Clinical practice guideline for chronic headache 2013

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The Chronic Headache Clinical Practice Guideline Development Committee of Japan.

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1 | INTRODUCTION

With the publication of The International Classification of Headache Disorders by the International Headache Society in 1988, standardized headache diagnostic criteria began to be used worldwide, which established the foundation for headache research. As a result of this development, research on chronic headache led by the Japanese Society of Neurology and Japanese Headache Society also progressed. In 2002, the “Chronic Headache Treatment Guideline 2002” was published as one of the Japanese Society of Neurology treatment guidelines. Then in 2004, the International Headache Society published the International Classification of Headache Disorders 2nd Edition (ICHD-II). In response to this development, the “Clinical Practice Guideline for Chronic Headache” was compiled in Japan by the Study Group for Chronic Headache Clinical Practice Guideline Development (Principal Researcher: Fumihiko Sakai) as a Mental Health Scientific Research Project funded by a grant-in-aid from the Ministry of Health, Labour and Welfare Research. In 2006, the book entitled “The Clinical Practice Guideline for Chronic Headache (edited by Japanese Headache Society)” was published by the publisher Igakushoin. Furthermore, in 2007, the ICHD-II was translated into Japanese language and published as the “Japanese Version of the International Classification of Headache Disorders 2nd Edition (translated by International Headache Classification Promotion Committee of Japanese Headache Society)”.

1.1 | New approaches for “Clinical Practice Guideline for Chronic Headache” from 2010

As triptans have become widely used, clinical practice for chronic headache has also been changed in Japan and there was a need
to revise the “Clinical Practice Guideline for Chronic Headache” (2006) developed by the Japanese Headache Society. With the objective to develop a new edition of "Clinical Practice Guideline for Chronic Headache," a guideline development committee consisting of 39 members was formed in November 2010. Then, in 2011, it was decided that the revision project would be carried out mainly by the Japanese Society of Neurology and Japanese Headache Society, with collaboration from the Japanese Society of Neurological Therapeutics and the Japan Neurosurgical Society. Among the 39 members on the Japanese Headache Society Guideline Committee, 12 group leaders served as guideline committee members and the other 27 members as coordinating members of the Japanese Society of Neurology. With the addition of seven evaluation/coordination members, the guideline development committee comprised 46 members to carry out the revision tasks.

1.2 | Procedures and organization

The first task was to decide how to structure the contents, and it was decided to adopt the same format as in the second edition. Since the second edition used the format of clinical questions (CQ), this format was maintained with the contents divided into the following eight chapters, as in the second edition.

I Headache: general considerations
II Migraine (1. diagnosis • epidemiology • pathophysiology • precipitating factors • prognosis, 2. acute treatment, 3. prophylactic therapy)
III Tension-type headache
IV Trigeminal autonomic cephalalgias
V Other primary headache disorders
VI Medication-overuse headache
VII Headaches in children
VIII Genetics

In addition to the above eight chapters, it was decided also to include the "Guideline for Self-injection of Sumatriptan at Home," “Guideline for Migraine Treatment by Valproic Acid (Provisional Edition),” and “Guideline for Migraine Treatment by Propranolol (Provisional Edition)” as Appendix A, Appendix B, and Appendix C.

Search for scientific evidence was conducted by a systematic approach. Using the criteria as shown in Table 1, the literature was searched on public databases including PubMed, Cochrane Library, and Ichushi, a database that contains bibliographic citations and abstracts from more than 2500 biomedical journals and other serial publications published in Japan. The results were consolidated, and recommendation grades were assigned for individual CQs (Table 2). During the execution of these tasks, Mr Masahiro Yoshida, Director of Medical Information Network Distribution Service (MINDS), kindly provided valuable guidance. Taking this opportunity, we would like to express our profound gratitude for his assistance. It was also decided to construct abstracts of important articles as far as possible and make them accessible on the website of the society.

1. After each committee member wrote the part that he or she was responsible for, the contents were discussed within each group. The results were opened to all committee members on the designated website, and the contents were brushed up. On June 3, 2012, all committee members met to brush up all the items. Then, on November 17, 2012, a symposium on the guideline was held during the Congress of Japanese Headache Society to invite opinions from a wide audience. In addition, the opinions from the evaluation/coordination members were collected, and public comments were invited from all society members. Final compilation of the guideline took place on March 20, 2013, and the guideline was published in May.

1.3 | Contents of guideline

As was also stated in the 2006 version, this guideline is intended to support clinical practice, and not to restrict clinical practice. In the clinical setting, in addition to the guideline, physicians’ experience is important. We hope that this guideline will facilitate better clinical decision-making and will improve patients’ quality of life (QOL).

The new guideline adopted the CQ used in the 2006 version and added 19 new CQs. All the previous CQs were reviewed and rewritten.

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**TABLE 1** Oxford center for evidence-based medicine levels of evidence (2001)

| Level | Descriptions |
|-------|--------------|
| 1a    | Systemic review (with homogeneity) of RCTs |
| 1b    | Individual RCT with narrow confidence interval |
| Ic    | All or none |
| IIa   | Systematic review (with homogeneity) of cohort studies |
| IIb   | Individual cohort study (including low quality RCT, for example, <80% follow-up) |
| IIc   | Outcomes research |
| III   | Systematic review (with homogeneity) of cohort studies |
| IV    | Case series (and poor quality cohort and case-control studies) |
| V     | Expert opinion without explicit critical appraisal, or based on physiology, bench research, or first principles |

**TABLE 2** Grades (strength) of recommendation

| Grade | Strongly recommended | Recommended | No clear evidence to support recommendation for use |
|-------|----------------------|-------------|-----------------------------------------------|
1.4 | Closing remark

Essentially based on the 2006 version of the Clinical Practice Guideline for Chronic Headache, the new guideline has added the latest information and presented the concept of international standards of chronic headache care. If the guideline of 2002 is considered the first edition of clinical practice guideline for chronic headache in Japan, then the 2006 guideline is the second edition, and the present guideline is the third edition. We hope that this guideline will become an indispensable document for physicians to provide effective and standardized treatments in their clinical care for chronic headache. We have also planned to produce an English version of the guideline to disseminate information to the world on the clinical practice guideline for chronic headache in Japan.

Last but not the least, we would like to convey our gratitude to all the committee members for their tremendous efforts and dedication that have led to the publication of this guideline.

May 2013
Nobuo Araki
Takao Takeshima
Representing the Chronic Headache Clinical Practice Guideline Development Committee

1.5 | On publication of the English edition of the guideline

While we were drawing up a plan to compile the English Edition of the Clinical Practice Guideline for Chronic Headache 2013 which was originally written in Japanese language, we were confronted with a dilemma: 1 month after we published the original guideline in Japanese, the International Classification of Headache Disorders 3rd Edition beta version (ICHD-3beta) was published. Since the diagnoses of headache disorders worldwide would be made according to the ICHD-3beta, we felt that a new guideline based on the diagnostic criteria of the 2nd edition (ICHD-II) would be less valuable. The Chronic Headache Clinical Practice Guideline Development Committee discussed over this issue and confirmed that there would be no problem to update the guideline based on the diagnostic criteria of ICHD-3beta. This guideline is the final product of the Committee’s efforts with editorial input from Teresa Nakatani. During the compilation of this guideline, we were greatly saddened by the sudden demise of Professor Junichi Hamada who had contributed enormously to the development of the guideline. We would like to convey our sincere condolences. We hope that this book will help many people around the world to understand the clinical practice for headache disorders in Japan.

February 24, 2015
Nobuo Araki
Takao Takeshima
Hisaka Igarashi
Toshihiko Shimizu
Representing the Chronic Headache Clinical Practice Guideline Development Committee

2 | HEADACHE: GENERAL CONSIDERATIONS

2.1 | CQ I-1 How is headache classified and diagnosed?

Recommendation

Headache should be classified and diagnosed according to the ICHD-3beta. Grade A.

2.2 | CQ I-2 How are primary headaches and secondary headaches differentiated?

Recommendation

Secondary headache should be suspected for the following: (1) headache with sudden onset, (2) headache never experienced before, (3) headache different from the customary headache, (4) headache that has increased in frequency and intensity, (5) headache begins after age 50, (6) headache with neurological deficit, (7) headache in a patient with cancer or immunodeficiency, (8) headache in a patient with psychiatric symptoms, and (9) headache in a patient with fever, neck stiffness, or meningeal irritation. Intensive investigations are required. Grade A.

2.3 | CQ I-3 How is subarachnoid hemorrhage diagnosed?

Recommendation

When subarachnoid hemorrhage is suspected, a rapid and precise diagnosis and treatment by a specialist are necessary. The typical symptom is “sudden excruciating headache never experienced before.”

Subarachnoid hemorrhage may manifest warning symptoms from mild bleeding. Pay attention when there is abrupt onset of headache accompanied by nausea or vomiting, dizziness, diplopia or impaired vision, and delirium.

Regarding neuroimaging, early-stage CT or fluid-attenuated inversion recovery (FLAIR) MR imaging has high diagnostic value. When subarachnoid hemorrhage is strongly suspected, a lumbar puncture should be considered even when neuroimaging is negative.

Several days following the onset of headache, cerebral ischemic symptoms may appear due to cerebral vasoconstriction. Grade A.

2.4 | CQ I-4 What are the procedures for managing headache in the emergency room?

Recommendation

For patients presenting with a major complaint of headache, differentiation between primary headache and secondary headache is the most important. First screening for life-threatening headaches should be performed, with special attention to headache due to subarachnoid hemorrhage. History taking, physical and neurological examination, and neuroimaging (CT/MRI) are important for diagnosis of headache. Even when neuroimaging shows no abnormality,
lumbar puncture should be considered if subarachnoid hemorrhage is strongly suspected. Grade A.

2.5 | CQ I-5 How should primary care physicians manage headache?

Recommendation
Primary care physicians should bear in mind to differentiate between primary headaches and secondary headaches and, in case of difficulties with diagnosis, should promptly refer the patient to a specialist. For primary headaches, primary care physicians should be able to correctly diagnose and treat especially migraine and tension-type headache. Grade A.

2.6 | CQ I-6 How should dentists manage headache?

Recommendation
Dentists should differentiate between headache and temporomandibular disorder.
In the differential diagnosis of toothache of unknown cause, the possibility of the involvement of the teeth by primary headaches and secondary headaches has to be considered.
Cases with concurrent headache which are difficult to diagnose should be referred promptly to specialists. Grade B.

2.7 | CQ I-7 Are headache clinic and headache specialists necessary? Is collaborative care useful for primary headaches?

Recommendation
Headache clinic is necessary to improve the satisfaction and QOL of patients with chronic headache. In the headache clinic, diagnosis and treatment should be provided by headache specialists with expert knowledge not only in highly emergent secondary headaches but also in chronic headaches. Especially, when primary care physicians have difficulties with diagnosis or treatment of headache, referral to or consultation with headache specialists is recommended. Collaboration between primary care physicians and headache specialists for the management of primary headaches increases the satisfaction and QOL of patients. Collaborative care for primary headaches should be further promoted. Grade A.

2.8 | CQ I-8 How are algorithms used?

Recommendation
The diagnosis and treatment of headache start from differentiating secondary headaches, especially the life-threatening headaches. Next, the primary headaches, including migraine, should be diagnosed. Simple diagnostic algorithms are a powerful tool that provides clues to the diagnosis of headaches in the clinical setting. Grade B.

2.9 | CQ I-9 How is the impact of headache on individuals measured?

Recommendation
Use of questionnaires that have been validated for reliability and validity is recommended to measure the impact of headache on individuals. Grade B.

2.10 | CQ I-10 How are questionnaires and screeners used?

Recommendation
Questionnaires on headache include those that measure the disability in daily living, QOL, treatment effect, and satisfaction, as well as diagnostic screeners for the diagnosis of migraine. Use of these questionnaires and screeners contributes to routine clinical care by improving the communication between patients and physicians, and providing simple and rapid diagnosis as well as objective evaluation of therapeutic effects. Grade B.

