

# **Clinical Practice Guideline for Chronic Headache 2013**

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# On Publication of Clinical Practice Guideline for Chronic Headache 2013

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In 2001, the Executive Board of the Japanese Society of Neurology decided to develop clinical practice guidelines for the major neurological diseases, according to a proposal by President Nobuo Yanagisawa. In 2002, “Treatment Guidelines 2002” for six diseases comprising “chronic headache”, “Parkinson disease”, “epilepsy”, “amyotrophic lateral sclerosis”, “dementia”, and “cerebrovascular disease” were published. The Japanese Headache Society developed and published the “Clinical Practice Guideline for Chronic Headache” in 2006 to improve and standardize clinical care for chronic headaches, and to disseminate this knowledge not only among specialists but also to primary care physicians.

Following the publication of “Treatment Guidelines 2002”, new knowledge had accumulated markedly. The 2008 Executive Board of the Japanese Society of Neurology (President, Shigeki Kuzuhara) decided to revise the guidelines, and inaugurated the guideline development committee for “Treatment Guidelines 2010”. From 2009 to 2011, guidelines on “genetic diagnosis of neurological disorders”, “epilepsy”, “dementia”, “multiple sclerosis”, and “Parkinson disease” were published. Furthermore, at the Executive Board of 2011, publication of new clinical practice guidelines for six neurological disorders (Guillain-Barré syndrome/Fisher syndrome, chronic inflammatory demyelinating polyneuropathy/multifocal motor neuropathy, amyotrophic lateral sclerosis, bacterial meningitis, Duchenne muscular dystrophy, and myasthenia gravis) in 2013 was decided. At the same time, with the accumulation of evidence for chronic headaches, mainly on pharmacotherapy, development of the “Clinical Practice Guideline for Chronic Headache 2013” was decided, to be jointly edited by the Japanese Society of Neurology and the Japanese Headache Society.

As procedures of guideline development, President/CEO of the Japanese Society of Neurology appointed the chairman for each guideline development committee, and each chairman recommended candidates as committee members, research collaborators, and evaluation/coordination members. Each candidate submitted a declaration of conflict of interest. Conforming to the review and advice of the Conflict of Interest Review Committee and upon coordinating with each chairman, appointment of the members was approved at the Executive Board. This guideline was developed with cooperation from the Japan Neurosurgical Society and the Japanese Society of Neurological Therapeutics. We would like to express our gratitude to the two societies for their gracious endorsement and support for guideline development.

As with the previous guidelines, the present guideline is developed based on the concept of evidence-based medicine (EBM), and presented in a question and answer (Q&A) format. The guideline is organized in an easy to read manner, as in the 2010 guidelines. Contents of the answers are based on careful review of the cited references, and recommendation grades based on the quality of evidence are provided. However, depending on diseases and symptoms, sufficient evidence is not available for some fields. Treatment contents vary among diseases, ranging from those with established pharmacotherapy and neurosurgical treatment to those in which pharmacotherapy has limitations and non-pharmacotherapy with long-term care are important. As a result, the grading of EBM is also diverse. Furthermore, objectives of treatment differ for diseases with freedom from symptom or symptom relief as the treatment goal and for diseases in which symptomatic relief is difficult and QOL improvement is the only goal. Even in these cases, the optimal guides available to date are provided in this guideline.

It should be noted that clinical practice guidelines do not necessarily present uniform treatment methods. Even for the same disease, the optimal treatment may vary depending on individual patients, and treatment may also vary according to the experience and the opinions of physicians. The guidelines are intended to provide physicians responsible for treatment decision a reference for selecting the best treatment method. For this purpose, the evaluations of individual medications and non-pharmacological treatments are presented based on evidence graded according to international systems.

Clinical practice for chronic headache continues to progress rapidly, and regular revisions are necessary in the future. We hope that many members of relevant societies will use this guideline actively and provide us with feedback, which will allow us to update and improve the contents of the guideline. We anticipate that this guideline will serve as an aid to physicians in their daily practice, and look forward to receiving opinions and feedback for future revisions.

May 2013

Hidehiro Mizusawa, President/CEO, Japanese Society of Neurology

Fumihiko Sakai, President, Japanese Headache Society

Sadatoshi Tsuji, Chairman, Guideline Executive Committee

# Preface

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## 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)”.

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

Accompanying the popularization of triptans, clinical practice for chronic headache also 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 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 7 evaluation/coordination members, the guideline development committee comprised 46 members to carry out the revision tasks.

## 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.

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. 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.

**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
1c	All or none
IIa	Systemic review (with homogeneity) of cohort studies
IIb	Individual cohort study (including low quality RCT; e.g., <80% follow-up)
IIc	Outcomes research
III	Systemic review (with homogeneity) of case-control studies, or individual case-control study
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 A	Use strongly recommended
Grade B	Use recommended
Grade C	No clear evidence to support recommendation for use

After each committee member wrote the part that he or she was responsible, the contents were discussed within each group. The results was opened to all committee members on the internet, 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.

## 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, physician's' experience is important. We hope that this guideline will facilitate better clinical decision-making, and will improve patients' quality of life.

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

## 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

## On publication of the English edition of the guideline

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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: one 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

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# Lists of members of Chronic Headache Clinical Practice Guideline Development Committee, members of Evaluation and Coordination Committee, collaborating societies

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## Chairman

Nobuo Araki                      Department of Neurology, Saitama Medical University

## Vice-chairman

Takao Takeshima                Department of Neurology, Headache Center, Tominaga Hospital

## Committee members

Eiichiro Nagata	Department of Neurology Tokai University School of Medicine
Hidehiro Takekawa	Department of Neurology Dokkyo Medical University
Hikaru Doi	Department of Neurology, Hiroshima Red-Cross Hospital and Atomic-Bomb Survivors Hospital
Hirohisa Ohkuma	Department of Neurology, Tokai University Tokyo Hospital
Hisaka Igarashi	Headache Care Unit, Fujitsu Clinic
Hisanori Kowa	Division of Neurology, Department of Brain and Neurosciences, Faculty of Medicine, Tottori University
Junichi Hamada	Department of Neurology Kitasato Institute Hospital
Karin Ogawa	Department of Neurology, Toshiba Rinkan Hospital
Kazumasa Saigoh	Department of Neurology, Kinki University Faculty of Medicine
Keiko Imamura	Center for iPS Cell Research and Application(CiRA), Kyoto University
Kentaro Kuwabara	Department of Pediatrics, Hiroshima City Hiroshima Citizens Hospital
Kiyomi Yamane	Department of Neurology, Neurological Institute, Ohta-Atami Hospital
Koichi Hirata	Department of Neurology Dokkyo Medical University
Koichi Shibata	Department of Medicine, Tokyo Women's Medical University Medical Center East
Koichi Wajima	Department of Dentistry and Oral Surgery, Keio University School of Medicine
Mamoru Shibata	Department of Neurology, Keio University School of Medicine
Masahiro Hashizume	Department of Psychosomatic Medicine, Toho University
Masako Kudo	Division of Neurology and Gerontology, Department of Internal Medicine, Iwate Medical University
Michiyasu Suzuki	Department of Neurosurgery, Yamaguchi University School of Medicine
Mieko Inagaki	Department of Obstetrics & Gynecology, Chibune General Hospital
Mitsue Fujita	Department of Pediatrics, Tsukuba Gakuen Hospital
Naoki Ando	Department of Pediatrics and Neonatology, Nagoya City University Graduate School of Medical Sciences
Naoto Fujiki	Department of Neurology, National Hospital Organization Hokkaido Medical Center
Shiori Hashimoto	Department of Neurology, Tokyo Women's Medical University
Shoji Kikui	Department of Neurology, Headache Center, Tominaga Hospital
Takahiro Iizuka	Department of Neurology, Kitasato University, School of Medicine

Takayuki Kitamura	Department of Neurological Surgery, Musashikosugi Hospital, Graduate School of Medicine, Nippon Medical School
Tomokazu Shimazu	Department of Neurology, Saitama Neuropsychiatric Institute
Toshihiko Shimizu	Department of Neurology, Keio University School of Medicine
Toshiya Nakano	Division of Neurology, Department of Brain and Neurosciences, Faculty of Medicine, Tottori University
Yasuo Ito	Department of Neurology, Saitama Medical University
Yuji Kato	Department of Neurology and Cerebrovascular Medicine, Saitama International Medical Center, Saitama Medical University
Yuji Takahashi	Department of Neurology, National Center Hospital, National Center of Neurology and Psychiatry
Yuka Watanabe	Department of Neurology Dokkyo Medical University Nikko Medical Center
Yukari Gono	Department of General Medicine, Kitasato University School of Medicine
Yukio Ikeda	Department of Neurosurgery, Tokyo Medical University Hachioji Medical Center

### **Evaluation/coordination members**

Fumihiko Sakai	Saitama International Headache Center
Kenji Nakashima	Division of Neurology, Department of Brain and Neurosciences, Faculty of Medicine, Tottori University
Makoto Iwata	Medical Clinic Kakinokizaka
Norihiro Suzuki	Department of Neurology, Keio University School of Medicine
Shinya Manaka	Manaka Hospital
Yasuhisa Kitagawa	Department of Neurology, Tokai University Hachioji Hospital
Yasuo Fukuuchi	Fukuuchi Pain Clinic

# I

## Headache: General Considerations

## How is headache classified and diagnosed?

### Recommendation

Headache should be classified and diagnosed according to the International Classification of Headache Disorders 3rd edition (beta version).

**Grade A**

### Background and Objective

In 2004, the International Headache Society (IHS) revised the first edition of the IHS guideline for the first time in 15 years, incorporating the latest advances in research, evidence and criticisms. The resulting document, International Classification of Headache Disorders 2nd Edition (ICHD-2) was published in *Cephalalgia*.<sup>1)</sup> In the same year, the ICHD-2 was translated into Japanese and published.<sup>2)</sup> From 2004, headache should be classified and diagnosed in accordance with the ICHD-2.

The first recorded classification of headache was by Aretaeus (a physician born in 81 BC) of Cappadacia in the present day Turkey, who classified headaches into cephalalgia, cephalea, and heterocrania.<sup>3)-5)</sup> Heterocrania was described as “half head” headache, which is equivalent to migraine in the present day classification.

The first consensus-orientated headache classification in history was the classification by the Ad Hoc Committee on Classification of Headache of the American Neurological Association (Ad Hoc classification) published in 1962.<sup>6)</sup> In this classification, headache was classified into 15 types, but no diagnostic criteria were included.

In 1988, the Headache Classification Committee of the International Headache Society chaired by Olesen proposed the first international classification of headache disorders (IHS Classification, 1<sup>st</sup> edition, 1988).<sup>7)</sup> The IHS Classification 1<sup>st</sup> edition first classified headache into 13 items, and further subdivided into 165 headache types. For each subtype, operational criteria were described. Since the IHS Classification 1<sup>st</sup> edition placed greater weight on the nervous system rather than the vascular system as the mechanism of migraine development, the concept of vascular headache was abandoned. Migraine and cluster headache were classified independently, and muscle contraction headache was renamed tension-type headache.

When the IHS Classification 1<sup>st</sup> edition was tested on 740 persons, only 2 persons (0.3%) had unclassifiable headache, verifying that the classification covers the vast majority of headaches.<sup>5)</sup> The consistency, reproducibility and reliability of the operational criteria in the IHS Classification 1<sup>st</sup> edition were validated by clinical evaluations.<sup>8)9)</sup>

Several commentaries on the ICHD-2 have been published.<sup>2)5)10)-12)</sup>

Due to clinical necessity, an appendix for chronic migraine and medication overuse headache (MOH) were added in 2006.<sup>13)14)</sup> Furthermore, revision of the diagnostic criteria for secondary headache was proposed.<sup>15)16)</sup> The Classification Committee of the International Headache Society has been preparing for the publication of the third edition of ICHD. The ICHD Third Edition (beta version) (ICHD-3beta) was published in 2013.<sup>17)</sup>

### Comments and Evidence

#### Headache classification according to the ICHD-3beta<sup>17)</sup>

The ICHD-3beta is composed of the following three parts

- |            |  |
|------------|--|
| Part one   | The primary headaches: 4 types (57 subtypes)   |
| Part two   | The secondary headaches: 8 types (117 subtypes)  |
| Part three | Painful cranial neuropathies, other facial pains and other headaches: 2 types (29 subtypes) supplement (17 subtypes) |
| Appendix   | (40 subtypes)  |

#### Broad Classification of Headache

- Part one: The primary headaches
  1. Migraine
  2. Tension-type headache (TTH)
  3. Trigeminal autonomic cephalalgias (TACs)

- 4. Other primary headache disorders
- Part two: The secondary headaches
  - 5. Headache attributed to trauma or injury to the head and/or neck
  - 6. Headache attributed to cranial or cervical vascular disorder
  - 7. Headache attributed to non-vascular intracranial disorder
  - 8. Headache attributed to a substance or its withdrawal
  - 9. Headache attributed to infection
  - 10. Headache attributed to disorder of homeostasis
  - 11. Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cranial structure
  - 12. Headache attributed to psychiatric disorder
- Part three: Painful cranial neuropathies, other facial and other headaches
  - 13. Painful cranial neuropathies and other facial pains
  - 14. Other headache disorders
- Appendix

## Notes

- While the 1<sup>st</sup> edition had 13 categories, the International Classification of Headache Disorders 2nd Edition (ICHD-2) has an added category “12. *Headache attributed to psychiatric disorder*” and thus a total of 14 categories.
- The ICHD-2 is an indispensable reference for the treatment and diagnosis, research, and education of headache disorders.
- At least, physicians should acquire a good knowledge of migraine (migraine without aura and migraine with aura), tension-type headache, cluster headache, and medication overuse migraine.
- Although the classification was revised by consolidating a vast volume of evidence on headache accumulated during 15 years since publication of the 1<sup>st</sup> edition, the basic policy is based on that of the 1<sup>st</sup> edition.
- Headache is classified based on the hierarchical classification system into group → type → subtype → sub-form. According to this system, each headache is coded in four digits. However, in clinical practice, classification up to two digits is sufficient.
- The following new headache disorders have been added: 1.5.1 *Chronic migraine*, 4.5 *Hypnic headache*, 4.6 *Primary thunderclap headache*, and 4.7 *Hemicrania continua*.
- For some headaches, the classification code was changed (for example; 1.3 *Ophthalmoplegic migraine* was moved to 13.17 *Ophthalmoplegic migraine*).
- Reflecting new concept of pathophysiology, the names of some headaches were changed [for example; trigeminal-autonomic cephalalgias (TAC)].
- In the Japanese translation of the ICHD-2, some translated terms were revised, such as “*Migraine not associated with aura*” to “*Migraine without aura*”.
- This classification is compiled in the same format as the World Health Organization (WHO) International Classification of Disease, and is compatible with the International Classification of Diseases, 10<sup>th</sup> revision: Neurological Adaptation (ICD-10NA).
- Soon after the publication of ICHD-2, the necessity to revise the diagnostic criteria for MOH was pointed out, and they were revised in March 2004. The major changes were (1) deletion of the characteristics of headache described in the subform of medication overuse headache; (2) addition of a new subform “8.2.6 *Medication overuse headache attributed to combination of acute medications*”. These two changes have been incorporated in the Japanese edition of the ICHD-2.<sup>2)18)</sup>
- The Japanese edition of ICHD-2 was published in 2004 in the official journal of the Japanese Headache Society.<sup>2)</sup> A book has since been published which detailed the errata of typographical errors and subsequent changes.<sup>19)</sup>
- An important point of the 2006 revision is that MOH can be diagnosed when there is misuse of medication, and the condition of headache improvement after drug discontinuation is no longer needed. For chronic migraine, while it was required in the past that the headache fulfills at least the diagnostic criteria for migraine without aura, at present it is not necessary that the headache shows the characteristics of migraine.<sup>16)</sup>
- The current diagnostic criterion D for secondary headaches is “Headache is greatly reduced or resolved within 3 months (this may be shorter for some disorders) after successful treatment or spontaneous remission of the causative disorder”. According to this, the headache should disappear completely or improve markedly after the causative disease is cured. However, some causative diseases cannot be cured and as a result headache is perpetuated. In the draft revision for ICHD-3, the diagnostic criterion C is revised substantially to better demonstrate the evidence of causal relationship.

Fulfillment of at least two of five sub-criteria is required. In other words, while the current criterion C focuses only on the temporal relation of the development of headache with the onset of causative disorder, the new proposal has additional items: (C1) headache has developed in temporal relation to the onset of the causative disorder; (C2) headache has worsened in parallel with the causative disorder; (C3) headache has improved in parallel with the presumed causative disorder; (C4) headache has characteristics typical for the causative disorder; (C5) other evidence exists of causation. Moreover, for criterion D, while the current required evidence is resolution or greatly reduced of headache by cure of the causative disorder, the new proposal abolishes this and added “not better accounted for by other diagnosis”.<sup>15)16)</sup>

- The Japanese edition of ICHD-3beta was published in 2014.<sup>20)</sup>

## Major References

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- **Search terms and secondary sources**

- Search database: Ichushi Web for articles published in Japan (2012/5/28)  
classification of headache 58  
headache classification 118 (headache/TH or headache/AL) and (classification/TH or classification/AL) 798
- Search database: PubMed (2012/5/28)  
classification of headache 3085  
international classification of headache 1030  
headache disorders/\*classification 889
- Database used: Ichushi Web for articles published in Japan (2012/5/28)  
(headache /TH or headache /AL) and diagnostic criteria /AL 242
- Database used: PubMed (2012/5/28)  
headache/diagnostic criteria 3107  
headache/\*classification/\*diagnosis 449

## 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**

### Background and Objective

Secondary headaches are headaches that develop due to some disorders, intracranial or otherwise, that cause the headache. In the International Classification of Headache Disorders 3rd Edition beta version (ICHD-3beta), the secondary headaches are coded under 5. “Headache attributed to trauma or injury to the head and/or neck”, 6. “Headache attributed to cranial or cervical vascular disorder”, 7. “Headache attributed to non-vascular intracranial disorder”, 8. “Headache attributed to a substance or its withdrawal”, 9. “Headache attributed to infection”, 10. “Headache attributed to disorder of homeostasis”, 11. “Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cranial structures”, and 12. “Headache attributed to psychiatric disorder”, and further subdivided into subtypes.<sup>1,2)</sup> There was an issue in the International Classification of Headache Disorders Second Edition regarding the classification and diagnosis of secondary headaches; which is, secondary headache cannot be diagnosed definitively if headache does not resolve after treatment.<sup>5)</sup> To address this issue, novel general diagnostic criteria for secondary headaches were proposed as a part of the revision task towards the publication of ICHD-3beta. As a result revision was adopted in ICHD-3beta.

Diverse disorders can cause secondary headaches, and some could be life-threatening. Therefore, careful examination is required. The phrase “Primary or secondary headache or both” is repeatedly discussed throughout the ICHD-3beta.<sup>1,2)</sup> The most important point in clinical care is that among the large number of disorders that may cause secondary headaches, do not miss the “headache for which a misdiagnosis will threaten life”.

### Comments and Evidence

The diagnostic criterion D of ICHD-2 for secondary headaches states “Headache is greatly reduced or resolves within 3 months (this may be shorter for some disorders) after successful treatment or spontaneous remission of the causative disorder”.<sup>5)</sup> According to this criterion, a diagnosis requires that the headache disappears completely or improves markedly after the causative disease is cured. However, some causative diseases cannot be cured, and as a result headache may be perpetuated. To address this issue, general diagnostic criteria for secondary headaches are proposed in ICHD-3beta,<sup>3,4)</sup> and they are presented below.

- A. Any headache fulfilling criterion C
- B. Another disorder scientifically documented to be able to cause headache has been diagnosed
- C. Evidence of causation demonstrated by at least two of the following:
  - 1. headache has developed in temporal relation to the onset of the presumed causative disorder
  - 2. one or both of the following:
    - a) headache has significantly worsened in parallel with worsening of the presumed causative disorder
    - b) headache has significantly improved in parallel with improvement of the presumed causative disorder
  - 3. headache has characteristics typical for the causative disorder
  - 4. other evidence exists of causation
- D. Not better accounted for by another ICHD-3 diagnosis.

Currently, the diagnostic criteria for each of the secondary headaches are being revised in line with the above general criteria.

