the RCTs were on topiramate（not eligible for health insurance coverage）and 1 was on sodium valproate. The number of days which adult patients aged 18 years old＋suffered from chronic migraine significantly decreased at around 4 weeks in the group who were orally administered with topiramate compared with the placebo. Researchers have not proven the preventive effects of valproic acid on reducing the number of days patients suffer from a migraine but compared with the placebo, the frequency of pain significantly decreased on the visual analogue scale（VAS）, maximum VAS level and pain frequency. There were no problems with safety in any of the research studies but in the preventive effects of oral drugs for chronic migraine, researchers did notice a slight risk of bias, for example a different oral drug was used or different outcomes and therefore, the strength of the evidence was medium.

In actual clinical settings when topiramate and valproic acid are not successful,

an RCT targeting patients with chronic daily headache used amitriptyline which was recognized to have preventive effects, and propranolol and romeridine were used to prevent 'migraines without warning signs' and 'migraines with warning signs.

Period		2001～2019
Database		Cochrane Library, PubMed, NPO Japan Medical Abstracts Society
Words searched	P	chronic migraine
	I/C	preventive therapy, prevention
Limitations		Limited by publication type, PubMed CER randomized controlled trial / systematic review search filter, Cochrane RCT search filter, other（cases of50＋）etc
Selection Summary		Of the 172 MEDLINE search hits, and 1 Cochrane search hit, we used 3 search hits which matched with the set PICO

CQ N-5-1：Is non-invasive（percutaneous）vagus nerve stimulation useful for chronic cluster headache？

Answer： Non-invasive（percutaneous）vagus nerve stimulation（nVNS）is useful for chronic cluster headache.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade：2（weak）： Implementation is weakly recommended 〔Consensus 100.0%〕

Summary of overall evidence：C（low）

Commentary：

There was 1 RCT which considered and compared the usefulness of nVNS for chronic cluster headache. This study targeted adults aged 18 years old＋with chronic cluster headache and used a standard-treatment group for the control, and performed non-invasive vagus nerve stimulation（nVNS）6 times a day, and found that the number of headache attacks and the actual attacks had significantly decreased by over 50%. There was 1 RCT which considered and compared the usefulness of nVNS on chronic migraine, and researchers confirmed its safety but although it was effective in reducing the number of days when patients had a migraine 2 months later in the nVNS group compared with a sham treatment group, the difference was not significant.

Period		2001～2019
Database		Cochrane Library, PubMed, NPO Japan Medical Abstracts Society
Words searched	P	chronic migraine, chronic headache
	I/C	nerve stimulation, brain stimulation, preventive therapy, prevention
Limitations		Limited by publication type, PubMed CER randomized controlled trial / systematic review search filter, Cochrane RCT search filter, other（cases of 50＋）etc
Selection Summary		Of the 172 MEDLINE search hits, 1 Cochrane search hit, we used 2 of them which matched with the set PICO

CQ N-5-2 : Is transcranial magnetic stimulation (TMS) useful for chronic migraine and chronic tension-type headache ?

Answer : Transcranial magnetic stimulation (TMS) is believed to be useful in reducing chronic migraine pain and reducing the usage of analgesics but there is insufficient evidence on this. There is insufficient evidence allowing us to believe that it is useful in reducing the intensity of pain from chronic tension-type headache (TTH). The equipment used for the research which would serve as evidence is different from the equipment used in Japan so we do not have certain grounds on which we can recommend TMS.

TMS : transcranial magnetic stimulation

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : Implementation is weakly recommended 〔Consensus 90.0%〕

Summary of overall evidence : C (low)

Commentary :

There are only 4 RCTs which have considered and compared the usefulness of TMS for chronic migraine. Three of them used repetitive magnetic stimulation, and the other one used deep transcranial magnetic stimulation. The transcranial magnetic stimulation study did not observe that it was effective in reducing the number of attacks and the number of days patients had a headache. In 2 of the studies, they observed that it was effective in reducing intensity of pain, and in 3 of the studies, it was effective in reducing the number of times analgesics were used. Overall, there were few cases, and some of the research poorly explained their methods regarding how they made the test blind, and the methods of treatment were different as well so the level of the evidence was low. There was only 1 RCT in which researchers observed a decrease in the intensity of pain from chronic tension-type headache and a rise in the pain threshold so the level of evidence was low.

Period		2001～2019
Database		Cochrane Library, PubMed, NPO Japan Medical Abstracts Society
Words searched	P	chronic migraine, chronic headache
	I/C	transcranial magnetic stimulation
Limitations		Limited by publication type, PubMed CER randomized controlled trial / systematic review search filter, Cochrane RCT search filter, other (cases50+) etc
Selection Summary		Of the 172 MEDLINE search hits etc, we used 6 of them which matched with the set PICO

CQ N-5-3 : Is acupuncture useful for chronic migraine/chronic tension-type headache ?

Answer : An acupuncture may be useful for preventing chronic migraine. Its effects for preventing chronic tension-type headache are not superior to those of physical therapy and relaxation.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : Implementation is weakly recommended 〔Consensus 83.3%〕

Summary of overall evidence : C (low)

Commentary :

There are 2 studies which considered the effects of acupuncture on chronic migraine by comparing it against taking oral medication and both of these studies found that it was significantly more effective in preventing it. However, compared with the oral medication, the placebo effect from acupuncture was fairly high and therefore one must consider the possibility that the significant difference may have been caused by the placebo effect. The effects from acupuncture in preventing chronic tension-type headache, as well as from sham treatments or physical therapy and relaxation, showed that it had reduced the intensity of pain compared with prior to treatment but there was no significant difference in the mitigating effects from acupuncture, sham treatments or physical therapy and relaxation. In terms of safety, there have been no reports mentioning severe adverse events and therefore it is believed to be generally safe.

Period		2001～2019
Database		Cochrane Library, PubMed, NPO Japan Medical Abstracts Society
Words searched	P	chronic migraine, chronic tension-type headache
	I/C	acupuncture
Limitations		Limited by publication type, PubMed CER randomized controlled trial / systematic review search filter, Cochrane RCT search filter, other (cases of50+) etc
Selection Summary		Of the 54 MEDLINE search hits and 1 Cochrane search hit, we used 6 of them which matched with the set PICO

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Chapter O. Herpes Zoster-Related Pain

: CQ O-1～CQ O-8

CQ O-1 : What kind of pathology is herpes zoster ?
CQ O-2 : How is herpes zoster-related pain categorized ?
CQ O-3 : Is vaccine useful for preventing herpes zoster and postherpetic neuralgia (PHN) ?
CQ O-4 : Is the administration of antiviral drugs, after onset of herpes zoster, useful for preventing postherpetic neuralgia ?
CQ O-5-1 : Is pregabalin useful for postherpetic neuralgia (PHN) ?
CQ O-5-2 : Is gabapentin useful for postherpetic neuralgia (PHN) ?
CQ O-5-3 : Is mirogabalin useful for postherpetic neuralgia (PHN) ?
CQ O-5-4 : Is amitriptyline useful for postherpetic neuralgia (PHN) ?
CQ O-5-5 : Is nortriptyline useful for postherpetic neuralgia (PHN) ?
CQ O-5-6 : Is tramadol useful for postherpetic neuralgia (PHN) ?
CQ O-6 : Is performing nerve block therapy soon after onset of herpes zoster, useful for preventing postherpetic neuralgia (PHN) ?
CQ O-7-1 : Is pulsed radiofrequency of the dorsal root ganglion (DRG-PRF) useful for herpes zoster-related pain ?
CQ O-7-2 : Is applying pulsed radiofrequency to the peripheral nerves useful for postherpetic neuralgia (PHN) ?
CQ O-8 : Is spinal cord stimulation useful for postherpetic neuralgia (PHN) ?

O. Herpes Zoster-Related Pain

CQ O-1 : What kind of pathology is herpes zoster ?

Answer : Herpes zoster is a painful small rash that occurs when a latent infection of the sensory ganglion by the varicella-zoster virus (VZV), after someone has had chickenpox, is reactivated. Normally, the rash is treated in a few weeks but sometimes there are various complications that arise afterwards.

VZV : varicella-zoster virus

Commentary :

Varicella-zoster virus (VZV) is a neurotropic virus which invades the sensory ganglion at the onset of chickenpox. However, even after the chickenpox is cured, there is a latent infection in the cranial ganglion and dorsal root ganglion. Due to a variety of factors, when the patient's specific cellular immunity is weakened, the latent infection of VZV is reactivated, causing herpes zoster[1-3]. Normally, this gives onset to acute painful herpes at one dermatome. Frequently, several days before the rash appears, premonitory symptoms manifest such as fever, headache, feeling of discomfort, and pain. Several weeks after onset, the skin lesions heal and may leave scars and pigmentation. The main risk factor is ageing, and in patients aged 50 years old and over, onset clearly increases. Various complications have been reported but the most frequently occurring complication is postherpetic neuralgia (PHN).

PHN : postherpetic neuralgia

CQ O-2 : How is herpes zoster-related pain categorized ?

Answer : Herpes zoster-related pain includes acute mainly inflammatory pain and chronic neuropathic pain.

Commentary :

Herpes zoster-related pain can range from acute to chronic pain[4,5]. The acute pain is a precursor pain and arises when a patient has herpes zoster and as the virus multiplies, patients mainly suffer from an inflammatory pain that arises when nerve cell tissue is damaged as a result of the body's immune response. As a result of chronic impairment of the peripheral nerves and central nerves and secondary sensation, it develops into postherpetic neuralgia (PHN), which is an intractable form of neuropathic pain. There is no standard definition of PHN but it is often defined as pain that persists after 90 days have passed since manifestation of the rash. Allodynia and hyperalgesia are frequent characteristics of PHN. Risk factors

of PHN include aging, precursor pain, severe rash, severe pain, and ocular complications[6].

CQ O-3 : Is vaccine useful for preventing herpes zoster and postherpetic neuralgia (PHN) ?

Answer : Either a live-virus vaccine or sub-unit vaccine works on the chickenpox/varicella-zoster virus (VZV) and prevents the onset of herpes zoster, and prevents the transition to postherpetic neuralgia (PHN). There are no severe side effects. The usefulness of the live-virus vaccine deteriorates over time. We are expecting that future research will investigate how long the sub-unit vaccine is effective.

PHN : postherpetic neuralgia

The sub-unit vaccine is more useful than the live-virus vaccine and although it is possible to vaccinate immunodeficient patients, there are often side reactions.

Recommendation Grade & Summary of Overall Evidence

1) Live-virus vaccine

Recommendation grade : 2 (weak) : Implementation is weakly recommended 〔Consensus 100.0%〕

Summary of overall evidence : B (moderate)

2) Sub-unit vaccine

Recommendation grade : 2 (weak) : Implementation is weakly recommended 〔Consensus 80.0%〕

Summary of overall evidence : B (moderate)

Commentary :

In Japan, the use of the live-virus vaccine for the prevention of herpes zoster was approved in 2016 and the use of the sub-unit vaccine was approved in 2018. The live-virus vaccine is administered once subcutaneously and the sub-unit vaccine is administered intramuscularly twice with a two-month interval between the first and second shot. The sub-unit virus has an adjuvant ($AS01_B$) added to the glycoprotein components of the varicella zoster virus.

Patients with immune function abnormalities and patients undergoing treatment for immunosuppression cannot be vaccinated with the live-virus vaccine. On the other hand, such patients can be vaccinated with the sub-unit virus. The Centers for Disease Control and Prevention (CDC) in the US, stated in 2017 that they recommend the sub-unit vaccine more for preventing herpes zoster and related complications[7].

The sub-unit vaccine may be beneficial for patients who are at high risk of se-

vere herpes zoster. As there is a possibility that systemic side reactions may manifest, it is necessary for the patients to understand this properly when administering it.

RCT : randomized controlled trial

1) Live-virus vaccine

According to 2 RCTs[8,9], during the observation period which is approximately 6 months～3 years, the live-virus vaccine reduced the onset of herpes zoster by 53%, thereby reducing PHN by 67%. There have been no severe adverse events from the live-virus vaccine. The efficacy of the live-virus vaccine deteriorates over time but, there have been reports that it inhibits the onset rate of herpes zoster up to 8 years after the vaccination[10].

2) Sub-unit vaccine

According to 2 RCTs[11,12], in an observation period of approximately 3～4 years, the sub-unite vaccine reduced the onset of herpes zoster by 93%, thereby reducing PHN by 89%. There were no severe adverse events from the sub-unit vaccine. Local reactions at the site of injection (pain, redness, swelling) and systemic side reactions (fatigue, gastrointestinal symptoms, headache, muscle pain, and the chills), a few days after the vaccine, were significantly higher than the placebo. At follow-up approximately 3 years later, researchers confirmed cellular immunity and humoral immunity had been maintained by the vaccine[13].

Period		2005～2019
Database		MEDLINE, Cochrane Central,NPO Japan Medical Abstracts Society
Words searched	P	adult
	I/C	herpes zoster vaccine, chickenpox vaccine/nothing specified
Limitations		Limited by publication type, Pubmed CER randomized controlled trial / systematic review search filter, Cochrane RCT search filter, etc
Selection summary		Of the 279 MEDLINE search hits, 315 Cochrane Central search hits, and 12 NPO Japan Medical Abstracts Society search hits, we used 7 references that matched with the set PICO

CQ O-4 : Is the administration of antiviral drugs, after onset of herpes zoster, useful for preventing postherpetic neuralgia ?