Background and objective
Although a careful medical interview is important for the diagnosis and treatment of headache, it is difficult to obtain sufficient information from patients during the busy consultation hours. Various interview sheets and screening tools have been developed to support the routine clinical care for primary headaches, with the objective to attain accurate diagnosis and treatment as well as effective communication between physicians and patients.

Comments and evidence
The following interview sheets and screening tools for headache have been evaluated for reliability and validity.

Diagnostic screening tools
1. 3-Question Headache Screen
2. ID Migraine

The 3-Question Headache Screen is useful for the diagnosis of migraine, with the following three items: (1) recurrent headaches that are disabling, (2) headaches lasting at least 4 hours, and (3) no new or different headaches in the past 6 months.

The ID Migraine is useful for the diagnosis of migraine, with the following three items: disability, nausea, and sensitivity to light. Because the screening tools are simple and can be self-administered, their usefulness in primary care is attracting attention. In Japan also, a similar validation study was conducted as a multicenter, blinded, clinical epidemiological study.

Questionnaires on disability and severity
1. Headache Impact Questionnaire (HImQ)
2. Migraine Work and Productivity Loss Questionnaire (MWPLQ)
3. Migraine Disability Assessment (MIDAS) Questionnaire
4. PedMIDAS
5. Headache Impact Test (HIT)
6. HIT-6
Migraine disability assessment and HIT are representative of short questionnaires.

The MIDAS questionnaire is a short questionnaire developed based on the HI-mQ. It divides daily living into work and school, household work, and leisure and social events and evaluates the degree of disability from the missed days of these activities. This scale is useful not only for migraine but also for headache in general. It has been translated into various languages including Japanese, and the reliability and validity have been evaluated. In addition, MIDAS for adolescents and children, Ped-MIDAS, has also been developed and is useful for the evaluation of headaches in children.

The HIT is a 6-item questionnaire, developed through the construction of the HIT. It can be used as a paper-based test and consists of six questions. The questions are on pain intensity, impact on daily activities, impact on social activities, and mental burden due to headache. There are five choices for each question. Each choice has a predetermined score, and the total score for all six questions is calculated. Based on the total score, the impact of headache on daily living is classified into four grades. The short questionnaire can be completed within one minute. The HIT-6 has been translated into more than 25 languages.

The reliability of the Japanese version has also been validated.

Questionnaires on patient QOL

1. Migraine-specific Quality of Life Questionnaire (MSQ)
2. Migraine-specific Quality of Life Measure (MSQOL)

The MSQOL is a questionnaire consisting of 25 items developed for the evaluation of the QOL of patients with migraine. High reliability and validity have been reported.

The MSQ version is composed of 14 items on family events, leisure activities, daily activities, work, concentration, tiredness, feeling energetic, canceled work or daily activities, needed help, stopped work or daily activities, social activities, frustration, burden, and afraid. The impact of migraine on QOL is assessed by three dimensions: role function restrictive, role function preventive, and emotional function. The Japanese version of MSQ version 2.1 has also been evaluated for reliability and validity.

Questionnaires on treatment

1. Migraine Therapy Assessment Questionnaire (MTAQ)
2. Migraine Assessment of Current Therapy (Migraine-ACT) questionnaire
3. Migraine Disability Assessment (MIDAS) questionnaire
4. Headache Impact Test (HIT)

The MTAQ is a 9-item questionnaire that requires a response of “yes or no” to each question. The questionnaire was developed to assess therapeutic effect and identify patients who require changes in treatment.

The Migraine-ACT further simplifies the MTAQ. The therapeutic effect and whether the patient need to change treatment can be assessed by answering “yes” or “no” to four questions: (1) Does your migraine medication work consistently, in the majority of your attacks? (2) Does the headache pain disappear within 2 hours? (3) Are you able to function normally within 2 hours? (4) Are you comfortable enough with your medication to be able to plan your daily activities? Due to its sensitivity and simplicity, this questionnaire is recommended to be used also in primary care.

Although the MIDAS questionnaire is a tool for evaluating disability, by performing this test before and after treatment, the change in score or grade may indicate the effectiveness of treatment.

For HIT and HIT-6 also, by performing the test before and after treatment, the change in score may indicate treatment efficacy.

- Search terms and secondary sources
- Search database: PubMed (2011/9/1)
  - Headache All fields 54 507
  - [screening] 23 380
  - [questionnaire] 1212 & [screener] 10
  - Migraine All fields 24 758
  - [screening] 7645
  - [questionnaire] 661
  - [screener] 9
  - Cluster headache 2766
  - [screening] 1062
  - [questionnaire] 63
  - [screener] 0
  - Tension-type headache 2416
  - [screening] 994
  - [questionnaire] 162
  - [screener] 0
  - Primary headache 5549
  - [screening] 2795
  - [questionnaire] 231
  - [screener] 4
- Search database: Ichushi Web for articles published in Japan (2011/12/21)
  - headache 795 & [questionnaire] 30
  - [interview sheet] 88
  - [screening] 0 & [screener] 0

2.11 How is the headache diary used?

Recommendation

The headache diary provides a wealth of information for the management of headache, including the number of days with headache, the number of days of taking medications, and the treatment effect. It is also useful from the viewpoint that it reinforces patient-physician...
communication. Use the headache diary in combination with clinical interview is recommended. Grade A.

2.12 | CQ I-12 What types of primary headaches require treatment?

Recommendation
The primary headache is a target for treatment if the patient is suffering from it, regardless of the severity. When it is evident that the headache causes disability in daily living, the headache should to be treated aggressively. Grade A.

2.13 | CQ I-13 What types of primary headache require hospitalized treatment and what are the treatment methods?

Recommendation
The primary headaches that require hospitalized treatment include (1) when life-threatening secondary headache cannot be excluded; (2) rare headaches that require diagnosis and treatment; (3) for the purpose of confirming the efficacy of special treatment; (4) status migrainosus and refractory or chronic cluster headache; and (5) for the purpose of treating medication overuse headache. Grade B, C (admission requirement: B, inpatient treatment: C).

2.14 | CQ I-14 How is pharmacotherapy using over-the-counter medications planned?

Recommendation
The choice of pharmacotherapy depends on the severity of headache, the frequency of headache, and the degree of disability. Among the primary headaches, mild headaches can be controlled by over-the-counter (OTC) medications. When the headache is moderate or severe and does not respond to OTC medications, or when OTC medications have been taken frequently, pharmacotherapy under a physician’s guidance is recommended. Physician should set a limit on the number of days of drug taking (not more than 10 days a month) to prevent patients from developing medication overuse headache and instruct patients who take medications relatively frequently to choose single-ingredient OTC drugs. Grade A.

2.15 | CQ I-15 Are herbal medicines (Kampo) effective?

Recommendation
Based on traditional medicine, herbal medicine (Kampo) is a treatment that had been used empirically. Various herbal medicines have been used empirically for headache and have shown effects. Scientific evidence has been accumulated in recent years, and the effectiveness for headache is being proven. Grade B.

2.16 | CQ I-16 What other therapies are available, apart from pharmacotherapy?

Recommendation
Apart from pharmacotherapy, other therapies for primary headaches include behavioral therapy, physical therapy, and supplements. Because these therapies are not covered by health insurance in Japan, and some adverse events have also been reported, use of these therapies should consider the characteristics of individual patients and also accountability. Details of nonpharmacotherapy for migraine and tension-type headache can be found in the respective sections. Grade B, C (depending on therapy).

2.17 | CQ I-17 Is cognitive-behavioral therapy effective for primary headaches?

Recommendation
As a nonpharmacotherapy for primary headaches, cognitive-behavioral therapy has been evaluated by randomized controlled trials in European and North American countries, and the therapeutic effect has been confirmed. Using cognitive-behavioral therapy, headache can be ameliorated in 30%-50% of the patients and therapeutic effect comparable to pharmacotherapy may be expected. The therapeutic effect increases when cognitive counselling therapy is combination with pharmacotherapy. However, the number of facilities in Japan offering cognitive-behavioral therapy for headache is limited. Grade B.

2.18 | CQ I-18 Does anxiety/depression coexist with primary headaches?

Recommendation
Patients with migraine and tension-type headache tend to develop psychological states such as anxiety and depression as a level of symptom, and these psychological states are associated with chronicity of headache. In addition, psychiatric disorders such as mood disturbances (major depression) and anxiety disorder (including panic disorder) are common comorbidities. Paying attention to the coexistence of these psychological states and psychiatric disorders is clinically important. Grade B.

2.19 | CQ I-19 How should occupational health physicians and brain health checkup physicians manage headache?

Recommendation
Occupational health physicians and brain health checkup physicians should participate actively in providing headache
medical care for workers and brain checkup examinees with headaches. Grade A.

2.20 | CQ I-20 How should school physicians manage headache?

Recommendation
In addition to primary headaches such as migraine and tension-type headache, headaches encountered in schools also include headache as one form of psychosomatic pain. In schools, school nurses look after children who complain of headache, but school physicians are also sometimes consulted regarding headaches. Therefore, school physicians should possess correct knowledge on primary headaches (especially migraine). Headaches may be related to the circumstances surrounding the children, such as stress with teachers and classmates in school or problems at home. Therefore, understanding the background of the children and the mental issues during the development process is sometimes necessary. Grade A.

2.21 | CQ I-21 What are the important points in patient education and doctor-patient relationship?

Recommendation
As for all disciplines of medical care, good doctor-patient relationship is necessary to provide high-quality headache care. A headache management program that puts emphasis on patient education improves disability and functional health status and increases satisfaction. When informing a patient of the accurate diagnosis, the doctor should at the same time explain the appropriate management and treatment of headache to the patient, and educate the patient where necessary. Grade A.

2.22 | CQ I-22 How to evaluate the medico-economic effect of appropriate treatment for migraine?

Recommendation
In Japan, it is estimated that migraine causes an economic loss of approximately three hundred billion yen per year.\(^1\) Compared to traditional migraine medications, proper use of triptan greatly improves patients’ QOL at an acceptable level of increase in medical expenses, and the health benefit leads to reduction in overall cost to the society. Grade B.

2.23 | CQ I-23 Is there a need for multidisciplinary team approach to headache treatment?

Recommendation
Despite advances in headache treatment, there remain many patients with chronic headache in whom pharmacotherapy alone is not adequately effective. For the treatment of refractory headache, a multidisciplinary team led by the headache specialists and supported by other health professionals including clinical psychotherapists, physical therapists, occupational therapists, nurses, pharmacists, and acupuncturists is essential. Grade A.

2.24 | CQ I-24 How is headache or facial or neck pain attributed to cervical carotid or vertebral artery dissection diagnosed?

Recommendation
Headache or facial or neck pain attributed to cervical carotid or vertebral artery dissection is new, acute-onset headache, with facial or neck pain, usually unilateral (ipsilateral to dissecting artery), and severe. The pain of vertebral artery dissecting aneurysm is mostly localized in the back of the head or the neck, whereas pain due to internal carotid artery dissection occurs commonly in the front of the head or the forehead.

The pain is persistent, but resolves within 1 month.

The modes of onset can be classified broadly into ischemic (cerebral infarction, transient ischemic attack), hemorrhagic (subarachnoid oozing), and others (headache, local symptoms, others).

For diagnosis, while cerebral angiography is essential for a definitive diagnosis, noninvasive imaging techniques such as MRI, magnetic resonance angiography (MRA), and three-dimensional CT angiography (3D-CTA) are useful and provide important imaging information especially on dissection. Grade A.

2.25 | CQ I-25 How is headache attributed to spontaneous intracranial hypotension diagnosed and treated?

Recommendation
1. Diagnosis
Headache attributed to spontaneous intracranial hypotension is diagnosed according to the ICHD-3beta. Confirmation of cerebrospinal fluid leak by diagnostic imaging is important. The ICHD-3beta does not indicate the criteria for diagnostic imaging; therefore, diagnosis should use the guidelines proposed by the Japanese Ministry of Health, Labour and Welfare Study Group (published in October 2011) as reference. Grade B.