First of all, differentiation between the primary headaches and the secondary headaches is important. The features that lead to a suspicion of secondary headache include “headache with sudden onset”, “headache never experienced before”, “headache different from the customary headache”, and “headache that tends to worsen”. The probability of secondary headache has to be considered for headaches that begin after age 50; headaches associated with neurological symptoms such as paralysis or abnormal visual acuity or visual field, change in consciousness level, and seizure; headaches associated with fever, rash, or neck stiffness; and headaches with a history of systemic disease.<sup>6)</sup> In clinical interview, the question “Have you experienced the same headache before?” is very useful. If the headache has never been experienced before or is the worst headache ever experienced in life, then it is important to conduct neurological examinations and evaluations, and select appropriate imaging studies, blood tests and cerebrospinal fluid test.<sup>7)</sup> Start treatment if the test and examination results exclude secondary headaches with high emergency, such as subarachnoid hemorrhage, and do not contradict with a diagnosis of primary headache. If the clinical course is not typical of primary headache or if response to treatment is poor, reconsider the possibility of secondary headache.<sup>8)</sup> Especially, in a patient with primary headache who becomes affected by a disease that causes secondary headache, careful examination is needed so as not to delay the diagnosis.

Secondary headache has to be suspected and imaging studies are required in children with headaches that do not respond to drugs within 6 months; headaches associated with papilloedema, nystagmus, or gait/motor disorder; headaches with no family history of migraine; headaches associated with impaired consciousness or nausea; recurring headaches during sleep causing waking; and headaches with a family history or medical history of central nervous system disease.<sup>9)</sup>

Although history taking and physical/neurological examinations are important for the differentiation between primary and secondary headaches, the significance of diagnostic imaging has also been pointed out.<sup>10)</sup> According to the study of Mayer et al.,<sup>11)</sup> 54 of 217 patients (25%) who had subarachnoid hemorrhage were misdiagnosed. The misdiagnoses included meningitis (15%), migraine (13%), headache of unknown etiology (13%), cerebral infarction (9%), headache attributed to arterial hypertension (7%), and tension-type headache (7%). Cautions in the diagnosis of subarachnoid hemorrhage are described in a separate CQ (CQ 1-3, page 8), and will not be discussed here.

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- Search database: Pub Med (2012/4/30)  
{secondary headache} & {diagnosis} 2351
- Search database: Ichushi for articles published in Japanese (2012/4/30)  
{secondary headache} & {diagnosis} 212
- One reference added by manual search (reference 7)

## How is subarachnoid hemorrhage diagnosed?

### Recommendation

- When subarachnoid hemorrhage is suspected, a rapid and precise diagnosis and treatment by 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**

### Background and Objective

Subarachnoid hemorrhage caused by a ruptured cerebral aneurysm has poor outcome. Since misdiagnosis or delay in diagnosis may worsen the outcome, the objective of this section is to improve the capability of the primary care physician to differentiate subarachnoid hemorrhage from other conditions.

In this section, the diagnostic criteria in the International Classification of Headache Disorders 3rd Edition beta version (ICHD-3beta) are provided, and updated knowledge is added.

### Comments and Evidence

Guidelines for the diagnosis and treatment of subarachnoid hemorrhage have been published in Japan and overseas.<sup>1)2)</sup> The prognosis of subarachnoid hemorrhage is poor; overall mortality of 25-53% has been reported.<sup>3)4)</sup> The most important factor that aggravates the prognosis is rebleeding from the ruptured cerebral aneurysm. Since rebleeding is a common cause of misdiagnosis and delay in diagnosis, an accurate diagnosis together with treatment provided by specialist are essential.<sup>5)6)</sup> Before the onset of the major attack of subarachnoid hemorrhage accompanied by “abrupt onset of the worst headache ever experienced”,<sup>3)</sup> minor leak occurs in around 20% of the patients. Misdiagnosis of these warning leaks would deteriorate the outcome; therefore attention has to be given to these cases.<sup>7)8)</sup> The most common symptom of minor leak is sudden headache, but may be accompanied by nausea or vomiting, dizziness, delirium,<sup>9)</sup> oculomotor paralysis, and visual disturbance.<sup>10)</sup> Careful history taking is essential. The common neck stiffness is not observed during the very early stage of subarachnoid hemorrhage, therefore be aware that “absence of neck stiffness does not exclude a diagnosis of subarachnoid hemorrhage”. CT is a useful neuroimaging modality. The diagnostic power increases by comparing with former images.<sup>11)12)</sup> The diagnostic rate is 98-100% when performed within 12 hours of onset.<sup>13)-15)</sup> When a CT scan shows no abnormality, FLAIR MR imaging is useful.<sup>8)16)-18)</sup> Even when imaging findings are negative, a lumbar puncture for cerebrospinal fluid examination is important, especially at 12 hours or later after onset.<sup>1)2)4)13)19)</sup>

#### • For Reference

According to the International Classification of Headache Disorders 3rd Edition beta version (ICHD-3beta) published in 2013, the diagnostic criteria for 6.2.2 *Headache attributed to non-traumatic subarachnoid hemorrhage* are as follows<sup>16)</sup>:

- A. Any new headache fulfilling criterion C
- B. Subarachnoid haemorrhage (SAH) in the absence of head trauma has been diagnosed
- C. Evidence of causation demonstrated by at least two of the following:
  1. headache has developed in close temporal relation to other symptoms and/or clinical signs of SAH, or has led to the diagnosis of SAH
  2. headache has significantly improved in parallel with stabilization or improvement of other symptoms or clinical or radiological signs of SAH

3. headache has sudden or thunderclap onset

D. Not better accounted for by another ICHD-3 diagnosis.

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## • Search terms and secondary sources

- Search database: PubMed (2011/10/15)  
Subarachnoid hemorrhage diagnosis  
& human  
& English/Japanese  
& 2005-  
& practical guideline/review = 457 articles  
Cerebral aneurysm  
& Subarachnoid hemorrhage diagnosis  
& human & English/Japanese & 2005-  
& RCT/metaanalysis = 51 articles

## 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 a diagnosis of headache. Even when neuroimaging shows no abnormality, lumbar puncture should be considered if subarachnoid hemorrhage is strongly suspected.

**Grade A**

### Background and Objective

Patients with diverse complaints of headaches visit the emergency room, ranging from highly emergent subarachnoid hemorrhage to primary headaches. According to the data (between January 1997 and December 1999) of the emergency outpatient department of Keio University Hospital, headache emergencies occupied 3.2% of all emergency cases, 38.3% of which were primary headaches (including migraine 6.6%) and 53.6% were secondary headaches, with subarachnoid haemorrhage constituting 8.1%.<sup>1)</sup> In an emergency department of a hospital in the United States, the vast majority of patients who presented with acute primary headache had migraine (95%).<sup>2)</sup> However, the emergency department physicians diagnosed migraine in only 32% of the patients, and only 7% of the patients received medications specific for migraine. Emergency physicians are required to have the competency to diagnose secondary headaches, and the knowledge to diagnose and treat primary headaches.

### Comment and Evidence

First, physicians should know about headache classification as described in the International Classification of Headache Disorders 2nd Edition (ICHD-II).<sup>3)4)</sup> A sinister headache should be suspected if the onset and clinical course fulfill the following criteria<sup>5)</sup>: patient is younger than 5 years or older than 50 years; new onset headache within the past 6 months; very acute course reaching the highest intensity within 5 minutes; atypical symptoms, headache accompanied by symptoms never before experienced; presence of local neurological abnormalities; non-resolving neurological symptoms; presence of rash, head tenderness, head injury, infection, and hypertension.

Dodick<sup>6)</sup> proposed concise and easy to understand clinical clues for the differentiation between primary and secondary headaches, abbreviated as SNOOP.

#### SNOOP: Clinical clues for clinical diagnosis

- Systemic symptoms/signs (fever, myalgias, weight loss)
- Systemic disease (malignancy, acquired immune deficiency syndrome)
- Neurologic symptoms or signs
- Onset sudden (thunderclap headache)
- Onset after age 40 years
- Pattern change (progressive headache with loss of headache-free periods, change in type of headache)

In a study connected on 264 patients visiting an internal medicine department with a complaint of headache but no neurological abnormalities, patients were asked three questions: Q1 “Is your headache the worst ever? (worst)”, Q2 “Is your headache getting worse? (worsening)”, and Q3 “Was the onset of headache sudden? (sudden)”.<sup>7)</sup> Among the three questions, Q2 (worsening) had the highest positive predictive value, followed by Q1 (worst). It is noteworthy that none of the patients who were negative for all three questions had red flag headaches.

Cortelli et al.<sup>8)</sup> proposed evidence-based diagnosis of non-traumatic headache in the emergency department (ER). They summarized the consensus regarding four clinical scenarios based on extensive literature review.

## Scenarios for the diagnosis of non-traumatic acute headache

### • Scenario 1

Adult patients admitted to ER for severe headache (“worst headache”)

\* with acute onset (“thunderclap headache”)

\* with focal neurological findings (or non-focal, such as decreased level of consciousness)

\* with vomiting or syncope at onset of headache

→ Perform head CT

→ If CT scan is negative or uncertain, or of poor quality, perform lumbar puncture

→ If lumbar puncture shows no abnormality, evaluation by a neurologist within 24 hours is necessary

### • Scenario 2

Adult patients admitted to ER for severe headache

\* With fever and/or neck stiffness

→ Perform head CT and lumbar puncture

### • Scenario 3

Adult patients admitted to ER for the following conditions:

\* headache of recent onset (days or weeks)

\* progressively worsening headache, or persistent headache

→ Perform head CT

→ Perform routine blood tests (including erythrocyte sedimentation rate and C-reactive protein)

→ If tests are negative, perform neurological evaluation within 7 days

### • Scenario 4

Adults with a past history of headache

\* Headache similar to previous headache in intensity, duration and associated symptoms

→ Perform vital signs examination, neurological evaluation and routine blood tests

→ If tests are negative, discharge patient from ER

→ After discharge, provide collaborated care

Although the medical care environment in Japan differs in some aspect from other countries, the above diagnostic scenarios provide useful references. When MRI is used as the first neuroimaging method for acute headache, FLAIR or T2-weighted imaging is essential.

Kowalski et al.<sup>9)</sup> conducted a cohort study on 482 patients with subarachnoid hemorrhage admitted to a tertiary hospital, to analyze the association of initial misdiagnosis with outcome. According to their study, 12% of the patients with subarachnoid hemorrhage were misdiagnosed, and migraine or tension-type headache (36%) was the most common incorrect diagnosis. Misdiagnosis was common in patients with mild bleeding or normal mental status. Misdiagnosis was associated with poor survival and functional outcome. More aggressive CT scanning in patients suspected of subarachnoid haemorrhage, even though the symptoms are mild, may reduce the frequency of misdiagnosis. Even when CT and cerebrospinal fluid test are negative, conducting FLAIR MRI may lead to a diagnosis of subarachnoid haemorrhage.<sup>10)</sup>

Lewis and Qureshi<sup>11)</sup> analyzed the cause of acute headache in children and adolescents (boys and girls). Their results showed that upper respiratory tract infection with fever, sinusitis, and migraine were the most common causes. Physicians have to pay special attention if the acute headache is located in the occipital region or if the patient is unable to describe the quality of the pain. Serious underlying diseases such as brain tumor and intracranial hemorrhage are rare; when present, they are accompanied by multiple neurological signs (such as ataxia, hemiparesis, and papilledema).

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No. Request & Records
  - 1 Headache 55659
  - 2 emergency 210382
  - 3 #1 & #2 1907
  - 4 etiology 6577149
  - 5 management 1654390
  - 6 diagnosis 7723671
  - 7 therapy 6548922
  - 8 treatment 7421136
  - 9 "differential diagnosis" 391173
  - 10 #3 & #4 1076
  - 11 #3 & #5 704
  - 12 #3 & #6 1405
  - 14 #3 & #8 1324
  - 15 #3 & #9 289
  - 16 #10 or #11 or #12 or #13 or #14 or #15 1829
  - 17 "Evidence-Based-Medicine"/all subheadings 49397
  - 18 guidelines 219788
  - 19 consensus 96334
  - 20 #16 & #17 11824
  - 21 #16 & #18 8
  - 22 #16 & #19 2 23 #20 or #21 or #22 11
- Search database: Ichushi for articles published in Japan (2012/5/5)  
(headache) & (emergency) 1103

## 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**

### Background and Objective

Headache is one of the common complaints encountered in routine clinical care. It is estimated that primary care physicians accurately diagnose headache at a rate of approximately 50%. The issue for primary care physicians is how to improve the precision of diagnosis and treatment of headache. When providing headache care, primary care physicians should first of all diagnose the cause of headache accurately. To do this requires knowledge regarding the classification of headaches. When primary care physicians with no access to head CT and MRI encounter difficulties in differentiating secondary headaches from primary headaches, they should refer the patient to a specialist as soon as possible. Especially in the case of sudden onset of headache in which subarachnoid hemorrhage cannot be excluded, the patient should be referred to a neurosurgeon.

Although primary headaches are considered not to cause residual organic damage to the brain, headache attacks cause disability in daily life. Therefore, appropriate treatment is required to improve the daily life of the patients.

For clinical care of headache, use simple screeners and headache diary for diagnosis, severity evaluation, and treatment; evaluate the treatment effect appropriately; and it is also important to give proper guidance to the patients about the timing of taking acute medications for headache and on prophylactic treatment.

### Comments and Evidence

First, primary care physicians should know about the International Classification of Headache Disorders 2nd Edition (ICHD-II) developed by the International Headache Society (IHS),<sup>1)</sup> which set out diagnostic criteria for each of the headache types. Furthermore, they should know that according to ICHD-II, headaches are classified into primary headaches and secondary headaches, and that primary headaches include migraine, tension-type headache, and cluster headache, while secondary headaches are caused by various neurological disorders and may include systemic diseases.<sup>1)</sup> When primary care physicians provide care for headache, it is important that first of all they have knowledge of the diagnostic criteria for primary headaches. Although ICHD-II classifies in a hierarchical manner, primary care physicians should be familiar with at least the first level (for example, the level to diagnose “migraine”). To diagnose primary headaches, it is necessary to exclude the possibility of secondary headaches. In practice, precise history taking, neurological evaluation, sometimes blood tests and neuroimaging are necessary to exclude secondary headaches. If eye disease or disease of other discipline is suspected from the beginning, refer the patient to the respective specialist as soon as possible. When a diagnosis of primary headache is established, plan treatment according to this guideline.

Simple screeners headache for use by primary care physicians have been developed, and reported to have high specificity for the diagnosis of migraine.<sup>2,3)</sup> One of them consists of questions on the frequency of headache, and the use of medications.<sup>2)</sup> Another screener contains questions based on the diagnostic criteria of ICHD-II, including the frequency and duration of headache, aura, and degree of disability.<sup>3)</sup> MIDAS and HIT-6 are tools that evaluate objectively the impact of headache on patient’s activities of daily living. Use these screeners to aid diagnosis and evaluation of severity, and provide treatment appropriate to individual patients. Use headache diary for follow-up observation. Advise patients on the timing of taking medications for migraine. Provide rescue treatment when the early treatment fails. Offer prophylactic treatment when headache occurs frequently. As such, primary care physicians also have to be engaged in many aspects of headache management.<sup>4,5)</sup>

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  - Headache & 'primary care' 1078
  - Headache & 'primary care' & diagnosis 710
  - Headache & general practitioner 326
  - Headache & general practitioner & diagnosis 190
  - Headache & algorithms 171
  - Headache & screener 15

## 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**

### Background and Objective

Temporomandibular disorder occurs overwhelmingly more often in women, and is known to be a disease with gender difference. Primary headaches, especially migraine and tension-type headache, tend to occur concurrently with temporomandibular disorder. Moreover, since the pain experienced by patients with cluster headache and migraine sometimes involves the face and the teeth, these patients may visit dentists with the major complaint of toothache or temporomandibular pain. Dentists are recommended to have the capability of differentiating these headaches from temporomandibular disorder and odontogenic pain.

On the other hand, it has been reported that dental disease may be a cause of secondary headaches.

### Comments and Evidence

In the International Classification of Headache Disorders 3rd Edition (beta version) (ICHD-3beta) of the International Headache Society (IHS),<sup>1)</sup> tension-type headache is subdivided into infrequent episodic tension-type headache, frequent episodic tension-type headache, and chronic tension-type headache; and each further subdivided into two subforms: with and without pericranial tenderness. Increased pericranial tenderness induced by palpation is the most significant abnormal finding in patients with tension-type headache. The tenderness increases with the intensity and frequency of headache, and is further increased during actual headache. Pericranial tenderness is in fact tenderness of the frontal muscle, temporal muscle, masseter muscle, lateral and medial pterygoid muscle, sternocleidomastoid muscle, splenius muscle, and trapezius muscle. In another words, tension-type headache and myogenic temporomandibular disorder may be regarded as similar diseases with the same source of pain but different pain reception sites. Because the muscles are affected, stiff shoulders and stiff neck often occur concurrently.<sup>2)3)</sup>

In addition, studies have shown a pathological association between temporomandibular disorder and headache, and between toothache and headache.<sup>4)5)</sup>

Migraine is a disease with high prevalence, and therefore may coexist incidentally with other diseases that have high prevalence. A report has indicated that one-half of the patients with temporomandibular disorder have migraine concurrently. Patients with migraine sometimes manifest allodynia in the craniocervical region both during headache and when in remission, probably a result of lowered threshold of pericranial tenderness.<sup>6)</sup> Furthermore, the pain in migraine not only involves the first division of the trigeminal nerve, but also the second and third divisions, and may sometimes be misdiagnosed as temporomandibular disorder or toothache.<sup>7)</sup> This is a result of sensitization of the central nervous system due to headache attack, and conversely deep pain in the craniocervical region may also sensitize the central nervous system. Consequently, temporomandibular disorder is a factor that contributes to aggravate headache frequency or induce chronicity of headache.<sup>4)5)</sup>

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  - TMD & migraine headache 33
  - TMD & tension-type headache 38

## Are headache clinic and headache specialist necessary?

## Is collaborative care useful for primary headaches?

### Recommendation

Headache clinic is necessary to improve the satisfaction and quality of life (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**

### Background and Objective

Many patients with chronic headaches have headaches that seriously interfere with their daily activities. Yet, the needs of the patients were not met. Many patients either never sought medical care or were not diagnosed and treated appropriately even if they had received medical care, while others were always anxious that as the doses of analgesics increased, the medications might become ineffective. To address this situation, the Japanese Headache Society started to certify headache specialists from 2005, and began to establish headache clinics nationwide. A nationwide epidemiological survey in Japan estimated that approximately 40 million persons were affected by chronic headache.<sup>1)</sup> The numbers of headache specialists and headache clinics remain insufficient.

### Comment and Evidence

According to a nationwide epidemiological survey in Japan, the number of persons affected by headache was estimated to be approximately 40 million, 8.5 million of whom had migraine and 74% of whom had serious disability in daily living because of the headache.<sup>1)</sup> The economic loss because of headache, including direct loss due to medical expenses and indirect loss due to the incapability to work, amounts to nearly three hundred billion yen a year.<sup>2)</sup> The World Health Organization (WHO) ranked migraine at the 19<sup>th</sup> place among diseases that shorten the healthy lifespan.<sup>3)</sup> Approximately 70% of migraine patients never consult medical facilities, and approximately 50% are taking only over-the-counter medications.<sup>1)4)</sup> Most of the patients with chronic headache who have never consulted a medical facility, patients who have not been appropriately diagnosed, and patients who are treated only with over-the-counter medications have serious disability in daily living. In addition, even among those who have consulted medical facilities, many are not accurately diagnosed and do not receive appropriate treatment.<sup>5)6)</sup> In the background of such situation, issues on the medical facility side include the following: (1) only neuroimaging is conducted to exclude organic diseases, and the diagnosis for migraine is inadequate; (2) even when migraine is diagnosed, knowledge on treatment is inadequate leading to patient dissatisfaction; and (3) diagnosis and treatment are not explained adequately to patients. On the other hand, there are also issues on the patient's side, including: (4) feel assured by exclusion of organic diseases alone, and do not ask for treatment; and (5) are embarrassed by consulting medical facilities because of headache, due to a lack of understanding that migraine is a condition that requires treatment.<sup>7)</sup> Through the establishment and publicity of headache clinics, the number of patients with chronic headache consulting headache specialists has increased.<sup>5)9)</sup> When the headache clinic was opened at the Department of Neurology at Yamaguchi University, the event was publicized in the press and television, resulting in an increase of new headache patients by 7.4-fold, especially with a significant increase in patients with migraine.<sup>8)</sup> Among patients with migraine consulting the headache clinic, their primary purpose is to seek treatment, followed by to know the cause of their headache.<sup>7)</sup> In a study of 38 patients with migraine referred by primary care physicians to a specialist headache clinic in Singapore, the pain intensity, MIDAS score, and SF-36 score improved after three months, and patient satisfaction also increased.<sup>10)</sup> Referral from general physicians to headache specialists benefits the patients by ameliorating the fear toward headache, improving the headache per se, and improving QOL.<sup>11)12)</sup>

To improve headache care, experienced headache specialists and headache clinics staffed by headache specialists are essential.<sup>9)</sup> An accurate diagnosis of headache and every possible approach to relieve the disease burden of headache patients should be provided.