Answer : By administering a patient with an anti-viral drug within 72 hours of onset of herpes zoster, it helps cure the rash and reduce acute pain. Acyclovir does not prevent herpes zoster transitioning into PHN. Famciclovir, valaciclovir, amenamevir may possibly prevent the transition to PHN but we are unable to say that the evidence on this is sufficient.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : Implementation is weakly recommended
〔Consensus 95.0%〕

Summary of overall evidence : C (low)

Commentary：

Antiviral drugs that are used against herpes zoster are acyclovir, famciclovir, valaciclovir, and amenamevir. Famciclovir is a penciclovir prodrug, and valaciclovir is an acyclovir prodrug, with a higher bioavailability rate than acyclovir. One should be careful about usage and dosage when it comes to acyclovir, famciclovir, and valaciclovir as side effects can easily arise in elderly patients and those with impaired kidney function. Amenamevir is a relatively new drug, approved for use in 2017, which by inhibiting the activation of helicase and primase in the chickenpox/varicella-zoster virus (VZV), blocks the duplication of its DNA. It is metabolized in the liver and excreted in the feces, so there is no need to regulate the dosage due to decreased renal function. Furthermore, administering patients once a day is fine. Amenamevir is believed to be easy to use in patients with impaired renal function and those with medication non-compliance. As it is a new drug, there are still few reports on its usefulness.

There are several placebo-controlled RCTs on the usefulness of acyclovir[14-17]. If administration is begun within 72 hours after the rash manifests, it reduces the time until the skin lesions are healed and reduces acute pain. The number of patients who had pain 4 months after onset did not decrease[14,15].

RCT：randomized controlled trial

There is an RCT on the usefulness of famciclovir[18] which used a group administered with acyclovir for the control[19-21]. It has the same effect as acyclovir on rash and acute pain. Among patients who commenced treatment within 48 hours, there were fewer patients with pain at between 1～6 months than with acyclovir[19].

There is also an RCT on the usefulness of valaciclovir which used a group administered with acyclovir for the control[22], and an RCT which used a group administered with famciclovir for the control[23]. It had the same effect on patients' rash as acyclovir and famciclovir[22,23]. The period in which pain disappeared in the acute to sub-acute phase was shorter in the group administered with valaciclovir than it was for the group administered with acyclovir. Furthermore, patients had less pain after 24 weeks in the group that were administered with valaciclovir for 14 days[22].

There is an RCT which investigated the usefulness of amenamevir using a group administered with valaciclovir for the control[24]. There was a higher number of patients in whom the formation of new lesions no longer manifested on the 4th day of treatment in the group administered with amenamevir. There was no difference between the groups in the amount of time that it took for the rash to turn into a scab, no difference in the amount of time it took for the pain to improve and at 91 days, there was no difference in the number of patients suffering from pain.

We are unable to say that there is sufficient evidence on the preventive effects of antiviral drugs for postherpetic neuralgia (PHN) and therefore further investigation is required in future[25]. However, it is clearly useful in the acute phase and therefore antiviral drugs should be administered early for herpes zoster.

Period		2005～2019
Database		MEDLINE, Cochrane Central, NPO Japan Medical Abstracts Society
Words searched	P	herpes zoster, postherpetic neuralgia, zoster associated pain
	I/C	antiviral agent, acyclovir, valacyclovir, famciclovir, Amenamevir/nothing specified
Limitations		Limited by publication type, Pubmed CER randomized controlled trial / systematic review search filter, Cochrane RCT search filter, etc
Selection summary		Of the 47 MEDLINE search hits, 163 Cochrane Central search hits, and 54 NPO Japan Medical Abstracts Society search hits, we utilized references that matched with the set PICO. We used references from before 2005 that we searched for and which were important as papers for reference purposes. From the above, we used 12 search hits

CQ O-5-1：Is pregabalin useful for postherpetic neuralgia（PHN）?

Answer： Pregabalin is useful for postherpetic neuralgia. Research indicates that it is effective in terms of dosage dependency but it does have a high incidence rate of side effects（sleepiness and drowsiness etc.）. One needs to be careful with its usage and dosage in patients with renal dysfunction.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade：1（strong）： Implementation is strongly recommended〔Consensus 100.0%〕

Summary of overall evidence：A（high）

Commentary：

There are several RCTs on the effects of pregabalin on PHN[26-32]. According to a systematic review which summarizes these studies[33], when the outcome was set at a 50%＋reduction in pain, the number needed to treat（NNT）when patients were administered with 150 mg, 300 mg, and 600 mg, was 8.3,5.1, and 3.9, respectively. There were no severe side effects from pregabalin but drowsiness and dizziness did increase with dosage dependence.

Period		2005～2019
Database		MEDLINE, Cochrane Central,NPO Japan Medical Abstracts Society
Words searched	P	postherpetic neuralgia, zoster associated pain
	I/C	pregabalin/nothing specified
Limitations		Limited by publication type, Pubmed CER randomized controlled trial / systematic review search filter, Cochrane RCT search filter, etc
Selection summary		Of the 55 MEDLINE search hits, 139 Cochrane Central search hits, and 9 NPO Japan Medical Abstracts Society search hits, we used 6 references that matched with the set PICO. We used some references from before 2005 which we searched for and were important. From the above, we used 8 references

CQ O-5-2：Is gabapentin useful for postherpetic neuralgia（PHN）?

Answer： Gabapentin is useful on postherpetic neuralgia（PHN）. One must be careful of side effects such as drowsiness and dizziness and be careful of its usage and dosage in patients with renal dysfunction.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 1 (strong) : Implementation is strongly recommended〔Consensus 94.7%〕

Summary of overall evidence : A (high)

Commentary :

Since 2018, gabapentin has been approved for use on neuropathic pain but is not eligible to be covered under the Japanese health insurance system. There are several RCTs on the effects of gabapentin on PHN. According to a systematic review which summarizes these studies[34], when the outcome was a 50%+reduction in pain, the number needed to treat (NNT) when patients were administered with between 1,200～3,600 mg, was 6.9. There were no severe side effects from gabapentin but there were side effects such as drowsiness and dizziness.

Period		2005～2019
Database		MEDLINE, Cochrane Central, NPO Japan Medical Abstracts Society
Words searched	P	postherpetic neuralgia, zoster associated pain
	I/C	gabapentin/nothing specified
Limitations		Limited by publication type,Pubmed CER randomized controlled trial / systematic review search filter, Cochrane RCT search filter, etc
Selection summary		Of the 55 MEDLINE search hits, 147 Cochrane Central search hits, and 1 NPO Japan Medical Abstracts Society search hits, we used 6 references which matched with the set PICO. We used some citations from references prior to 2005 that were important. From the above, we used 1 review

CQ O-5-3 : Is mirogabalin useful for postherpetic neuralgia (PHN) ?

Answer : Mirogabalin is useful for postherpetic neuralgia (PHN). The incidence rate of side effects such as drowsiness and dizziness increase as the dosage increases and therefore physicians need to be careful of this. One must also be careful about its usage and dosage when administering it to patients with renal dysfunction.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : Implementation is weakly recommended〔Consensus 90.0%〕

Summary of overall evidence : B (moderate)

Commentary :

Mirogabalin is a new drug, which became available for clinical use for treating peripheral neuropathic pain as of 2019. According to an RCT which investigated its effects on PHN[35], in groups who had been administered with 15 mg/day, 20 mg/day, and 30 mg/day of mirogabalin, after 14 weeks of treatment, there was a significantly higher number of patients from the mirogabalin groups who had experi-

enced a reduction in pain of 30% or more, compared with the placebo group. (group administered 15mg/day : risk ratio 1.30 ; group administered with 20 mg/day : risk ratio 1.29 ; group administered with 30 mg/day : risk ratio 1.42). The number of patients who had experienced a reduction in pain of 50% or more was significantly higher in the group administered with 30 mg/day than in the placebo group (risk ratio 1.47). It was unclear whether there were any severe side effects related to mirogabalin. The frequency of incidence of side effects such as drowsiness, dizziness and edema tended to increase with a higher dosage. There are few reports yet on the usefulness of mirogabalin ; further accumulation of clinical research is required.

Period		2005～2019
Database		MEDLINE, Cochrane Central, NPO Japan Medical Abstracts Society
Words searched	P	postherpetic neuralgia, zoster associated pain
	I/C	mirogabalin/nothing specified
Limitations		Limited by publication type, Pubmed CER randomized controlled trial / systematic review search filter, Cochrane RCT search filter, etc.
Selection summary		Of the 3 MEDLINE search hits, 15 Cochrane Central search hits, and 0 NPO Japan Medical Abstracts Society search hits, we used 1 search hit which matched with the set PICO.

CQ O-5-4 : Is amitriptyline useful for postherpetic neuralgia (PHN) ?

Answer : We believe that amitriptyline is useful for postherpetic neuralgia (PHN) but we cannot say that there is sufficient evidence and therefore cannot evaluated the size of its effect.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : Implementation is weakly recommended 〔Consensus 100.0%〕

Summary of overall evidence : C (low)

Commentary :

Amitriptyline is a tricyclic antidepressant which was approved in Japan in 2015 as a drug for treating peripheral neuropathic pain. There are placebo-controlled RCTs which have investigated the effects of amitriptyline for PHN[36,37], and researchers observed its analgesic effects after administering patients with the drug for 6～8 weeks. There was a large number of side effects such as drowsiness and dry mouth in the group administered with amitriptyline. However, there was a small number of patients the study targeted and therefore we cannot say that there was a high level of evidence on its analgesic effects. According to a systematic review which summarized the effects of amitriptyline on neuropathic pain[38], it was unclear whether there were severe side effects caused by amitriptyline. There was at least 1 or more patients in the amitriptyline group who more frequently had

adverse events than in the placebo group (risk ratio 1.5, NNH 5.2).

Period		2005～2019
Database		MEDLINE, Cochrane Central, NPO Japan Medical Abstracts Society
Words searched	P	postherpetic neuralgia, zoster associated pain
	I/C	amitriptyline/nothing specified
Limitations		Limited by publication type, Pubmed CER randomized controlled trial / systematic review search filter, Cochrane RCT search filter, etc
Selection summary		Of the 10 MEDLINE search hits, 29 Cochrane Central search hits, and 3 NPO Japan Medical Abstracts Society search hits, we used 1 search which matched with the set PICO. We used some citations from prior to 2005 that were important for reference purposes. From the above, we used 3 references

CQ O-5-5 : Is nortriptyline useful for postherpetic neuralgia (PHN) ?

Answer : Nortriptyline may possibly be useful for postherpetic neuralgia (PHN) but we cannot say that there is sufficient evidence.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : Implementation is weakly recommended 〔Consensus 100.0%〕

Summary of overall evidence : C (low)

Commentary :

Nortriptyline is a tricyclic antidepressant which is the main metabolite of amitriptyline. In Japan, it is not applied for the treatment of pain. There are some RCTs which have reported that nortriptyline has equivalent effects on PHN as gabapentin and amitriptyline[39,40]. However, these studies targeted a small number of patients and did not use a placebo for the control, and therefore we are unable to say that there is sufficient evidence on the analgesic effects of nortriptyline. It is unclear whether there are severe side effects from nortriptyline but there are side effects such as dry mouth, constipation and drowsiness.

Period		2005～019
Database		MEDLINE, Cochrane Central, NPO Japan Medical Abstracts Society
Words searched	P	postherpetic neuralgia, zoster associated pain
	I/C	nortriptyline/nothing specified
Limitations		Limited by publication type, Pubmed CER randomized controlled trial / systematic review search filter, Cochrane RCT search filter, etc.
Selection summary		Of the 6 MEDLINE search hits, 9 Cochrane Central search hits, 1 NPO Japan Medical Abstracts Society search hit, we used 1 search that matched with the set PICO. We used some citations from prior to 2005 which were important for reference purposes. From the above, we used 2 references.

CQ O-5-6 : Is tramadol useful for postherpetic neuralgia (PHN) ?

Answer : Tramadol might possibly be useful for postherpetic neuralgia (PHN). The amount of evidence is insufficient but this does not mean that we should dis-

miss its usefulness.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : Implementation is weakly recommended
〔Consensus 100.0%〕

Summary of overall evidence : C (low)

Commentary :

There is 1 RCT on the effects of tramadol on postherpetic neuralgia (PHN)[41]. By administering patients with the drug for 6 weeks, there was a larger number of patients in the tramadol group who experienced a 50%+reduction in pain compared with the placebo group (risk ratio 1.37, NNT 4.8). However, the number of patients they targeted was small, so the amount of evidence is insufficient. According to a systematic review which summarized the usefulness of tramadol for neuropathic pain[42], it was unclear whether there were any severe side effects from administering patients with tramadol. There was at least 1 more patient who more frequently experienced adverse events in the tramadol group than the placebo group (risk ratio 1.6, NNH 4.2). Adverse events that were particularly common were nausea, constipation, a feeling of fatigue, and dizziness.