2. Treatment
Conservative treatments such as bed rest and fluid infusion should be conducted. When there is no improvement and whether the site of cerebrospinal fluid leak can be identified by diagnostic imaging, invasive treatments such as epidural blood patch should be considered. Grade A.

3 | MIGRAINE

3.1 | Diagnosis, epidemiology, pathophysiology, precipitating factors, prognosis

3.1.1 | CQII-1-1 How is migraine classified?

Recommendation
Migraine is classified in accordance with the ICHD-3beta. The ICHD-3beta adopts a hierarchical classification system. Although classification to the first digit level (headache type) or second digit level (subtype) is usually applied to general practice, classification to the third digit level (subform) is recommended for clinical settings such as specialist practice and headache center. Grade A.

3.1.2 | CQII-1-2 How is migraine diagnosed?

Recommendation
Migraine is diagnosed according to the diagnostic criteria of the ICHD-3beta. The ICHD-3beta adopts a hierarchical classification system. In general practice, the use of the diagnostic criteria up to the second digit level (subtype) is recommended. In specialist practice and headache centers, diagnosis according to the diagnostic criteria to the second digit level (subtype) or to the highest level of the third digit (subform) is recommended. Grade A.

3.1.3 | CQII-1-3 What is the prevalence of migraine in Japan?

Recommendation
In Japan, the annual prevalence of migraine is 8.4%; comprising migraine with aura 2.6% and migraine without aura 5.8%. The prevalence of migraine is high in women aged 20-40 years. In juveniles, the prevalence is 9.8% among senior high students and 4.8% among junior high students. Grade A.

3.1.4 | CQII-1-4-1 What hypotheses have been proposed for the pathophysiology of migraine?

Recommendation
The definite pathophysiological mechanisms of migraine have not been established. In the past, the vascular theory, neuronal theory, and trigeminovascular theory were proposed as the pathological hypotheses of migraine. Currently, the trigeminovascular system, the descending pain modulatory network in the brainstem, and various peptides are considered to play important roles in migraine. Especially, serotonin and its receptor (5-HT1B/1D receptor) as well as calcitonin gene-related peptide (CGRP) released from the trigeminal nerve endings may be closely associated with the pain in migraine attacks. On the other hand, aura of migraine is considered to be a phenomenon due to cortical spreading depression (CSD). Grade A.

3.1.5 | CQII-1-4-2 What are the types of auras in migraine?

Recommendation
Apart from the typical aura observed in migraine with aura, migraine aura also includes the aura observed in hemiplegic migraine and migraine with brainstem aura.

Typical aura observed in migraine consists of visual symptoms, sensory symptoms, and speech symptoms. Aura in hemiplegic migraine includes motor weakness in addition to the typical aura. Aura in migraine with brainstem aura includes dysarthria, vertigo, tinnitus, hypacusis, diplopia, ataxia, and decreased level of consciousness. Grade A.

3.1.6 | CQII-1-4-3 What is the proposed mechanism for aura in migraine?

Recommendation
At present, aura in migraine is considered to be caused by CSD or spreading oligemia. Grade B.

3.1.7 | CQII-1-4-4 What is the proposed mechanism for pain in migraine?

Recommendation
No definitive mechanism has been established for the pathophysiology of pain in migraine. Two main hypotheses regarding the genesis of pain have been proposed: the peripheral origin theory of pain generated from cerebral blood vessels and trigeminal nerve endings, and the central origin theory of pain generated from the brainstem. Currently, the trigeminovascular system, the descending pain modulatory system in the brainstem, and various peptides are considered to play important roles in migraine pain. Especially, there is high probability that serotonin and its receptor (5-HT1B/1D receptor) and CGRP released from the trigeminal nerve endings are closely associated with pain in migraine attack. Grade A.

3.1.8 | CQII-1-4-5 How is migraine related to serotonin abnormality?

Recommendation
The involvement of platelet serotonin (5-hydroxytryptamine: 5-HT) abnormality in the pathology of migraine was hypothesized. However, subsequent examinations of plasma or serum serotonin levels yielded no consensus, and there are few reports on serotonin and its metabolism. On the other hand, serotonin receptors; 5-HT1B and 5-HT1D receptors, are widely distributed in the trigeminovascular system consisting of intracranial large oculus blood vessels, trigeminal peripheral nerve endings, trigeminal ganglion, and subnucleus caudalis of the spinal trigeminal nucleus. Since the advent of triptan (5-HT1B/1D receptor agonist), the relationship between migraine and serotonin receptor has been highlighted. Grade A.

3.1.9 | CQII-1-4-6 How does cerebral blood flow change during migraine attack?

Recommendation
Change in cerebral blood flow during migraine attack is discussed focusing on CSD. In an attack of migraine with visual aura, reduced cerebral blood flow in the occipital lobe is observed. In an attack of migraine without aura, the opinion is divided. In addition, regional
cerebral blood flow has been shown to increase during headache attack. Grade B.

3.1.10 | CQII-1-5 What are the precipitating/aggravating factors of migraine?

Recommendation

The precipitating factors of migraine (from epidemiological studies) include the followings:

- Psychological factors: stress, mental strain, fatigue, sleep (too much or too little)
- Endogenous factors: menstrual cycle
- Environmental factors: weather change, temperature change, frequent travels, odor
- Dietary factors: hunger, alcohol (for other food groups, since response differs individually, there is no need to restrict intake)

Grade B

3.1.11 | CQII-1-6-1 What is the prognosis of migraine (including chronification of migraine)?

Recommendation

Most migraine patients show a tendency of improvement with age. It is also known that approximately 3% of the patients per year show deterioration of symptoms, with increases in frequency of headache attacks and number of days with headache. The known risk factors for chronification of migraine include (1) congenital factors, (2) headache conditions, (3) comorbidities, and (4) external factors. Especially, (3) and (4) contain elements that are modifiable, and therapeutic interventions may lead to improved outcome. Grade A.

Background and objective

Literature was searched to identify the risk factors associated with the outcome and chronification of migraine and to clarify the current assumptions of the biological mechanism for the chronification of migraine.

Comments and evidence

The outcome of migraine can be broadly classified into four patterns: A. no change; B. partial remission (symptomatic improvement); C. remission; D. progression. For D. progression, apart from increases in intensity and frequency of attacks, chronification defined as overlap of chronic headache and increase in number of days with headache are also classified in this category.17

According to the evolution of headache prevalence with age published by the American Migraine Prevalence and Prevention Study (AMPP), the prevalence in men was 9% in the 30-39 year group, decreasing to 5.9% in the 50-59 year group, and further to 2.1% at 60 years.18 In women also, the prevalence reached 38.1% in the 30-39 age-group and decreased to 6.4% after 60 years of age. These figures suggest that many patients achieve remission with age, in both men and women. There are few longitudinal studies on the long-term outcome of migraine. Lyngberg et al19 studied 64 migraine patients and reported that 42% showed complete or partial remission after 12 years, 38% showed no change, and 20% evolved to transformed migraine. A 30-year prospective cohort study conducted in Switzerland also shows that migraine tends to remit in the long term.20 However, regarding the change in disease state 1 year after onset, 83.29% show no change, 9.85% show partial remission, and 3.26% show complete remission. However, in 2.97% of the patients, the frequency of headache attacks increases and headache-related disability becomes more severe. In other words, although the overall percentage is low, migraine progresses in some patients who gradually complain of more chronic headache over time. Even on days without migraine attack, these patients experience headache symptoms similar to tension-type headache. As a result, the number of days without headache becomes even less. As explained in a different section, the headache symptoms of patients with episodic migraine become chronic and are eventually diagnosed as chronic migraine when headache occurs on 15 days or more per month (see “CQII-1-8; What kind of disease is chronic migraine?”). The mechanisms leading to progression or chronification remain unclear. However, epidemiological studies identified several risk factors related to chronic migraine. These risk factors are listed below.21-26

1. Congenital factors
   - Family history
     The risk of onset in a child increases when the mother has chronic daily headache.
   - Prenatal exposure
     Mother’s drinking and smoking during gestation are risk factors.

2. Headache conditions
   - The number of days with headache at baseline
     Migraine tends to become chronic when the number of days with headache at baseline is high.

3. Comorbid conditions
   - Obesity
     The prevalence of chronic daily headache (including chronic migraine) is increased threefold in persons with BMI 25-29 and fivefold in those with BMI 30 or above, compared to normal-weight individuals.
   - Snoring and sleep apnea
   - Psychiatric disorder or stressful life
     Mood disturbances such as depression and anxiety have been related to chronic migraine. Stressful life events (such as moving and losing job) are triggers of alteration in migraine.
   - Temporomandibular disorder

4. External factors
   - Analgesic overuse
     The focus here is not on the aggravation of medication-overuse headache, but on the relationship between analgesics and chronification of migraine. The use of opioid and barbiturate is a risk of migraine chronification, though this may not be an issue in Japan because of the tight regulation of opioid use. Triptan and non-steroidal anti-inflammatory drugs (NSAIDs) contribute to chronification when given to patients with headache on 10 days or more per month.
2. Caffeine consumption
3. Traumatic injury to the head

The incidence of cutaneous allodynia (CA) in terms of semiology is known to increase accompanying chronification of migraine. Cutaneous allodynia is considered to be a phenomenon indicating the presence of central sensitization in second-order trigeminal neurons (subnucleus caudalis of the spinal trigeminal nucleus) or above. The periaqueductal gray (PAG) modulates pain transmission in the subnucleus caudalis of the spinal trigeminal nucleus. The possibility that PAG dysfunction changes the threshold of headache leading to chronification of headache is hypothesized. In this connection, iron deposition in the PAG has been demonstrated by high-resolution MRI in patients with episodic migraine and patients with chronic daily headache, and the degree of deposition is proportional to the disease stage.27 Whether iron deposition in the PAG is a cause or the result of migraine chronification is not clear. However, several studies using voxel-based morphometry of MRI in patients with chronic migraine reported changes in volume of brain tissues in these patients, indicating a possibility of the presence of organic changes in the central nervous system structures.28-31

3.1.12 | CQII-1-6-2 To what extent does migraine impair the healthy life expectancy and QOL of patients?

Recommendation
The healthy life expectancy and QOL of patients with migraine are significantly compromised in terms of physical, mental, and social functions, compared with healthy individuals without headache. When compared with other chronic diseases, migraine patients experience greater impairment in QOL in some domains. Grade B.

3.1.13 | CQII-1-7 What are the comorbid disorders associated with migraine?

Recommendation
The comorbid disorders of migraine include hypertension, heart diseases, cerebrovascular diseases, depression, bipolar disorder, anxiety disorder, epilepsy, asthma, allergic diseases, and autoimmune diseases. Grade B.

3.1.14 | CQII-1-8 What kind of disease is chronic migraine?

Recommendation
Chronic migraine is a condition that starts off as episodic migraine but migraine attacks increase in frequency during the course of disease resulting in headache occurring on many days of a month.

3.1.15 | CQII-1-9 Is migraine a risk factor for cerebral infarction?

Recommendation
In women younger than 45 years of age, the presence of migraine with aura may slightly increase the risk of cerebral infarction. However, the annual incidence of ischemic stroke in this age group is very low. However, the risk is increased by smoking and oral contraceptive (OC). Migraine without aura does not increase the risk. Grade A.

3.1.16 | CQII-1-10 Is it safe for migraine patients to use low-dose oral contraceptives?

Recommendation
Estrogen-containing OCs are in principle contraindicated in women who have migraine with aura, and other contraceptive methods are recommended. Although these OCs are not contraindicated in women who have migraine without aura, these agents should be administered with caution. Grade B.

Background and objective
Hormonal contraception is one of the most effective contraceptive methods and include low-dose combined OC containing estrogen and progesteron, progestin-releasing intrauterine contraceptive device (IUD), and progestin-only pill (not yet approved in Japan). In Japan, OC is the most widely used method.

Migraine is prevalent in women reaching sexual maturity. Apart from contraception, use of combined OC is often considered for the purpose of treating oesailing and dermatological diseases. Literature was searched to examine the tolerability and safety of OC use in migraine patients.