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- Search database: PubMed (2012/4/30)  
 {headache clinic} 3175  
 & ({role} OR {necessity}) 232  
 &specialist 62  
 (1) & {medical treatment} & {migraine} 73
- Search database: Ichushi Web for articles published in Japan (2012/4/30)  
 headache clinic 142  
 specialist headache clinic 12  
 headache center 28  
 headache specialist 7
- Secondary source: 4 references from manual search (references 1, 3, 4 and10)



## How are algorithms used?

### Recommendation

The diagnosis and treatment of headache start from differentiating secondary headaches, especially the dangerous (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

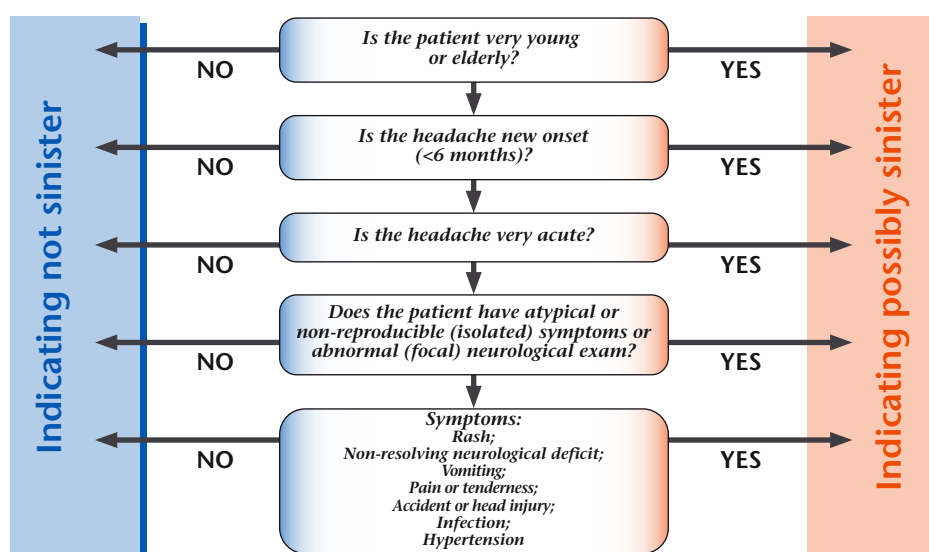
### Background and Objective

The objective of this section is to illustrate how algorithms can be used for effective diagnosis of headache in the busy routine clinical setting.

### Comments and Evidence

The diagnosis and treatment of headache start from excluding the secondary headaches that are dangerous headaches. An algorithm for use by primary care physicians is available (Figure 1). After screening for dangerous headaches, the diagnosis of chronic headaches that are primary headaches including migraine then begins.<sup>1-4)</sup> The algorithm comprises four major questions: “What is the impact of the headache on daily life?”, “How many days of headache in a month?”, “how many days per week are medications taken?” and “Does the attack start with reversible homonymous visual symptoms or unilateral sensory symptoms?”<sup>2)</sup> (Figure 2).

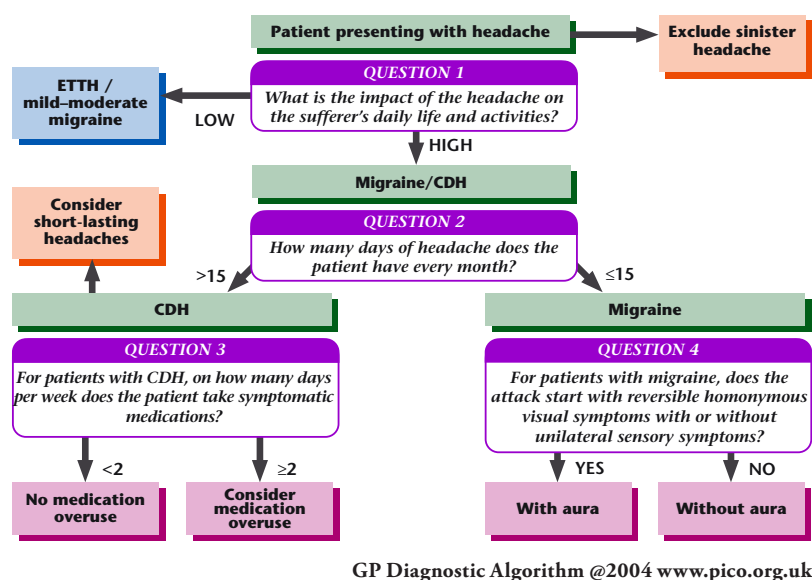
For migraines, “POUNDing” that is composed of the acronyms characterizing the five symptoms of migraine is useful.<sup>4)</sup> POUNDing stands for Pulsating, duration of 4-72 hOurs, Unilateral, Nausea, and Disabling. If four of the five are satisfied, then there is a high probability of migraine (Figure 3). Moreover, another algorithm examines the common clinical question of what kinds of patients require neuroimaging. Six items: “cluster-type headache”, “abnormal findings on neurologic examination”, “undefined headache (not cluster-, migraine-, or tension-type)”, “headache with aura”, “headache aggravated by exertion or valsalva-like maneuver”, and “headache with vomiting”, are useful in judging whether neuroimaging is necessary (Figure 4). An algorithm for differentiating chronic daily headaches<sup>5)</sup> and another algorithm for the management of primary headaches in the emergency setting<sup>6)</sup> have also been reported.



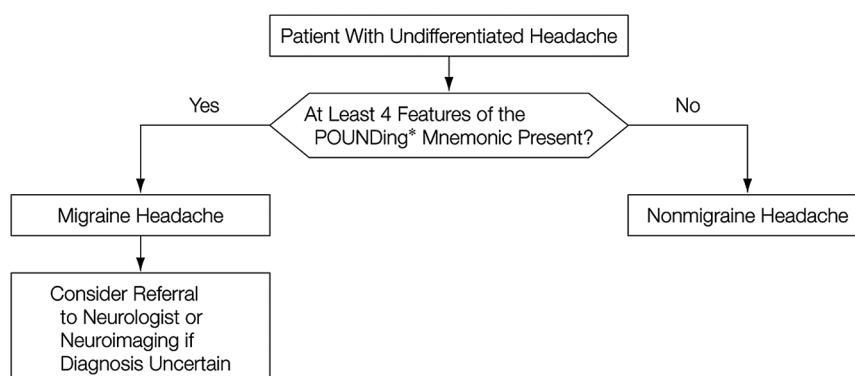
Sinister Headache Algorithm @2004 [www.pico.org.uk](http://www.pico.org.uk)

Figure 1. Simple diagnostic algorithm for screening sinister headache.

Reproduced with permission from Migraine Action.



**Figure 2. Algorithm for screening headache.**  
Reproduced with permission from Migraine Action.

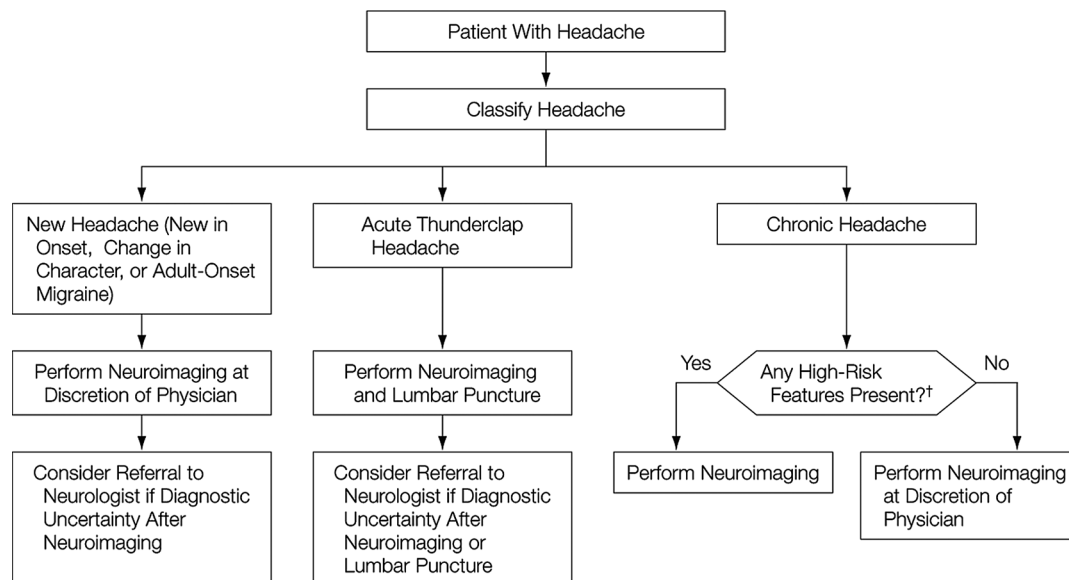


**Figure 3. Algorithm for the approach to headache: Does this patient have a migraine headache?**

\*POUNDiNg: Pulsatile; duration 4-72 hOurs; Unilateral; Nausea; Disabling  
[Detsky ME, McDonald DR, Baerlocher MO, Tomlinson GA, McCrory DC, Booth CM: Does this patient with headache have a migraine or need neuroimaging? JAMA 2006;296(10):1274-1283. Copyright © (2006) American Medical Association. All rights reserved.]

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**Figure 4. Algorithm for the approach to headache: Does this patient need neuroimaging?**

†Cluster-type headache, abnormal findings on neurologic examination, undefined headache (not cluster-, migraine-, or tension-type), headache with aura, headache aggravated by exertion or valsalva-like maneuver, headache with vomiting [Detsky ME, McDonald DR, Baerlocher MO, Tomlinson GA, McCrory DC, Booth CM: Does this patient with headache have a migraine or need neuroimaging? JAMA 2006;296(10):1274-1283. Copyright © (2006) American Medical Association. All rights reserved.]

## • Search terms and secondary sources

- Search database: PubMed (2011/10/18)  
headache 54858  
& diagnosis 32183  
& algorithm 170
- Search database: Ichushi Web for articles published in Japan (2011/10/18)  
headache 22226  
& diagnosis 12004  
& algorithm 21

## 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**

### Background and Objective

Impact has a similar connotation to “disability” as defined by the WHO, which is the limitation or incapability of normal activities as a human being. Rather than the subjective manifestation of signs and symptoms and health-related quality of life (HRQOL), the impact of headache is rated as the objective influence of the disease on life activities such as work and leisure activities. Among the primary headaches, the disability caused by migraine has been reported worldwide. The evaluate the severity of migraine, assessing the impact of migraine is important.

### Comments and Evidence

Several scales are available for the evaluation of the disability in daily living caused by chronic headache; however, the scales that can be used in Japanese language are limited. This section comments on several questionnaires, including Japanese versions, for the evaluation of the impact of headache in general, which have been reported to have high reliability and validity.

#### • Headache Impact Questionnaire (HImQ)

This is a scale developed based on the Chronic Pain Inventory (CPI) for measuring the impact of headache. The scale is a 16-item self-administered questionnaire: number of headaches; headache duration; pain intensity; disability; and time lost in work for pay, housework and non-work activities. The scale can be applied to all headaches and has wide utility. However, scoring is complicated, and is therefore more suitable for research than for primary care.<sup>1)</sup>

#### • Migraine Disability Assessment (MIDAS)

This is a brief questionnaire based on a part of HImQ. The MIDAS divides daily living into work or school, household work, and non-work activities. The missed days in work and other activities are scored and the total score is used to evaluate the disability. The scale is useful not only for migraine but also for headache in general.<sup>2)</sup> The MIDAS has been translated into various languages including Japanese, and the reliability and validity have been evaluated.<sup>3)</sup>

#### • Headache Impact Test (HIT)

The HIT is composed of items from several widely used QOL and daily living disability scales with proven validity; the Headache Disability Inventory (HDI), Headache Impact Questionnaire (HIQ), MIDAS, and Migraine-Specific Quality of Life Questionnaire (MSQ), together with added questions from clinicians and QOL specialists. It is a tool for measuring the impact of headache on individuals in their ability to function on the job, at school, at home and in social situations. The scale is in the form of an internet-administered questionnaire (only available in English).<sup>4)</sup>

#### • HIT-6

The HIT-6 was developed through the construction of the HIT. The questionnaire can be administered as a short paper-based test consisting of six questions that can be responded within one minute. The questions are on pain intensity, impact on daily activities, impact on social activities, and mental burden due to headache. The respondent chooses from one of 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 on daily living is classified into four grades.<sup>5)</sup> A high correlation has been found between the HIT-6 score and HIT score. The scale has been translated into more than 25 languages. The reliability of the Japanese version has also been validated.<sup>6)</sup>

- **Migraine Work and Productivity Loss Questionnaire (MWPLQ)**

The impact of headache can be measured by focusing on productivity at work.<sup>7)</sup>

- **Headache Needs Assessment (HANA)**

The HANA is a questionnaire consisting of 7 items that evaluate the frequency of loss of QOL and bothersomeness.<sup>8)</sup>

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- **Search terms and secondary sources**

- Search database: PubMed(2011/8/28)  
Headache All fields 54478  
& {impact} 1284  
& {burden} 94  
& {QOL} 32
- Search database: Ichushi Web for articles published in Japan (2011/12/21)  
headache 795  
& {QOL and/or quality of life}12  
& {disability}1  
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## 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 doctors, 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 screeners 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 doctors and patients.

### Comments and Evidence

The following interview sheets and screeners for headache have been evaluated for reliability and validity.

#### Diagnostic screeners

- (1) 3-Question Headache Screen
- (2) ID Migraine

The 3-Question Headache Screen<sup>1)</sup> diagnoses migraine from three features: (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<sup>2)</sup> diagnoses migraine from three items: disability, nausea and sensitivity to light. Because the screener is simple and can be self-administered, its usefulness in primary care is attracting attention. In Japan also, similar validation study was conducted as a multi-center, blinded, clinical epidemiological study<sup>2b)</sup>.

#### 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

MIDAS and HIT are examples of short questionnaires.

The MIDAS questionnaire<sup>3)-5)</sup> is a short questionnaire developed based on the HImQ. It divides daily living into work or school, household work and non-work activities, and evaluates the degree of disability from the missed days of these activities.<sup>3)4)</sup> This scale is useful not only for migraine but also for headache in general. It has been translated in various languages including Japanese,<sup>5)</sup> and the reliability and validity have been evaluated. In addition, MIDAS for adolescents and children, PedMIDAS<sup>6)</sup> has also been developed and is useful for the evaluation of pediatric headache.

The HIT is composed of items from several widely used QOL and daily living disability scales with proven validity; the Headache Disability Inventory (HDI), Headache Impact Questionnaire (HIQ), MIDAS, and Migraine-Specific Quality of Life Questionnaire (MSQ), together with added questions from clinicians and QOL specialists. It was developed as a tool for measuring the impact of headache on individuals in their ability to function on the job, at home, at school and in social situations. The scale is only available in English. The test is internet-administered, and evaluates the impact of headache comprehensively.<sup>7)</sup>

The HIT-6<sup>8)</sup> was developed through the construction of the HIT. The questionnaire 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.<sup>9)</sup>

### Questionnaires on patient QOL

(1) Migraine-Specific Quality of Life Questionnaire (MSQ)

(2) Migraine-Specific Quality of Life Measure (MSQOL)

The MSQOL<sup>10)</sup> 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 ver. 2.1<sup>11)</sup> is composed of 14 items on family, 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 ver 2.1 has also been evaluated for reliability and validity.<sup>12)</sup>

### 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<sup>13)</sup> 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<sup>14)</sup> 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.<sup>15)</sup>

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- Search database: PubMed (2011/9/1)  
 Headache All fields 54507  
 & {screening} 23380  
 & {questionnaire} 1212 & {screeener} 10  
 Migraine All fields 24758  
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 & {screeener} 9  
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- Search database: Ichushi Web for articles published in Japan (2011/12/21)  
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 & {interview sheet} 88  
 & {screening}0 & {screeener}0

## 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**

### Background and Objective

Patients themselves often do not remember accurately information about their headache, such as the number days with headache, the number of days they have taken medication, and the relation between menstruation and headache. Hence, it is difficult to communicate the information to the physicians. The purpose of the headache diary is to allow the patient to understand the condition of his/her headache and to communicate it effectively to the physician, so as to promote appropriate treatment.

### Comments and Evidence

The headache diary provides prospective information of headache, and its usefulness in clinical care and research of headache has been reported.<sup>1)</sup> Using headache diaries, it is possible to confirm objectively (1) the number days with headache, (2) the property of headache, (3) the intensity of pain, (4) the duration, (5) the accompanying symptoms, (6) the trigger factors, (7) the status of medication use, and (8) the degree of disability.<sup>1)–6)</sup> Hence for the physicians, their rate of accurately diagnosing individual headaches is increased by using also the headache diary compared to conducting clinical interview alone,<sup>7)</sup> and they can also monitor the treatment effects. The diagnosis rate of individual headaches is especially high in patients who have headaches in many days, and differentiation between migraine and tension-type headache is possible.<sup>8)</sup> For the patients, they benefit from being able to monitor their own headache, improvement in drug taking according to the headache type, and improvement in the timing of drug use.<sup>5)</sup> Moreover, the headache diary is also useful in facilitating patient–physician communication.<sup>9)</sup>

When using the headache diary, it is necessary to explain to the patients how it is used and its usefulness, and to obtain their cooperation.

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- Search database: PubMed (2011/12/21)  
headache & diary (all field) 504
- Search database: Ichushi Web for articles published in Japan (2011/12/21)  
headache & diary (AL) 44  
headache & diary 23

## 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 be treated aggressively.

**Grade A**

### Background and Objective

The prevalence of migraine in Japan is 8.4%, and 74% of the affected persons experience disability in daily living.<sup>1)</sup> The prevalence of chronic tension-type headache is 1.5%, and 40.5% of the affected persons have disability in daily living.<sup>2)</sup> The medical facility consultation rate is 30% for migraine, and 73% for chronic tension-type headache.<sup>2)</sup> However, consulting a medical facility does not guarantee that appropriate treatment is received.

With emphasis being placed on exclusion of secondary headaches, many patients do not receive explanations of the pathophysiology and diagnosis of primary headaches, or receive adequate treatment. Regarding the level of headache care in Japan, reports have indicated that patient needs are not met.<sup>3,4)</sup> This section examines the primary headaches that should be treated.

### Comment and Evidence

The prevalence of migraine in Japan was 8.4%. Among all migraine sufferers, 74% experienced disability in daily living; comprising 4% who frequently required bed rest, 30% who sometimes required bed rest, and 40% who did not require bed rest but had disability.<sup>1)</sup> Including borderline cases ('borderline' tension-type headache with no clinical features of migraine), the prevalence of tension-type headache was 22.3% (including episodic tension-type headache 20.6%, chronic tension-type headache 1.5%), 29.2% of whom had disability in daily living; comprising 0.5% who always required bed rest, 4.7% who frequently required bed rest, and 24% who did not require bed rest but had disability.<sup>2)</sup> Tension-type headache tends to have a milder impact than migraine. However, for chronic tension-type headache sufferers, 40.5% were affected by disability.<sup>2)</sup>

The Migraine Disability Assessment (MIDAS) questionnaire<sup>5)-7)</sup> and the Headache Impact Test (HIT-6)<sup>8)</sup> are practical tools for the assessment of disability caused by headache. They are used for assessing the degree of disability and for monitoring treatment effectiveness. MIDAS Grade III (score 11) or above, or an HIT-6 score 50 or above indicates moderate or severe disability, and are targets of intensive treatment. In Japan, two reports on the assessment of migraine patients by the MIDAS questionnaire have been published. Igarashi<sup>9)</sup> evaluated 1,760 nurses or pharmacists with migraine using the MIDAS questionnaire, and reported the distribution of the degree of disability as follows: grade I (minimal or infrequent disability) 63.3%, grade II (mild or infrequent disability) 14.0%, grade III (moderate disability) 8.0%, and grade IV (severe disability) 5.7%. These results are similar to those of an epidemiological survey conducted in France (no response 9.0%).<sup>10)</sup> According to the study of Igaya et al.<sup>7)</sup> on 101 migraine patients who visited a neurological outpatient department, the MIDAS grade distribution was grade I or II 46.5%, grade III 22.2%, and grade IV 31.3%.