Period		2005～2019
Database		MEDLINE, Cochrane Central, NPO Japan Medical Abstracts Society
Words searched	P	postherpetic neuralgia, zoster associated pain
	I/C	tramadol/nothing specified
Limitations		Limited by publication type,Pubmed CER randomized controlled trial / systematic review search filter, Cochrane RCT search filter, etc.
Selection summary		Of the 7 MEDLINE search hits, 35 Cochrane Central search hits, and 4 NPO Japan Medical Abstracts Society search hits, we used 1 search hit that matched with the set PICO. We used citations from prior to 2005 that were important for reference purposes. From the above, we used 2 references.

CQ O-6 : Is performing nerve block therapy soon after onset of herpes zoster, useful for preventing postherpetic neuralgia (PHN) ?

Answer : There are many reports on preventing postherpetic neuralgia (PHN) using various types of nerve blocks. There is also a report by a systematic review which globally scrutinized this therapy. However, there were problems such as a lack of uniformity between the trials and with the control group settings. However, rather than performing a nerve block just once, performing a nerve block continuously or several times has been shown to prevent acute-stage pain after 6 months and after 12 months, and therefore we think that it does prevent PHN.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : Implementation is weakly recommended
〔Consensus 100.0%〕

Summary of overall evidence : C (low)

Commentary :

There is a systematic review based on 9 research studies related to stellate ganglion block, epidural block, paraspinal nerve block and PHN. At 6 months, the incidence rate of PHN was 13.3～33.9% in the control group, and 0～26.7% in the block groups ; at 12 months it was 16～34.4% in the control group, and 2～5.9% in the block group, indicating a significant difference. However, taking into consideration the lack of uniformity between the research studies, researchers concluded that for each type of nerve block, it was more effective when performed continuously or repetitively. Furthermore, they claimed that there were no reports of serious adverse events due to nerve block[43].

Period		2005～2019
Database		MEDLINE, Cochrane Central, NPO Japan Medical Abstracts Society
Words searched	P	mainly postherpetic neuralgia, words similar to this (herpes zoster, postherpetic neuralgia* etc)
	I/C	nerve block/nothing specified
Limitations		Nothing
Selection summary		Of the 53 MREDLINE search hits, 46 Cochrane CENTRAL search hits, and 57 NPO Japan Medical Abstracts Society search hits, we used 1 search hit that matched with the set PICO

*Searches were conducted in English and in Japanese

CQ O-7-1 : Is pulsed radiofrequency of the dorsal root ganglion (DRG-PRF) useful for herpes zoster-related pain ?

Answer : In a randomized controlled trial (RCT) which compared the usefulness before and after a block, researchers indicated in each case that pulsed radiofrequency of the dorsal root ganglion (DRG-PRF) was useful on herpes zoster-related pain. However, the longest period of observation was relatively short at 3 months, so it is unclear whether it is useful over the long-term. They did not mention anything about adverse events but caution is advised.

PRF: : pulsed radiofrequency
DRG : dorsal root ganglion

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : Implementation is weakly recommended
〔Consensus 100.0%〕

Summary of overall evidence : C (low)

Commentary :

There is an RCT which investigated the effects of pulsed radiofrequency of the dorsal root ganglion (DRG-PRF) on 160 patients with PHN currently being administered gabapentin. Researchers reported that the visual analogue scale (VAS) scores were significantly lower in the group which underwent DRG-PRF at 1

VAS : visual analogue scale

week, 2 weeks and 4 weeks after the procedure[44]. In a retrospective study which targeted 59 patients with herpes zoster who underwent DRG-PRF, researchers reported that intensity of pain was significantly lower at 12 weeks, in the acute-stage (within 90 days) group of patients who underwent PRF-DRG (29 patients) than the chronic-phase (90 days+) patients who underwent the procedure (29 patients)[45]. In a retrospective controlled trial on continuous epidural block and DRG-PRF, researchers considered 42 cases. In each case, NRS decreased over time but in the DRG-PRF group, researchers reported that the dosage of the drug decreased and there were fewer patients who transitioned to PHN[46]. Ninety patients who were diagnosed with PHN and had symptoms for 3 months or more underwent DRG-PRF, and researchers reported that 1 week, 4 weeks, 8 weeks, and 12 weeks later, their VAS scores had significantly decreased and their SF-36 scores had improved[47]. In 49 of the patients with PHN who underwent DRG-PRF, researchers reported that the treatment had been effective in alleviating pain at 4 weeks, 8 weeks, and 12 weeks after treatment[48]. There are many reports from one single institution that PRF is useful for herpes zoster-related pain and PHN. In future, researchers will need to consider unified conditions such as method of performing DRG-PRF, time since onset and the site of procedure.

NRS : numerical rating scale

Period		2005～2019
Database		MEDLINE, Cochrane Central, NPO Japan Medical Abstracts Society
Words searched	P	mainly postherpetic neuralgia, words similar to this (herpes zoster, postherpetic neuralgia* etc.)
	I/C	pulsed radiofrequency/nothing specified
Limitations		Limited by publication type,PubMed CER randomized controlled trial / systematic review search filter, Cochrane RCT search filter, other (cases of50+) etc
Selection summary		Of the 17 MREDLINE search hits, 30 Cochrane CENTRAL search hits, 5 NPO Japan Medical Abstracts Society search hits, We used 5 search hits that matched with the set PICO

*Searches were conducted in English and in Japanese

CQ O-7-2 : Is applying pulsed radiofrequency to the peripheral nerves useful for herpes zoster-related pain ?

Answer : There are several double-blind RCTs on applying pulsed radiofrequency (PRF) to the peripheral nerves to treat PHN. These studies indicated that it was effective in each case in providing analgesic effect, had an effect on the dosage of the drug used and on QOL. Furthermore, they indicated that there was no significant difference in severe complications as compared with the control group.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : Implementation is weakly recommended
〔Consensus 100.0%〕

Summary of overall evidence : B (moderate)

Commentary：

There are placebo-controlled double-blind RCTs which have investigated the application of pulsed radiofrequency to the peripheral nerves (intercostal nerve) and performing a nerve block for patients with chest PHN. In one of the controlled trials, one group of patients (30 patients) was administered pregabalin and underwent PRF while the other group (30 patients) was administered pregabalin and given a sham treatment. Researchers reported that pain significantly decreased 4 weeks and 8 weeks later in the PRF group, QOL improved, and patients tended to have a reduced dosage of analgesics[49]. Furthermore, there is a controlled trial which targeted patients with chest PHN, in which one group (48 patients) underwent PRF to the peripheral nerves (intercostal nerves) and one group (48 patients) underwent a sham treatment for 6 months. This study reported that were no severe complications in the PRF group, patients' dosage of analgesics (tramadol) decreased and there was a significant difference in improved physical function QOL (SF-36)[50]. Furthermore, there is a placebo-controlled double-blind RCT in which PRF was applied to the intercostal nerve under ultrasound guidance and while patients were observed over a period of 12 months, researchers reported seeing a significant decrease in VAS scores and a decreased dosage of the patients' drug (pregabalin and acetaminophen)[51].

PRF：pulsed radiofrequency

QOL：quality of life

Period		2005～2019
Database		MEDLINE, Cochrane Central, NPO Japan Medical Abstracts Society
Words searched	P	mainly postherpetic neuralgia, words similar to this (herpes zoster, postherpetic neuralgia*) etc
	I/C	pulsed radiofrequency/nothing specified
Limitations		Limited by publication type, PubMed CER randomized controlled trial / systematic review search filter, Cochrane RCT search filter, Other (50 cases＋) etc
Selection summary		OF the 17 MREDLINE search hits, 30 Cochrane CENTRAL search hits, and 5 NPO Japan Medical Abstracts Society search hits, we used 3 search hits that matched with the set PICO

*Searches were conducted in English and in Japanese

CQ O-8：Is spinal cord stimulation useful for postherpetic neuralgia (PHN)？

Answer： There are few reports on the usefulness of spinal cord stimulations (SCS) to treat postherpetic neuralgia (PHN) and few cases used in the reports. Furthermore, there were no research studies which were compared against a placebo. However, we saw reports indicating an improvement in analgesic effect and activities of daily living (ADL) due to SCS. We also saw several reports on temporary SCS reducing long-term pain in the acute and sub-acute phase.

SCS：spinal cord stimulation

Recommendation Grade & Summary of Overall Evidence

Recommendation grade：No recommendation [Consensus 100.0%]

Summary of overall evidence：D (very low)

Commentary：

There is some researchs which has looked at the analgesic effects of spinal-cord stimulation (SCS) on patients with PHN. Researchers reported performing SCS on 28 patients, in which it had a long-term effect on 23 of them. At the same time, they performed SCS on 4 patients with acute-phase herpes zoster, and in each case it had a long-term effect on the patients[52].

There is one report in which PHN patients with kidney failure underwent SCS and did not have to increase their dosage of the drug and it raised their quality of life (QOL)[53]. In addition, some other reporters performed temporary SCS on patients from the acute phase to around 6 months, and reported that patients had passed through this period without a recurrence of pain[54].

Period		2005～2019
Database		MEDLINE, Cochrane Central, NPO Japan Medical Abstracts Society
Words searched	P	Mainly chronic pain, postherpetic neuralgia, words similar to this (Herpes zoster,Postherpetic neuralgia* etc.)
	I/C	Spinal cord stimulation etc./nothing specified
Limitations		Limited by publication type, PubMed CER randomized controlled trial / systematic review search filter, Cochrane RCT search filter, other (50 cases＋) etc.
Selection summary		Of the 24 MREDLINE search hits, 21 Cochrane CENTRAL search hits, 29 NPO Japan Medical Abstracts Society search hits, we used 3 references that matched with the set PICO. Reference # 52 is outside of our targeted period but it was used in previous guidelines and was considered to be important so we used it this time as well.

*Searches were conducted in English and in Japanese.

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Chapter P. Painful Diabetic Peripheral Neuropathy : CQ P-1～CQ P-7

P. Painful Diabetic Peripheral Neuropathy

CQ P-1 : What kind of pathology is painful diabetic peripheral neuropathy (PDPN) ?

PDPN : painful diabetic peripheral neuropathy

Answer : Painful diabetic peripheral neuropathy (PDPN), is a form of symmetric sensorimotor polyneuropathy, dependent upon nerve length, which arises when high blood sugar persists in diabetic patients, and it is estimated that over 1 million patients are affected by the disease in Japan. Researchers have indicated that advanced glycation end products (AGEs) are involved in the mechanism of onset.

Commentary :

PDPN occurs when high blood sugar persists in diabetic patients, and is a form of symmetric sensorimotor polyneuropathy which is dependent upon nerve length, based upon diabetic neuropathy[1,2].

According to the National Health and Nutrition Survey published by the Ministry of Health, Labor and Welfare (MHLW) in 2016[3], the number of people who are estimated to have diabetes or who are in danger of developing diabetes is approximately 10 million people in each case. On the other hand, the European EURODIAB study and a survey conducted by Japan's 'Society for Thinking about Diabetic Neuropathy', reported that approximately 30% of patients with diabetes suffer from neuropathy, and the prevalence rate of patients with pain which was diagnosed as DN was 40～50%[4-6], and as 75% of these cases are PDPN[7], we roughly calculated that there exists more than 1 million people in Japan with PDPN, and therefore the prevention and treatment of PDPN is a matter that should be tackled to improve the health of the Japanese people.

The incidence rate of people who have suffered from PDPN throughout their whole life consists of 54～59% of patients with type 1 diabetes, and 45% with type 2 diabetes, indicating a higher incidence rate of type 1 diabetes[8]. The prevalence rate of PDPN is known to increase both with a low age of onset of diabetes and length of sickness and also there is a statistically-significant correlation with people with a high BMI, women, and smokers[8]. Researchers have indicated that factors such as increased polyol metabolism, increased oxidative stress, abnormal protein kinase C activity, an accumulation of advanced glycation end products (AGEs), elevated inflammatory cytokines, a decrease in neurotrophic factors, and abnormalities in Na^+ and Ca^{2+} channels are involved. In particular, it is claimed that reactive dicarbonyl and α-oxoaldehyde, which are precursors of advanced glycation end products (AGEs), are factors involved in the onset and development of PDPN. Methylglyoxal is known for its depolarization of sensory nerves, hyperalgesia via

voltage-gated Na^+ channels (Na_V 1.8), promoting neurosecretions of CGRP, and provoking heat and mechanical hyperalgesia via activation of TRPA1[9].

We should also point out that in these guidelines we have not touched upon acute transient PDPN, which may arise at any stage of the disease, and treatment-induced neuropathy of diabetes (TIND), which arises in a short period of time due to blood-sugar control.

CQ P-2 : What are the symptoms of painful diabetic peripheral neuropathy ?

PDPN : painful diabetic peripheral neuropathy

Answer : Typical painful diabetic peripheral neuropathy (PDPN) exhibits glove-and-stocking type dysesthesia, and its pain symptoms match with the characteristics of neuropathic pain. As time passes, hypalgesia, hypanakinesis, and autonomic dysfunction become salient, and diabetic foot ulcers are formed. As for the local form of neuropathy, one sees single nerve dysfunction as well as multifocal neuropathy.