Comments and evidence
Combined OC exhibits contraceptive effect by acting on the hypothalamic-pituitary-ovarian endocrine system to suppress follicle development and ovulation and by exerting effects on the cervical mucosa and endometrium.

Combined OC is generally taken for 21-24 consecutive days, followed by 3-7 days of no pills or placebo pills. During this period, the endometrium sloughs off resulting in withdrawal bleeding. For women who desire no bleeding, continuous taking of OC without a pill-free period is also possible.32 The types of hormone contained in combined OC differ depending on the formulation, which may be one-phase pills containing the same doses of hormones every day or multiple-phase pills containing different amounts of hormones on different days.

Headache has been reported to be one of the most common adverse effects associated with taking OC.33 Use of OC may aggravate oesaling headache or induce new onset of headache.34 In the ICHD-II, exogenous hormone-induced headache and estrogen-withdrawal headache are defined. However, in most of the patients with
aggravated and new-onset headache, the headache occurs during early cycles of OC use, and with continued use, the difference between OC use and control becomes insignificant.\(^3^4\)

Headache associated with OC use tends to occur during the placebo or pill-free period, and the impact on headache has been reported to differ depending on the administration regimen. To control headache during the pill-free period, continuous OC regimen\(^3^5\) and estrogen supplementation during the pill-free period have been used.\(^3^6\)

A large number of studies have been conducted to examine the impact of OC on migraine, some of which have various issues. For example, the observation period and interval between OC administration and headache onset are not well defined in some studies, combined OC and progestin-only pill are not differentiated in others, and the majority of the studies are case-control research.

In a large-scale cross-sectional study, the incidence of migraine among 13,944 women using OC was approximately 18%, and the odds ratio of OC use compared with non-OC use was 1.4 (95% confidence interval: 1.2-1.7).\(^3^7\) A cohort study in patients who had migraine without aura comparing subjects using and those not using OC reports that use of OC exerts only subtle differences on the course of migraine.\(^3^8\) In several retrospective studies, use of OC aggravates the frequency and intensity of migraine in 24.1%-34.8% of patients who had migraine without aura, and in 18.6%-69.2% of patients who had migraine with aura.\(^3^9\)-\(^4^2\)

In a meta-analysis of 13 case-control studies and 10 cohort studies reported in 2009, the relative risk of cerebral infarction was 7.02 (1.51-32.68) in patients with migraine (including with and without aura) using OC, while the risk was 10.0 (1.4-73.7) in migraine with aura accompanied by OC use and smoking.\(^4^3\) The current WHO medical eligibility criteria for contraceptive use (WHOMEC) classifies migraine with local neurological signs as category 4 (unacceptable health risk), whereas UKMEC does not provide age stratification and classifies continuation as category 3 (risks outweigh advantages). In the case of using OC not for contraception but for treatment of disease, careful evaluation of risk and benefit in individual patient is necessary.

- Search terms and secondary sources
- Search database: PubMed (2011/1/11)
  - Oral contraceptives & headache 851
  - Contraceptive & headache 869
  - Migraine & contraceptives 504
  - Migraine & oral contraceptives 494
  - Migraine & contraception 187
- 2.1 and stroke 149
- Search database: Ichushi Web for articles published in Japan

### 3.2 | Acute treatment

#### 3.2.1 | CQII-2-1 What are the acute treatments for migraine and how are they used?

**Recommendation**

The mainstay of acute treatment for migraine is pharmacotherapy. The drugs used include (1) acetaminophen, (2) NSAIDs, (3) ergotamines, (4) triptans, and (5) antiemetics. Stratified treatment according to the severity of migraine is recommended: use NSAIDs such as aspirin and naproxen for mild-to-moderate headache, and use triptans for moderate-to-severe headache, or even mild-to-moderate headache when NSAIDs were ineffective in the past. It is necessary to give guidance and cautions to patients having acute attacks and explain the methods of using medications (timing, dose, frequency of use) and medication use during pregnancy and breast-feeding. Grade A.

**Background and objective**

The objective of acute treatment is to resolve the migraine attack completely and rapidly and restore the patient’s normal functions. An ideal treatment should have the following characteristics: (1) resolves pain and associated symptoms rapidly; (2) is consistently effective; (3) no recurrence; (4) no need for additional use of medication; (5) no adverse effects; (6) can be administered by the patients themselves; and (7) low cost. Literature was searched to identify acute treatments that satisfy the above conditions.

**Comments and evidence**

The acute treatment drugs for migraine generally include (1) acetaminophens, (2) NSAIDs, (3) ergotamines, (4) triptans, and (5) antiemetics. For severe migraines including status migrainosus and migraine attacks refractory to treatment, (6) anesthetics, and (7) corticosteroids (dexamethasone) are used (Tables 3 and 4).\(^4^6\)-\(^5^4\) There are two approaches to the selection and sequencing of these medications: "step care" and "stratified care." In step care, safe and low-cost drugs are initially selected, and if treatment fails, then more expensive and specific drugs such as triptans are used. In stratified care, drugs are selected according to the degree of disability caused by migraine. A randomized trial has proven the effectiveness of stratified care and recommended...
| Drug                                | Quality of evidence | Scientific evidence | Clinical impression | Adverse effect | Recommendation grade | Efficacy group | Recommended dose          |
|------------------------------------|---------------------|---------------------|---------------------|----------------|----------------------|----------------|--------------------------|
| **Triptans**                       |                     |                     |                     |                |                      |                |                          |
| Sumatriptan                        | I                   | +++                 | +++                 | Occasional     | A                    | 1              | 50 mg/dose, 200 mg/d     |
| Sumatriptan (nasal spray)          | I                   | +++                 | +++                 | Occasional-frequent | A                  | 1              | 20 mg/dose, 40 mg/d      |
| Sumatriptan (injection ampoule)    | I                   | +++                 | +++                 | Frequent       | A                    | 1              | 3 mg/dose, 6 mg/d        |
| Sumatriptan (self-injection)       | I                   | +++                 | +++                 | Frequent       | A                    | 1              | 3 mg/dose, 6 mg/d        |
| Sumatriptan (suppository)          | I                   | +++                 | −                   | −              | A<sup>b</sup>       | 1              | −                        |
| Sumatriptan (subcutaneous)         | II                  | ++                  | −                   | −              | A<sup>b</sup>       | 1              | −                        |
| Zolmitriptan                       | I                   | +++                 | +++                 | Occasional     | A                    | 1              | 2.5 mg/dose, 10 mg/d     |
| Zolmitriptan (nasal spray)         | I                   | +++                 | −                   | −              | A<sup>b</sup>       | 1              | −                        |
| Eletriptan                         | I                   | +++                 | +++                 | Occasional     | A                    | 1              | 20 mg/dose, 40 mg/d      |
| Rizatriptan                        | I                   | +++                 | +++                 | Occasional     | A                    | 1              | 10 mg/dose, 20 mg/d      |
| Naratriptan                        | I                   | +++                 | +++                 | Occasional     | A                    | 1              | 2.5 mg/dose, 5 mg/d      |
| Naratriptan (injection)            | I                   | +++                 | −                   | −              | A<sup>b</sup>       | 1              | −                        |
| Almotriptan                        | I                   | +++                 | −                   | −              | A<sup>b</sup>       | 1              | −                        |
| Frovatriptan                       | I                   | +++                 | −                   | −              | A<sup>b</sup>       | 1              | −                        |
| **Anxiolytics, antipsychotics, anesthetics, antiemetics** |                     |                     |                     |                |                      |                |                          |
| Metoclopramide                     | I                   | +++                 | ++                  | Occasional     | A<sup>b</sup>       | 2              | 5 mg/dose, 30 mg/d       |
| Metoclopramide (intramuscular/ intravenous) | I                | +++                 | ++                  | Occasional     | A<sup>b</sup>       | 2              | 10 mg/dose, 20 mg/d      |
| Domperidone                        | II                  | ++                  | ++                  | Occasional     | A<sup>b</sup>       | 2              | 5 mg/dose, 30 mg/d       |
| Domperidone (suppository)          | II                  | ++                  | −                   | Occasional     | B<sup>b</sup>       | 4              | 60 mg/dose               |
| Prochlorperazine                   | I                   | +++                 | −                   | Occasional-frequent | B<sup>b</sup>       | 4              | 5 mg/dose                |
| Prochlorperazine (intramuscular)   | I                   | +++                 | −                   | Occasional-frequent | B<sup>b</sup>       | 4              | 5 mg/dose                |
| Chlorpromazine                     | I                   | +++                 | −                   | Occasional-frequent | B<sup>b</sup>       | 4              | 30 mg/dose               |
| Chlorpromazine (intramuscular)     | I                   | +++                 | −                   | Occasional-frequent | B<sup>b</sup>       | 4              | 10 mg/dose               |
| Droperidol (intramuscular)         | II                  | ++                  | −                   | Occasional-frequent | C<sup>b</sup>       | 4              | −                        |
| Propofol (intravenous)             | III                 | +                   | −                   | Frequent       | C<sup>b</sup>       | 4              | −                        |
| Diazepam (intramuscular/intravenous) | III               | +                   | −                   | Frequent       | C<sup>b</sup>       | 4              | −                        |
| **Acetaminophen/NSAIDs**            |                     |                     |                     |                |                      |                |                          |
| Acetaminophen                      | I                   | +++                 | ++                  | Occasional     | A                    | 2              | 0.5 (–10) g/dose, 1.5 (–4) g/d |
| Aspirin                            | I                   | +++                 | ++                  | Occasional     | A                    | 2              | 330 mg/dose, 990 mg/d    |
| Ibuprofen                          | I                   | +++                 | ++                  | Occasional     | A<sup>b</sup>       | 2              | 100-200 mg/dose, 600 mg/d |

(Continues)
| Drug                          | Quality of evidence | Scientific evidence | Clinical impression | Adverse effect     | Recommendation grade | Efficacy group | Recommended dose              |
|-------------------------------|---------------------|---------------------|---------------------|--------------------|----------------------|-----------------|------------------------------|
| Diclofenac                    | I                   | +++                 | ++                  | Occasional         | A<sup>a</sup>         | 2               | 25-50 mg/dose, 75-100 mg/d  |
| Naproxen                      | I                   | +++                 | ++                  | Occasional         | A<sup>b</sup>         | 2               | 100-300 mg/dose, 300-600 mg/d |
| Etodolac                      | II                  | ++                  | ++                  | Occasional         | A<sup>b</sup>         | 2               | 100-200 mg/dose, 400 mg/d   |
| Celecoxib                     | II                  | ++                  | ++                  | Rare-occasional    | A<sup>b</sup>         | 2               | 100-200 mg/dose, 400 mg/d   |
| Mefenamic acid                | II                  | ++                  | ++                  | Occasional         | A                    | 2               | 250-500 mg/dose, 1,500 mg/d |
| Zaltoprofen                   | III                 | +                   | ++                  | Occasional         | A<sup>b</sup>         | 2               | 80-160 mg/dose, 240 mg/d    |
| Pranoprofen                   | III                 | +                   | ++                  | Occasional         | A<sup>b</sup>         | 2               | 75-150 mg/dose, 225 mg/d    |
| Lornoxicam                    | III                 | +                   | ++                  | Occasional         | A<sup>b</sup>         | 2               | 60-120 mg/dose, 240 mg/d    |
| Ergotamines                   |                     |                     |                     |                    |                      |                 |                              |
| Ergotamine-caffeine combination| II                  | ++                  | ++                  | Frequent           | B                    | 4               | Withdrawn from market in Japan |
| Ergotamine-caffeine-pyrene combination| II                 | ++                  | ++                  | Frequent           | B                    | 4               | 1 tablet/dose, 3 tablets/d, up to 10 tablets/week, combined use with triptans contraindicated |
| Dihydroergotamine             | II                  | ++                  | ++                  | Frequent           | B                    | 4               | 1 mg/dose, 3 mg/d, combined use with triptans contraindicated |
| Steroids                      |                     |                     |                     |                    |                      |                 |                              |
| Dexamethasone (intravenous)   | III                 | +                   | ++                  | Occasional         | C<sup>b</sup>         | 3               | 2-8 mg/dose                 |
| Hydrocortisone                | III                 | +                   | ++                  | Occasional         | C<sup>b</sup>         | 3               | 200-500 mg/dose             |
| Others                        |                     |                     |                     |                    |                      |                 |                              |
| Tramadol                      | III                 | +                   | –                   | Occasional-frequent | C<sup>b</sup>         | 4               | 100 mg/dose, 300 mg/d       |
| Tramadol-acetaminophen combination| III                 | +                   | –                   | Occasional-frequent | C<sup>b</sup>         | 4               | 1 tablet/dose, 4 tablets/d  |
| Tramadol (intramuscular)      | III                 | +                   | –                   | Occasional-frequent | C<sup>b</sup>         | 4               |                               |
| Magnesium preparation         | III                 | +                   | –                   | Rare               | C<sup>b</sup>         | 2               |                               |

Quality of evidence: I. Evidence from systematic review or meta-analysis or from at least one randomized controlled trial. II. Evidence from nonrandomized controlled trials or analytical epidemiological studies (cohort studies or case-control studies). III. Evidence from descriptive studies (case reports or case series). IV. Evidence from opinions of expert committees or individual experts, not based on patient data. Clinical impression: -, little experience of use, currently difficult to evaluate; +, somewhat effective: significant clinical improvement in few patients; ++, effective: significant clinical improvement in some patients, ++++, markedly effective: significant clinical improvement in most patients.