The objectives of treating primary headaches are to reduce the headache frequency, headache intensity, and duration; to reduce the time of disability caused by headache and improve QOL; and to prevent the exacerbation of headache by medication overuse. Stratified care according to the degree of disability is recommended for the treatment of acute migraine.<sup>11)</sup> Stratified care is a treatment approach based on the degree of disability, in which analgesic is prescribed for low-degree disability, while triptan is prescribed from the first treatment for patients with high-degree disability.

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## • Search terms and secondary sources

- Search database: PubMed (2011/11/8)  
Chronic headache OR Primary headache  
& {strategy OR stratified} 484

## 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)

### Background and Objective

Serious life-threatening secondary headache encountered in the emergency outpatient setting obviously require admission and treatment on an inpatient basis. However, the criteria of admitting patients with primary headaches and the treatment methods are decided by individual medical facilities and physicians. There are no clear guidelines.

### Comments and Evidence

The evidence level for patients who require admission is grade B, and that for treatment method is grade C. The guidelines on headache management published overseas provide recommendations according to consensus of specialists based on the medical care situation of individual countries or regions. Among these guidelines, the Danish guidelines describe the patients who require hospitalized management, and give the following criteria:

- (1) When a serious disease that require immediate treatment is diagnosed
- (2) When diagnosis and evaluation of headache are not achieved within the limited time at the outpatient clinic
- (3) In the case of rare headache that can be diagnosed by observing a headache attack
- (4) In the case of investigating whether a special treatment is effective
- (5) For the purpose of stopping medications in severe acute medication overuse cases of migraine and tension-type headache (if outpatient treatment fails, admission for 1-3 weeks<sup>2)</sup>)

In addition, patients with severe status migrainosus and refractory or chronic cluster headache<sup>3)</sup> who have serious symptoms untreatable in outpatient clinic may desire hospitalized treatment. Regarding hospital treatment methods for these primary headaches, evidence is available for acute-phase treatment of status migrainosus, but evidence is lacking for the treatment of the other headaches. For discontinuing medications on an inpatient basis for patients with severe overuse of acute medications described in (5),<sup>4)-7)</sup> a metaanalysis on outcome has been conducted by reviewing literature up to 1998.<sup>8)</sup> Regarding short- and long-term outcome, the 50% headache improvement rate was approximately 80% within 6 months, and 60% over 6 months. However, the types of headaches treated, the types of acute medications, the doses, and the misuse durations varied widely among the articles. There is no clear evidence for treatment method.

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- **Search terms and secondary sources**

- Search database: PubMed (2011/8/9)
  - #1 primary headache 5527
  - #2 hospitalization OR inpatient 215346
  - #3 primary headache and (hospitalization OR inpatient) 104
  - #4 primary headache and guideline 79;
  - #5 #3 or #4 181

## 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**

### Background and Objective

Some 40 million persons in Japan are estimated to be affected by chronic headache.<sup>1)2)</sup> Among 8.4 million persons estimated to be affected by migraine, approximately 74% have disability in daily living, indicating that pharmacotherapy can play a big role. On the other hand, there is a lack of awareness about migraine, and only 2.7% of the migraine sufferers consult a medical facility regularly.<sup>1)2)</sup> Most of the headache patients presumably manage by taking OTC medications. The major primary headaches comprise migraine, tension-type headache, and cluster headache. OTC medications can be expected to be effective against only mild migraine and episodic tension-type headache. Before starting pharmacotherapy, life-threatening secondary headaches should be excluded.<sup>3)</sup> Then, OTC medications may be one of the options of pharmacotherapy for migraine and episodic tension-type headache.

### Comments and Evidence

Headache is classified by severity and disability into three grades: (1) mild: not disabling; (2) moderate: has impact on daily living or work; and (3) severe: not able to carry out activities of daily living or work, requiring bed rest. Among the primary headaches, when the headache is always mild, afflicts minimal suffering and does not impair daily living, this type of headache can be managed by observation, lifestyle improvement and self-care such as stretching. Even when the headache inflicts suffering, mild cases can be controlled by OTC medications.

For OTC antipyretic analgesics, single-ingredient or combination products approved by the Ministry of Health, Labour and Welfare in Japan are shown in [Table 1](#).<sup>4)</sup> Acetaminophen 1,000 mg,<sup>5)</sup> aspirin 1,000 mg,<sup>6)</sup> and ibuprofen 200 mg and 400 mg<sup>7)</sup> have been reported to be effective for migraine and tension-type headache.<sup>8)</sup> A combination preparation of aspirin, acetaminophen and caffeine has been evaluated in a double-blind randomized control trial (RCT) and reported to be effective for migraine.<sup>9)</sup> This fixed combination preparation has also been reported to be more effective than single substances.<sup>10)</sup> In recent year, loxoprofen has been added as a switch OTC, but there is no report at RCT level.

Since patients can obtain unlimited OTC medications, it is necessary to explain and draw the patients' attention to the fact that frequent use for long periods of time may cause medication-overuse headache.

**Table 1. Ingredients of OTC antipyretic analgesics.**

Antipyretic analgesic ingredients	Aspirin, acetaminophen, isopropylantipyrine, ibuprofen, ethebamide
Sedative hypnotic ingredients	Enhancement of analgesic effect of antipyretic analgesic, also sedative effect Allylisopropylacetylurea, bromvalerylurea
Antacid ingredient	Suppresses gastric discomfort due to antipyretic analgesic ingredients
Herbal medicine ingredients	Exhibit antipyretic effect (Jiryu, etc.) and analgesic effect (Shakuyaku)
Other ingredients	Supplement the analgesic effect of antipyretic analgesics Anhydrous caffeine



According to the criteria for medication-overuse headache described in the International Classification of Headache Disorders 3rd Edition (beta version) published in Cephalalgia in June 2013,<sup>11)</sup> medication-overuse headache is diagnosed when headache is associated with regular intake of simple analgesic on  $\geq 15$  days per month or combination analgesics on  $\geq 10$  days per month for  $> 3$  months. Therefore, for patients who are taking OTC medications on  $\geq 10$  days per month and patients who have been taking OTC medications despite no response, a change to acute medications according to physicians' instructions and administration of prophylactic medications should be considered.

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- Search database: PubMed (2011/12/21)  
Headache & OTC 50 & aspirin 530  
& acetaminophen 372  
& ibuprofen 185  
& self-medication 371  
& guideline 405
- Search database: Ichushi Web for articles published in Japan (2011/12/21)  
Headache & OTC 58  
& aspirin 194  
& acetaminophen 165  
& ibuprofen 96  
& pharmacy 138  
& pharmacist 180

## 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**

### Background and Objective

Since herbal medicine (Kampo) is a treatment that was developed through empirical use, it cannot be denied that scientific evidence such as basic and clinical research remains insufficient. In this section, the effectiveness of Kampo is examined by reviewing articles with evidence level of case series or above.

### Comments and Evidence

Comments are given below by Kampo formula.

#### 1. Goshuyuto (呉茱萸湯 in Japanese, Evodia Decoction in English)

One report of double-blind randomized controlled trial (DB-RCT) on responders only, one report of randomized controlled (open label, cross-over) trial, one report of comparative study between Kampo formulas, and two reports of case series were identified. Taking into account the prescription system of Kampo medicines, Odaguchi et al.<sup>1)</sup> conducted a DB-RCT on a selected subgroup of 53 patients with chronic headache who responded to Goshuyuto, and observed significant decrease in headache frequency and decrease in frequency of analgesic intake. According to the Kampo prescription system, even with the same diagnosis of migraine, different Kampo formulas may be prescribed depending on the constitution of individuals. Therefore, it is difficult to conduct conventional clinical research such as DR-RCT on Kampo prescriptions. Maruyama<sup>2)</sup> conducted an open-label crossover study of Goshuyuto and lomerizine hydrochloride in patients with migraine. Despite limitations of a relatively small number of cases and short wash-out period, the study showed higher efficacy of Goshuyuto compared to lomerizine hydrochloride. Seki et al.<sup>3)</sup> and Maeda et al.<sup>4)</sup> used Goshuyuto for chronic headache, and observed high improvement rates of 79.5% and 89%, respectively. Especially, Maeda et al.<sup>4)</sup> reported high improvement rate in vascular headache patients with severe pain, and the effect appeared mostly within 2 weeks, suggesting that early effectiveness may be expected for migraine. Akamine et al.<sup>5)</sup> reported effectiveness in 76.7% of patients with tension-type headache. Thus, Goshuyuto is highly effective for both migraine and tension-type headache.

#### 2. Keishininjinto (桂枝人参湯 in Japanese, Cinnamon Twig and Ginseng Decoction in English)

One report of randomized controlled study comparing with Goshuyuto and one report of non-randomized crossover study between Keishininjinto and Chotosan were identified. In the randomized controlled study for chronic headache comparing with Goshuyuto,<sup>3)</sup> Keishininjinto was used as a comparator for Goshuyuto and showed an improvement rate of 61.4%. In the crossover study between Keishininjinto and Chotosan for chronic headache,<sup>6)</sup> the number of cases in which Keishininjinto was more useful tended to be greater although there was no significant difference.

#### 3. Chotosan (釣藤散 in Japanese, Uncaria Decoction in English)

One report of non-randomized crossover study between Chotosan and Keishininjinto and five reports of case series were identified. In the non-randomized crossover study between Chotosan and Keishininjinto for chronic headache, Chotosan was effective although the number of effective cases was slightly smaller compared to Keishininjinto.<sup>6)</sup> In a case series of 54 cases of chronic headache, the improvement rate was 74.1%.<sup>7)</sup> In two case series of chronic tension-type headache, high improvement rates of 94% in 150 cases<sup>8)</sup> and 70% in 20 cases<sup>9)</sup> were reported. Unfortunately, the evidence level of these reports is low because the time of symptom improvement was unclear and the age group was biased. In a study on chronic headache caused by intracranial organic disease, 80% of the patients showed slight improvement or better.<sup>10)</sup> In another study on chronic headache caused by cerebrovascular disease, slight or better improvement was shown in 78.3% of the patients and effectiveness was observed within 4 to 7 weeks in nearly 70%.<sup>11)</sup>

#### 4. Kakkonto (葛根湯 in Japanese, Kudzu Decoction in English)

One case series report of 23 cases of chronic tension-type headache not sufficiently treated by anxiolytic medication was

identified.<sup>12)</sup> Improvement rates of 50% for headache and 60.9% for heavy headiness were reported. Kakkonto is conventionally taken short-term or on an as-needed basis. However, in this study, the period of intake was not fixed. Among the patients, some used the formula for more than one month and there was one case of adverse event including gastric discomfort. Study design based on the conventional usage of Kampo formulas should be considered.

#### 5. Goreisan (五苓散 in Japanese, Five Ingredient Powder with Poria in English)

Two reports of case series for headache accompanying hemodialysis were identified. Although the method of intake lacked consistency, significant improvement of headache as assessed by VAS score was observed in 11 hemodialysis patients with headache.<sup>13)</sup> In another questionnaire study on 16 hemodialysis patients, “marked response” or “response” was obtained in 12 patients.<sup>14)</sup> Headache associated with hemodialysis may be caused by transient cerebral edema. According to the pharmacological study conducted by Isohama,<sup>15)</sup> Goreisan regulates water metabolism by acting on aquaporin (AQP) in cell membrane. Especially, AQP4 is involved in cerebral edema, and Goreisan has been shown to suppress AQP4. Clinical use of Goreisan for chronic subdural hematoma has been reported but only as case report.

As shown by the above reports, evidence at a level of case series or above is available for only five Kampo formulas. Only two studies have high evidence level; a DB-RCT and an open-label crossover study for Goshuyuto. Almost all the other reports are case series. One of the reasons is that the prescription system for Kampo formula is that “even for the same diagnosis, prescription differs depending on constitution”, and this feature hampers research development. In the future, development of study design that is adapted to Kampo prescription system is necessary.

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- Search database: Ichushi Web for articles published in Japan (2011/10/24)  
{kampo}or {Kampo medicine}  
& {headache}or {migraine}or {tension headache}or {chronic headache}1213
- Search database: PubMed (2011/10/24)  
{kampo} or {herbal medicine} or {traditional medicine} or {oriental medicine}  
& {headache} or {migraine} 387

## 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, and some adverse events have also been reported, use of these therapies should consider the characteristics of individual patients and also accountability. Details of non-pharmacotherapy for migraine and tension-type headache can be found in the respective sections.

**Grade B, C** (depending on therapy)

### Background and Objective

Other than pharmacotherapy, other prophylactic treatments have been anticipated to be effective for primary headaches. A literature search was conducted focusing on non-pharmacotherapies that have been tested by randomized controlled trials (RCT).

### Comments and Evidence

Treatments for primary headaches other than pharmacotherapy include the following:

- (1) Behavioral therapy: Relaxation training, biofeedback, cognitive-behavioral therapy, and hypnosis → <migraine, tension-type headache>
- (2) Physical therapy: Acupuncture, transcutaneous electrical nerve stimulation → <migraine, tension-type headache>
- (3) Supplements: Feverfew, magnesium, vitamin B<sub>2</sub> (riboflavin) → <migraine>

These are therapeutic options for patients who prefer nonpharmacologic treatment, patients with poor tolerance to pharmacologic treatments, patients with medical contraindications for pharmacologic treatments, patients showing no response to pharmacologic treatment, patients who are pregnancy or planning pregnancy, patients with a history of medication overuse headache, and patients with significant stress.<sup>1)</sup>

#### (1) Behavioral therapy

Relaxation training, thermal biofeedback combined with relaxation training, electromyogram biofeedback, cognitive-behavioral therapy, and hypnosis are useful prophylactic treatments for tension-type headache and migraine.<sup>1)2)</sup> A meta-analysis revealed that relaxation and biofeedback training improved migraine in over 20% of the patients.<sup>3)</sup> Clinical improvement may be expected by a combination of prophylactic pharmacotherapy and relaxation/feedback training (recommendation grade B). In recent years, cognitive-behavioral therapy has been reported to be effective especially for migraine in children (recommendation grade B).<sup>4)</sup>

#### (2) Physical therapy

Acupuncture and transcutaneous electrical nerve stimulation as acute and prophylactic treatments for primary headaches have been tested by RTCs and reported to be effective. However, these trials lack quality and quantity. Further evidence has to be accumulated<sup>5)-7)</sup> (recommendation grade B).

RCTs of chiropractic and spinal manipulation have been reported.<sup>8)9)</sup> However, the opinions of experts are divided. Since risk is involved depending on the manipulation, caution has to be exercised when used in therapy (recommendation grade C).

#### (3) Supplements

Feverfew, magnesium, vitamin B<sub>2</sub> (riboflavin) have been reported to be effective prophylactic agents for migraine<sup>10)-12)</sup> (recommendation grade B).

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- **Search terms and secondary sources**

- Search database: PubMed (2013/3/11)  
 headache (All Fields) 59278  
 headache (All Fields) & alternative medicine 1758 +Limits1 (English, Randomized Controlled Trial, Human) 392  
     & acupuncture 479 +Limits1 0  
     & biofeedback 561 +Limits1 0  
     & chiropractic 176 +Limits1 0  
     & hypnosis 161 +Limits1 0  
     & herbal medicine 103 +Limits1 0
- Search database: Ichushi Web for articles published in Japan  
 (headache /TH or headache /AL) 5405  
 & (alternative medicine/TH or alternative therapy/AL) 183

## Is cognitive-behavioral therapy effective for primary headaches?

### Recommendation

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

**Grade B**

### Background and Objective

The cognitive-behavioral therapeutic approach for primary headaches has been conducted since more than 30 years ago. Most of the previous research studied relaxation (including stress management), biofeedback therapy and cognitive therapy, either alone or in combination. These therapies are grouped together and called cognitive-behavioral therapy. Although there are reports on relaxation alone and biofeedback therapy alone, there are few reports on cognitive therapy alone in the literature.

In this section, the usefulness of cognitive behavioral therapy for primary headaches is presented.

### Comments and Evidence

Validation of the usefulness of cognitive-behavioral therapy for primary headaches has been conducted mainly in European and American countries, and many randomized controlled trials have reported the usefulness of this therapy.<sup>1)-8)</sup> For tension-type headache, headache reduction rates of 37 to 50% have been reported,<sup>9)</sup> and cognitive-behavioral therapy has been reported to have equivalent therapeutic effect as amitriptyline.<sup>3)</sup> For migraine also, cognitive-behavioral therapy reduced headache by 32 to 49%, and a combination of relaxation and biofeedback therapy achieved equivalent prophylactic effect as propranolol and even better long-term effectiveness than propranolol.<sup>6)</sup> Apart from randomized controlled trials, several metaanalyses and reviews showing the effectiveness of behavioral therapy have been reported.<sup>9)-13)</sup> As of present, cognitive-behavioral therapy has been shown to be effective for migraine and tension-type headache, but little therapeutic effect for cluster headache.<sup>9)</sup>

For primary headaches, the therapeutic effect is further improved when cognitive-behavioral therapy is used in combination with pharmacotherapy, compared with cognitive-behavioral therapy alone.<sup>6)14)15)</sup> Furthermore, superior and long-lasting clinical effect has been reported for cognitive-behavioral therapy (biofeedback therapy) in children, and the efficacy is even higher than in adults.<sup>11)16)</sup>

However, in a survey in which therapy was administered by persons who were not experienced in behavioral therapy, no significant difference in clinical improvement rate was observed, suggesting an issue in using this therapy as regular treatment in routine clinical setting.<sup>17)</sup> Another report found no difference in efficacy between relaxation alone and combined relaxation and biofeedback therapy.<sup>18)</sup>

Behavioral therapy has several merits: no risk of drug dependence because it is a non-pharmacotherapy, very few adverse events, and low cost. On the other hand, the demerits include inconsistent methods used in different facilities due to the lack of standardized method, requirement of therapists to possess certain level of knowledge and skills, and lack of immediate response. Recent research is heading for the direction of examining the effectiveness and impact on medical cost by comparing or combining with representative existing pharmacologic treatments.<sup>3)</sup>

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## • Search terms and secondary sources

- Search database: PubMed (2011/12/1)  
Cognitive-behavioral therapy 44110  
& {headache OR tension-type headache OR migraine} 553

{Cognitive-behavioral therapy}  
OR {biofeedback} OR {relaxation} 98049  
& tension-type headache 128

{Cognitive-behavioral therapy}  
OR {biofeedback} OR {relaxation}  
& migraine 405

Limits: English, Randomized Controlled Trial, Humans 38



## 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**

### Background and Objective

Psychological factors such as anxiety and depression have been known to be closely associated with the onset and progression of migraine and tension-type headache. In addition, many studies have reported various psychiatric disorders that tend to coexist with primary headaches, such as mood disturbances (such as major depression, dysthymia, and bipolar disorder), drug addiction, anxiety disorders (panic disorder, phobia, generalized anxiety disorder), somatoform disorder (such as somatization disorder, and pain disorder). Especially, the involvement of abnormal serotonin metabolism in the relationship between migraine and panic disorder or major depression has gained attention.

The objective of this section is to collect available literature and present the knowledge concerning the relationship between primary headaches and depression or anxiety.

### Comment and Evidence

For migraine, large epidemiological surveys have been conducted actively. The annual prevalence of major depression among migraine patients has been reported to be approximately 8.6%,<sup>1)</sup> with odds ratio of 2.2.<sup>2)</sup> The lifetime prevalence of major depression in migraine patients has been reported to range from 18 to 40%, and many epidemiological studies have shown odds ratios of 3 to 4.<sup>1(3)-6)</sup> The relations between migraine and various anxiety disorders such as panic disorder, generalized anxiety disorder, phobia, and obsessive-compulsive disorder have been studied. High odds ratios for panic disorder ranging from 2.8 to 6.0 have been reported,<sup>1(3)(6)-8)</sup> similar to depression. Many studies so far have demonstrated an association of migraine with major depression, panic disorder, and phobia, but no significant relationship with obsessive-compulsive disorder and substance abuse. Psychiatric comorbidities in migraine patients in headache centers also showed similar high association<sup>9)-11)</sup> as in epidemiological studies. The prevalence of psychiatric comorbidities in migraine patients is especially high in migraine with aura, chronic migraine, and migraine with medication overuse.<sup>12)</sup>

Research on the association of psychosocial factors and psychiatric disorders with tension-type headache is less abundant than that with migraine. The association with psychological states including psychosocial stress and anxiety/depression has been found, and psychiatric comorbidities including mood disturbances (such as depression), anxiety disorders (such as panic disorder, generalized anxiety disorder, and obsessive-compulsive disorder), and somatoform disorders have also been reported<sup>9)(10)(13)</sup> as in migraine.