Commentary :

Pain due to PDPN is often the initial symptom for patients who undergo treatment at a healthcare facility[10]. With diabetic neuropathy (DN), which is the basis of PDPN, as small-diameter neuropathy comes first, PDPN begins with bilateral and symmetrical numbness, pain, and dysesthesia in distal sites of the lower limbs and over time, exhibits the glove-and-stocking type symptoms[11,12]. Patients complain of for example a 'pins and needles' like pricking pain, a 'stinging' pain, a burning-hot like pain, a shooting pain like an electric shock, an unpleasant sensation that is accompanied by pain from a stimulus, hyperalgesia, and allodynia. While walking, some patients have described the pain as "a pain like one is walking barefoot over marbles" and "a pain like one is walking barefoot over hot sand".[13] These symptoms match with the characteristics of neuropathic pain. The pain increases at night, and patients may also complain of insomnia, lack of sleep and a feeling of fatigue[5]. Furthermore, some researchers have also observed paresthesia like muscle cramps in the lower limbs[14]. In the initial stage, motor function does not deteriorate, but gradually hypalgesia, hypanakinesis and autonomic dysfunction become salient and there is an elevated risk of the patient falling over[15]. In the final stage, sufferers experience a lack of sensation in the lower limbs and leg ulcers are formed.

With local symptoms, patients may exhibit single nerve or multifocal nerve symptoms[11], and impaired blood flow of a single nerve, due to for example the blockage of a neurotrophic blood vessel, can be the cause of mononeuropathy. On the other hand, multifocal nerve dysfunction, which is seen in the nerve plexus of

the lumbosacral spinal cord, exhibits for example pain and muscular atrophy of the femur as well as unilateral or bilateral hip pain.

CQ P-3 : How is painful diabetic peripheral neuropathy (PDPN) diagnosed ?

PDPN : painful diabetic peripheral neuropathy

Answer : Painful diabetic peripheral neuropathy (PDPN) is diagnosed if the patient's underlying disease is diabetes and also through for example a questionnaire on the patient's pain symptoms and neuropathic pain. Each diagnostic criteria for neuropathic pain is useful for diagnosing PDPN as well.

Commentary :

When diagnosing painful diabetic peripheral neuropathy (PDPN), the basic assumption is that diabetic neuropathy exists as an underlying condition, physicians need to hear the patient's history and clinical conditions, and confirm on the blood test whether the patient's fasting blood glucose is 126mg/d*l* or higher and whether their HbA1C is 6.5% or higher[15]. Pain is generally observed bilaterally and symmetrically and at distal sites, and patients complain of pain symptoms mentioned in the previous CQ[16]. Their condition often deteriorates at night, and as it progresses, symmetrical loss of sensation becomes salient, and this sensory loss may extend to the calf muscles and upper limbs. For example, a Neuropathic Pain Screening Questionnaire, Neuropathic Pain Questionnaire (NPQ), and the McGill Pain Questionnaire may be used to confirm that the pain is neuropathic pain[17,18] Note P1. Neuro-QoL is used to evaluate a decline in quality of life (QOL)[13], while VAS and NRS are used to evaluate intensity of pain. A tactile test using a Semmes-Weinstein filament is widely used for screening, in many cross-sectional studies, the monofilament is known as a useful tool for identifying patients with foot ulcers[19]. Normally, patients experience a reduction or loss of their Achilles tendon reflex, and in some cases a reduction in the kneecap reflex. An abnormality on a nerve conduction study (NCS) and a microfiber nerve function test are required in order to confirm a neurological disorder[20,21]. A skin biopsy to evaluate a patient's intraepidermal nerve fiber density can also be beneficial for diagnosis but such occasions are limited and can be useful in cases where small fiber neuropathy is suspected in patients whose condition has followed an atypical course.

Note P1 : Refer to CQ B-8, B-9

VAS : visual analogue scale

NRS : numerical rating scale

Simple tools used for diagnosing diabetic neuropathy (DN) include the 'Simple Diagnostic Criteria for Diabetic Polyneuropathy' by the 'Society for Thinking About Diabetic Neuropathy' (Table P-1)[22], the 'Toronto Consensus' by the Toronto Diabetic Neuropathy Expert Group (Table P-2)[23], as well as the 'Michigan Neuropathy Screening Instrument (MNSI)' and the Italian Society of Diabetology questionnaire (on neuropathy syndromes). In clinical conditions in Japan, the 'Simple Diag-

nostic Criteria for Diabetic Polyneuropathy' is frequently used.

Table P-1 Simple Diagnostic Criteria for Diabetic Polyneuropathy (distal symmetric polyneuropathy) (Cited from Reference #22)

Essential Criteria
Patient meets the following 2 criteria 1. Diabetes is present 2. Peripheral neuropathy other than diabetic polyneuropathy can be ruled out
Conditional Criteria
Patient has 'neuropathy' if he / she meets 2 or more of the 3 criteria below 1. Exhibits subjective symptoms believed to be based on diabetic polyneuropathy 2. Bilateral reduction of loss of Achilles tendon reflex 3. Bilateral hypopallesthesia of the inner ankles
Precautions
1. Subjective symptoms believed to be based on diabetic polyneuropathy are 1) Bilateral symptoms 2) Patient complains of one of these symptoms: 'numbness' 'pain' or 'dysesthesia' in the toes or sole of the foot When the above 2 criteria are met This does not include when only the above symptoms are present or when only 'psychroesthesia' is present 2. The Achilles tendon reflex test confirms knee standing position 3. Hypopallesthesia is under 10 seconds on a C-128 tuning fork used as a guideline 4. Carefully consider effects due to ageing in elderly patients
Referential Criteria
If any of the following referential criteria are met, patients are considered to 'have neuropathy' even if conditional criteria are not met : 1. Clear abnormality is recognized for one of the test criteria (conduction velocity, amplitude, latency) at 2 or more nerves, for 1 criteria or more at each nerve, on a nerve conduction study 2. From the clinical symptoms, there is clear diabetic autonomic dysfunction. However, it is recommended that an abnormality is confirmed on an autonomic (nerve) function test

Table P-2 The Toronto Consensus by the Toronto Diabetic Neuropathy Expert Group (Cited from Reference #23)

Defined as 'may possibly have diabetic neuropathy' if patient meets 2 or more of the following criteria
1. Symptoms of neuropathic pain 2. Reduced distal sensation in all 4 limbs 3. Reduction or lack of Achilles tendon reflex
Precautions
In some cases, patients have a normal reduction or loss of Achilles tendon reflex. Sometimes patients will have a reduced kneecap reflex as well.

CQ P-4-1 : Is blood-sugar control useful for alleviating symptoms of painful diabetic peripheral neuropathy (PDPN) ?

PDPN : painful diabetic peripheral neuropathy

Answer : There is no evidence on the effects of blood-sugar control in alleviating pain from painful diabetic peripheral neuropathy (PDPN). There is no correlation between the indicators of blood-sugar management, blood-sugar levels and HbA1C, and the severity of diabetic neuropathy (DN). There is also a small-scale research study which indicated that treatments which introduced insulin therapy did not alleviate pain due to PDPN.

Commentary :

Blood-sugar control and administering for example aldose reductase inhibitor drugs are recommended to alleviate symptoms of DN, and there is much evidence indicating a correlation between poor blood-sugar control and aggravated DN. However, there is no research which has investigated the relationship between blood-sugar control and the alleviation of PDPN symptoms.

In the Diabetes Control and Complications Trial (DCCT), a research study which investigated the relationship between blood-sugar levels and DN, researchers indicated that there was no correlation between fluctuations in blood-sugar levels and severity of neuropathy[25]. Furthermore, in the secondary outcome of a research study which targeted diabetic patients with coronary artery disease (BARI-2D)[26], researchers investigated the relationship between HbA1C and neuropathy but they indicated that there was no relationship between a reduction in HbA1c and alleviated neuropathy. Furthermore, other researchers indicated that compared with a non-insulin treatment group, the incidence rate of DN was 30%+higher in the insulin treatment group (OR=1.34 (95% CI 1.08 ～ 1.67)), in which patients who were being treated with a hypoglycemic drug were then transitioned to an insulin treatment and without using an oral hypoglycemic drug, even when they performed reinforced insulin therapy through administering insulin subcutaneously, it did not reduce PDPN-related pain[27]. Therefore, after onset of PDPN, even if blood-sugar control is performed, using blood-sugar levels and HbA1C as indicators, there is a low possibility that pain will be reduced.

CQ P-4-2 : Is blood-sugar control useful for preventing the onset of painful diabetic peripheral neuropathy (PDPN) ?

Answer : There is no direct evidence that prevents the onset of painful diabetic peripheral neuropathy (PDPN). Due to the epidemiological fact that onset of PDPN has diabetic neuropathy as an underlying condition and the fact that blood sugar

regulation prevents the onset of DN, we can indirectly recommend that reinforced blood-sugar control prevents the onset of PDPN.

Commentary：

There are no research studies which have investigated the relationship between blood-sugar control and preventing the onset of PDPN[27]. It has been known that blood-sugar control could prevent the onset of DN in the past, and in a 2012 systematic review[28], reinforced blood-sugar control significantly prevented the onset of DN in type 1 diabetic patients (annual RD 1.84% (95% CI −1.11～−2.56), high recommendation), and reinforced blood-sugar control indicated that it tended to prevent the onset of DN in type 2 diabetic patients as well (annual RD −0.58% (95% CI 0.01-1.17), moderate recommendation). Furthermore, researchers observed that these preventive effects continued for 3～6 years[29]. Therefore, based on the epidemiological fact that 75% of DN patients will develop PDPN and also the fact that blood-sugar regulation prevents the onset of DN, we can verify, albeit indirectly, that reinforced blood-sugar control probably prevents the onset of PDPN. However, as the risk of developing hypoglycemia is elevated while patients are undergoing reinforced blood-sugar control[30], patients need to be treated carefully by a specialist and monitored closely. In recent years, there was a report on the relationship between PDPN and abnormal glucose tolerance, not blood-sugar levels[31], and therefore we expect future research to be conducted on the prevention of PDPN using abnormal glucose tolerance as an indicator.

Period	2004～2019
Database	PubMed, Cochrane Central,NPO Japan Medical Abstracts Society
Words searched	chronic pain,chronic pain treatment,painful diabetic neuropathy, diabetic neuropathic pain, glucose control, hyperglycemia, insulin
P	chronic pain*/painful diabetic peripheral neuropathy
I/C	Treatment/placebo or standard treatment
Limitations	Limited by publication type,PubMed randomized controlled trial/systematic review search filter, Cochrane RCT search filter, other（cases of50＋）etc
Selection summary	Of the 23,620 search hits (painful diabetic neuropathy) and 164,742 search hits (glucose control), we took 19 from our search history, and used 5 of them from a second screening. In addition we used 1 supplementary reference for the commentary

CQ P-5-1：Are Ca^{2+} channels and $\alpha_2\delta$ ligands useful for painful diabetic peripheral neuropathy（PDPN）?

Answer： Ca^{2+} channels and $\alpha_2\delta$ ligands (gabapentinoids) are recommended as first-line drug therapies for neuropathic pain in general and gabapentin and pregabalin are useful for alleviating pain from painful diabetic peripheral neuropathy (PDPN). Furthermore, researchers have indicated that a novel Ca^{2+} channel and $\alpha_2\delta$ ligand, mirogabalin, may possibly be useful for alleviating pain due to PDPN.

PDPN： painful diabetic peripheral neuropathy

Recommendation Grade & Summary of Overall Evidence

1) Gabapentin

Recommendation grade : 1 (strong) : Implementation is strongly recommended 〔Consensus 100.0%〕

Summary of overall evidence : A (high)

2) Pregabalin

Recommendation grade : 1 (strong) : Implementation is strongly recommended 〔Consensus 100.0%〕

Summary of overall evidence : A (high)

3) Mirogabalin

Recommendation grade : 2 (weak) : Implementation is weakly recommended 〔Consensus 100.0%〕

Summary of overall evidence : B (moderate)

Commentary :

In a 2017 systematic review of the effects of gabapentin on PDPN[31], researchers observed that by administering patients with 1,200 mg of gabapentin/day, there was a significant analgesic effect (pain was reduced by 30% or more) in 52% of patients who were administered the drug, and there was an improvement in the Patient Global Impression of Change (PGIC) (RR 1.4 (95% CI 1.3～1.6)). Furthermore, researchers observed a 50% or more reduction in pain in 38% of cases and an improved PGIC (RR 1.7 (95%CI 1.4～2.0)), indicating a high level of evidence on the usefulness of gabapentin for PDPN. However, as they are unable to make a proportion of the dosage for the C_{max} (maximum serum concentration) for administrating gabapentin, researchers claim that fine adjustments need to be made to the dosage[32].

A 2019 systematic review[33] indicated that 47% of patients who were administered 300 mg of pregabalin/day experienced a 30% or more reduction in pain (RR 1.1 (95% CI 1.01～1.2)), and 31% of cases experienced a 50% or more reduction in pain (RR 1.3 (95% CI 1.2～1.5)). Furthermore, PGIC improved in 51% of the patients (RR 1.8 (95% CI 1.5～2.0)). In addition,63% of patients who were administered 600 mg of pregabalin/day experienced a 30% or more analgesic effect (RR 1.2 (95% CI 1.04～1.4)), and 41% of cases experienced a 50% or more analgesic effect (RR 1.4 (95% CI 1.2～1.7)). As for side effects, although there was a low incidence of severe complications, researchers observed many cases of drowsiness (11% of patients administered 300 mg/day,15% of patients administered 600 mg/day) and dizziness (13% of patients administered 300 mg/day, and 22% of patients administered 600 mg/day). In a domestic long-term administration study on PDPN patients[34], the incidence rate of side effects was high at 87% (28% had drowsiness, 27% gained weight, 26% had dizziness, and 19% edema). Therefore, the dosage of

pregabalin needs to be set carefully.