Recommendation grade: according to the descriptions in the main text of this guideline. Drugs covered by health insurance in Japan and drugs with high level of evidence are described.

Recommended dose: According to the evidence and consensus obtained in Japan, all doses are for adults.

In recommended dose, “–” denotes difficult to assess currently regarding evaluation and doses.

Drugs not currently available in Japan are written in italics.

<sup>a</sup>Covered by health insurance as off-label use for migraine.

<sup>b</sup>Not covered by health insurance.
stratified treatment according to the severity of migraine. The recommended treatment is to use NSAIDs or NSAIDs + antiemetic for mild-to-moderate headache; and use triptans for moderate-to-severe headache, or even mild-to-moderate headache if NSAIDs were ineffective in the past. In any case, combined use with antiemetic is useful. In Japan, triptan tablet, nasal spray, and subcutaneous injection are available. From these various formulations, the appropriate drug is selected taking into consideration the attack frequency, intensity, degree of disability, associated symptoms, patient's preference, past treatment history, and medical history. When prescribing acute treatment, physicians has to explain to and caution the patients that regardless of the medication, regular overuse for more than 3 months may cause medication-overuse headache. Moreover, while prescribing medications, it is necessary to confirm whether the patients have conditions for which certain drugs are contraindicated or whether they are pregnancy or breast-feeding. Finally, as counselling for patients having acute attacks, physicians have to provide personalized lifestyle guidance appropriate for individual patients, such as to rest in a quiet and dark place, to cool the painful site, and to avoid taking a bath (for details usage of different drugs, see the corresponding sections in this guideline).

• Search terms and secondary sources
• Search database: PubMed (2012/2/10)

migraine & management 2260
migraine & management & acute 423
migraine & management & acute & treatment 335
migraine & management & acute & treatment & review 201
migraine & management & acute & treatment & guideline 37
migraine & management & acute & treatment & RCT 15

3.2.2 | CQII-2-2 What is the timing of taking triptans?

Recommendation

Triptans are effective if taken when headache is mild or in the early stage of headache attack (up to around one hour after onset). When taken during the aura phase or the premonitory phase of migraine, triptans have no negative effect but may fail to relieve headache. Grade A.

3.2.3 | CQII-2-3 How should patient preference for multiple triptans be determined?

Recommendation

Although all the triptans have proven efficacy, individual triptans differ slightly in characteristics. The efficacy and preference vary depending on patients, but adequate evidence is lacking. Grade C.

3.2.4 | CQII-2-4 When and how are nonoral formulations of triptans used for the treatment of migraine?

Recommendation

As acute treatment for migraine, nonoral formulations of triptan are effective for severe migraine attacks. Especially, use of injection and nasal spray formulations is indicated when severe migraine attacks cause serious disability in daily and social living, or when frequent vomiting impairs oral administration resulting in poor headache control. The time to response is the shortest for injection, followed by nasal spray. The appropriate formulation should be selected depending on the intended use in individual patients. Grade A (injection, nasal spray).

3.2.5 | CQII-2-5 How should the acute phase of migraine with brainstem aura and hemiplegic migraine be managed?

Recommendation

The acute phase of migraine with brainstem aura and hemiplegic migraine is managed in the same manner as acute treatment for migraine. However, the use of triptans and ergotamines is not actively recommended at present. Grade B.

3.2.6 | CQII-2-6 How are ergotamines used?

Recommendation

Ergotamine-caffeine combination has little effect when headache has already become moderate to severe, but there is value to use in patients with frequently relapsing headache while on triptans. Its use is limited because early treatment is as effective as or inferior to NSAIDs and adverse effects including vomiting are present. In addition, its use during pregnancy and breast-feeding is contraindicated. Grade B.

3.2.7 | CQII-2-7 Are acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) effective acute treatments for migraine?

Recommendation

Acetaminophen monotherapy and NSAIDs monotherapy are safe and low-cost treatments and are recommended as first-choice drugs for mild-to-moderate migraine attacks. However, their effectiveness is limited compared with triptans. For migraine patients not responding to acetaminophen or NSAIDs, early use of triptan should be considered. Grade A.

3.2.8 | CQII-2-8 Are antiemetics useful acute treatment for migraine?

Recommendation

Antiemetics are effective against nausea and vomiting which are associated symptoms of migraine. Various options of administration routes are available, including oral, intravenous, intramuscular, and suppository. Adverse effects are few. Hence, active combined use is recommended. Especially, combined use with triptans, ergotamines, and NSAIDs is useful. Grade B.
3.2.9 | CQII-2-9 What other acute treatment drugs for migraine are available?

**Recommendation**

For acute treatments of migraine, intravenous corticosteroids (dexamethasone), intravenous magnesium, intramuscular tramadol, and oral tramadol-acetaminophen combination may be considered. However, because of a lack of adequate evidence, they are not the first-choice drugs. Intravenous, intramuscular, suppository, and combination formulations of prochlorperazine are recommended in the literature, but their use for migraine treatment is not covered by health insurance in Japan. Grade B and C (prochlorperazine: B; dexamethasone: B; magnesium: B; tramadol: B; tramadol-acetaminophen combination: C).

3.2.10 | CQII-2-10 What are the acute treatments for severe migraine attacks and status migrainosus?

**Recommendation**

1. Rule out secondary headaches.
2. Fluid replacement (secure intravenous route): improvement of dehydration due to vomiting and be prepared for hypotension and other drug-related adverse effects.
3. Subcutaneous injection of sumatriptan 3 mg: pay attention to the total dose within 24 hours and headache recurrence.
4. Intravenous or intramuscular injection of antiemetic: intravenous metoclopramide 10 mg or intramuscular prochlorperazine 5 mg.
5. Intravenous dexamethasone. Grade B.

3.2.11 | CQII-2-11 How should migraine be treated (acute and prophylactic) during pregnancy and breastfeeding?

**Recommendation**

When attacks are severe and require treatment, acetaminophen is recommended as an acute treatment. The safety of using triptans during pregnancy has not been established, but there is no report that using triptans during early pregnancy increases the rate of fetal teratogenicity. Since most migraine patients experience reduced frequency of migraine attacks during pregnancy, few patients require prophylactic drugs. Although administration of prophylactic drugs is not recommended, beta-blocker may be used where necessary. For breast-feeding women who are using triptans, it is recommended to avoid breast-feeding for 12 hours after taking sumatriptan and for 24 hours after taking other triptans. Grade B.

3.2.12 | CQII-2-12 The diagnosis and treatment of menstrual migraine

**Recommendation**

Menstrual migraine is diagnosed according to the ICHD-3beta. To establish the relationship between menstrual cycle and migraine attack, confirmation of the headache diaries is required (for three menstrual cycles). Since headache attacks tend to be severe in menstrually related migraine without aura, triptan is recommended for acute treatment when previous attacks did not respond to NSAIDs. Prophylactic treatment is conducted according to that used for
general migraine, but when attacks occur mainly in association with menstruation, short-term prophylactic therapy may be one option. Grade B.

3.3 | Prophylactic therapy

3.3.1 | CQII-3-1 What kinds of patients requires prophylactic therapy?

Recommendation

For patients who have migraine attacks two times or more or 6 days or more a month, consideration of prophylactic therapy is recommended. Prophylactic therapy is recommended when migraine-induced disability in daily living remains with acute treatment alone, when acute treatment drugs cannot be used, and for special types of migraine with a risk of causing permanent neurological defects. Grade B.

3.3.2 | CQII-3-2 What kinds of drugs are available for prophylactic therapy?

Recommendation

The drugs used in prophylactic therapy for migraine are shown in Table 5.

Furthermore, the prophylactic drugs for migraine can be classified into five efficacy groups as shown in Table 6, taking into consideration various factors including the strength of evidence, the effects, and risk of adverse events. Grade B.

Background and objective

In many guidelines, various medications have been evaluated based on evidence and consensus. These medications have also been classified into efficacy groups based on evidence and consensus concerning their effectiveness and safety.

Comments and evidence

Table 5 (list of prophylactic medications for migraine) and Table 6 (efficacy groups) were constructed by reviewing the guidelines published to date and adding the consensus of our study group.

The prophylactic medications for migraine covered by health insurance in Japan are lomerizine, valproic acid, propranolol, and dihydriodergotamine. As of March 2013, verapamil and amitriptyline are approved for off-label use.

Search terms and secondary sources

- Benefit of prophylactic therapy for migraine patient (2012/5/30)
- & benefit 55
- & QOL 8
- & guideline 27
- & efficacy 195

3.3.3 | CQII-3-3 How should multiple prophylactic therapies be used differentially?

Recommendation

For prophylactic therapy, select a drug with scientific evidence-based efficacy and few adverse effects, and start from a low dose. In the absence of adverse events, increase the dose gradually until a dose that yields adequate clinical efficacy and evaluate the effectiveness for a period of 2-3 months. If no adequate response is obtained even after increasing to an adequate dose and after a sufficiently long observation period, then change to another drug. Select drugs taking into account comorbid conditions other than migraine as well as the physical condition. Grade B.

3.3.4 | CQII-3-4 How long should prophylactic therapy be continued?

Recommendation

It takes at least 2 months before the effectiveness of prophylactic therapy can be evaluated. Continue prophylactic therapy for 3-6 months if there is no adverse event. If good migraine control is achieved, taper the prophylactic drug slowly, and discontinue where possible. Grade B.

3.3.5 | CQII-3-5 Are beta-blockers (propranolol) effective for migraine prevention?

Recommendation

Beta-blockers (propranolol) are effective in preventing migraine attacks. Propranolol at an initial dose of 20-30 mg/day followed by 30-60 mg/day is recommended as one of the first-choice drugs for patients with migraine attacks that impair QOL. Beta-blockers have the additional merit that they can be used in patients with coexisting hypertension and coronary artery disease and that they can be used to treat these comorbid conditions simultaneously. Grade A.

3.3.6 | CQII-3-6 Are calcium channel blockers (lomerizine) effective for migraine prevention?