Various tools have been used for the screening of these psychiatric disorders, such as SDS, HAM-A, HAM-D, and the Hospital Anxiety and Depression Scale (HADS). The reliability and validity of HADS for the evaluation of primary headaches have been studied.<sup>14)-17)</sup>

Almost all previous reports have pointed out a relationship between primary headaches and anxiety or depression. However, the evaluation methods for psychological states or psychiatric disorders are not standardized. While the high association has been attributed to the involvement of serotonin, a consensus is yet to be arrived.

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- Search database: PubMed (2011/12/1)
- Major depression 93622
- & {migraine} 389
- & {tension type headache} 1668
- & {headache} 12274 Panic disorder 9209
- & {migraine} 105
- & {tension type headache} 12
- & {headache} 109

# How should occupational health physicians and brain health check-up physicians manage headache?

## Recommendation

Occupational health physicians and brain health check-up physicians should participate actively in providing headache medical care for workers and health check-up receivers with headaches.

**Grade A**

## Background and Objective

The objective of this section is to search for literature on the frequency and status of persons with primary headaches in the workplace and brain health check-up setting to examine the roles of occupational health physicians and brain health check-up physicians in providing medical care for headache.

## Comment and Evidence

Migraine has been reported to cause reduction in working hours and socio-economic loss.<sup>1)</sup> According to a survey of primary headaches in the workplace, the prevalence of migraine was 13.2% (male 11.6%, female 26.6%), episodic tension-type headache 29.15% (male 27.6%, female 41.3%), and chronic tension-type headache 0.9% (male 0.8%, female 1.3%). Although the majority (84.3%) of workers suffering from migraine reported decrease in working efficiency, the rate of consulting a medical facility was as low as 23.7%.<sup>2)</sup> In a study on persons receiving brain health check-up, the prevalence of migraine was 10.2% (male 6.1%, female 19.4%). Most (75.4%) were mild cases, and the rate of consulting a medical facility was also low at 15.1%. The rates of medical facility consultation were 9.8% among persons suffering from migraine without aura and 48.0% among persons suffering from migraine with aura. Brain health check-up findings of those who had migraine revealed cerebral aneurysm (1.1%) and cerebral arteriovenous malformation (0.6%).<sup>3)</sup>

In the workplace and brain health check-up, the number of persons affected by migraine is more than 10% higher than the prevalence of migraine reported in other epidemiological surveys.<sup>4)5)</sup> Despite this high prevalence, the studies have confirmed that appropriate medical care for headache is not being implemented.

Occupational health physicians and brain health check-up physicians should identify serious secondary headaches and promptly refer the affected workers and health check-up receivers to appropriate medical facilities, organize headache educational activities in the workplace to detect persons with primary headaches that cause disability in daily living, and guide these persons to receive appropriate medical care.

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## Search terms and secondary sources

- Search database: PubMed (2011/12/21)  
Headache & {Epidemiology} 3263  
& {Migraine} 785  
& {Japan} 7

## 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 developmental process is sometimes necessary.

**Grade A**

### Background and Objective

Among the complaints of children at school, headache is one of the most common symptoms. Although headache can be a symptom of acute diseases such as upper respiratory tract infection, primary headaches represented by migraine and tension-type headache are also frequently encountered in school settings. While the teacher in charge of the class is usually the first to deal with headache, the actual care is provided by the school nurse. The school physician provides health consultation for school children and students, and is also consulted about headache through the school nurse during health check-ups and other situations. In students who refuse to go to school or enter classroom, headache is a common reason. Therefore school physicians may also be consulted on psychosocial issues through the school counselor. A literature search was conducted on the management of headache by school physicians

### Comments and Evidence

The School Health and Safety Act in Japan (final revision in 2008) stipulates the staffing of school physicians in schools. However, when searching for literature in English language, the search term “school doctor” or “school physician” does not exist. Therefore, it is not possible to compare the school physician system among countries. Instead, relatively abundant literature was identified for “psychologist” as a profession related to children and adolescents. These psychologists probably play similar roles as school counselors in Japan. School counselors in Japan work mainly in public junior high schools, part-time, and the majority hold a certificate of clinical psychotherapist. There are few articles on school physicians in Japan; nevertheless a review article that serves as a useful reference was identified. This article points out that school physicians and school nurses should possess correct knowledge about migraine, and that migraine is fundamentally not a disease with a mental problem and should not be linked unnecessarily to the mental aspect. However, in some cases, it is important to discern psychosocial issues including family environment.<sup>1)</sup>

#### • Population-based survey

Children with migraine and tension-type headache reported neck pain, facial and jaw pain, and sleep disorder significantly more frequently than children without headache. Fatigue was more frequent in children with migraine than in children with tension-type headache or children without headache. The number of children visiting the school nurse because of headache did not differ significantly between migraine and tension-type headache. Children with migraine were absent from school significantly more often than children with tension-type headache (aged 7-15 years, Sweden).<sup>2)</sup> Approximately 6.7% of children experienced severe headache during the previous 12 months, and from the mental health aspect, children with severe headache were 3.2 times more likely than children without severe headache to have difficulties and 2.7 times more likely to have impairment (aged 4-17 years, United States).<sup>3)</sup> School stressors (harassment by peers, schoolwork pressure, and being treated poorly by teachers) were strongly associated with psychosomatic pain (headache and abdominal pain) as well as psychological symptoms (aged 10-18 years, Sweden).<sup>4)</sup> Headaches were associated with emotional problems from parent-reported questionnaire, and with general anxiety disorder from child-reported questionnaire (aged 6-11 years, France).<sup>5)</sup> Frequent headache was significantly associated with teacher unfairness, and classmate social support acted as a protective factor but not as a buffering mechanism (aged 11, 13 and 15 years, Italy).<sup>6)</sup>

- **School-based activity study of patients attending headache center of pediatric hospital**

School children with headache did not differ from the healthy control children without headache in terms of social goodwill and friendship. Elementary school children with migraine had fewer friends at school, but middle school students with migraine were identified by peers as displaying higher levels of leadership and popularity (aged 8-14 years, United States).<sup>7)</sup>

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- **Search terms and secondary sources**

- Search database: PubMed (2011/10/2)  
Headache 54748 & children 7917  
& children adolescents 4900  
& (school) 752 OR (doctor) 35 OR (physician) 49 OR (nurse) 14 OR (psychologist) 136
- Search database: Ichushi Web for articles published in Japan (excluding proceedings) (2011/10/16)  
School physician 705  
& primary school middle school 30  
& primary school middle school kindergarten 4  
& headache 2

## 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 obtain 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**

### Background and Objective

The effectiveness of prophylactic and acute treatments for chronic headache is directly linked to the understanding and appropriate management of headache by the patient him/herself. Patient education is extremely important in headache care. Furthermore, to promote patient education, building a good doctor–patient relationship is essential.

### Comments and Evidence

Several non-controlled studies have shown that patient education program or comprehensive headache treatment program including patient education improves patients' QOL regardless of the type of headache.<sup>1)-11)</sup> By explaining to patients with headache regarding the type of headache they have, the mechanisms by which symptoms appear, self-management skills, therapies, medications and their mechanisms of action as well as adverse effects, and instructing them about what to pay attention in daily life, disability and functional health status are improved and satisfaction is increased. Patient education has to be conducted thoroughly. To increase the motivation of patients toward treatment, building a good doctor–patient relationship is important. Furthermore, studies in recent years have indicated the association between chronicity of migraine and health problems such as sleep<sup>12)</sup> and obesity.<sup>13)</sup> Increasing emphasis is being put on education of these research results as well as interventions.

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- Search database: PubMed (2012/6/5)  
headache.mp. [mp=title, original title, abstract, name of substance, mesh subject heading] & education.mp. [mp=title, original title, abstract, name of substance, mesh subject heading] limited to (review) 260  
headache.mp. [mp=title, original title, abstract, name of substance, mesh subject heading] & doctor patient relationship.mp. [mp=title, original title, abstract, name of substance, mesh subject heading] limited to (review) 95

# 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.<sup>1)</sup> 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**

## Background and Objective

In Japan, headache causes an estimated economic loss of approximately six hundred billion yen per year, and migraine contributes to a half of this loss.<sup>1)</sup> Since triptan is a costly medication, many studies from European and American countries evaluated the cost-effectiveness of triptan in the 1990s. A representative economic assessment of triptan is the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) conducted by a health department. The study concluded that incremental health benefits were obtained from using oral triptan rather than oral ergotamine and that these benefits were achieved at acceptable incremental costs to healthcare resources. When society as a whole was considered, the health benefits also resulted in a net reduction of overall costs to society. In other words, a conclusion has been arrived that triptan is superior in terms of cost-effectiveness. In Japan, an article examining the cost-effectiveness of triptan tablet has been published.

## Comments and Evidence

In an assessment conducted by the Canadian health department, from the societal perspective, using sumatriptan instead of caffeine/ergotamine resulted in an incremental cost-effectiveness ratio of 25 Canadian dollars (\$Can) per attack suppressed, an increment of \$Can7,507 for obtaining each quality-adjusted life-year (QALY), and a net economic benefit to the society of \$Can42 per patient per year.<sup>2)</sup> From the perspective of the insurance payer, the incremental cost-effectiveness ratio was \$Can98 per attack suppressed, and the increment was \$Can29,366 per QALY. The grade of recommendation based on decisions regarding health technology for adoption into health insurance plans was 'moderate'. Sensitivity analysis showed that the results were robust despite relatively large changes in the input variables.

In the evaluation conducted by Shimizu et al.,<sup>3)</sup> avoiding an episode of migraine required an extra economic burden of only approximately 600 yen. In addition, an extra expenditure of more than two million yen is required to live healthily without being troubled by attack for one year. Comparing this extra expenditure with the Canadian insurance reimbursement standard, it is equivalent to a recommendation grade of "moderate". The authors concluded that sumatriptan tablet for migraine is a treatment with high cost-effectiveness.

In recent years, medication overuse headache due to excessive use of triptan has become a problem. For this reason, there is a concern that this situation will increase medical expenditure and lower labor productivity, consequently lowering the medico-economic value of triptan. Proper use of triptan is an issue that should always be borne in mind.

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<http://homepage2.nifty.com/uoh/gakubu/keizaigakubu.htm> (In Japanese)
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## Search terms and secondary sources

- Search database: Ichushi Web for articles published in Japan (2011/12/21)  
migraine/ and medical economics 6, migraine and cost-effectiveness 9
- Search database: PubMed (2011/12/21)  
Migraine and cost-effectiveness 162, Migraine and economic evaluation 143, Migraine and pharmacoeconomics

## 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 specialist and supported by other health professionals including clinical psychotherapist, physical therapist, occupational therapist, nurse, pharmacist and acupuncturist is essential.

**Grade A**

### Background and Objective

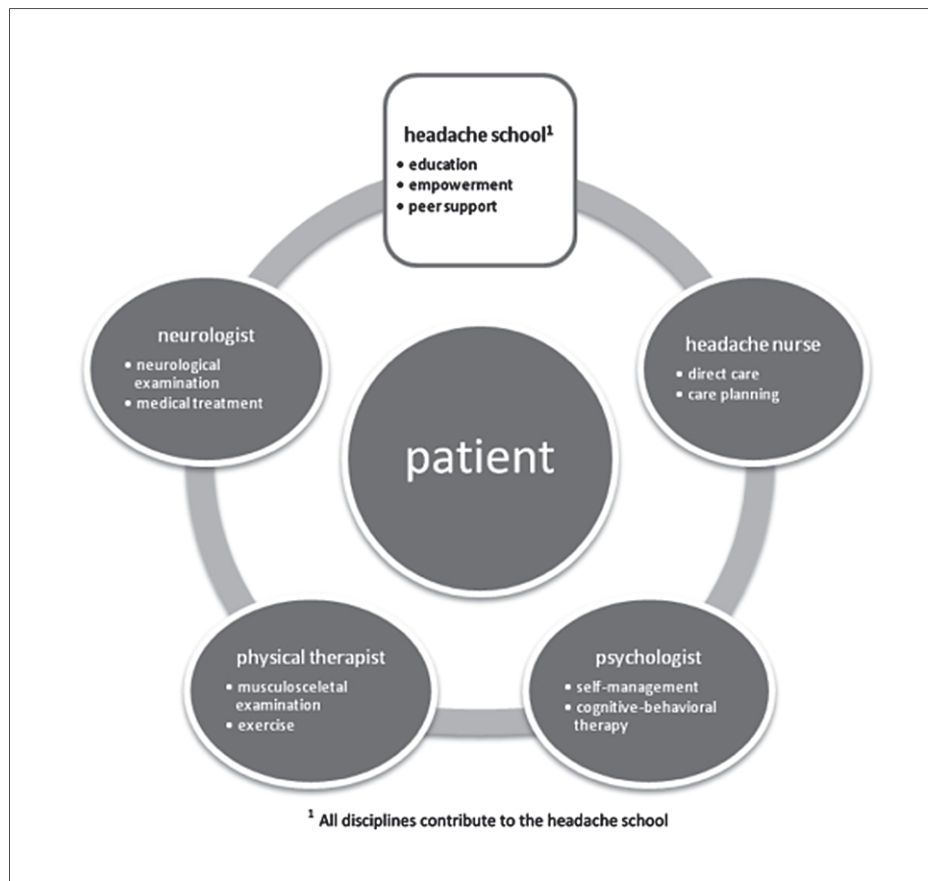
Despite the advances in acute treatment and prophylactic therapy for chronic headache, there are still many patients who do not respond adequately to pharmacotherapy alone. A scientific session on multidisciplinary treatment of headache was organized at the European Headache and Migraine Trust International Congress (EHMTIC) in 2010. The session concluded that effective multidisciplinary headache program (MTP) can be expected to reduce the frequency of headache and the disease burden, as well as decrease the risk for medication overuse headache.<sup>1</sup> In the future, MTP provided by a headache team led by the headache specialist and supported by other health professionals including clinical psychotherapist, physical therapist, occupational therapist, nurse, pharmacist and acupuncturist is indispensable for the treatment of refractory headache. The Japanese Headache Society has started board certification of headache specialist from 2005, and subsequently headache outpatient clinics began to be established around the country. The challenge ahead will be to educate and train headache specialists and other health professionals specializing in headache treatment.

### Comments and Evidence

A nationwide epidemiological survey in Japan estimated that approximately 40 million people suffered from chronic headache, 8.4 million of whom had migraine, and that headache impaired the activities of daily living in 74% of those affected.<sup>2</sup> These figures show that despite the recent advances in headache treatment, many patients still do not achieve improvement in symptoms.

Recent reports have indicated that MTP provided by a headache team led by physician and supported by other health professionals from multiple disciplines is essential, and that MTP is effective in alleviating the impairing and disabling effects of chronic headache, and increasing the patients' level of satisfaction.<sup>1(3)-9)</sup> The MTP usually involves three disciplines comprising physicians, physical therapists and psychotherapists,<sup>4(5)</sup> or four disciplines with the addition of nurses.<sup>6-9)</sup> In the headache school of the MTP, the team participants work together to educate patients with chronic headache about the diagnosis of headache, acute treatment, prophylactic treatment, risk factors and mechanisms of medication overuse headache, and implementation of non-pharmacological prophylactic treatment strategies (**Figure 1**).<sup>1)</sup> The physician is responsible for performing neurological examinations on patients with chronic headache, excluding secondary headache, establishing the correct diagnosis, prescribing pharmacotherapy, and at the same time playing a leading role in deciding the therapy plans within the team.<sup>1)</sup> The physical therapist evaluates the musculoskeletal system, and verifies the effectiveness of various interventions such as exercise therapy, exercise for relief of headache, massage, and hot pack.<sup>1(10)</sup> The psychotherapist implements cognitive-behavioral therapy and is sometimes essential as a bridge to the psychiatrist or psychosomatic physician.<sup>1(10)</sup> The roles of the headache nurse include taking a headache history from patients with chronic headache, listening to their complaints or anxiety, obtaining information on individual and social background, and providing technical guidance on self-injection of sumatriptan at home. Acupuncture has been reported to be effective in the prevention of migraine.<sup>11)</sup> Although evidence is currently inadequate, trial of this approach is worthwhile. Instructions provided by the pharmacist regarding taking of the prescribed medications is expected to increase the level of satisfaction of patients with chronic headache, and improve the therapeutic effect. At the Saitama International Headache Center, occupational therapists analyze the patients' headache diaries in detail by conducting interviews with the patients.<sup>10)</sup> Lemstra et al.<sup>4)</sup> assigned migraine patients to MTP (n = 44) or non-MTP group (n = 36) for six weeks, and observed significant improvements in





**Figure 1. All disciplines contribute to the headache school.**

[Reproduced from Gaul C, Visscher CM, Bhola R, Sorbi MJ, Galli F, Rasmussen AV, Jensen R: Team players against headache: multidisciplinary treatment of primary headaches and medication overuse headache. *J Headache Pain* 2011; 12(5): 511-519, under the Creative Commons Attribution license]

headache frequency, headache intensity, quality of life, and depression in the MTP group, at the end of intervention and after 3 months. Gunreben-Stempfle et al.<sup>5)</sup> reported that a 96-hour MTP was more effective than a 20-hour program. Zeeberg et al.<sup>6)</sup> showed that MTP reduced headache intensity, headache frequency, and headache-related absence from work for headaches other than post-traumatic headache, while Jensen et al.<sup>7)</sup> reported that female gender, migraine, and triptan overuse predicted good outcome from MTP. Gaul et al.<sup>9)</sup> conducted a four-discipline MTP for 5 days in 295 patients with primary headache, and reported that the mean headache frequency decreased from 13.4 to 8.8 days per month after 12-18 months, and that 43% of the subjects accomplished the primary outcome which was 50% reduction of headache frequency.

From the above findings, MTP implemented by a headache team is undoubtedly essential for the treatment of chronic headache. However, the methodology lacks adequate scientific evidence, and further discussion is therefore necessary. In recent years, there is an increase in nurses specializing in chronic diseases, such as Japanese Nursing Association-certified nurses in dementia nursing and certified nurses in diabetes nursing. There is also a need for the training of nurses and other health professionals specializing in headache treatment.

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- Search database: PubMed (2012/4/30)  
 {headache} & {team play} 7  
 {headache} & {multidisciplinary treatment} 193  
 {headache} & {management program} 269
- Search database: Ichushi Web for articles published in Japan  
 headache outpatient 142  
 headache outpatient clinic 12  
 headache center 28  
 headache specialist 7
- Secondary source: 2 additional references from manual search (references 2 and 11)

## 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 one month.
- The modes of onset can be classified broadly into ischemic (cerebral infarction, transient ischemic attack), hemorrhagic (subarachnoid hemorrhage), 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**

### Background and Objective

Approximately 70% of the patients with dissecting aneurysm of the internal carotid artery or cervical artery have headache. In recent years, with increasing attention given to this disease due to widespread use of noninvasive diagnostic imaging techniques such as MRI and MRA, the opportunity of detection has also increased. The natural course of this disease is good in most patients. However, in some cases, the clinical state changes greatly in the early stage, with rebleeding and brainstem ischemia that may result in serious sequelae or even death. The objective of this section is to describe differential diagnosis by physicians attending the patients in the early stage.

### Comments and Evidence

In the International Classification of Headache Disorders, 3rd edition (beta version) of the International Headache Society, this disease is classified as 6.5.1 “*Headache or facial or neck pain attributed to cervical carotid or vertebral artery dissection*”.<sup>1)</sup> The diagnostic criteria are as follows:

- A. Any new headache and/or facial or neck pain fulfilling criterion C
- B. Cervical carotid or vertebral dissection has been diagnosed
- C. Evidence of causation demonstrated by at least two of the following:
  1. pain has developed in close temporal relation to other local signs of cervical artery dissection, or has led to the diagnosis of cervical artery dissection
  2. either or both of the following:
    - a) pain has significantly worsened in parallel with other signs of the cervical artery lesion
    - b) pain has significantly improved or resolved within 1 month of its onset
  3. either or both of the following:
    - a) pain is severe and continuous for days or longer
    - b) pain precedes signs of acute retinal and/or cerebral ischemia
  4. pain is unilateral and ipsilateral to the affected cervical artery
- D. Not better accounted for by another ICHD-3 diagnosis.