In 2019, there was 1 RCT which studied the newly-available Ca^{2+} channel and $\alpha_2\delta$ ligand, mirogabalin, in a study targeting Asian patients with PDPN[35]. Administering 15 mg of mirogabalin/day, 20 mg/day, and 30 mg/day randomly to subjects, resulted in an average daily reduction in pain scores by −1.34, −1.47 and −1.81, respectively, with the group administered 30 mg of mirogabalin/day experiencing a significant reduction in pain compared with the control group. (RR ?0.5 (95%CI −0.82～−0.17)). However, the amount of research was small so it did not indicate a high level of evidence. Furthermore, researchers observed mild to moderate side effects in each of the groups administered with 15 mg of mirogabalin/day, 20 mg/day, and 30 mg/day, including sleepiness, dizziness, peripheral edema, and weight gain.

Based on the above, by setting and administering the optimal dosage for a Ca^{2+} channel and $\alpha_2\delta$ ligand (gabapentinoids), PDPN-related pain is significantly reduced and the benefits of using mirogabalin may possibly increase through the accumulation of research studies conducted in future.

CQ P-5-2 : Are serotonin-noradrenaline reuptake inhibitors useful for painful diabetic peripheral neuropathy ?

Answer : There is a high amount of evidence on the serotonin-noradrenaline re-uptake inhibitor, duloxetine, and painful diabetic peripheral neuropathy (PDPN). Researchers have indicated that administering 60 mg of duloxetine / day is useful for alleviating PDPN-related pain.

SNRI : serotonin-noradrenaline re-uptake inhibitor

PDPN : painful diabetic peripheral neuropathy

Recommendation Grade & Summary of Overall Evidence

Duloxetine

Recommendation grade : 1 (strong) : Implementation is strongly recommended〔Consensus 100.0%〕

Summary of overall evidence : A (high)

Commentary :

Compared with the tricyclic antidepressant, amitriptyline, SNRIs are safe and easy to use and a good choice for patients with heart disease.

In a research study which evaluated the analgesic effects of SNRI, duloxetine, on PDPN[36], researchers confirmed that pain had decreased by 30% or more in the group administered with 40 mg of duloxetine/day (RR 1.57 (95% CI 1.18～2.07)), and 60 mg/day (RR 1.53 (95% CI 1.3～1.75)). Furthermore, the number of patients who experienced a 50% or more reduction in pain was 20.4% higher in the

group administered 60 mg of duloxetine/day compared with the placebo (RR 1.73, (95%CI 1.44～2.08)), and those who had changed from baseline according to the SF-36 was 2.65 physically speaking (95% CI 1.38 ～ 3.92), thereby confirming a significant improvement (mentally speaking, there was a significant improvement in some of the patients, but the difference was not significant at 1.08 (95%CI-0.32 ～2.48)). In addition, the average change from baseline in the level of patient satisfaction according to the Patient Reported Global Impression (PGI) was －0.6 (95% CI －0.07 ～－0.44), indicating a significant improvement. Side effects manifest from duloxetine depending on the dosage used but severe side effects are rare and there was no significant difference compared with the placebo. However, caution is required with using antidepressants, including SNRIs, in cases of serotonin syndrome. (It should also be pointed out that researchers considered a 120 mg of duloxetine/day group but as the maximum dosage for duloxetine in Japan is set at 60 mg/day, an evaluation was not conducted).

Other SNRI in Japan are venlafaxine and milnacipran. In a Cochrane systematic review, they indicated that 150～225 mg of venlafaxine/day significantly reduced pain compared with the control group or a 75 mg of venlafaxine/day group. (pain reduced by 50% in the 150～225 mg/day group, by 32% in the 75 mg/day group, and 27% in the control group[37]. However, the sample size in the selected research studies was small and the period of observation was also short. Furthermore, there was no meta-analysis so the quality of evidence was not high.

CQ P-5-3 : Are tricyclic antidepressants useful for painful diabetic peripheral neuropathy (PDPN) ?

TCA : tricyclic antidepressant

Answer : Tricyclic antidepressants (TCAs) have the effect of alleviating neuropathic pain, and so are useful for alleviating pain due to painful diabetic peripheral neuropathy (PDPN). However, there are a small number of research studies which have targeted PDPN, and so the quality of evidence is not high and as there is a large number of side effects, one needs to approach this treatment cautiously.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : Implementation is weakly recommended
〔Consensus 100.0%〕

Summary of overall evidence : B (moderate)

Commentary :

It is widely known that the tricyclic antidepressants (TCAs), amitriptyline and nortriptyline have an analgesic effect on neuropathic pain. However, nortriptyline is

not eligible to be used in Japan for neuropathic pain.

In a Cochrane systematic review[38], it was apparent from the analysis of 2 cross-over studies that amitriptyline was useful compared with the placebo, and there is also a report of a meta-analysis which concluded that TCAs are useful for treating PDPN[39]. However, the number of these research reports and the number of patients in them were both small so the accuracy is low. In terms of the side effects, it is known that TCAs tend to cause for example narrow-angle glaucoma, prostatic hypertrophy and orthostatic hypotension as they have an anticholinergic effect[40]. Furthermore, there is a risk of Torsade de Pointes due to extended QT, and therefore it is contraindicated in patients with cardiac circulatory disorders, including heart failure, arrythmia, and recent myocardial infarction.

Based on the above, TCAs have the effect of alleviating neuropathic pain but as the number of research studies which have targeted PDPN is small, the quality of evidence is not high, and also there was much harm caused in cases where the drug was not chosen suitably. However, as the price of TCA drugs is reasonable, we expect further research to be conducted in future focusing on its cost-effectiveness from a healthcare economical point of view.

CQ P-5-4 : Are antiepileptic drugs useful for painful diabetic peripheral neuropathy (PDPN) ?

Answer : Administering 400 mg of lacosamide, an antiepileptic drug, to patients a day reduces pain from painful diabetic peripheral neuropathy (PDPN) by 50% or more. However, there are few high-quality RCTs on the effects of other antiepileptic drugs (carbamazepine, lamotrigine, topiramate, oxycarbazepine) on PDPN. Therefore, it can be considered as an option in cases where other drugs prove to be ineffective. However, there are no drugs in Japan which have an indication for PDPN and one must pay plenty of attention to the fact that they are many side effects.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : No recommendation 〔Consensus 100.0%〕

Summary of overall evidence : B (moderate)

Commentary :

Antiepileptics such as carbamazepine, phenytoin, sodium valproate, clonazepam have long been used for treating neuropathic pain and other neurological disorders. Out of these drugs, there have only been high-quality research studies conducted on carbamazepine ; there is no research on phenytoin and clonazepam.

In a Cochrane systematic review, there was a report indicating that administering 200～600 mg of carbamazepine/day had a significant analgesic effect on neuropathic pain, including PDPN, compared with the placebo. However, as the study targeted a small number of patients, there was no obtainable evidence limited to PDPN[41]. On the other hand, there are many side effects from administering carbamazepine such as drowsiness, dizziness, constipation, nausea, and ataxia, and as there is a risk of developing toxic epidermal necrolysis and Steven-Johnson syndrome, and the risk of incidence is 10 times more frequent in patients with human leukocyte antigen B*1502, which is common among Asians[42], it can be used for trigeminal neuralgia in Japan but one needs to administer it carefully.

In the 2 RCTs on lamotrigine[43], PDPN-related pain had decreased by 50% or more within 12 weeks of being administered between 200～400 mg/day of lamotrigine. However, an assessment of its comprehensive effects were that it was not significant compared with the placebo (RR 1.1 (95% CI −0.8～1.4)). In addition, there was a relatively high number of side effects due to lamotrigine compared with the placebo (RR 1.1 (95%CI 1.01～1.2)), and one should especially pay attention to how common rashes appear (RR 1.4 (95% CI 1.01～2.0)).

In a Cochrane systematic review, research on the usefulness of administering 200～400 mg of tramadol/day was not limited to PDPN, and the sample size was small as well so we were unable to conduct an effective analysis[44]. On the other hand, there was a significantly higher number of occasions when administration of topiramate was discontinued due to side effects, compared with the placebo (RR 3.4 (95%CI 2.4～4.7)), and therefore it was evaluated as not being of high usefulness.

A small-scale research study indicated that administering 300～2,400 mg/day of oxycarbazepine was useful for treating PDPN, but in a systematic review, researchers did not recognize a significant difference compared with the placebo[45]. On the other hand, adverse events were seen to be slightly higher in the group who had been administered oxycarbazepine.

In a systematic review, administering 400 mg/day of lacosamide contributed to a 50%＋decrease in pain (RR 1.4 (95% CI 1.01～1.9)) and improved symptoms with PGIC (RR 1.5 (95% CI 1.2～1.9)). However when 600 mg of the drug were administered per day, researchers did not observe a significant analgesic effect or improved symptoms with PGIC[46,47].

Based on the above, administering 400 mg/day of lacosamide reduced PDPN-related pain by 50% or more but as there are few high-quality RCTs on other antiepileptics, we decided assign a 'no recommendation' grade, and so this drug should be considered as an option in cases where other highly-recommended drugs prove to be ineffective, while at the same time paying attention to preventing and avoiding side effects. Furthermore, one must also pay attention to the fact that there are no antiepileptic drugs which have an indication for PDPN in Japan.

CQ P-5-5 : Is tramadol useful for painful diabetic peripheral neuropathy (PDPN) ?

Answer : Researchers have reported that opioid analgesics are effective in alleviating neuropathic pain, and tramadol is useful for alleviating pain from painful diabetic peripheral neuropathy (PDPN). However, long-term administration of opioid analgesics does not improve physical function in patients and as it leads to an elevated risk of drug dependence and overdose, its disadvantages increase. While being aware that the risk of dependence or overdose on tramadol is low, we do not recommend that anyone other than a pain management specialist treat the patient, someone who can screen the patient prior to administration and conduct rigorous monitoring of the patient once administration of the drug commences.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : Implementation is weakly recommended 〔Consensus100.0%〕

Summary of overall evidence : B (moderate)

Commentary :

Some researchers have reported that opioid analgesics were effective in alleviating neuropathic pain compared with the placebo[40] but there have only been small-scale research studies which have investigated the efficacy of opioid analgesics limited to their effects on PDPN alone[48].

In a systematic review[49], researchers indicated that administering 100～400 mg/day of tramadol, which overseas applies as an opioid analgesic 〔mild〕, reduced neuropathic pain, including PDPN, by 50% or more (RR 2.2 (95%CI 1.02～4.6)). However, considering things like the research was a small size study and there was a high amount of latent bias, the quality of the evidence was low. In other small-scale research studies, researchers reported that the odds of achieving 50% analgesic effect from administering 210 mg of tramadol per day were 3.8 (95% CI 1.8～8.0).

In an RCT on administering 4～8 tablets of tramadol-acetaminophen to treat PDPN, pain due to PDPN decreased significantly in those who took the tramadol-acetaminophen tablets compared with the placebo, and contributed to improved sleep, quality of life (QOL) and mood[50]. However, the sample size was small and the quality of evidence was low and nausea was a frequently observed side effect and therefore one cannot ignore the amount of harm it causes.

Research has indicated that opioid analgesics are effective in treating neuropathic pain over the short-period but according to a systematic review[51] conducted by the US Centers for Disease Control and Prevention (CDC), researchers did not recognize that long-term administration of opioid analgesics improved physical func-

CDC : Centers for Disease Control and Prevention

tion in patients and indicated a strong correlation with the risk of opioid analgesic dependence and an elevated risk of overdose. Furthermore, in a report on prescribing opioid analgesics to patients with neuropathic pain[52], 66% of patients were prescribed with at least 1 type of opioid analgesic, and they reported that 9% of these patients were undergoing long-term administration and only a mere 26% of these patients had used a drug recommended by guidelines prior to being administered with an opioid analgesic. While being conscious of the fact that there is a low risk of dependence and abuse from tramadol, these drugs and psychotropic drugs are not indicated in Japan[53], and we do not recommend that patients be treated by anyone other than a pain management specialist who can conduct rigorous patient screening prior to administration of opioid analgesics and also conduct rigorous monitoring of the patient once administration commences.

CQ P-5-6 : Are opioid analgesics〔strong〕useful for painful diabetic peripheral neuropathy (PDPN) ?

Answer : In the treatment of painful diabetic peripheral neuropathy (PDPN) with opioid analgesics〔strong〕, some research on the usefulness of oxycodone has been reported. However, as mentioned above, researchers did not observe an improvement in physical function through long-term administration of opioid analgesics〔strong〕and this leads to an elevated risk of dependence on opioid analgesics and overdose, we do not recommend that patients be treated by anyone other than a pain management specialist.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : No recommendation〔Consensus 100.0%〕

Summary of overall evidence : B (moderate)

Commentary :

Just like with opioid analgesics〔weak〕, researchers have not proven that opioid analgesics〔strong〕are effective in alleviating neuropathic pain[41], and there are few research studies which have investigated the usefulness of opioid analgesics〔strong〕limited to its effects on PDPN alone[49].