Recommendation

When migraine patients who have two or more attacks per month are given the oral calcium channel blocker lomerizine 10 mg/day, reduction in frequency and severity of migraine attacks can be expected after 8 weeks in 64% of the patients. Adverse events are similar to placebo, indicating safety of the drug. Lomerizine is recommended as one of the first choice drugs for migraine prevention. Grade B.
### TABLE 5  Summary of evidence for prophylactic therapies

| Drug                   | Quality of evidence | Scientific evidence | Clinical impression | Adverse effect          | Recommendation grade | Efficacy group | Recommended dose |
|------------------------|---------------------|---------------------|---------------------|-------------------------|----------------------|----------------|------------------|
| **Antiepileptic drugs** |                     |                     |                     |                         |                      |                |                  |
| Valproic acid          | A                   | +++                 | +++                 | Occasional-frequent     | A                    | 1              | 400-600 mg/d     |
| Topiramate             | A                   | +++                 | +++                 | Occasional-frequent     | A^b                  | 1              | 50-200 mg/d      |
| Gabapentin             | B                   | ++                  | ++                  | Occasional-frequent     | 2                    |                |                  |
| Levetiracetam          | B                   | ?                   | ?                   | Occasional-frequent     | 2                    |                |                  |
| **Antidepressants**    |                     |                     |                     |                         |                      |                |                  |
| Amitriptyline          | A                   | +++                 | +++                 | Frequent                | A^a                  | 1              | 10-60 mg/d       |
| Nortriptyline          | C                   | ?                   | +++                 | Frequent                | 3                    |                |                  |
| Imipramine             | C                   | ?                   | +                   | Frequent                | 3                    |                |                  |
| Clomipramine           | C                   | ?                   | +                   | Frequent                | 3                    |                |                  |
| Trazodone              | C                   | ?                   | +                   | Occasional-frequent     | 3                    |                |                  |
| Mianserin              | C                   | ?                   | +                   | Occasional-frequent     | 3                    |                |                  |
| Fluvoxamine            | C                   | ?                   | +                   | Occasional              | 3                    |                |                  |
| Paroxetine             | C                   | ?                   | +                   | Occasional              | 3                    |                |                  |
| Sulpride               | C                   | ?                   | +                   | Rare                    | 3                    |                |                  |
| Duloxetine             | C                   | ?                   | ?                   | Occasional              | 3                    |                |                  |
| Fluoxetine             | B                   | +                   | +                   | Occasional              | 2                    |                |                  |
| **Beta-blockers**      |                     |                     |                     |                         |                      |                |                  |
| Propranolol            | A                   | ++                  | +++                 | Rare-occasional         | A                    | 1              | 20-60 mg/d       |
| Metoprolol             | A                   | ++                  | +++                 | Rare-occasional         | A^b                  | 2              | 40-120 mg/d      |
| Atenolol               | B                   | ++                  | +                   | Rare-occasional         | 2                    |                |                  |
| Nadolol                | B                   | +                   | +++                 | Rare-occasional         | 2                    |                |                  |
| Timolol                | A                   | +++                 | +                   | Rare-occasional         | 1                    |                |                  |
| **Calcium channel blockers** |                  |                     |                     |                         |                      |                |                  |
| Lomerizine             | B                   | +                   | ++                  | Rare                    | B                    | 2              | 10-20 mg/d       |
| Verapamil              | B                   | +                   | ++                  | Rare-occasional         | B^a                  | 2              | 80-240 mg/d      |
| Diltiazem              | C                   | ?                   | ++                  | Rare-occasional         | 3                    |                |                  |
| Nicardipine            | C                   | +                   | ++                  | Rare-occasional         | 3                    |                |                  |
| Flunarizine            | A                   | ++                  | +++                 | Frequent                | 4                    |                |                  |
| **ARB/ACE inhibitors** |                     |                     |                     |                         |                      |                |                  |
| Candesartan            | B                   | +                   | +                   | Rare                    | B^b                  | 2              | 8-12 mg/d        |

(Continues)
### TABLE 5 (Continued)

| Drug                  | Quality of evidence (1) | Scientific evidence | Clinical impression (2) | Adverse effect | Recommendation grade (3) | Efficacy group (4) | Recommended dose |
|-----------------------|-------------------------|---------------------|-------------------------|----------------|--------------------------|--------------------|------------------|
| Lisinopril            | B                       | +                   | +                       | Occasional     | B<sup>b</sup>             | 2                  | 5-20 mg/d        |
| Enalapril             | C                       | ?                   | ?                       | Occasional     | 3                        |                    |                  |
| Olmesartan            | C                       | ?                   | ?                       | Occasional     | 3                        |                    |                  |
| Others                |                         |                     |                         |                |                          |                    |                  |
| Dihydroergotamine     | A                       | ++                  | ++                      | Occasional     | B                        | 4                  | 2-3 mg/d         |
| Methysergide          | A                       | +++                 | +++                     | Frequent       |                          | 4                  |                  |
| Botulinum toxin type A (acute/chronic) | B/A                | ++                  | ?                       | Rare           | C<sup>i</sup>/A<sup>b</sup> | 2                  |                  |
| Feverfew              | B                       | ++                  | +                       | Rare           | B                        | 2                  |                  |
| Magnesium preparation | B                       | +                   | +                       | Rare           | B<sup>i</sup>             | 2                  |                  |
| Vitamin B2            | B                       | ++                  | +++                     | +              | Rare                     | B<sup>i</sup>     | 2                |
| Tizanidine            | B                       | +                   | +                       | Rare           | 2                        |                    |                  |
| Melatonin             | C                       | ?                   | ?                       | Rare           | C                        | 4                  |                  |
| Olanzapine            | C                       | ?                   | ?                       | Frequent       | C<sup>i</sup>             | 4                  |                  |

(1) Quality of evidence: A. Consistent results obtained from multiple RCT. B. Evidence from RCT exists but not complete. C. No evidence from RCT, but consensus obtained from the US MCH Consortium or Guideline Study Group of Japanese Ministry of Health, Labour and Welfare. RCT: randomized controlled trials.

(2) Clinical impression: 0, ineffective, no improvement in most patients. +, somewhat effective: significant clinical improvement in a few patients. ++, effective: significant clinical improvement in some patients. ++++, markedly effective: significant clinical improvement in most patients.

(3) Recommendation grade: according to the descriptions in the main text of this guideline. Drugs approved for health insurance in Japan and drugs with high-quality evidence are described. Quality of evidence is not necessarily equal.

(4) See Table 6.

(5) Recommended dose: according to the evidence and consensus obtained in Japan.

Drugs not currently available in Japan are written in italics.

*Covered by health insurance as off-label use for migraine in Japan.

<sup>b</sup>Not covered by health insurance in Japan.
3.3.7 | CQII-3-7 Are angiotensin-converting enzyme (ACE) inhibitors and angiotensin II blockers (ARB) effective for migraine prevention?

**Recommendation**

Lisinopril and candesartan are effective for the prevention of migraine. They are recommended for patients with migraine and coexisting hypertension. Start lisinopril at around 5 mg/day and increase up to 20 mg/day where necessary. Candesartan at a dose of 8 mg/day is recommended for migraine prevention. Grade B.

3.3.8 | CQII-3-8 Are antiepileptic drugs (valproic acid) effective for migraine prevention?

**Recommendation**

When migraine patients with 2 or more headache attacks per month are treated with oral valproic acid, reduction in the number of attacks per month can be expected (Grade A recommendation). In adults, oral sodium valproate 400-600 mg/day is recommended (Grade A recommendation). When used in women of child-bearing potential, explain to the patients about adverse effects and teratogenicity, select sustained release formulation, and do not use in combination with other antiepileptic drugs (Grade A recommendation). Valproic acid is contraindicated in women who are pregnant or has a possibility of being pregnant. Grade A.

3.3.9 | CQII-3-9-1 Are antidepressants effective for migraine prevention?

**Recommendation**

Amitriptyline is effective for migraine prevention. In September 2012, amitriptyline was approved for off-label use for migraine and tension-type headache in Japan. Start from a low dose (5-10 mg/day before bedtime) and titrate upward while confirming the effect. A dose of 10-60 mg/day is recommended. Grade A.

3.3.10 | CQII-3-9-2 Is combined use of antidepressants (SSRI/SNRI) and triptan safe?

**Recommendation**

Combined use of triptans and antidepressants (SSRI/SNRI) is possible. However, attention must be paid to serotonin syndrome. Grade B.

3.3.11 | CQII-3-10 Are magnesium, vitamin B12, feverfew, and analgesics effective for migraine prevention?

**Recommendation**

Magnesium, vitamin B2, and feverfew can be expected to prevent migraine to some extent. Because of the absence of serious adverse reactions and the low cost, these medications may be considered as an option for migraine prophylaxis. Non-steroidal anti-inflammatory...
drugs and naproxen have significant migraine prophylactic effect compared with placebo, but medication-overuse headache and drug dependence are issues and therefore should be used only for short-term prophylactic therapy. Grade B and C (magnesium, vitamin B2, and feverfew: B; NSAID short-term prophylaxis: C).

3.3.12 | CQII-3-11 Are other prophylactic therapies effective for migraine prevention?

**Recommendation**

Since dihydroergotamine has long been used as a migraine prophylactic drug, and large-scale trials have proven its effectiveness, this drug can be considered appropriate as a prophylactic agent. In actual fact, however, dihydroergotamine is not used as the first choice drug for prophylaxis because combined use with triptan is contraindicated. For melatonin, although occasional reports have indicated its prophylactic effect for migraine, RCT has not demonstrated its usefulness. However, since serious adverse reactions are not observed, this drug may be considered for migraine prophylaxis in cases not responding to other prophylactic therapies. Regarding olanzapine, there are occasional reports of effectiveness, but evidence is insufficient. Paying close attention to adverse effects, this drug may be considered in cases not responding to other prophylactic therapies.

Grades B and C (dihydroergotamine: B, melatonin and olanzapine: C).

3.3.13 | CQII-3-12 Is botulinum neurotoxin (BoNT) effective for migraine prevention?

**Recommendation**

Multiple randomized placebo-controlled trials have proven that botulinum neurotoxin type A is effective in reducing symptoms of chronic migraine. Moreover, several studies have verified that its symptom-reducing effect for chronic migraine is equivalent to that of topiramate. On the other hand, the effect on episodic migraine is not clear. Therefore, botulinum neurotoxin type A may be considered for chronic migraine when other treatments have failed. In Japan, this treatment is not covered by health insurance. Grade A.

3.3.14 | CQII-3-13 How is typical aura without headache diagnosed and treated?

**Recommendation**

1. Diagnosis
   - Typical aura without headache is diagnosed according to the diagnostic criteria of the International Classification of Headache Disorders 2nd Edition (ICHD-II). Grade A.

2. Treatment
   - Although the absolute number of cases is small, the risk of cerebral infarction is increased in patients who have migraine with aura. On the other hand, there is no report that typical aura without headache increases the risk of cerebral infarction. Therefore, active treatment is currently considered unnecessary for typical aura without headache. However, in the case of frequent occurrence and long duration, and in the case of strong patient anxiety, use of prophylactic drugs such as valproic acid and lomerizine may be considered. Grade C.

3.4 | Tension-type headache

3.4.1 | CQ III-1 How is tension-type headache classified?

**Recommendation**

Since 1962, various classifications for tension-type headache have been proposed. Currently, classification according to the ICHD-3beta published in 2013 is recommended. Grade A.

3.4.2 | CQ III-2 How is tension-type headache diagnosed?

**Recommendation**

Tension-type headache is diagnosed according to the diagnostic criteria of the ICHD-3beta. Grade A.

3.4.3 | CQ III-3 How common is tension-type headache? What are the risk factors, triggers, and prognosis? What is the real prevalence of tension-type headache?

**Recommendation**

Tension-type headache is the most common headache among the primary headaches, and the prevalence varies widely among surveys. To find the precise prevalence, it is necessary to establish suitable survey methods and correct the problems of diagnosis. The risk factors and triggers of tension-type headache have not been defined. The prognosis of episodic tension-type headache is good in majority of the cases, but there exist some cases of poor outcome with progression to chronic tension-type headache. Grade B.

3.4.4 | CQ III-4 What is the proposed pathophysiology for tension-type headache?

**Recommendation**

The pathophysiology and the pathogenetic mechanism of tension-type headache remain unknown. Evidence is accumulating
supporting the possibility that peripheral pain mechanism plays a role in infrequent episodic tension-type headache and frequent episodic tension-type headache, while central pain mechanism plays a more important role in chronic tension-type headache. Grade B.