Sudden and severe headache or neck pain is an important characteristic of artery dissection. The frequency of headache or neck pain associated with dissection has been reported to be 60 to 80%. Headache or neck pain arises due to dissection of the vascular wall, and is considered to be referred pain along the blood vessel. In the vertebral artery territory, distribution of the 2<sup>nd</sup> and 3<sup>rd</sup> spinal nerves gives rise to pain in the back of the head and the neck. In the internal carotid artery territory, distribution of the trigeminal nerve often gives rise to pain in the front of the head and the forehead. It should be noted that there is no specific pattern of headache onset, as is also commented in the International Headache Classification. This condition

is often misdiagnosed as other headaches including migraine, cluster headache, and primary thunderclap headache.<sup>2)-10)</sup> Since a suspicion of this condition as well as early diagnosis and treatment are vital, MRI, MRA and 3D-CTA should be conducted. Furthermore, performing conventional angiography is important to confirm a definitive diagnosis. In addition, since cerebral aneurysm is an important cause of cerebral infarction in young adults, the possibility of dissecting cerebral aneurysm should always be borne in mind in younger stroke patients aged below 50 years.<sup>11)</sup> In recent years, cervical artery dissection manifesting headache or neck pain only has received attention. In cases with mild lumen formation, the natural course is favorable. However, some cases progress to serious conditions such as subarachnoid hemorrhage and cerebral infarction.<sup>12)</sup> At present, evidence-based treatment for cases manifesting headache or neck pain only has not been established.<sup>13)14)</sup>

For further studies of headache and pain associated with dissecting cerebral aneurysm, cases should be accumulated to examine the characteristics not only for the vertebrobasilar artery territory but also for other territories of the internal carotid artery, anterior cerebral artery, and middle cerebral artery.<sup>15)-18)</sup>

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## • Search terms and secondary sources

- This search (2012/4/10)
- PubMed: Headache & Dissecting cerebral aneurysm = 197 articles, Dissecting cerebral aneurysm & Diagnosis & Clinical Features = 76 articles
- Ichushi Web for articles published in Japan  
Dissecting cerebral aneurysm = 248 articles

• **Note 1**

The diagnostic criteria for cerebral artery dissection have been reported by the Cerebral and Cardiovascular Disease Commissioned Study Group in Japan. They are shown below for reference.

**1. Vascular lumen findings**

- a.* Either intimal flap or double lumen observed on cerebral angiography
- b.* Intimal flap or double lumen observed on CTA images
- c.* Hyperintensity suggesting intramural hematoma on T1-weighted MRI
- d.* Findings suggesting artery dissection (dilatation and stenosis, retention of the contrast media, string sign, tapered occlusion) on cerebral angiography
- e.* Dilatation and stenosis observed on MRA or CTA
- f.* Intimal flap or double lumen observed on MRI, MRA or contrast-enhanced T1-weighted MRI
- g.* Fusiform dilatation in the main branch of artery observed on angiography, MRA or CTA

**2. Arterial surface appearance findings**

Surface appearance of artery showing fusiform dilatation on contrast-enhanced (volume) T1-weighted image or basiparallel anatomic scanning (BPAS) or 3D-T2-weighted MRI.

**3. Change in imaging finding during follow-up**

Definitive changes (reduced or augmented) of **1** or **2** on follow-up images.

**4. Surgical and histopathological findings**

- a.* Artery dissection observed during surgery
- b.* Histopathological examination of resected or autopsied specimen showing cerebral artery dissection

**[Definite dissection]**

When one of the following three applies:

- Among *a*, *b* and *c* of **1** above, one is fulfilled
- **3** above is fulfilled and causes other than dissection are excluded
- For **4** above, either *a* or *b* is fulfilled

**[Probable dissection]**

When one of the following three applies:

- For **1** above, either *d* or *e* is fulfilled
- Either *f* of **1** above or **2** is fulfilled
- Stenosis or obstruction is observed in artery, and **2** is fulfilled

**[Possible dissection]**

- Either *f* and *g* of **1** above, or **2** is fulfilled

[Tsukahara T: Status of cerebral artery dissection (1) Outline of disease state, symptoms, diagnosis and treatment of cerebral artery dissection. Guidance for examination of cerebral artery dissection. Cardiovascular Disease Study Commission Grant 18 Ko-5 (SCADS-Japan) Disease state of cerebral artery dissection and treatment development (principal investigator: Minematsu K) Cerebrovascular Division, Department of Internal Medicine, National Cerebral and Cardiovascular Center 2009: pp 1-7.]

• **Note 2**

Descriptions related to cerebral artery dissection in the Japanese Guideline for the Management of Stroke are shown below:

II. Cerebral infarction/transient ischemic attack (TIA)

2. Treatment of cerebral infarction caused by special conditions

2-1. Cerebral artery dissection

For cerebral infarction caused by cerebral artery dissection, select treatment method for individual cases according to the degree of vascular stenosis and aneurysm formation (grade C1)

2-2. Aorta dissection

For cerebral infarction complicating aortic dissection, intravenous alteplase therapy is contraindicated (grade D).

VI. Other cerebrovascular diseases

1. Intra-/extra-cranial artery dissection

1-1. Medical treatment for intra-/extra-cranial artery dissection (anti-thrombotic therapy)

1. For extracranial cervical artery dissection with onset of ischemic symptoms, antithrombotic therapy (anticoagulant therapy or antiplatelet therapy) should be considered in the acute stage (grade C1).

2. For intracranial artery dissection with onset of ischemia, antithrombotic therapy (anticoagulant therapy or antiplatelet therapy) may be considered in the acute stage (grade C1). However, since intracranial dissection may have a risk of subarachnoid hemorrhage, antithrombotic therapy should be withheld if aneurysm formation is clearly observed in the dissecting site (grade C2).
  3. To prevent recurrence in cases of cerebral artery dissection with onset of ischemia, antithrombotic therapy (anticoagulant therapy or antiplatelet therapy) should be considered. Since the findings in the dissection site change over time, conduct imaging examination every three months, and consider change or continuation of antithrombotic therapy based on the imaging findings (grade C1).
- 1-2. Surgical treatment for intra-/extra-cranial artery dissection
1. For hemorrhagic cerebral artery dissection, early diagnosis and treatment are recommended because of the high risk of rebleeding (grade C1). When surgical treatment is selected, conducting surgery within 24 hours of bleeding is recommended (grade C1).
  2. For nonhemorrhagic cerebral artery dissection, conservative treatment is usually selected if the natural history is unknown. In that case, regular follow-up by MRI or angiography is recommended (grade C1).
  3. Direct surgery and endovascular treatment both have advantages and disadvantages. Evaluate the indication individually (grade C1). Direct surgery is useful when revascularization is necessary. On the other hand, endovascular treatment is less invasive and treatment can be started earlier, and is frequently selected as the surgical treatment (grade C1). From the viewpoint of preventing rebleeding, trapping of the lesion site is recommended. If trapping is difficult, consider proximal occlusion of the parent artery (grade C1).
- [Shinohara Y, Ogawa A, Suzuki N, Katayama Y, Kimura A (Eds.) Japanese Guidelines for the Management of Stroke 2009. Kyowa Kikaku, 2009, quoted and abstracted from p. 74, 75, 244 and 247]

## 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 International Classification of Headache Disorders 3rd Edition beta version (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 if the site of cerebrospinal fluid leak can be identified by diagnostic imaging, invasive treatments such as epidural blood patch should be considered.

Grade A

### Background and Objective

According to the International Classification of Headache Disorders 3rd Edition beta version (ICHD-3beta), headache attributed to low cerebrospinal fluid pressure is coded under 7 “*Headache attributed to non-vascular intracranial disorder*” type 7.2 “*Headache attributed to low cerebrospinal fluid pressure*”, and is further classified into the following subforms<sup>1)</sup>:

7.2.1 “*Post-dural puncture headache*”

7.2.2 “*CSF fistula headache*”

7.2.3 “*Headache attributed to spontaneous intracranial hypotension*”

Previously used terms for headache attributed to spontaneous intracranial hypotension include “spontaneous low CSF pressure; ICHD second edition (ICHD-II)”, “primary intracranial hypotension”, “low CSF-volume headache”, and “hypoliquorrhoeic headache”. In the ICHD-3beta, 7.2.3 “*Headache attributed to spontaneous intracranial hypotension*” was adopted.<sup>1)</sup>

Headache attributed to spontaneous intracranial hypotension is considered to be fundamentally caused by a loss in cerebrospinal fluid volume.<sup>1)-5)</sup> Although cerebrospinal fluid hypovolemia can give rise to diverse symptoms, the core symptom is orthostatic headache. According to the Monro-Kellie doctrine, cerebrospinal fluid pressure is compensated and becomes normalized.<sup>5)</sup> Therefore, the disease name “cerebrospinal fluid hypovolemia” has been advocated for headache attributed to spontaneous *intracranial hypotension*.<sup>6)</sup>

Despite having the word “spontaneous” in the disease name, recently several etiologies have been proposed for headache attributed to spontaneous *intracranial hypotension*, such as leak from the dural sleeve that passes through the nerve root (dural tear) and leak from meningeal diverticulum.<sup>4)-6)</sup> The triggers include straining, coughing, drastic lowering of atmospheric pressure, sexual activity, craniocervical injury, falling on the rear, and dura weakness due to abnormal connective tissue. Note that other causes of low cerebrospinal fluid pressure may exist, including reduced production of cerebrospinal fluid due to vitamin A deficiency.<sup>7)</sup>

Reports from Japan have shown that “cerebrospinal fluid hypovolemia” may be included among cases diagnosed as post-head injury sequel, whiplash injury, autonomic ataxia, general malaise, chronic fatigue syndrome, and depression.<sup>6)8)</sup>

### Comments and Evidence

In the ICHD-II,<sup>1)</sup> the diagnostic criteria for 7.2.3 “*headache attributed to spontaneous low CSF pressure*” are as follows:

- A. Diffuse and/or dull headache that worsens within 15 minutes after sitting or standing, with at least one of the following and fulfilling criterion D:
  - 1. neck stiffness

2. tinnitus
  3. hypacusia
  4. photophobia
  5. nausea
- B. At least one of the following:
1. evidence of low CSF pressure on MRI (eg, pachymeningeal enhancement)
  2. evidence of CSF leak on conventional myelography, CT myelography or cisternography
  3. CSF opening pressure <60 mm H<sub>2</sub>O in sitting position
- C. No history of dural puncture or other cause of CSF fistula
- D. Headache resolves within 72 hours after epidural blood patching

**In the recently published ICHD-3beta,<sup>2)</sup> the diagnostic criteria for 7.2.3 “headache attributed to spontaneous intracranial hypotension” are described below:**

- A. Any headache fulfilling criterion C
- B. Low CSF pressure (<60 mm CSF) and/or evidence of CSF leakage on imaging
- C. Headache has developed in temporal relation to the low CSF pressure or CSF leakage, or has led to its discovery
- D. Not better accounted for by another ICHD-3 diagnosis.

As shown above, the ICHD-II criteria provide concise definitions for the symptoms, test findings and treatments for headache attributed to spontaneous low CSF pressure [hereinafter referred to as spontaneous intracranial hypotension: SIH]. For the diagnosis and treatment of SIH, it is appropriate to start from these diagnostic criteria. Criterion D concerns symptom improvement after blood epidural blood patch. However, this does not imply that headache attributed to spontaneous low CSF pressure cannot be diagnosed without conducting a blood patch. This criterion should be interpreted as “headache resolves within 72 hours in the case that blood patching is conducted for SIH”.

After publication of the ICHD-II, renowned researchers from the United States proposed new criteria as the basis for change in future revision of the classification criteria.<sup>9)</sup> The proposed diagnostic criteria are shown in [Table 1](#). A characteristic of these criteria is that the time requirement was eliminated. Subsequently, in the ICHD-3beta published in 2013, the time factor described in the ICHD-II has been removed, as shown above.

## Headache

The typical headache is orthostatic headache. However, cases of unremarkable orthostatic headache, or paradoxically rare cases of postural headache,<sup>4)</sup> and cases manifesting thunderclap headache<sup>9)</sup> have been reported. Most patients experience orthostatic headache at some point during the disease course. Apart from spontaneous intracranial hypotension syndrome, other causes of orthostatic headache such as postural orthostatic tachycardia syndrome (POTS)<sup>11)</sup> have to be included in the differential diagnosis.

## Symptoms other than headache

The ICHD-II listed other symptoms such as neck stiffness, tinnitus, hypacusia, photophobia, and nausea. The symptoms of cerebrospinal fluid hypovolemia described by the Japanese Cerebrospinal Fluid Hypovolemia Study Group are presented in [Table 2](#). These symptoms are exacerbated by a mild state of dehydration such as fever and diarrhea.<sup>6)</sup> In the proposed criteria for future revision mentioned above,<sup>9)</sup> symptoms other than orthostatic headache included in the ICHD-II were

**Table 1. Diagnostic criteria for headache due to spontaneous intracranial hypotension.**

A. Orthostatic headache
B. The presence of at least one of the following:
1. Low opening pressure ( $\leq 60$ mmH <sub>2</sub> O)
2. Sustained improvement of symptoms after epidural blood patching
3. Demonstration of an active spinal CSF leak
4. Cranial MRI changes of intracranial hypotension (eg, brain sagging or pachymeningeal enhancement)
C. No recent history of dural puncture
D. Not attributable to another disorder

[Schievink WI, Dodick DW, Mokri B, Silberstein S, Bousser MG, Goasdsby PJ]: Diagnostic criteria for headache due to spontaneous intracranial hypotension: a perspective. *Headache* 2011; 51(9): 1442-1444.]



**Table 2. Symptoms of cerebrospinal fluid hypovolemia (Cerebrospinal Fluid Hypovolemia Study Group).**

(1) Major symptoms	
	Headache, neck pain, vertigo, tinnitus, visual disturbance, weariness/fatigability
(2) Accompanying symptoms)	
1. Cranial nerve symptoms	blurred vision, nystagmus, oculomotor palsy (pupil dilation, ptosis of eyelid), diplopia, photophobia, visual field disturbance, facial pain, facial numbness, hearing loss, abducens palsy, facial palsy, hypacusia
2. Nerve dysfunction other than cranial nerve symptoms	Impaired consciousness, apathy, cerebella ataxia, gait disturbance, Parkinson syndrome, dementia, dysmnnesia, radiculopathy, pain/numbness of upper extremity, vesicorectal disturbance, etc.
3. Endocrinologic abnormality	Galactorrhoea, etc.
4. Others	Nausea/vomiting, neck stiffness, interscapular pain, lumbar pain, etc.

[Guideline Committee of Cerebrospinal Fluid Hypovolemia Study Group (Ed.): Cerebrospinal fluid hypovolemia guideline 2007 (in Japanese). Cited and abstracted from p. 16, 2007]

**Table 3. Image diagnostic criteria for cerebrospinal fluid hypovolemia.**

(1) Findings of low cerebrospinal fluid pressure (indirect finding)	
MRI [plain + gadolinium enhancement, sagittal + coronal]	
(a) Brain shift finding	Enlargement of subdural space, descent of amygdala, disappearance of suprasellar cistern, flattening of brainstem (pons)
(b) Congestion findings	Diffuse pachymeningeal enhancement, dilation of superficial veins of the brain, enlargement of pituitary gland
(2) Diagnosis of cerebrospinal fluid leak (direct findings)	
RI cisternography, CT/MR myelography, spinal MRI	
(a) Cerebrospinal fluid leak finding	
(3) Diagnosis of cerebrospinal fluid leak (indirect findings)	
RI cisternography	
(a) Early renal uptake of RI	
(b) Increased RI clearance	
(c) Cerebrospinal fluid circulatory failure	

deleted (Table 1). Subsequently, in the ICHD-3beta, accompanying symptoms have been removed from the *diagnostic criteria*, but the *description* carries a sentence that “It is usually accompanied by neck stiffness and subjective hearing symptoms”.

### Cerebrospinal fluid pressure

For the diagnosis of SIH, although it is important to perform a lumbar puncture to prove low cerebrospinal fluid pressure, the lumbar puncture per se may elicit further cerebrospinal fluid leak. Therefore, in patients with already positive MRI findings such as pachymeningeal enhancement, lumbar puncture should be performed upon consideration of its necessity for treatment. In SIH also, the cerebrospinal fluid pressure may be normalized according to Monroe-Kellie doctrine (Miyazawa<sup>5</sup>) and Mokri et al.<sup>12</sup>) both reported normal pressure in 18%).

### Diagnostic imaging

The modalities of diagnostic imaging for cerebrospinal fluid hypovolemia include radionuclide (RI) cisternography for detecting cerebrospinal fluid leak, CT/MR myelography and spine MRI for obtaining direct findings, and cranial MRI for detecting indirect findings due to reduced cerebrospinal fluid. Table 3 summarizes the imaging modalities examined in many reports.<sup>4)-6)</sup> Conventional CT has little diagnostic value. Occasionally, spontaneous intracranial hypotension syndrome is complicated by bilateral chronic subdural hematomas. In this case, CT would help the diagnosis. Pachymeningeal enhancement on MRI is a strong evidence for a suspicion of spontaneous intracranial hypotension syndrome. However, this finding is not always depicted. On the other hand, pachymeningeal enhancement is observed in many diseases including dura invasion of malignant tumor and hypertrophic pachymeningitis, and exclusion of these conditions is necessary.<sup>3)</sup>

In recent years, to solve the confusion over the disease concept and diagnostic criteria of headache attributed to spontaneous



**Table 4. Image diagnostic criteria for cerebrospinal fluid leak (partially abstracted).**

Image diagnosis of cerebrospinal fluid leak
<ul style="list-style-type: none"><li>• If “definitive” cerebrospinal fluid leak findings are present, the diagnosis is “definite” cerebrospinal fluid leak.</li><li>• If “probable” cerebrospinal fluid leak are present, the diagnosis is “probable” cerebrospinal fluid leak.</li><li>• If RI cisternography and MRI/MR myelography show a combination of “strongly suspected” and “strongly suspected” findings, respectively, or “strongly suspected” and “suspected” findings at the same site, the diagnosis is “strongly suspected” cerebrospinal fluid leak.</li><li>• If RI cisternography and MRI/MR myelography show a combination of “suspected” and “suspected” findings, respectively, or only one of the two examinations showed “strongly suspected” or “suspected” findings at the same site, the diagnosis is “suspected” cerebrospinal fluid leak.</li></ul>
<b>“Definitive” finding</b>
CT myelography:
Finding of epidural leak of contrast medium continuous with the subarachnoid space
<b>“Probable” finding</b>
CT myelography:
Finding of epidural leak of contrast medium not continuous with the puncture site
Spinal MRI/MR myelography
Unenhanced epidural water signal lesion continuous with the subarachnoid space
RI cisternography:
Unilateral localized abnormal RI uptake + cerebrospinal fluid circulatory failure
<b>“Strongly suspected” finding</b>
Spinal MRI/MR myelography:
(1) Unenhanced epidural water signal lesion
(2) Epidural water signal lesion continuous with subarachnoid space
RI cisternography:
(1) Unilateral localized abnormal RI uptake
(2) Asymmetrical abnormal RI uptake or symmetrical uptake from neck to chest region, + cerebrospinal fluid circulatory failure
<b>“Suspected” finding</b>
Spinal MRI/MR myelography:
Epidural water signal lesion
RI cisternography:
(1) Asymmetrical abnormal RI uptake
(2) Symmetrical uptake from neck to chest region

[Sato S, Kayama T: Guidelines for Diagnosis and Treatment of Cerebrospinal Fluid Leak. Noshinkei Geka Sokuho 2012; 22(2): 200-206 (in Japanese)]

low CSF pressure (spontaneous intracranial hypotension syndrome) and cerebrospinal fluid hypovolemia, which has become a social problem, a research project funded by the Japanese Ministry of Health, Labour and Welfare Grant-in-aid for Scientific Research on the “Establishment of Diagnosis and Treatment of Cerebrospinal Fluid Hypovolemia (principal investigator: Kayama Takamasa)” was started in 2007. This Study Group published the “Guidelines for diagnosis and treatment of cerebrospinal fluid leak” in October 2011,<sup>13)</sup> which was approved by the Japan Neurosurgical Society, Japanese Society of Neurology, the Japanese Orthopaedic Association, the Japanese Headache Society, the Japan Society of Neurotraumatology, Japanese Society of Spinal Surgery, The Japanese Society for Spine Surgery and Related Research, and Japan Medical Society of Spinal Cord Lesion. The Study Group reasoned that “even if the pathological condition of ‘loss of cerebrospinal fluid volume’ advocated by Mokri et al. does exist, the volume of cerebrospinal fluid cannot be measured clinically. At this point in time, the only diagnoses possible are ‘intracranial hypotension’ and ‘cerebrospinal fluid leak’”. Based on this rationale, the Study Group first developed the criteria to diagnosis cerebrospinal fluid leak (Table 4). Given that cerebrospinal fluid leak is closely related to intracranial hypotension, the diagnostic criteria for spontaneous intracranial hypotension syndrome were also published (Table 5). The patients diagnosed according to these criteria are eligible for the advanced medical care (blood patch) which was approved for health insurance in June 2012 (to be described below). For this guideline, the detailed image diagnostic criteria are published elsewhere,<sup>13)</sup> and are not provided here due to space limitation.