According to 3 research studies which targeted 537 patients with PDPN[54], results indicated that oxycodone controlled-release (CR) tablet reduced moderate pain due to PDPN (RR 1.7 (1.3～2.1), NNT 5.7 (4.0～9.9). Furthermore, according to 2 research studies which targeted 259 patients with PDPN[55], results indicated that oxycodone controlled-release (CR) tablet alleviated pain by 30% or more in 45% of the patients in the studies and the RR of alleviating PDPN-related pain by

30% or more from oxycodone controlled-release tablet was 2.1 (95% CI 1.4～3.1). Researchers indicated that the effective dosage from oxycodone was between 10～120 mg/day, with the average being between 40～60 mg/day.

However, as mentioned above, researchers did not recognize an improvement in physical function through long-term administration of opioid analgesics and as it leads to an elevated risk of dependence and overdose, we do not recommend that patients be treated by anyone other than a pain management specialist.

CQ P-5-7：Is Kampo medicine useful for painful diabetic peripheral neuropathy (PDPN)?

Answer： There are no clear grounds to suggest that Kampo medicine is useful for alleviating pain due to painful diabetic peripheral neuropathy (PDPN).

PDPN：painful diabetic peripheral neuropathy

Recommendation Grade & Summary of Overall Evidence

Recommendation grade：2 (weak)： Implementation is weakly recommended 〔Consensus 95.0%〕

Summary of overall evidence：C (weak)

Commentary：

In a Cochrane systematic review on the effects of pharmacology on PDPN[56], there were 2 research studies which investigated the effects of treatment through Kampo medicine. In 1 of the research studies used, researchers evaluated aspects such as reduced pain, improvement in PGIC, and side effects but as the results were inconsistent and as the scale of the research study was small, there was a high amount of bias, meaning the quality of the evidence was not high. In 10 research studies that were used in another Cochrane systematic review, researchers reported on the usefulness of Kampo medicine but the quality of the evidence used in these research reports was low[57], and researchers had not set objective outcome indicators when conducting the RCT. Therefore, the quality of evidence on the usefulness of Kampo medicine for PDPN is extremely low, and therefore we decided to assign a recommendation grade of '2 (weak)'.

In Japan, there have been reports on the usefulness of gosha-jinki-gan[58,59], a kidney-supporting medicine, for pain and numbness due to PDPN, and the usefulness of shakuya-kukanzo-to[60] on painful muscle cramps (leg cramps) resulting from diabetic neuropathy (DN) and recommend that Kampo (Chinese herbal) medicine treatments be conducted according to the characteristics of each patient's 'individual constitution' (known as 'sho' in this field).

DN：diabetic neuropathy

Period	2004～2019
Database	PubMed, Cochrane Central,NPO Japan Medical Abstracts Society
Words searched	chronic pain,chronic pain treatment,painful diabetic neuropathy, drug therapy, pharmacological treatment, alpha2-delta ligands, gabapentinoids, gabapentin, pregabalin, mirogabalin, antidepressants, serotonin-noradrenaline reuptake inhibitors, duloxetine, venlafaxine, tricyclic antidepressants, anticonvulsants, antiepileptic agents, carbamazepine, lamotrigine, topiramate, oxcarbazepine, lacosamide, opioid analgesics, tramadol, tramadol-acetaminophen, oxycodone, herbal medicine, Kampo medicine
P	chronic pain*/painful diabetic peripheral neuropathy
I/C	Pharmacotherapy/placebo
Limitations	Limited by publication type,PubMed randomized controlled trial/systematic review search filter, Cochrane RCT search filter, other（cases of50＋）etc.
Selection summary	Of the 23,620 search hits on painful diabetic neuropathy, 3,266,997 search hits on pharmacological treatment, we used 15,000 from our search history, and used 15 search hits as a result of our secondary screening process. In addition to this, we used 9 references to supplement the Commentary.

CQ P-6-1：Is nerve block useful for painful diabetic peripheral neuropathy（PDPN）?

PDPN：painful diabetic peripheral neuropathy

Answer： Lumbar sympathetic ganglion block is often used clinically, for the purpose of alleviating pain due to painful diabetic peripheral neuropathy（PDPN）. However, there are no high-quality research studies on this. There are some small-scale research studies which have indicated the usefulness of using radiofrequency thermocoagulation（RF）and pulsed radiofrequency（PRF）in combination with a neurolytic agent.

Recommendation Grade & Summary of Overall Evidence

1）Lumbar sympathetic nerve block

Recommendation grade：No recommendation〔Consensus 95.0%〕

Summary of overall evidence：C（low）

2）Pulsed radiofrequency（PRF）

Recommendation grade：No recommendation〔Consensus 95.0%〕

Summary of overall evidence：C（low）

Commentary：

There is no high-quality evidence on the usefulness of nerve block for treating PDPN[61]. In a retrospective-controlled trial, the findings indicated that the group which underwent a combination of radiofrequency thermocoagulation（RF）of the lumbar sympathetic nerve as well as a neurolytic agent experienced a significant decrease in pain compared with the sympathetic nerve block groups which either had only a neurolytic agent or only RF treatment[62]. Furthermore, in a research study which compared the efficacy of transcutaneous electrical nerve stimulation（TENS）and pulsed radiofrequency（PRF）[63], both groups experienced a significant decrease in pain as a result of the treatments but reported that the PRF group ex-

RF：radiofrequency thermocoagulation

TENS：transcutaneous electrical nerve stimulation

PRF：pulsed radiofrequency

perienced a longer period of reduced pain than the TENS group. In addition to this, we have seen examples of scattered case reports[64] reporting that a lumbar sympathetic nerve block reduced intractable PDPN pain and improved QOL. Therefore, as the quality of evidence on the usefulness of nerve block for treating PDPN is not high, we decided to assign a "no recommendation" grade.

CQ P-6-2 : Is transcutaneous electrical nerve stimulations (TENS) useful for painful diabetic peripheral neuropathy (PDPN) ?

Answer : The research studies on using transcutaneous electrical nerve stimulation (TENS) to manage painful diabetic peripheral neuropathy (PDPN) targeted a small number of cases, and so there is no high-quality evidence. However, as there have been few severe adverse events from using TENS, it is useful for PDPN patients as a form of adjuvant treatment.

TENS : transcutaneous electrical nerve stimulation

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : No recommendation 〔Consensus 100.0%〕

Summary of overall evidence : B (moderate)

Commentary :

A Cochrane systematic review which evaluated the usefulness of transcutaneous electrical nerve stimulation (TENS) for PDPN used 2 research studies[65], but the number of cases was small and the control was not set so the quality of evidence is not high. According to the guidelines of the European Federation of Neurological Societies (EFN)[66], ultra-high frequency TENS has more analgesic effect on the leg muscles in PDPN patients than low frequency TENS, and while they propose that low frequency TENS has a higher analgesic effect than sham stimulation treatments, the number of patients used in each of the research studies cited was small and the bias was high so the quality of evidence is low. Therefore, we decided to assign a "no recommendation" grade. However, as there are few severe adverse events from TENS, excluding the possibility of a cardiac pacemaker intervention, it is useful as a form of adjuvant therapy as it indicates that it provides temporary analgesic effects for PDPN pain.

EFN : The European Federation of Neurological Societies

CQ P-6-3 : Is low level laser therapy (LLLT) useful for painful diabetic peripheral neuropathy (PDPN) ?

Answer : There are no high-quality research studies on using low level laser

LLLT : low level laser therapy

therapy (LLLT) to manage painful diabetic peripheral neuropathy (PDPN). However, there have been few severe adverse events from LLLT, so it is useful as a form of adjuvant therapy for treating PDPN pain.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : No recommendation 〔Consensus 100.0%〕

Summary of overall evidence : C (low)

Commentary :

According to a systematic review which evaluated the effects of LLLT on PDPN[67], 5 out of the 6 research studies which used VAS and screening scores as indicators, indicated that LLLT reduced pain due to PDPN. However, the light wavelength and average output used in these 6 studies varied so in the systematic review, they did not provide adequate analysis and as it had a high amount of research bias, we judged that there was no high-quality evidence available, so we decided to assign a "no recommendation" grade. However there are few severe adverse events from LLLT, and therefore it is useful as a form of adjuvant therapy which indicates that it provides temporary analgesic effects on PDPN pain.

In Japan, there is 1 review article on the efficacy of LLLT for treating diabetic neuropathy (DN), including PDPN[68], which describes an example of their own test on the usefulness of LLLT based on the analgesic mechanism.

Period	2005～2019
Database	PubMed, Cochrane Central,NPO Japan Medical Abstracts Society
Words searched	chronic pain, pain treatment, painful diabetic neuropathy, neural blockade, nerve block, sympathetic nerve block, radiofrequency, pulsed radiofrequency, transcutaneous electrical nerve stimulation, TENS, low level laser therapy, LLLT
P	chronic pain
I/C	Interventional treatment (nerve block, pulsed radiofrequency, transcutaneous electrical nerve stimulation, low reactive-level laser therapy) /nothing specified
Limitations	Limited by publication type,PubMed randomized controlled trial/systematic review search filter, Cochrane RCT search filter, other (cases of 50+) etc.
Selection summary	Nerve block : We used one NeuPSIG recommendation which was found through a manual search, and 2 controlled trials which had different controls. TENS : Of the 14 search hits, we used 4 after a secondary screening, and in addition used 1 other guideline. LLLT : Of the 9 search hits, we used one after secondary screening.

CQ P-7 : Is spinal cord stimulation (SCS) useful on intractable painful diabetic peripheral neuropathy (PDPN) ?

Answer : In cases where no analgesic effect is obtained from other forms of treatment for intractable pain, it is worth trying the surgical treatment of spinal cord stimulation (SCS), but there is a risk that severe complications may arise.

SCS : spinal cord stimulation

Recommendation Grade & Summary of Overall Evidence

Recommendation grade：2（weak）：Implementation is weakly recommended〔Consensus 90.0%〕

Summary of overall evidence：B（moderate）

Commentary：

Spinal cord stimulation（SCS）, which had a peculiar analgesic mechanism called 'neuromodulation', is a surgical treatment which is worth trying in cases of intractable pain and when analgesic effect was not obtained from other forms of treatment[Note P2], and its usefulness for PDPN has been reported on. There are 2 RCTs which have considered the usefulness of SCS for treating PDPN[69,70], and researchers found that pain significantly decreased and QOL improved in the group that underwent SCS compared with the control group. Furthermore, in a research study which observed the long-term results over a 2-year period, researchers reported obtaining an analgesic effect of 50% or higher through using SCS in 65% of patients with PDPN.[71]. Moreover, in a 5-year observational study which investigated 48 patients[72], 80% of patients who underwent implant surgery continued to use SCS, and researchers indicated that the weakened effects of treatment were related to an increase in their Michigan Diabetic Neuropathy Score（MDNS）（RR 3.9（95% CI 1.3～11.6））. However,3 of these research studies had been conducted under the initiative of one single institution, and therefore there was a high risk of bias, and there was a higher number of dropout cases, and therefore the quality of evidence was not high. In addition, we believe it can be harmful for patients as in these RCTs, there was a report of a death（details are unknown）for example, due to the complication of an epidural hematoma. Therefore, we assigned a recommendation grade of '2B' but physicians should exercise plenty of caution when deciding whether to apply SCS and when performing this procedure.

Note P2：Refer to CQ D-9

PDPN：painful diabetic peripheral neuropathy

Period	2005～2019
Database	PubMed, Cochrane Central,NPO Japan Medical Abstracts Society
Words searched	chronic pain, painful diabetic neuropathy, spinal cord stimulation
P	chronic pain*
I/C	Surgical treatment（spinal cord stimulation）/nothing specified
Limitations	Limited by publication type, PubMed randomized controlled trial/systematic review search filter, Cochrane RCT search filter, other（cases of50＋）etc.
Selection summary	Of the 21 search hits, we used 4 of them which matched with the set PICO.

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Chapter Q. Fibromyalgia : CQ Q-1～CQ Q-7

Q. Fibromyalgia

CQ Q-1：What kind of pathology is fibromyalgia ?

FM：fibromyalgia,
FMS：fibromyalgia syndrome

FSS：functional somatic syndromes

Answer： Fibromyalgia (FM) is a form of chronic pain of unknown cause which manifests at a wide number of sites on the body. The cardinal sign is a systemic stiffness, and its accompanying symptoms are diverse physical symptoms and mental symptoms. With each of these symptoms, just like with chronic pain, clinical tests including a physical examination and general image testing will not detect any abnormalities which can explain the symptoms. Symptomatically, it is a form of rheumatoid arthritis which belongs to the functional somatic syndromes (FSS), frequently occurs in middle-aged women, and although there are no problems with their vital prognosis, apart from suicide, their quality of life (QOL) and activities of daily living (ADL) are remarkably impaired. Similar to reports in the West to date, it is a disease with a relatively high incidence rate with 1.7～2.1% of the population suffering from this condition. Through future advances into the causes of this disease and research into its pathology, there is the possibility that our concept of FM as a disease may undergo a significant transformation. For ICD-11, we have used the chronic pain categories that were issued by the International Association for the Study of Pain (IASP) in 2015, in which fibromyalgia is classified into chronic primary pain and chronic widespread pain.