### 3.4.5 CQ III-5 What is the relationship between transformed migraine and tension-type headache?

**Recommendation**

When headache episodes are diagnosed individually, differentiation between transformed migraine and chronic tension-type headache is difficult. The two can be discriminated by a comprehensive approach to diagnosis considering the treatment, headache response and clinical course. Chronic migraine in the ICHD-3-beta includes the concept of transformed migraine. Grade B.

### 3.4.6 CQ III-6 How is tension-type headache treated?

**Recommendation**

Various types of tension-type headache exist, and the types that cause disability in daily living should be treated. Among them, frequent episodic tension-type headache and chronic tension-type headache require treatment. Therapies can be divided into acute treatment and prophylactic treatment, each of which can be pharmacotherapy and nonpharmacotherapy. For acute treatment, attention has to be paid to medication-overuse headache. For prophylactic therapy, occurrence of adverse effects should be monitored. Grade A, C.

### 3.4.7 CQ III-7 What kinds of acute treatment (during headache) are available for tension-type headache? How effective are they? How should these drugs be used differentially?

**Recommendation**

Pharmacotherapy is the mainstay of acute treatment for tension-type headache. Medications are primarily analgesics and NSAIDs, and their efficacy has been proven. There is little evidence on differential use of these drugs. It is important to always pay attention to medication-overuse headache that results in treatment failure. Specifically, use for more than two to three times per week should be avoided. Grade A-C.

### 3.4.8 CQ III-8 How should prophylactic therapy for tension-type headache be conducted?

**Recommendation**

Prophylactic therapy for tension-type headache can be broadly divided into pharmacotherapy and nonpharmacotherapy. Pharmacotherapy using mainly antidepressants and nonpharmacotherapies using electromyographic biofeedback therapy, physical therapy, acupuncture, exercise therapy (exercise to relax neck and occipital muscles), psychotherapy, and cognitive-behavioral therapy (such as lifestyle guidance) are being conducted. Regarding the treatment duration for pharmacotherapy using mainly antidepressants, assess the outcome after around 3 months (the longest 6 months) and decide whether to continue or discontinue medication. On the other hand, evidence for the treatment duration for nonpharmacotherapies has not been established. Grade A-C.

### 3.4.9 CQ III-9 Apart from pharmacotherapy, what other therapies are used for tension-type headache?

**Recommendation**

Nonpharmacotherapies for tension-type headache include psycho-behavioral therapy, physical therapy, acupuncture, and Tiger Balm®, and those with proven usefulness warrant recommendation as treatment. Among them, combined use of electromyographic biofeedback (psycho-behavioral therapy) and relaxation training is recommended. Grade A.

### 3.4.10 CQ III-10 Is botulinum toxin effective for tension-type headache?

**Recommendation**

At the present time, the effectiveness of botulinum toxin (BTX) for tension-type headache has not been established. Most of the adverse effects of BTX are due to excessive pharmacological action, and no serious effects have been reported. Therefore, BTX may be used to reduce symptoms of chronic tension-type headache when other treatments have failed. However, BTX is not fast-acting and is currently not covered by health insurance in Japan. Grade C.

### 3.5 Trigeminal autonomic cephalalgias

#### 3.5.1 CQ IV-1 How are trigeminal autonomic cephalalgias classified and typed?

**Recommendation**

The International Classification of Headache Disorders 3rd Edition beta version classifies cluster headache together with related diseases under “Trigeminal autonomic cephalalgias”. Furthermore, “Trigeminal autonomic cephalalgias” is further divided into five subtypes: cluster headache, paroxysmal hemicrania, short-lasting unilateral neuralgiform headache attacks, hemicrania continua, and probable trigeminal autonomic cephalalgia. Grade A.

#### 3.5.2 CQ IV-2 How are trigeminal autonomic cephalalgias diagnosed?

**Recommendation**

Trigeminal autonomic cephalalgias are diagnosed according to the ICHD-3 beta. Grade A.
3.5.3 | CQ IV-3 How common is trigeminal autonomic cephalalgias? What are the risk factors and aggravating factors? What is the prognosis?

**Recommendation**

The prevalence of cluster headache has been reported to be around 56-401 per 100 000 population and is lower than that of migraine. The onset age of cluster headache is usually from the twenties to the forties. The prevalence is three to five times higher in men than in women. During the cluster period, attacks occur regularly and may be provoked by alcohol, histamine or nitroglycerin. Grade B.

3.5.4 | CQ IV-4 What is the proposed pathophysiology for trigeminal autonomic cephalalgias?

**Recommendation**

The hypotheses of the pathophysiology for cluster headache and other trigeminal autonomic cephalalgias are classified as follows:

1. Generator in the hypothalamus.
2. Explanation by the association of trigeminal nerve activity with vascular response based on changes in serum neuropeptide concentrations.
3. Pain generation around the internal carotid artery.
4. Parasympathetic activation due to hyperexcitation of trigeminal nerve Grade B.

3.5.5 | CQ IV-5 What kinds of acute treatments are available for cluster headache, and how effective are they?

**Recommendation**

1. For triptans, subcutaneous injection of sumatriptan 3 mg (up to 6 mg/day) is recommended (covered by health insurance in Japan). The effectiveness of sumatriptan nasal spray 20 mg/dose and oral zolmitriptan 5-10 mg has been reported, but evidence has not been established, and they are currently not covered by health insurance in Japan.
2. Pure oxygen delivered via a side tube of a face mask at 7 L/minute for 15 minutes has been reported to be useful.
3. The somatostatin analog octreotide has been reported to be effective in overseas countries, but clinical trials have not been conducted in Japan. Lidocaine, cocaine, ergotamine, and general analgesics [NSAIDs] have no effect. Grade A-C (1. triptans: sumatriptan subcutaneous injection; A, sumatriptan nasal spray, oral zolmitriptan; B. 2. oxygen inhalation; A. 3. somatostatin, lidocaine, cocaine, ergotamine, NSAIDs; C).

3.5.6 | CQ IV-6 What kinds of medications for prophylactic therapy are available for cluster headache, and how effective are they?

**Recommendation**

1. Prophylactic therapy for episodic cluster headache
   1. Among calcium channel blockers, verapamil 360 mg/day has been shown overseas to have prophylactic effect but the adverse effect of delayed cardiac conduction causing bradycardia and heart failure is a concern. For lomerizine, some prophylactic effect is expected in the clinical trial stage, but this drug is not covered by health insurance in Japan (as of March 2013).
   2. Ergotamine tartrate (1-2 mg) taken orally before bedtime may be effective as prophylaxis.
2. Prophylactic therapy for chronic cluster headache
   Lithium carbonate, valproic acid, gabapentin, topiramate, divalproex sodium, and baclofen have been reported to be effective, but the effects have not been established.
3. Treatments other than pharmacotherapy
   Patients who do not respond to pharmacotherapy are sometimes treated with nerve block therapies (including trigeminal nerve block, stellate ganglion block, sphenopalatine ganglion block, and greater occipital nerve block), trigeminal rhizotomy, and sphenopalatine ganglion resection. Gamma knife treatment and deep brain stimulation have also been conducted, but the effect has not been established. Grade B and C. [1. Prophylactic therapy for episodic cluster headache: (1) verapamil; B (off-label use approved in Japan), lomerizine; C, (2) ergotamine tartrate; C, (3) cimide; C, (4) corticosteroids (off-label use approved in Japan); B, (5) others (triptans, melatonin); C. 2. Prophylactic therapy for chronic cluster headache: lithium carbonate, valproic acid, gabapentin, topiramate, divalproex sodium, baclofen; C. 3. Treatments other than pharmacotherapy: nerve block therapies, others; C].

3.5.7 | CQ IV-7 What kinds of medications are available for the treatment of paroxysmal hemicrania, and how effective are they?

**Recommendation**

Paroxysmal hemicrania responds absolutely to indomethacin, and indomethacin is therefore recommended as a treatment drug for paroxysmal hemicrania [highest dose up to 75 mg for oral formulation, and up to 100 mg for rectal administration (suppository) in Japan]. Other drugs such as verapamil, NSAIDs, and topiramate have been reported
to be effective, but clear evidence is yet to be established. Grade A (indomethacin: A; verapamil, NSAIDs, and topiramate: C).

3.5.8 | CQ IV-8 What kinds of medications are available for the treatment of SUNCT and SUNA, and how effective are they?

Recommendation

The prevalence of SUNCT and SUNA is low, and no controlled trial has been conducted. However, case studies have suggested that lamotrigine is the most effective, while gabapentin and topiramate are also effective. During headaches that severely impact daily living, intravenous lidocaine has been reported to be effective. Grade C.

3.5.9 | CQ IV-9 How do trigeminal autonomic cephalalgias impact the patients' healthy life expectancy and QOL?

Recommendation

In patients with cluster headache, disability in daily living and economic loss during the headache attack period have been reported. Furthermore, the pain and disability in daily living in patients with cluster headache are at least as severe as those in migraine patients. Grade B.

3.6 | Other primary headache disorders

3.6.1 | CQ V-1 Apart from migraine, tension-type headache and cluster headache, what are the other types of primary headache disorders?

Recommendation

In the ICHD-3beta, primary headache disorders other than migraine, tension-type headache, and cluster headache are grouped together as "Other primary headaches disorders." They are classified into primary cough headache, primary exercise headache, primary headache associated with sexual activity, primary thunderclap headache, cold-stimulus headache, external-pressure headache, primary stabbing headache, nummular headache, hypnic headache, and new daily persistent headache. Grade A.

3.6.2 | CQ V-2 How are primary stabbing headache, primary cough headache, and primary exercise headache diagnosed and treated?

Recommendation

1. Diagnosis
Primary stabbing headache, primary cough headache, and primary exercise headache are diagnosed according to the ICHD-3 beta. Grade A.

2. Treatment
Although no randomized controlled trials of treatment for these headaches have been reported, indomethacin is considered effective in most cases for these headaches. As adverse effect of indomethacin, gastrointestinal symptoms may be an issue when used long-term. Other drugs have been tried, but are limited to case reports and small case series. Grade C.

3.6.3 | CQ V-3 How is primary headache associated with sexual activity diagnosed and treated?

Recommendation

1. Diagnosis
Primary headache associated with sexual activity is diagnosed according to the ICHD-3beta. This headache is precipitated by sexual activity and is diagnosed after excluding intracranial disorders by brain imaging study and cerebrospinal fluid examination. Grade A.

2. Treatment
To treat primary headache associated with sexual activity, it is necessary for the patient and the partner to understand the disorder. Pharmacotherapy using indomethacin, triptans and propranolol is effective in some cases. Grade C.

3.6.4 | CQ V-4 How is hypnic headache diagnosed and treated?

Recommendation

1. Diagnosis
Hypnic headache is diagnosed according to the ICHD-3beta. Grade A.

2. Treatment
Caffeine is used not only as an acute treatment but also as a prophylactic drug. Lithium is another frequently used prophylactic drug. Grade C.

3.6.5 | CQ V-5 How is primary thunderclap headache diagnosed and treated?

Recommendation

1. Diagnosis
Primary thunderclap headache is diagnosed according to the ICHD-3beta. Grade A.

2. Treatment
Differentiating primary thunderclap headache from diseases that cause thunderclap headache secondarily is most important. There is no established treatment. Grade C.

3.6.6 | CQ V-6 How is hemicrania continua diagnosed and treated?

Recommendation

1. Diagnosis
Hemicrania continua are diagnosed according to the ICHD-3 beta. Grade A.

2. Treatment
Complete remission is obtained by treatment with indomethacin. Grade A.
3.7 | Medication-overuse headache

3.7.1 | CQ VI-1 How is medication-overuse headache diagnosed?

**Recommendation**

Medication-overuse headache (MOH) is diagnosed according to the diagnostic criteria for “8.2 Medication-overuse headache” described in the ICHD-3beta, which was published in Cephalalgia in 2013. Grade A.

3.7.2 | CQ VI-2 How common is medication-overuse headache among primary headache disorders?

**Recommendation**

In oversea countries, the annual prevalence of medication-overuse headache in the general population is approximately 1%-2%, and women occupy approximately 70%. In headache clinics or headache centers, the percentage of medication-overuse headache is up to 30% in Europe and over 50% in the United States. Grade A.