Cerebrospinal fluid leak (CSF leak) is a disease already included in the International Classification Diseases (ICD-10). Moreover, in a paper published in 2008, Schievink from the United States also advocated that the term cerebrospinal fluid leak should be used because “the underlying cause is a spontaneous spinal cerebrospinal fluid (CSF) leak”.

**Table 5. Diagnostic criteria for spontaneous intracranial hypotension.**

• With orthostatic headache as prerequisite, if diffuse pachymeningeal enhancement and cerebrospinal fluid pressure (supine or prone) of 60 mmH <sub>2</sub> O or lower are fulfilled, the diagnosis is “definite” spontaneous intracranial hypotension syndrome.
• With orthostatic headache as prerequisite, if either diffuse pachymeningeal enhancement or cerebrospinal fluid pressure (supine or prone) of 60 mmH <sub>2</sub> O or lower is fulfilled, the diagnosis is “probable” spontaneous intracranial hypotension syndrome.
• If multiple “suggestive” findings are present, the diagnosis is “suspected” spontaneous intracranial hypotension syndrome.
* Diffuse pachymeningeal enhancement on cranial MRI alone is a “strongly suspected” finding.
* Since diffuse pachymeningeal enhancement (hypertrophic pachymeninges) may not be observed immediately after onset, repeated examination after an interval of several weeks is recommended.
* Dilation of epidural venous plexus, descent of amygdala, flattening of brainstem, enlargement of anterior lobe of the pituitary (superior convexity) are “suggestive” findings for spontaneous intracranial hypotension syndrome since it is not possible to clearly differentiate from normal findings.

[Sato S, Kayama T: Guidelines for Diagnosis and Treatment of Cerebrospinal Fluid Leak. Noshinkei Geka Sokuho 2012; 22(2): 200-206. (in Japanese)]

**Table 6. Treatment methods for spontaneous intracranial hypotension syndrome (Mokri, 2004).**

1. Bed rest	8. Epidural blood patch
2. Hydration/over-hydration	9. Continuous epidural saline infusion
3. Caffeine	10. Epidural infusion of dextran
4. Theophylline	11. Epidural injection of fibrin glue
5. Abdominal binder	12. Intrathecal fluid infusion
6. Corticosteroids	13. Surgical repair of the leak
7. Anti-inflammatory analgesic	

[Mokri B: Spontaneous intracranial hypotension spontaneous CSF leaks. Headache Currents 2005; 2(1): 11-22.]

## Treatment

Mokri<sup>3)</sup> described the treatments for SIH as shown in **Table 6**.

The treatments for SIH are divided into conservative treatments and invasive treatments. SIH may remit spontaneously. Conservative treatments such as bed rest and fluid infusion (1,000-1,500 mL/day) are effective, and treatment for approximately 2 weeks is recommended.<sup>5)6)</sup> Invasive treatments include the so called blood patch (epidural blood patch; EBP).<sup>4)-8)</sup> If the leak site is identified, epidural blood patching is conducted from near the leak.

Previously this procedure was not covered by health insurance. However, advanced medical care (Ministry of Health, Labour and Welfare Notification No. 379-63, Epidural blood patch) for patients fulfilling the diagnostic criteria proposed by the above-mentioned Study Group was approved for health insurance since June 2012. The approved procedure is described below.

- (1) The patient is placed in a lateral or prone position on the operating table.
- (2) An epidural needle of around 17G is used to perform an epidural puncture, using the loss of resistance method.
- (3) Autologous blood is prepared by collecting approximately 15-30 mL of venous blood. 4-10 mL of contrast medium is added for monitoring the injecting area during injection.
- (4) Injection is performed under fluoroscopic guidance.
- (5) After treatment, the patient bed rests for 1-7 days, and is then discharged.

The efficacy of blood patching has been reported. According to Sencakova et al.,<sup>15)</sup> 36% (9/25 patients) responded well to the first blood patch, 33% (5/15 patients) became asymptomatic after the second blood patch, and 50% (4/8 patients) responded well after 3 or more (4 on average) blood patch procedures. For traumatic spontaneous intracranial hypotension syndrome, 65% (95/147 patients) achieve improvement or better outcome.<sup>7)</sup> However, since the diagnostic criteria of the disease are still being debated, precise evaluation of the efficacy of blood patch is a future subject of research.

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# II

## Migraine

## How is migraine classified?

### Recommendation

Migraine is classified in accordance to the International Classification of Headache Disorders 3rd Edition beta version (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**

### Background and Objective

The classification of migraine has evolved with advances in the understanding of the disease concept and pathophysiology of migraine. The International Classification of Headache Disorders 2nd Edition and 3rd edition beta version are intended for use in research and clinical practice in the same manner as the first edition published in 1988, and is based on the most widely accepted disease concept and pathophysiology.

### Comments and Evidence

#### International Classification of Headache Disorders 2nd Edition (ICHD-II) <sup>1)</sup> and 3rd edition beta version (ICHD-3beta) <sup>2)</sup>

The ICHD-3beta adopts the hierarchical classification system, allowing descriptions of headache disorders using higher hierarchies (subtype, subform) for more specialized levels of research and clinical care.

Use the hierarchy of headache classification which corresponds to the condition and objective of clinical care and research.

Most of the evidence-based treatments for headache were developed based from using the first edition of the International Headache Society classification (1988). Since the major principles concerning the classification and diagnosis of primary headaches have not changed, the evidence obtained from using the first edition remains valid for most of the diagnoses made using the second edition. When looking for patients who will responds to triptan, it is recommended to diagnose the patients according to the diagnostic criteria for migraine with aura and migraine without aura described in the classification.

The ICHD-3beta is one of the most important references that should be read by physicians and researchers with an interest in the diagnosis and treatment of headache patients.

First, all the headaches are classified into major groups. In each group, headaches are subdivided 1, 2 or 3 times into type, subtype, and subform, respectively.

1. “Migraine” is a group containing one type of headache (migraine). The subtypes of migraine, such as 1.2 “Migraine with aura”, are a group of the next level (second digit level). Migraine with aura is further classified into subforms such as 1.2.1 “Migraine with typical aura”. For general practitioners, in order to select acute phase treatment, diagnosis to the first digit level; in other words, migraine, is usually sufficient. When problem arises with differential diagnosis, then coding to the second or third level may be necessary. Neurologists or headache specialists would be able to correctly diagnose the subform of migraine using the third digit level. This system has proven to be useful at various levels of healthcare system. In the ICHD-3beta, migraine is classified hierarchically as shown in [Table 1](#).

An important change from the first edition of the International Classification of Headache Disorder (1988) is the introduction of chronic headache and the accompanying adoption of the diagnostic criteria for medication overuse headache. A provision for chronic migraine is the absence of medication overuse. In the diagnosis of medication overuse headache, the criterion that headache improves after discontinuation of overused medication has to be fulfilled. In June 2006, the Headache Classification Committee of International Headache Society published new criteria that expands the concept of chronic headache as Appendix in Cephalalgia, the official journal of International Headache Society.<sup>3)</sup>

#### First edition of the International Classification of Headache Disorder (IHS classification 1988)<sup>4)</sup>

The first edition describes the classification and diagnostic criteria proposed by the International Headache Society in 1988. Since then, international standardization of headache diagnoses was initiated and accumulation of data on diagnosis

**Table 1. Classification of migraine in the International Classification of Headache Disorders 3rd Edition (ICHD-3beta)**

<b>1.</b>	<b>Migraine</b>
1.1	Migraine without aura
1.2	Migraine with aura
1.2.1	Migraine with typical aura
1.2.1.1	Typical aura with headache
1.2.1.2	Typical aura without headache
1.2.2	Migraine with brainstem aura
1.2.3	Hemiplegic migraine
1.2.3.1	Familial hemiplegic migraine (FHM)
1.2.3.1.1	Familial hemiplegic migraine type 1
1.2.3.1.2	Familial hemiplegic migraine type 2
1.2.3.1.3	Familial hemiplegic migraine type 3
1.2.3.1.4	Familial hemiplegic migraine, other loci
1.2.3.2	Sporadic hemiplegic migraine
1.2.4	Retinal migraine
1.3	Chronic migraine
1.4	Complications of migraine
1.4.1	Status migrainosus
1.4.2	Persistent aura without infarction
1.4.3	Migrainous infarction
1.4.4	Migraine aura-triggered seizure
1.5	Probable migraine
1.5.1	Probable migraine without aura
1.5.2	Probable migraine with aura
1.6	Episodic syndromes that may be associated with migraine
1.6.1	Recurrent gastrointestinal disturbance
1.6.1.1	Cyclical vomiting syndrome
1.6.1.2	Abdominal migraine
1.6.2	Benign paroxysmal vertigo
1.6.3	Benign paroxysmal torticollis

and treatment as well as comparative studies became possible. Most of the migraine classification in the first edition have been continued in ICHD-II. The main changes are the abolishment of “*Migraine with acute-onset aura*”, and moving “*Ophthalmoplegic migraine*” from the subtype of migraine to the subtype of “*Cranial neuralgias and central causes of facial pain*”.

1.7 “*Migrainous disorder not fulfilling above criteria*” was abandoned, and “*Probable migraine*” has been added.

The Ad Hoc Committee classification in 1962<sup>5)</sup> classified migraine from the viewpoint that migraine is a vascular headache, and the classification was wide used until the IHS classification was proposed in 1988. Although it is of historic value now, “*classic migraine*” and “*common migraine*” correspond nowadays to *migraine with aura* and *migraine without aura*, respectively. Although *cluster headache* was considered to be one type of migraine, it is now classified into an independent headache group. In addition, *migraine* and *muscle contraction headache* (corresponds to *tension-type headache* in ICHD-II) are grouped together under *Combined headache* and coded independently in ICHD-II.

As seen in Table 1, the classification of migraine has been further developed in the ICHD-3beta.

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- 3) Takeshima T, Nakama N, Igarashi H, Hirata Y, Sakani F; New International Headache Classification and Promotion Committee of Japanese Headache Society: On the addition of appendix diagnostic criteria for chronic migraine and medication overuse headache. Japanese Journal of Headache 2007; 34(2): 192-193. (In Japanese)
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## How is migraine diagnosed?

### Recommendation

Migraine is diagnosed according to the diagnostic criteria of the International Classification of Headache Disorders 3rd Edition beta version (ICHD-3beta). The ICHD-3beta adopts a hierarchical classification system. In general practice, 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**

### Background and Objective

Since the proposal of the diagnostic criteria by the International Headache Society in 1988, international standardization of the diagnosis for migraine was initiated and accumulation of data on diagnosis and treatment as well as comparative studies became possible. The International Classification of Headache Disorders 2nd Edition (ICHD-II) and 3rd Edition beta version (ICHD-3beta)<sup>(1)(2)</sup> follow the major classification of the first edition. The diagnosis of subtype and subform of migraine is structured on the basis that diagnosis is conducted based on semiology including the characteristics of headache and those of associated symptoms. The classification and diagnostic criteria of the ICHD-II and ICHD-3beta are voluminous. The documents are not intended to be learnt by heart, but to be consulted any time as necessary.

### Comments and Evidence

The major subtypes of migraine are 1.1 “*Migraine without aura*” and 1.2 “*Migraine with aura*”. The major subform is 1.2.1 “*Migraine with typical aura*”.

The diagnostic criteria are shown below:

#### 1.1 *Migraine without aura*

##### • Comments

This type of migraine is a recurrent headache disorder with attacks lasting 4-72 hours. Characteristics of the headache are unilateral, pulsating headache, moderate to severe in intensity, and aggravated by routine physical activity; with nausea, photophobia and phonophobia as associated symptoms.

##### • Diagnostic criteria

- A. At least five attacks fulfilling criteria B–D
- B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
- C. Headache has at least two of the following four characteristics:
  1. unilateral location
  2. pulsating quality
  3. moderate or severe pain intensity
  4. aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
- D. During headache at least one of the following:
  1. nausea and/or vomiting
  2. photophobia and phonophobia
- E. Not better accounted for by another ICHD-3 diagnosis.

#### 1.2 *Migraine with aura*

##### • Comments

This type of migraine is a disorder with recurrent attacks of reversible focal neurological symptoms that usually develop gradually over 5-20 minutes and last for less than 60 minutes. Headache with the characteristics of *migraine without aura* usually follows the aura symptoms. In rare cases, headache may lack migrainous characteristics, or headache may be completely absent.



- **Diagnostic criteria**

- A. At least 2 attacks fulfilling criterion B
- B. Migraine aura fulfilling criteria B and C for one of the subforms 1.2.1-1.2.6
- C. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded.

### 1.2.1 Typical aura with migraine headache

- **Comments**

Typical aura consists of visual, sensory, and speech symptoms that develop gradually, with duration no longer than one hour. Aura is characterized by a mixture of positive and negative features, is complete reversible, and is associated with a headache fulfilling the criteria for 1.1 “Migraine without aura”.

- **Diagnostic criteria**

- A. At least two attacks fulfilling criteria B and C
- B. One or more of the following fully reversible aura symptoms:
  - 1. visual
  - 2. sensory
  - 3. speech and/or language
  - 4. motor
  - 5. brainstem
  - 6. retinal
- C. At least two of the following four characteristics:
  - 1. at least one aura symptom spreads gradually over  $\geq 5$  minutes, and/or two or more symptoms occur in succession
  - 2. each individual aura symptom lasts 5-60 minutes<sup>Note 1</sup>
  - 3. at least one aura symptom is unilateral<sup>Note 2</sup>
  - 4. the aura is accompanied, or followed within 60 minutes, by headache
- D. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded.

**Notes:**

- 1. When, for example, three symptoms occur during an aura, the acceptable maximal duration is  $3 \times 60$  minutes. Motor symptoms may last up to 72 hours.
- 2. Aphasia is always regarded as a unilateral symptom; dysarthria may or may not be.

In June 2006, the Headache Classification Committee of International Headache Society reported new criteria that expand the concept of chronic headache as Appendix in Cephalalgia, the official journal of International Headache Society.

The main point of the appendix criteria for chronic migraine is that headache attack that responds to triptan or ergotamine may show no headache characteristic of migraine. However, fulfilling the diagnostic criteria for migraine without aura at least in the past is mandatory. This is based on the evidence from research results that while pure tension-type headache does not respond to triptan, the headache of migraine patients always responds to triptan even though they fulfill the diagnostic diagnosis of tension-type headache.<sup>3)</sup>

This appendix criteria have been developed into ICHD-3beta criteria,<sup>2)</sup> which are shown below.

### 1.3 Chronic migraine<sup>Notes 1,2</sup>

- **Diagnostic criteria**

- A. Headache (tension-type-like and/or migraine-like) on  $\geq 15$  days per month for  $>3$  months<sup>Note 2</sup> and fulfilling criteria B and C
- B. Occurring in a patient who has had at least five attacks fulfilling criteria B-D for 1.1 *Migraine without aura* and/or criteria B and C for 1.2 *Migraine with aura*
- C. On  $\geq 8$  days per month for  $>3$  months, fulfilling any of the following<sup>Note 3</sup>:
  - 1. criteria C and D for 1.1 Migraine without aura
  - 2. criteria B and C for 1.2 Migraine with aura
  - 3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
- D. Not better accounted for by another ICHD-3 diagnosis.

## Notes:

1. The diagnosis of 1.3 *Chronic migraine* excludes the diagnosis of 2. *Tension-type headache* or its subtypes because tension-type-like headache is within the diagnostic criteria for 1.3 *Chronic migraine*.
2. The reason for singling out chronic from episodic migraine is that it is impossible to distinguish the individual episodes of headache in patients with such frequent or continuous headaches. In fact, the characteristics of the headache may change not only from day to day but even within the same day. It is extremely difficult to keep such patients medication-free in order to observe the natural history of the headache. In this situation, attacks with or without aura are both counted, as well as tension-type-like headaches. The most common cause of symptoms suggestive of chronic migraine is medication overuse, as defined under 8.2 *Medication-overuse headache*. Around 50% of patients apparently with 1.3 *Chronic migraine* revert to an episodic migraine subtype after drug withdrawal; such patients are in a sense wrongly diagnosed as 1.3 *Chronic migraine*. Equally, many patients apparently overusing medication do not improve after drug withdrawal, and the diagnosis of 8.2 *Medication-overuse headache* may in a sense be inappropriate (assuming that chronicity induced by drug overuse is always reversible). For these reasons, and because of the general rule, patients meeting criteria for 1.3 *Chronic migraine* and for 8.2 *Medication-overuse headache* should be given both diagnoses. After drug withdrawal, migraine will either revert to the episodic subtype or remain chronic, and be re-diagnosed accordingly; in the latter case, the diagnosis of 8.2 *Medication-overuse headache* may be rescinded. In some countries, it is usual practice to diagnose 8.2 *Medication-overuse headache* only on discharge.
3. Characterization of frequently recurring headache generally requires a headache diary to record information on pain and associated symptoms day-by-day for at least 1 month. Sample diaries are available at <http://www.i-h-s.org>.

## • References

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## 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**

### Background and Objective

In the past, migraine was thought to be not highly prevalent in Japan. Accompanying the popularization of the international headache classification, epidemiology studies using standardized diagnostic criteria have been conducted in various countries worldwide. In Japan also, epidemiology surveys of the general population have been undertaken.

### Comments and Evidence

Sakai and Igarashi<sup>1)</sup> conducted a nationwide survey on a sample population aged 15 years or older in Japan and reported an overall prevalence of migraine in the past year of 8.4% (migraine without aura 5.8%, and migraine with aura 2.6%). When stratified by gender and age, the prevalence of migraine was highest among women in their thirties, reaching approximately 20%, while the prevalence in women in their forties was also high at approximately 18%.

In a survey conducted in Daisen, Tottori Prefecture, targeting residents aged 20 years or older, 6.0% of the residents had migraine (migraine with aura 0.9%, migraine without aura 5.2%). The prevalence reported in various countries differs: 3.0% in China, 9.0% in Malaysia, 9.1% in Taiwan, 12.1% in France, 13.0% in the United State, 13.2% in Sweden, 27.5% in Germany, and 29.1% in Thailand. Although the differences are likely due to the differences in survey method, diagnostic sensitivity, lifestyle, and regional characteristics, the estimated prevalence is 5-10% in Asia including Japan and 10-15% in European and American countries. All these figures portray a very high prevalence, indicating that migraine is a disorder requiring control measures. When analyzed by age, the prevalence of migraine is high in young to middle-aged women; with prevalence reaching 17.6% and 18.4% in women in the thirties and forties, respectively.<sup>2)</sup>

In a survey of Japanese senior high school students conducted by Suzuki et al.,<sup>3)</sup> the prevalence of migraine (including migraine with aura and without aura) was 9.8%, which is almost the same level as reported in other countries.

In a survey of Japanese junior high school students conducted by Ando et al.,<sup>4)</sup> the prevalence of migraine was 4.8%; 29.1% of those students had migraine with aura. In addition, approximately one-half of the migraine patients had migraine attacks with short duration, ranging from 1 to 3 hours.

In Japan, a small proportion of migraine patients consult medical facilities, even though migraine causes disability in everyday life.<sup>1)-4)</sup>

### • References

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### • Search terms and secondary sources

- Search database: PubMed (2011/11/4)  
migraine and (prevalence or epidemiology) and (Japan or Japanese) 60

## 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-HT<sub>1B/1D</sub> 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**

### Background and Objective

Various hypothesis for the pathophysiology of migraine have been proposed. Literature was searched with the aim to verify the pathophysiological hypothesis of migraine based on scientific evidence.