Commentary：

In terms of fibromyalgia (FM) as a disease concept, we came up with 231 search hits on PubMed for "concept," and 177 of these reports were in English. There were 114 search hits related to its "definition", and 101 of these reports were in English. Of these, 7 reports were related to either the disease concept of FM or a definition of the disease[1-7]. On the other hand, we came up with 45 search hits for "definition" and "concept" on NPO Japan Medical Abstracts Society. Of these, 12 were either about disease concept or gave a definition of the disease, and we used 11 of these search hits[8-18]. Considering these points, we decided on the following disease concept at this present stage in Japan.

FM is not a new and emerging disease；it has been known for a while under the same pathology, and is called various names such as non-articular rheumatism, psychogenic rheumatism, soft tissue rheumatism, fibrositis, fibrositis syndrome, fibromyalgia (FM), fibromyalgia syndrome (FMS). Fibrositis gives us the picture of a pathological inflammation in the connective tissue but as the existence of a classical image of inflammation cannot be confirmed with FM and in clinical tests, as it does not detect findings which would suggest the existence of inflammation, in 1990

the American College of Rheumatology proposed a definition of the disease and proposed highly useful classification criteria so FM/FMS became commonly used. Furthermore, pathologies which resemble FM include chronic fatigue syndrome (CFS), irritable bowel syndrome (IBS), temporomandibular joint disorder, young children skipping school, panic disorder, Gulf War syndrome, sick building syndrome, chemical sensitivity, interstitial cystitis. There is also functional somatic syndromes (FSS), and mental illnesses such as depression and somatoform disorders (somatic symptom disorders : DSM-5), and differentiating them from FM is a constant problem but at the present stage, no clear difference between them has been shown. Furthermore, there have been some cases of young (child) cases, although the number of such cases is small, and unlike in adult cases, these cases share the same psychosocial background prior to onset, and non-drug treatments are more important than pharmacotherapy.

ACR : American College of Rheumatology

CFS : chronic fatigue syndrome

At the present stage, the concept and definition for FM is, "a form of chronic pain of unknown origin which covers a wide area of the body and its cardinal sign is a systemic stiffness, with various physical symptoms and nerve / mental symptoms as its accompanying symptoms, and with each of its symptoms, just like with chronic pain, clinical tests including a physical examination and general image testing will not detect any abnormalities which can explain the symptoms." FM is an isolated form of rheumatoid arthritis belonging to FSS, occurs frequently among middle-aged women, and although there are no problems with its vital prognosis, apart from suicide, their quality of life (QOL) and activities of daily living (ADL) are remarkably impaired. Similar to reports in the west to date, it is a disease with a relatively high incidence rate with 1.7 ～ 2.1% of the population suffering from this condition. On the other hand, FM pain is not nociceptive pain ; it is a neuropathic central pain with lesions that cannot be pinpointed, which established what is called 'central sensitization,' one type of central nervous system syndrome (CSS). Another common characteristic is that these pathologies tend to mutually coexist. It is also sometimes called for example "central dysfunctional pain" and "psychosocial pain".

CSS : central sensitization syndrome

CQ Q-2 : What are the clinical symptoms of fibromyalgia in Japan ?

Answer : The clinical symptoms of fibromyalgia in Japan are basically the same clinical symptoms exhibited as in cases in the Western countries (clinical signs / clinical images) (Table Q-1, Table Q-2). However, there is a large number of studies that have reported differences in how frequently clinical symptoms have manifested depending on the patient's ethnicity and region. Moreever, in cases of juvenile fibromyalgia, although basically they exhibit the same symptoms as adult pa-

Table Q-1 Positive rate of clinical symptoms among Japanese fibromyalgia patients
(Cited from reference #28)

Clinical symptoms	+Rate [%]
Pain	
Systemic pain	91.7
Arthritic pain	82.0
Muscular pain	70.9
Other soft tissue pain	47.2
Rheumatoid arthritis-like symptoms	
Stiffness	63.7
Dry symptoms	49.3
Hand swelling	23.8
Mouth ulcer	22.4
Fever	17.6
Itchy skin	17.5
Raynaud's phenomenon	12.9
Rash	10.9
Photosensitivity	9.8
Physical symptoms	
Fatigue	90.9
Abdominal symptoms	44.2
Abnormal BM	43.1
Cold sensation	32.5
Palpitations	30.1
Burning sensation	26.8
Difficulty breathing	24.3
Weight fluctuations	23.7
Snoring	19.1
Allergic symptoms	17.1

Clinical symptoms	+Rate [%]
Neurological symptoms	
(Dull) headache	72.9
Numbness	64.8
Dizziness	44.6
Anacatesthesia	25.4
Photophobia	15.8
Hand root canal syndrome	5.5
Mental symptoms	
Sleep disorder	73.1
Anxiety	64.3
Depressive mood	60.5
Feeling frustrated	41.1
Reduced concentration	38.7
Forgetfulness	18.5
Sleep apnea	7.8
Disturbance of consciousness	2.0
(Dull) headache	
Headache	66.2
Tension-type headache	37.0
Vascular headache	6.0
Migraine	57.0
Dull headache	33.8
Cystitis symptoms	
Pollakiuria	15.0
Residual urine	15.0
Painful urination	10.3

Clinical symptoms	+Rate [%]
Systemic pain	
Upper-right of body	89.9
Upper-left of body	81.9
Right half of body	91.4
Left half of body	79.1
Dull headache	59.7
Arthritic pain	
Knee	64.4
Shoulder	63.5
Elbow	49.5
Fingers	45.2
Feet	44.7
Crotch	44.2
Toes	29.8
Sternoclavicular	19.2
Jaw	16.3
Cough	16.3
Odynophagia	12.2
Wheeze	11.0
Menstrual pain	13.0
Dysmenorrhea	22.3

Table Q-2 Positive rate of clinical symptoms among American fibromyalgia patients
(Cited from reference #31)

Clinical symptoms	+Rate [%]
Sleep disorder	89.1
Fatigue / lethargy	88.6
Myalgia	85.2
Muscle weakness	70.2
Numbness	67.6
Cognitive impairment	66.3
Headache	64.7
Xerostomia	53.3
Insomnia	51.8
Sensitive	49.1
Dry eyes	47.5
Depressive mood	47.5
Impaired eyesight	47.0

Clinical symptoms	+Rate [%]
Irritable bowel syndrome (IBS)	46.3
Heartburn	44.4
Itch	44.3
Dizziness	42.1
Constipation	41.9
Abdominal colic	41.5
Upper abdominal pain	40.3
Tinnitus	41.4
Neurotic	39.7
Nausea	37.7
Diarrhea	33.6
Difficulty breathing	32.3
Difficulty hearing	29.8

Clinical symptoms	+Rate [%]
Hair loss	23.6
Stomatitis (mouth ulcer)	22.4
Wheeze	21.4
Reduced appetite	21.1
Raynaud's phenomenon	20.1
Chest pain	29.2
Rash	17.1
Photosensitivity	16.7
Loss of taste / dysgeusia	14.4
Fever	13.4
Allergy	9.3
Vomiting	9.1
Epileptic fit	1.7

n = 2,784

tients, it is unclear whether there is any difference in the positive rate of symptoms.

Commentary :

We cited 12 cases in total, including reports with analytical data on a large number of cases, and reports which targeted patients with juvenile fibromyalgia. However, there were zero reports on Japanese patients. We had 13 search hits for "clinical symptoms" "clinical pictures" and "clinical signs" on the NPO Japan Medical Abstracts Society site[5,19–33], and we cited 1 report which had a relatively high number of cases analyzed. Furthermore, there was 1 survey report by a research team from the Ministry of Health, Labour and Welfare (MHLW)[31], and we cited 1 study on juvenile fibromyalgia[33].

The frequency of incidence of clinical symptoms, clinical signs or clinical pictures was reported on based on observation studies of various patient groups. At the current stage, there are almost no clear reports on whether there are any differences in symptoms according to the patient's country, region, ethnicity, gender, age group, religion, culture or economic situation. As these guidelines are for Japanese residents of Japan, we collected data on Japanese people residing in this country. In other words, there are analytical data based on an analysis of adult patients undergoing treatment at 1 facility[30] and studies from a large number of facilities obtained from a nationwide epidemiological survey[31], whereas for children, we only have the analytical results from 1 facility cases[33].

CQ Q-3 : What kinds of pathology coexist with fibromyalgia ?

Answer : There is no common consensus on what comorbidities exists but myalgic encephalomyelitis (ME) and chronic fatigue syndrome (CFS) very frequently coexist with fibromyalgia. Other (comorbid) diseases we can cite include various types of rheumatoid arthritis, self-immune disorders, autoimmune endocrine disorders, functional somatic syndromes (FSS), and mental diseases and disorders.

ME : myalgic encephalomyelitis
CFS : chronic fatigue syndrome syndrome
FSS : functional somatic syndromes

Commentary :

In an analysis of 1.7 million American fibromyalgia (FM) patients who were discharged from hospital (a retrospective study), the most common comorbidities for primary FM were non-specific chest pain, mood disorder, and spondylosis/disc disorder/other low-back pain (LBP). The most frequent underlying disease of secondary FM were essential hypertension, dyslipidemia, coronary atherosclerosis/other heart disease and mental disorder[34]. In a review by Giacomelli et al.[35], their analysis focused particularly upon patients with FM and autoimmune rheumatoid arthri-

tis and non-rheumatic disease as comorbidities and found that among the FM cases, the prevalence rates were systemic lupus erythematosus (SLE) in 32% of cases, Sjogren's syndrome in 18% of cases, primary antiphospholipid syndrome in 16.7% of cases, rheumatoid arthritis in 15～43% of cases, psoriatic arthritis in 53.3% of cases, Behcet's disease in 18% of cases, Hashimoto's disease in 31% of cases, autoimmune thyroiditis in 19% of cases, and diabetes in 17% of cases.

Furthermore, in a retrospective study into the medical records of 1,100 adult patients with FM, they found that more than 50% of the patients had 7 or more existing comorbidities. The most common comorbidities were chronic joint pain and osteoarthritis (OA) (88.7%), followed by depression (75.1%), migraine and headache (62.4%) and anxiety (56.5%)[36]. Often diseases with the same pathophysiology as FM (for example, irritable bowel syndrome, interstitial cystitis, tension-type headache) coexist, and there are reports also of coexisting peripheral disorders and inflammation (for example, self-immune disorders, osteoarthritis)[37].

The results of a US study of the prevalence rate of FM adults among 8,446 patients have been described below. We have estimated the prevalence rate among the general population (prevalence rate of fibromyalgia), and the odds of the FM prevalence rate among the general population (corrected by age, gender, ethnicity, education, obesity, smoking history, region). The following were reported as significant : myocardial infarction (2.9/95% CI 1.31～3.64), heart disease (2.47/1.43～4.28), stroke (2.37/1.09～5.15), liver disease (5.07/2.11～12.21), kidney disorder (4.16/1.97～8.81) high blood pressure (2.32/1.44～3.75), diabetes (2.73/1.74～4.30), chronic obstructive pulmonary disease (2.64/1.47～4.75), asthma (2.88/1.88～4.04), stomach ulcer (4.15/2.59～6.66), rheumatoid arthritis (5.76/3.25～10.12), systemic lupus erythematosus (SLE) (1.65/0.46～5.86), migraine (7.68/4.70～12.53), hepatitis (1.15/0.39～3.37), influence/pneumonia (3.38/2.26～5.07), depression (7.9/4.94～12.65), anxiety (7.62/4.84～11.99), bipolar disorder (7.03/3.21～15.39), other mental diseases (9.40/5.39～16.41), colorectal cancer (0.4/1.1～5.09), liver cancer (41.25/2.99～569), pancreatic cancer (32.86/2.69～401)[38]. The prevalence rate of mental comorbidities for fibromyalgia (FM) and widespread chronic pain among Japanese patients was 96.9% in the case of FM and 93.5% in the case of widespread chronic pain[39]. Although widespread chronic pain does not meet the diagnostic criteria for FM, it is a disease in which patients complain of pain throughout the whole body and its pathology and method of treatment are believed to be the same. Somatoform disorder (somatic symptom disorders : DSM-5), dysthymic disorder, major depressive disorder, personality disorder, pervasive developmental disorder (PDD), dissociative disorder, and schizophrenia are highly frequent comorbidities. For a diagnosis of fibromyalgia (FM), the medical practitioner needs to be an expert on psychiatric disorders.

CQ Q-4 : Is pharmacotherapy useful for fibromyalgia ?

Answer : Administering between 300～600 mg/day of pregabalin and 60 mg/day of duloxetine has been shown to provide analgesic effects. Generally, considering how adverse events and severe side-effects manifest with pharmacotherapy, one should confirm improvement in analgesic effect and QOL before administering medication.

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : Implementation is weakly recommended 〔Consensus 100.0%〕

Summary of overall evidence : QOL : C (low), Adverse events : B (moderate)

Commentary :

Administering between 300～600 mg/day of pregabalin continuously over a period of 12～26 weeks reduces medium to strong pain[40]. Furthermore, other conditions, QOL and ADL improved in the same way. Although administering 60 mg/day of duloxetine has analgesic effects, the NNT for indicating an analgesic effect of 50% or more is 8[41].