3.7.3 | CQ VI-2 What are the treatment and prognosis of medication-overuse headache?

**Recommendation**

The treatment principles for medication-overuse headache are as follows: (1) discontinue the overused medication, (2) treat the headache after discontinuing the overused medication, and (3) administer prophylactic medications. However, there is no established treatment method. Discontinuation of the overused medication may be conducted on an outpatient basis, but hospitalization may be required for detoxification therapy in severe cases. Simple medication-overuse headache may improve with suitable counseling, but severe cases may require hospitalization. As for prognosis, the relapse rate is approximately 30%. Even after discontinuation, patients should be given suitable counseling, and headache diary should be used to confirm the frequency of using triptans, ergotamine, and analgesics. Grade B.

3.8 | Headaches in children

3.8.1 | CQ VII-1 What types of headache are common in children?

**Recommendation**

The representative primary headaches in children are migraine and tension-type headache. The prevalence of migraine in children in population-based surveys conducted in various countries worldwide is 3.8%-13.5%, and the prevalence in school-based (number of students) surveys is 1.7%-21.3%, while the prevalence of tension-type headache is 17.4% and 0.7%-27.6%, respectively. According to Japanese data, the prevalence of migraine in children is 4.8% (boys 3.3%, girls 6.5%) among junior high school students and 15.6% (boys 13.7%, girls 17.5%) among senior high school students, while the prevalence of tension-type headache is 26.8% (boys 23.0%, girls 30.6%) among senior high school students. Grade B.

3.8.2 | CQ VII-2 How is migraine in children diagnosed?

**Recommendation**

Migraine and tension-type headache, which are representative primary headaches in children, are diagnosed according to the ICHD-3beta. Grade A.

3.8.3 | CQ VII-3 What types of secondary headache are common in children?

**Recommendation**

The most common secondary headache in children is headache attributed to infection, followed by traumatic injury to the head. Secondary headaches are not frequently seen at headache clinics. Headaches encountered in pediatric emergency departments are most commonly infections other than neurological diseases, such as viral diseases and sinusitis, followed by traumatic injury to the head. Although serious central nervous system disorders are rare, brain CT or MRI should be conducted in the presence of risk factors. Grade B.

3.8.4 | CQ VII-4 What kinds of acute and prophylactic medications are available for the treatment of migraine in children, and how effective are they?

**Recommendation**

As first-choice acute medications for migraine in children, ibuprofen and acetaminophen are effective, safe, and low-cost drugs, and ibuprofen exhibits the best analgesic effect. Among triptans, sumatriptan nasal spray is effect and safe for migraine in children, and rizatriptan tablet is also effective and safe. The recommended strategy is to start acute medication as early as possible after onset of headache and at an adequate dose. For prophylactic treatment of migraine in children, the anti-epileptic drug topiramate is effective and well tolerated, but is currently not covered by health insurance in Japan. Grade A.

3.9 | Genetics

3.9.1 | CQ VIII-1 Are there genetic factors associated with migraine?

**Recommendation**

Migraine occurs commonly among family members. The existence of genetic factors in migraine is almost certain from linkage analyses and twin studies. Multiple genes are speculated to be involved in the development of migraine. However, the definitive causative genes and susceptibility genes have not been identified except for the three types of familial hemiplegic migraine. Grade B.
3.9.2 | CQ VIII-2 Are there genetic factors associated with cluster headache?

**Recommendation**

Cluster headache occurs significantly more commonly among family members, and the involvement of genetic factors is highly probable. Due to the coexistence of environmental factors and the genetic heterogeneity, the causative genes and susceptibility genes for cluster headache have not been identified. Grade B.

3.9.3 | CQ VIII-3 Are there genetic factors associated with tension-type headache?

**Recommendation**

Environmental factors are considered to be strongly associated with the development of tension-type headache. However, the presence of genetic factors in some subtypes is possible. Grade C.

3.9.4 | CQ VIII-4 Does familial (hereditary) migraine caused by single gene mutations exist?

**Recommendation**

Familial hemiplegic migraine types 1, 2, and 3 have been reported to be familial migraine caused by single gene mutations. In addition, single gene disorders that may coexist with migraine include cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), retinal vasculopathy with cerebral leukodystrophy (RCL), hereditary hemorrhagic telangiectasia type 1 (HHT1), mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), and myoclonus epilepsy associated with ragged-red fibers (MERRF). Grade A.

3.9.5 | CQ VIII-5 Is genetic diagnosis for migraine possible?

**Recommendation**

Genetic diagnosis of familial hemiplegic migraine may be possible by analyzing CACNA1A, ATP1A2, and SCN1A. While it is rare to find causative mutations in sporadic hemiplegic migraine patients, genetic diagnosis is possible in some young-onset cases. Although migraine susceptibility genes have been identified by genomewide association studies, the contribution of individual gene is low and not useful for genetic diagnosis. Grade B.

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**CONFLICT OF INTEREST**

The authors declare no conflict of interests related to this guideline.

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APPENDIX A

GUIDELINE FOR SELF-INJECTION OF SUMATRIPTAN AT HOME

CQ1 What kinds of patients receive treatment by self-injection of sumatriptan at home (indication, adverse effects, contraindications)?

Recommendation
Self-injection of sumatriptan at home is indicated for patients with a definitive diagnosis of migraine or cluster headache. Cluster headache may be considered the best indication for self-injection of sumatriptan at home, because of its fast-acting feature and convenience. Migraine is an indication when severe attacks cause severe disability in daily and social lives, or when frequent vomiting impedes administration of oral medications. The safety of this treatment has not been established in children. This treatment has to be used with caution in elderly persons.

The major adverse effects include nausea, chest discomfort, palpitation, bleeding at injection site, malaise, and somnolence.

This treatment should not be given to patients with familial hemiplegic migraine, sporadic hemiplegic migraine, basilar-type migraine (migraine with brainstem aura), or ophthalmoplegic migraine; patients with a history of heart disease, cerebrovascular disorders, or periphery circulatory disturbance; patients with uncontrolled hypertension; patients with severe liver disorder; and patients on treatment with monoamine oxidase (MAO) inhibitor or within 2 weeks after discontinuation. For patients who are prescribed sumatriptan self-injection while also taking oral ergotamine or triptans other than sumatriptan, they should be instructed to use the two agents separately with an interval of at least 24 hours. Grade A

CQ2 How should self-injection of sumatriptan at home be initiated and explained to the patient? What is the appropriate amount to be prescribed?

Recommendation
Initiation of self-injection of sumatriptan at home starts when the doctor prescribes the drug to the patient who is judged to be capable of using self-injection properly. At the time of prescription, provide patient education including method of use. Use “Imigran Kit Subcutaneous Injection 3 mg Training Set” to instruct and explain to patients. Explain in detail the adverse effects that may occur by self-injection of this drug. Instruct patients to follow doctor’s directions if any abnormality occurs after self-injection. Also instruct the patients on appropriate method to dispose of the used injection product.

Since sumatriptan is highly effective and fast acting, self-injection of sumatriptan is recommended for patients with migraine or cluster headache who do not respond adequately to other treatments. Prescribe an appropriate amount taking into consideration for use on an as-needed basis.

For migraine, the amount of each prescription is two kits (four ampoules) to five kits (10 ampoules). However, for patients who have difficulties with frequent hospital visits, it is possible to prescribe an amount deemed appropriate considering the severity and frequency of attacks. For cluster headache, the amount of each prescription is usually seven kits (14 ampoules). Grade A

CQ3 What instructions should be given for the first sumatriptan self-injection at home, and what measures should be taken during emergency (when serious adverse event occurs)?

Recommendation
For patient who has never received sumatriptan subcutaneous injection and patient who self-injects at home for the first time, instruct the patient to inject in the presence of an observer such that contact with a medical institution is possible in case of emergency. For self-injection of sumatriptan at home, instruct the patient about the adverse events that may occur and the method of access to medical institutions, in order to be prepared for the occurrence of serious adverse events. Grade A

APPENDIX B

GUIDELINE FOR MIGRAINE TREATMENT BY VALPROIC ACID (PROVISIONAL EDITION)

CQ1 Is valproic acid effective for migraine prevention? Is there international consensus for valproic acid as prophylactic medication for migraine?
Recommendation
Oral administration of valproic acid to migraine patients with headache attacks two or more times a month can be expected to reduce the number of attacks per month.

Guidelines in European and American countries also recommend valproic acid as the first choice of prophylactic medication for migraine. Grade A

CQ2 What kind of migraine patients are treated by valproic acid?
Recommendation
Valproic acid can be expected to reduce headache attacks in patients who have migraine attacks two times or more a month. In addition, valproic acid prophylactic therapy is recommended when migraine-induced disability in daily living is not adequately resolved with acute treatment alone; when acute treatment drugs are contraindicated, ineffective, or resulted in overuse; and for special types of migraine with a risk of causing permanent neurological defects. Grade A

CQ3 What doses of valproic acid are used for the treatment of migraine? What are the precautions during administration of valproic acid?
Recommendation
In adults, sodium valproate 400-600 mg/day taken orally is recommended for migraine prophylaxis. Grade B
Valproic acid is contraindicated in women who are pregnant or has a possibility of being pregnant. When used in women of child-bearing potential, explain to the patients about adverse effects and teratogenicity, select sustained release formulation, and do not use in combination with other antiepileptic drugs. Considering the possibility of pregnancy, recommend the patient to check the menstruation period, basal temperature, and take folic acid 0.4 mg/day. Grade A

CQ4 What is the significance of measuring blood levels of valproic acid in the treatment of migraine?
Recommendation
When oral valproic acid therapy is used for the prevention of migraine attacks, the optimal blood level is considered to range from 21 to 50 µg/mL, and response does not improve even when the blood level increases to above 50 µg/mL. Therefore, regular measurement of blood valproic acid level during prophylactic therapy and adjustment of the dose to maintain the optimal blood level are recommended. Grade B

CQ5 Is valproic acid safe and effective in preventing migraine in children?
Recommendation
For migraine in children, valproic acid should be restricted for patients with high-level disability not responding to other drugs, or patients with migraine while showing epileptic discharge on EEG (or epilepsies-related headache), and should be used with caution. Grade B

APPENDIX C
GUIDELINE FOR MIGRAINE TREATMENT BY PROPRANOLOL (PROVISIONAL EDITION)

CQ1 Is propranolol effective for migraine prevention? Is there international consensus for propranolol as prophylactic medication for migraine?
Recommendation
Oral administration of propranolol to migraine patients with headache attacks two or more times a month can be expected to reduce the number of attacks per month. Guidelines in European and American countries also recommend propranolol as the first choice of prophylactic medication for migraine. Grade A

CQ2 What kinds of migraine patients are treated by propranolol?
Recommendation
Propranolol prophylactic therapy is recommended when migraine attacks occur two or more times a month and disability in daily living is not adequately resolved with acute treatment alone; when acute treatment drugs cannot be used; and for special types of migraine with a risk of causing permanent neurological defects. In addition, propranolol is recommended as the first-choice prophylactic therapy when patients have comorbidities of hypertension, coronary artery diseases, or tachyarrhythmia. Grade A

CQ3 What doses of propranolol are used for the treatment of migraine?
Recommendation
For adults, start with propranolol 20-30 mg/day. If response is inadequate, titrate up to 60 mg/day, to be taken orally in 2 or 3 divided doses per day. Grade A

CQ4 What precautions have to be taken during administration of propranolol (adverse reactions, interactions)?
Recommendation
Propranolol prophylactic therapy is recommended when migraine attacks occur two or more times a month and disability in daily living is not adequately resolved with acute treatment alone; when acute treatment drugs cannot be used; and for special types of migraine with a risk of causing permanent neurological defects. In addition, propranolol is recommended as the first-choice prophylactic therapy when patients have comorbidities of hypertension, angina pectoris, and arrhythmia. Adequate data including meta-analysis indicates good tolerability. The same applies to interactions. When used as a prophylactic drug for migraine, special attention has to be given to the contraindication for co-administration with rizatriptan. Grade A