NNT : number needed to treat

The results of a systematic review were that 7 reports met the eligibility criteria, and 3 of these reports[42-44] were used for meta-analysis. As the drugs that were used in the research papers that were eligible for meta-analysis were limited to mirtazapine, nonsteroidal anti-inflammatory drugs (NSAIDs) and oxycodone, the validity of other forms of pharmacotherapy is low. The indicators used for meta-analysis were NRS (an indicator of analgesic effect), improvement in the pain scale of 30%+, and the SF-36 (QOL). The 3 reference papers which were eligible for meta-analysis were mirtazapine, NSAIDs, and oxycodone and the drugs used in each respective one were different so there was a high amount of inconsistency. Researchers indicated that in terms of both analgesic effect and QOL, there was possibly no significant difference in analgesic effect that was clinically significant between the pharmacotherapy group and placebo group, and considering factors such as the small size of the sample and the lack of consistency, the evidence was low. It was possible that there were more adverse events in the pharmacotherapy group but the strength of the evidence was moderate.

With standard fibromyalgia (FM), 10～50 mg / day of amitriptyline is recommended but when depression is also present or for FM patients with general anxiety, they recommend 60 mg/day of duloxetine. When depression is not a comorbidity, one should consider administering 50～450 mg/day of duloxetine and pregabalin. There are some guidelines which do not recommend opioid analgesics 〔strong〕[45-48]. In a Cochrane review, researchers evaluated intensity of pain, physi-

cal function, mental function, and level of patient satisfaction after administering 60 mg/day of duloxetine over a period of 8～12 week for patients with FM. The % of patients who experienced a 50% reduction in pain or more, compared with the placebo, was high for FM at 13.1% (RR：1.57, 95% CI：1.2 ～ 2.06). Physical and mental function were evaluated using the SF-36, and the difference in the average change from the baseline was 1.28 for physical aspects (95% CI：－0.33～－2.89), and 3.11 for mental aspects (95% CI：0.59～6.02)；in both cases it had improved significantly. The level of patient satisfaction was evaluated using the Patient Reported Global Impression (PGI), and the difference in the average change from baseline was －0.45 (95% CI：－0.37～－0.18), in any case it had improved significantly. Mirtazapine significantly and greatly reduced patients' average NRS scores (pain scores) compared with the placebo (difference：0.44,95% CI：－0.72 ～ －0.17). Compared with the placebo, from 6 weeks onwards, there was a larger number of patients in the group who were administered mirtazapine whose NRS scores decreased by 30% from the baseline. (45.5% vs. 30.8%). Furthermore, with mirtazapine, both the pain-related QOL , which is evaluated on the survey of the impact of FM (Japanese version) and the SF-36, had improved. There were more adverse events from mirtazapine than the placebo (68.8% vs. 56.7%), which included drowsiness (32.1% vs. 7.4%), weight gain (17.7% vs. 0.9%), and increased appetite (11.6% vs. 3.3%)[48]. In a systematic review of 3 RCTs on fibromyalgia (FM), researchers evaluated changes in intensity of pain and QOL in a group that was only administered tramadol, a group that was administered a combination of tramadol/acetaminophen and a group that was administered a combination of tramadol/amitriptyline. The differences in the average changes in pain intensity from the baseline were －13 (95%：CI：－25.37 ～－0.63), －12 (95% CI：－18.77 ～ －5.23), and －13 (95% CI：－19.08～－6.92), respectively；showing a significant improvement. QOL was evaluated using the Fibromyalgia Impact Questionnaire (FIQ) and the average change in FIQ from baseline in the tramadol／acetaminophen group was －6.00 (95% CI：－9.55～－2.45), indicating an improvement but in the Tramadol alone group it was －2.9 (95% CI：－10.86～5.06)；a significant effect was not observed. In light of the above, tramadol is not useful enough when implemented alone.

Period		2005～2019
Database		MEDLINE, Cochrane Central,NPO Japan Medical Abstracts Society
Words searched	P	Fibromyalgia
	I/C	Pharmacotherapies etc./placebo etc
Limitations		Limited by publication type,PubMed CER randomized controlled trial / systematic review search filter, Cochrane RCT search filter, etc
Selection summary		Of the 14 MEDLINE search hits, and 1 Cochrane Central search hit, we used 9 of them which matched with the set PICO

CQ Q-5：Is exercise therapy useful for fibromyalgia ?

Answer： Exercise therapy improves the severity of fibromyalgia (FM), quality of life (QOL), pain, fatigue, physical function, and muscle stiffness so we believe it is useful.

QOL：quality of life

Recommendation Grade & Summary of Overall Evidence

Recommendation grade：1 (strong)： Implementation is strongly recommended〔Consensus 100.0%〕

Summary of overall evidence：B (moderate)

Commentary：

There have been 4 reports of Cochrane systematic reviews which investigated the effects of exercise therapy (aerobic exercise, aquatic exercises, muscle-strengthening exercises etc.) on chronic pain[49–52]. These studies targeted adults aged 18 years old + with chronic pain and used a waiting-list group or regular-treatment group for the control. There were problems with the bias risk and sample size in these research studies but researchers indicated that with each outcome (QOL, pain, fatigue, physical function, muscle stiffness), there was a high possibility that exercise therapy was effective on fibromyalgia (FM) both 3 months after and 4 months after intervention. Furthermore, in the EULAR (European League Against Rheumatism) guidelines (2016)[53], they recommend aerobics and stretching exercises. Therefore, we believe we can recommend implementing exercise therapy.

Period		2005～2019
Database		MEDLINE, Cochrane Central,NPO Japan Medical Abstracts Society
Words searched	P	Fibromyalgia*
	I/C	Exercise/nothing in particular
Limitations		Limited by publication type,PubMed CER randomized controlled trial / systematic review search filter, Cochrane RCT search filter, etc
Selection summary		Of the 20 MEDLINE search hits,and 19 Cochrane Central search hits, we used 5 of them which matched with the set PICO

CQ Q-6：Are alternative therapies useful for fibromyalgia ?

Answer： Although cognitive-behavioral therapy (CBT) alone improves depression, it is unable to improve pain and quality of life (QOL). CBT which uses hypnotherapy and guided imagery (image therapy) do improve pain and QOL. Although mind-body exercise therapy (Qigong, Tai chi, Yoga) does not improve pain, it does significantly improve depression and QOL. Balneotherapy (hot-spring therapy) and hydrotherapy do improve pain and QOL. We do not recommend transcranial magnetic stimulation (TMS) or massage therapy (including myofascial release). No particular adverse events or severe side effects have been reported.

CBT：cognitive-behavioral therapy

TMS：transcranial magnetic stimulation

myofascial release

Recommendation Grade & Summary of Overall Evidence

1) Transcranial magnetic stimulation (TMS)

Recommendation grade : No recommendation 〔Consensus 100.0%〕

Summary of overall evidence : B (moderate)

2) Cognitive-behavioral therapy (CBT)

Recommendation grade : 2 (weak) : Implementation is weakly recommended 〔Consensus 94.7%〕

Summary of overall evidence : C (low)

3) Cognitive-behavioral therapy (CBT) using hypnotherapy, guided imagery (image therapy)

Recommendation grade : 2 (weak) : Implementation is weakly recommended 〔Consensus 86.4%〕

Summary of overall evidence : B (moderate)

4) Balneotherapy, hydrotherapy

Recommendation grade : 2 (weak) : Implementation is weakly recommended 〔Consensus 85.7%〕

Summary of overall evidence : C (low)

5) Massage therapy

Recommendation grade : 2 (weak) : No implementation is weakly recommended 〔Consensus 100.0%〕

Summary of overall evidence : C (low)

Commentary :

Even though cognitive-behavioral therapy (CBT) improved depression, it did not improve pain or QOL. Patient's self-efficacy for their own pain improved significantly. In CBT performed for around 6～12 weeks (for a total of 6～72 hours), researchers found that its effects still persisted from 2 months later to 4 years later[54].

CBT using hypnotherapy significantly improved pain and QOL. When CBT was used in combination with hypnotherapy over a period of 12～14 weeks, in which patients underwent training for about 90～120 minutes every week, effects persisted up to 6 months later. When training was used with a combination of hypnotherapy and physical therapy (conducted 8 times over a 12-week period/1 hour per session), researchers recognized its effects up to 3 months later and 6 months later. CBT which used guided imagery (image therapy) significantly improved pain and improved QOL. With training using image therapy (over a period of 4～6 weeks, with patients undergoing around 1～1.5 hour sessions each time/day for 4 consecutive days/week), researchers observed its effects up to 6～10 weeks later[55-60].

Although exercise therapy which used mind-body exercise therapy (Qigong, Tai chi, Yoga) did not improve pain, depression and QOL significantly improved[61]. Through undergoing a total of 6～24 hours of training over a 4～12 week period,

researchers observed that it was effective up to 3～6 months later[62,63]. There is a report that repetitive transcranial magnetic stimulation (rTMS) did improve fibromyalgia (FM) pain and depression, as well as QOL but there was some reporting bias, and some inconsistencies in the results[64]. Subjects underwent 10～14 sessions of rTMS from between 2 weeks up to 3 months, and researchers observed its effects 30 days later. Balneotherapy (hot-spring therapy) and hydrotherapy improve pain and QOL. A total of 200-300 minutes of balneotherapy and hydrotherapy over a period of 2～5 weeks had significantly improved pain and QOL 14 weeks later[65].

Massage therapy (including Swedish style massage, connective tissue massage, lymph drainage, myofascial release, acupressure, Chinese style massage, tui na, etc.) did not have a clear effect on pain or depression[66-71]. In EULAR, no implementation is weakly recommended[53].

Period		2005～2019
Database		MEDLINE, Cochrane Central,NPO Japan Medical Abstracts Society
Words searched	P	Fibromyalgia*
	I/C	alternative medicine etc.
Limitations		Limited by publication type,PubMed CER randomized controlled trial / systematic review search filter, Cochrane RCT search filter, etc
Selection summary		Of the 19 MEDLINE search hits, and 7 Cochrane CENTRAL search hits, we used 20 that matched with the set PICO

CQ Q-7 Is multidisciplinary treatment useful for fibromyalgia ?

Answer : Compared with pharmacotherapy, multidisciplinary treatment improves Fibromyalgia Impact Questionnaire (FIQ) results and pain. However, its effects on other parameters such as physical capabilities and mental aspects remain unclear.

FIQ : Fibromyalgia Impact Questionnaire

Recommendation Grade & Summary of Overall Evidence

Recommendation grade : 2 (weak) : Implementation is weakly recommended
〔Consensus 100.0%〕

Summary of overall evidence : B (moderate)

Commentary :

In many cases single forms of treatment, such as conventional pharmacotherapy, provide insufficient effects on fibromyalgia (FM). Therefore, one considers the efficacy of providing multidisciplinary treatment from the start to patients, instead of combining individual therapies together based on the individual patient. Researchers have reported that multidisciplinary treatment has a tendency to improve QOL and pain, rather than just using pharmacotherapy alone[72-74]. QOL and pain are closely interrelated, and therefore multidisciplinary treatment is recommended as a strategy for treating FM.

There are individual reports indicating the efficacy and harmlessness of multidis-

ciplinary treatment on many parameters including physical capabilities such as ADL, as well as mental aspects such as depression. In Japan, it already has the objective of establishing uniform accessibility to a chronic pain treatment system and they are pushing ahead with the construction of multidisciplinary centers. We hope that between these numerous facilities, widespread mutual research will progress, for example with reducing medication due to multidisciplinary treatment, facilitate a return-to-work for patients, and seek out ways to provide even better treatment programs for them.

Period		2005～2019
Database		MEDLINE, Cochrane Central, NPO Japan Medical Abstracts Society
Words searched	P	Fibromyalgia*
	I/C	Multidisciplinary treatment/pharmacotherapy
Limitations		Limited by publication type,PubMed CER randomized controlled trial / systematic review search filter, Cochrane RCT search filter, etc
Selection summary		Of the 46 MEDLINE search hits, and 11 Cochrane Central search hits, we used 3 of them which matched with the set PICO

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慢性疼痛診療ガイドライン

2021 年 6 月 30 日　第 1 版第 1 刷発行©

編集・発行　慢性疼痛診療ガイドライン
作成ワーキンググループ

このガイドラインは「厚生労働行政推進調査事業費補助金（慢性の痛み政策研究事業）：慢性疼痛診療システムの均てん化と痛みセンター診療データベースの活用による医療向上を目指す研究」で作成された.

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発 行 所　真興交易㈱
医書出版部

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東京都港区南麻布 2-8-18
電　話　03-3798-3315㈹
振　替　00170-0-147227

印刷・製本　㈱リーブルテック

Clinical Practice Guideline for the Management Chronic Pain

The Committee for Clinical Practice Guideline
for the Management of Chronic Pain
First edition first published in 2021
by Publication Department, Shinko Trading Co. Ltd.

These guidelines are prepaired by “Health, Labour and Welfare Policy Research Grants (Research on chronic pain) in Japan : Research for the Uniform Accessibility to Chronic Pain Management Systems and Improved Healthcare Utilizing Pain Center Treatment Databases”

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Produced by Livretech Co. Ltd.