### Comments and Evidence

The pathophysiology of migraine has not been definitively established, although the vascular theory, the neuronal theory and the trigeminovascular theory were proposed in the past. Currently, visual aura is no longer considered a phenomenon due to cerebral vasoconstriction, and headache attack is not regarded as a phenomenon caused by cerebral vasodilation. The aura of migraine is now believed to be a phenomenon due to cortical spreading depression (CSD). As for the origin of headache, the theory of peripheral origin from cerebral blood vessels and trigeminal nerve endings, and the theory of central origin from the brainstem have been proposed, but a conclusion is yet to be arrived. In addition, the involvement of both central sensitization and peripheral sensitization in pain has been proven. Many reports have shown that nitric oxide (NO), histamine, serotonin, glutamic acid, dopamine, orexin, and various neuropeptides including calcitonin gene-related peptide (CGRP) are involved in the pathology of migraine attacks. In these reports, however, human data are mixed with results of animal studies. As a result, the evidence-based pathophysiological mechanisms that can explain all the neural symptoms observed during migraine attacks and the accompanying physiological changes have not been elucidated. Many phenomena observed in humans cannot be verified by animal experiments. In the future, it is necessary to further accumulate findings in humans to better elucidate the pathophysiological mechanisms based on scientific evidence. Therefore, several representative references with a review nature are given here.<sup>1)-6)</sup>

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### • Search terms and secondary sources

- Search database: PubMed (2011/11/8)
- Migraine
- & pathogenesis or pathophysiology or mechanism or hypothesis 14683

## 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**

### Background and Objective

This section explains the types of aura in migraine by describing the typical aura observed in migraine with aura, aura in hemiplegic migraine, and aura in migraine with brainstem aura.

### Comments and Evidence

#### 1. Typical aura

This type of aura is totally reversible focal neurological symptoms occurring immediately before or at the same time as pain starts in a migraine attack, which usually develops gradually over 5-20 minutes and lasts for less than 60 minutes. The first edition of International Headache Classification (1988) lists typical aura as visual symptoms, sensory symptoms, weakness, and speech symptoms. In the International Classification of Headache Disorders 2nd Edition (ICHD-II), typical aura consists of visual symptoms, sensory symptoms, and speech symptoms.<sup>1,2)</sup>

Visual aura is fully reversible symptoms including positive features (for example, flickering lights, spots or lines) and/or negative features (loss of vision). This is the most common type of aura, and often presents as fortification spectrum. In other words, a zigzag figure near the fixation point gradually spreads in a right or left direction and assumes a laterally convex shape with an angulated scintillating edge, resulting in absolute or relative scotoma. Next in frequency are sensory disturbances, which is fully reversible sensory symptoms including positive features (pins and needles spreading slowly from the point of origin and affecting the body and face to various extents) and/or negative features (numbness). Numbness may occur in its wake, but numbness may also be the only symptom. Less frequent are speech disturbances, usually fully reversible dysphasic but often hard to categorize.

#### 2. Aura of hemiplegic migraine

Aura of hemiplegic migraine consists of fully reversible motor weakness and at least one symptom of the typical aura. The duration of each aura is 5 minutes or longer and less than 24 hours.

#### 3. Aura of migraine with brainstem aura

Migraine with brainstem aura is described as migraine with aura symptoms clearly originating from the brainstem, but no motor weakness. According to the ICHD 3rd edition (beta version),<sup>3)</sup> the diagnostic criteria include: aura consisting of visual, sensory and/or speech/language symptoms, each fully reversible; and at least two of the following brainstem symptoms: dysarthria, vertigo, tinnitus, hypacusis, diplopia, ataxia, and decreased level of consciousness but no motor or retinal symptoms.

Aura has at least two of the following four characteristics: 1. at least one aura symptom spreads gradually over 5 minutes, and/or two or more symptoms occur in succession; 2. each individual aura symptom lasts 5-60 minutes; 3. at least one aura symptom is unilateral; 4. the aura is accompanied, or followed within 60 minutes, by headache.

### • References

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- **Search terms and secondary sources**

- Search database: PubMed (2011/12/21)  
Migraine 24757  
& aura 3464  
& diagnosis 1886

## What is the proposed mechanism for aura in migraine?

### Recommendation

At present, aura in migraine is considered to be caused by cortical spreading depression (CSD) or spreading oligemia.

**Grade B**

### Background and Objective

Several hypotheses for the physiopathology of migraine have been proposed. For aura, research so far suggests that aura manifests because of the occurrence of cortical spreading depression (CSD) in the cerebrum. Aura of migraine is explained by referring to some review articles.

### Comments and Evidence

In the past, the typical aura of migraine was thought to be caused by local contraction of cerebral blood vessels.<sup>1)</sup> Cortical spreading depression (CSD) was first observed in an animal study,<sup>2)</sup> and this phenomenon was suggested to resemble the process of spreading of fortification spectrum. Subsequent study reported the phenomenon of spreading oligemia. During migraine attack, regional cerebral blood flow in the occipital lobe is lowered (oligemia), and the reduced blood flow spreads anteriorly in the cerebrum at a speed of 2–3 mm/minute.<sup>3)</sup> Since spreading oligemia and CSD both propagate at almost the same speed, and are both almost independent of the vascular territory, it is currently hypothesized that spreading oligemia is caused by abnormal neural activities such as CSD. Currently, the neural theory that typical aura occurs due to abnormality activities of cerebral cortical neurons is being advocated.

With recent advances in functional neuroimaging, the involvement of CSD in visual aura has been demonstrated in humans using functional MRI, and the hypotheses proposed are gradually being tested and verified.<sup>4)</sup>

The mechanisms for aura in migraine with brainstem aura and aura in hemiplegic migraine have not been elucidated at present.

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### • Search terms and secondary sources

- Search database: PubMed (2011/9/1)
- Migraine 24757
- & aura 3464
- & pathophysiology 1427 or mechanism 213



## 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-HT<sub>1B/1D</sub> receptor) and calcitonin gene-related peptide (CGRP) released from the trigeminal nerve endings are closely associated with pain in migraine attack.

**Grade A**

### Background and Objective

Regarding the genesis of pain in migraine, the central origin theory and the peripheral origin theory have been proposed from the past. Literature was searched to clarify the origin of pain and its physiopathology based on scientific evidence.

### Comments and Evidence

The definitive mechanisms of the pathophysiology of pain in migraine remain to be established. For the genesis of pain also, two hypotheses have been proposed; the central origin theory of pain generated in the superior brainstem and the peripheral theory of pain generated from cerebral blood vessels and trigeminal nerve endings, but no conclusion has been arrived. Nevertheless, currently headache attack as a phenomenon caused by cerebral vasodilation is no longer considered valid. Recent research has shown that sensitization, which is the perception of pain caused by innocuous stimuli, occurs both peripherally and centrally. There is no dispute that skin allodynia caused by central sensitization of central nociceptive neurons and peripheral sensitization caused by trigeminovascular activation (neurogenic inflammation) are both prominently involved in migraine pain. Moreover, nitric oxide (NO), histamine, serotonin, glutamic acid, dopamine, and various chemical mediators including calcitonin gene-related peptide (CGRP) are involved in the pathology of migraine. In addition, the existence of the nociceptive receptor TRPV1 (transient receptor potential cation channel, subfamily V, member 1) has been demonstrated, and considered to be related to the pathology of migraine.

However, since previous reports contain a mixture of human and animal study data, they do not provide evidence-based pathophysiological mechanisms that can explain all the neural symptoms observed during migraine attacks as well as the accompanying physiological changes. Further elucidation of the pathophysiological mechanism based on scientific evidence is necessary. Therefore, several representative references with a review nature are given here.<sup>1)-8)</sup>

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### • Search terms and secondary sources

- Search database: PubMed (2011/11/8)
- Migraine
- & pathogenesis or pathophysiology or mechanism or hypothesis 14683

## 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-HT<sub>1B</sub> receptor and 5-HT<sub>1D</sub> receptor, are widely distributed in the trigeminovascular system consisting of intracranial large caliber blood vessels, trigeminal peripheral nerve endings, trigeminal ganglion, and subnucleus caudalis of the spinal trigeminal nucleus. Since the advent of triptan (5-HT<sub>1B/1D</sub> receptor agonist), the relationship between migraine and serotonin receptor has been highlighted.

**Grade A**

### Background and Objective

Serotonin abnormality in migraine was debated mainly in the 1960s. The majority of serotonin is present in the platelets. A few reports described the release of large amounts of serotonin from platelets, and others described the induction of migraine attack by intravenous injection of serotonin. However, subsequent studies did not lead to a unified opinion, and there are few reports of serotonin studies in humans. Literature was searched to clarify the role of abnormalities in serotonin, including serotonin receptors, in the pathology of migraine.

### Comments and Evidence

The relationship between serotonin and migraine was advocated from the 1960s. A low serotonin state in the central nervous system during the period in between attacks and the release and increase of serotonin during attack suggest an association between serotonin and migraine pathology. However, a consistent mechanism of serotonin kinetics (in blood or in platelet) during interictal and ictal periods has not yet been established. On the other hand, the serotonin receptor 5-HT<sub>1B/1D</sub> is widely distributed in the trigeminovascular system. Since triptan (5-HT<sub>1B/1D</sub> receptor agonist) is effective for the relief of migraine attack, there is no doubt that 5-HT<sub>1B/1D</sub> receptor plays an important role in migraine attack. Recent studies in humans have demonstrated increased 5-HT synthesis and augmented activity of 5-HT<sub>1A</sub> receptor in the raphe nucleus during migraine attacks. Here, only important references are provided.<sup>1)-11)</sup>

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### • Search terms and secondary sources

- Search database: PubMed (2011/11/8)
- Migraine
- & {serotonin} 2928

## How does cerebral blood flow change during migraine attack?

### Recommendation

Change in cerebral blood flow during migraine attack is discussed focusing on cortical spreading depression (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**

### Background and Objective

The change in cerebral blood flow during migraine attack was originally discussed focusing on cortical spreading depression (CSD). To prove the hypothesis, regional cerebral blood flow has been measured using Xe/CT, SPECT, PET, transcranial Doppler (TCD), or functional MRI. Literature was searched to clarify the scientific evidence for regional cerebral blood flow during migraine attacks.<sup>1)-10)</sup>

### Comments and Evidence

The articles searched and cited are all reports of human studies, in which cerebral blood flow was measured using noninvasive imaging methods such as Xe/CT, SPECT, PET, TCD, and functional MRI. However, due to the small number of cases in each study and the resolution limitation of imaging techniques, the timing of imaging during attack remains an issue. While the results of previous clinical studies concur on a reduction of cerebral blood flow in the occipital lobe in migraine with aura, the opinions regarding migraine without aura are divided. Moreover, increase in cerebral blood flow has also been shown during headache attack. In migraine with aura, because headache attack starts from the time when cerebral blood flow is lowered, vasodilation in the brain alone is not considered the cause of headache. Furthermore, in hemiplegic migraine, which is a special type of migraine associated with hemiplegia, consistent results have not been obtained for regional cerebral blood flow in the affected hemisphere.

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### • Search terms and secondary sources

- Search database: PubMed (2011/10/30)
- Migraine
- & {cerebral blood flow} 999

## What are the precipitating/aggravating factors of migraine?

### Recommendation

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

- 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**

### Background and Objective

Many migraine patients are aware that attack occurs easily under specific conditions. Since migraine may be prevented by avoiding the precipitating/aggravating factors in daily life, it is important that individual patients know the factors that precipitate/aggravate their own migraine. Literature was searched to identify the precipitating/aggravating factors of migraine.

### Comments and Evidence

Approximately 75% of migraine patients have some kind of precipitating factors.<sup>1)</sup> The common migraine precipitating/aggravating factors identified in various epidemiological studies include stress, mental strain, fatigue, sleep, menstrual cycle, weather change, temperature change, frequent travels, odor, hunger, and alcohol.<sup>1)-8)</sup> Apart from alcohol, the other factors are also precipitating factors of tension-type headache.

Stress is one of the most prominent precipitating factors.<sup>1)</sup> Stress triggers migraine in approximately 60% of the patients, and 25% of these patients feel that headache occurs when they are relieved from stress.<sup>2)</sup> While lack of sleep is perceived as the trigger in approximately 30% of the migraine patients, too much sleep is implicated in 25%.<sup>2)</sup> Weather is cited as the precipitating factor in 53% of the migraine patients, and 11% of the patients felt that weather is the precipitant in two-thirds of the headache attacks.<sup>1)</sup>

Among alcoholic beverages, red wine is a famous precipitating/aggravating factor. Histamine that is related to pain, and alcohol and polyphenol that possess vasodilating effect are probably involved in the precipitating/aggravating effect. In a study on a group of migraine patients who believed that red wine provoked migraine and a group who did not, migraine was triggered by red wine only in the group that believed that red wine provoked migraine.<sup>9)</sup> This finding suggests that the precipitating factors may differ depending on individual patients with migraine. Even from the old days, foods containing amines represented by tyramine, such as cheese, chocolate, citrus fruits, and nuts are well known to precipitate migraine.<sup>9)</sup> In a survey conducted in England, 16 to 18% of respondents cited chocolate or cheese as precipitating factor.<sup>10)11)</sup> A double-blind placebo controlled study in 20 patients who believed that chocolate provoked migraine found that chocolate ingestion triggered migraine attacks in many patients.<sup>12)</sup> On the other hand, a double-blind study using chocolate and placebo in patients with chronic headache (including migraine and tension-type headache) found no difference in the rate of migraine provocation between chocolate and control even in patients who believed that chocolate was a precipitating factor.<sup>13)</sup> Despite the fact that dietary factors are widely known, few patients have actually experienced the precipitating/aggravating factors.<sup>14)</sup> While a large number of foods have been implicated as precipitating/aggravating factors, they do not apply to all the patients. Even in the same patient, a given food does not always provoke headache. Few patients mention specific foods apart from alcohol. Therefore unnecessary dietary restriction may have the opposite effect of lowering patients' QOL. The American Headache Society publishes views on triggers of migraine on its website.<sup>15)</sup>

According to a survey conducted by Takeshima et al.,<sup>3)</sup> persons with migraine consume more fatty/oily foods, coffee, and tea than persons without headache. From these data, regular consumption of a well balanced diet is recommended. Although there is no correlation between obesity and the prevalence of migraine, study has shown that obesity is associated with chronic progression of migraine.<sup>16)</sup>

Despite recent advances in the treatment of migraine, many patients still do not achieve symptomatic relief. However,

even in such patients, lifestyle improvement, for example through sleep and dietary guidance and stress management, may mitigate symptoms, and maintenance of appropriate weight may prevent chronification of migraine.

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- Search database: PubMed (2012/4/30)
  - (migraine or headache) & "trigger factor" 28
  - (migraine or headache) & "precipitating factor" 51
  - (migraine or headache) & "risk factor" 583
  - migraine & food 462
  - migraine & diet 260
  - migraine & glucose 122
  - migraine & wine 39
  - migraine & chocolate 44
  - migraine & cheese 32
- Search database: Ichushi Web for articles published in Japan (2012/4/30)
  - (migraine) and (food) 40
- Secondary source, 1 reference added by manual search (No. 15)

## 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.<sup>1)</sup>

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.<sup>2)</sup> 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 al.<sup>3)</sup> 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.<sup>4)</sup> However, regarding the change in disease state one year after onset, 83.29% show no change, 9.85% show partial remission, and 3.26% show complete remission.<sup>1)</sup> However, in 2.97% of the patients, the frequency of headache attacks increases and headache-related disability becomes more severe.<sup>1)</sup> 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 chronification of migraine (note: these epidemiological studies often target chronic daily headache). These risk factors are listed below.<sup>5)-10)</sup>

#### (1) Congenital factors

##### 1. Family history

The risk of onset in a child increases when the mother has chronic daily headache.

##### 2. Prenatal exposure

Mother's drinking and smoking during gestation are risk factors.

#### (2) Headache conditions

##### 1. 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

##### 1. Obesity



The prevalence of chronic daily headache (including chronic migraine) is increased three-fold in persons with BMI 25-29 and five-fold in those with BMI 30 or above, compared to normal-weight individuals.

2. Snoring and sleep apnea

3. 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.

4. Temporomandibular disorder

(4) External factors

1. Analgesic overuse

The focus here is not on the aggravation of medication-overuse headache, but on the relationship between analgesics and chronification of migraine. Although this may not be an issue in Japan, use of opioid and barbiturate is a risk for migraine chronification. Triptan and 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. CA 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.<sup>11)</sup> 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.<sup>12)-15)</sup>

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## • Search terms and secondary sources

- Search database: PubMed (2011/12/7)
- migraine & chronification 63



## 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**

### Background and Objective

Migraine is a chronic disease, and is known to cause a wide variety of functional disabilities from the physical, mental and social aspects. According to a survey conducted by World Health Organization (WHO), migraine is ranked as the 19<sup>th</sup> disease (7<sup>th</sup> for women alone) that shortens healthy life expectancy.<sup>1)</sup> Many attempts have been made to quantitatively evaluate the quality of life (QOL) of migraine patients by comprehensively assessing functional disability from various aspects. To evaluate the deleterious impact of migraine on QOL, tools that assess overall health-related quality of life (HRQoL) such as the Short Form Health Survey (SF)-20<sup>2)</sup> and SF-36,<sup>3)</sup> as well as tools specific for migraine such as the Migraine Disability Assessment (MIDAS),<sup>4)5)</sup> Headache Impact Test-6 (HIT-6),<sup>5)</sup> and Migraine-Specific Quality of Life Questionnaire (MSQ)<sup>6)</sup> have been developed and used. This section examines the QOL impairment in migraine patients, focusing on reports of QOL studies in migraine patients using representative evaluation methods.

### Comments and Evidence

Healthy life expectancy refers to the number of years that a person can expect to live healthily and independently both physically and mentally. The WHO publishes the years of life lived with disability (YLDs) for various diseases, and migraine is ranked as number 19. In the Global Burden of Disease (GBD) Study, diseases were classified by the severity of disease sequelae into seven disability classes; class I to class VII. Parkinson disease and deafness are classified as class IV, Alzheimer and other dementias as well as blindness as class VI, and severe migraine together with quadriplegia, terminal stage cancer and others as the most severe class VII.<sup>7)</sup>

In a survey of migraine patients using SF-20 and SF-36, HRQoL score was significantly lower in migraine patients compared with healthy population without chronic disease.<sup>3)</sup> In a large-scale telephone interview survey conducted in the United States and United Kingdom comparing persons who had migraine with a non-migraine control group<sup>8)</sup>, HRQoL scores both in the mental health and physical health components were significantly lower in subjects with migraine. A correlation was observed between the degree of disability in HRQoL and migraine attack frequency. The comorbid rate of migraine and depression was significantly high, and each independently impaired HRQoL.<sup>8)</sup> Although migraine is an episodic disease, migraine patients have lower QOL and perceive greater emotional stress even between attacks compared with non-headache controls.<sup>9)</sup> In an evaluation using the MIDAS questionnaire, the mean MIDAS total score was 23.4 (n = 234) in patients who had migraine without aura and 79.2 (n = 150) in patient who had chronic migraine, both groups showing lower HRQoL.<sup>10)</sup> Compared to subjects with episodic migraine, those with chronic migraine reported significantly higher health care resource utilization rate, significantly lower HRQoL, and higher levels of anxiety and depression.<sup>11)</sup> Iigaya et al.<sup>12)</sup> developed the Japanese version of the MIDAS questionnaire and reported its reliability and validity.

When the eight SF-36 subscales were analyzed, patients with migraine had almost the same degree of HRQoL impairment as patients with other chronic primary headaches.<sup>10)</sup> In some of the subscales, patients with migraine had more severely impaired QOL compared to patients with other chronic diseases such as hypertension and diabetes.<sup>3)</sup> Since QOL depends to some extent on culture and lifestyle, scales suitable for measuring QOL in Japanese have been established and used for the evaluation of drug treatment.<sup>13)</sup>

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- Search database: PubMed (2012/3/17)  
{Migraine} or {vascular headache} or {hemicrania} 69836  
& Quality of Life 1755  
& disability 1575
- Search database: Ichushi Web for articles published in Japan (2012/3/17)
- Secondary source, 2 references added by manual search (Nos. 1 and 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**

### Background and Objective

Comorbid disorders of migraine are an important concept when considering the etiology, pathophysiology and treatment of migraine. The relationship of comorbid disorders with migraine may be (1) incidental coexistence; (2) comorbid disorder causing migraine or migraine causing comorbid disorder; (3) common risk factors causing migraine and comorbid disorder; (4) given hereditary and environmental factors triggering specific cerebral conditions, and the conditions causing migraine and comorbid disorder.<sup>1)</sup>

Studies on migraine comorbidities, such as case series and epidemiological surveys, have been conducted from various viewpoints.

### Comments and Evidence

Migraine is a disease with high prevalence, and often coexists incidentally with other diseases that also have high prevalence. Even if incidental, when planning treatments for migraine and the comorbid disorders, it is important to select drugs that do not exert adverse effects on both conditions.

Many case series have reported a high percentage of hypertension in migraine patients, but the results are not consistent. Large-scale epidemiological studies often found no correlation between migraine and hypertension. The prevalence of hypertension is high, hence the number of patients with both conditions is large, even though the association is incidental.<sup>2)(3)</sup>

Although reports have suggested an association between migraine and heart diseases such as mitral valve prolapse, ischemic heart disease and arrhythmia, no large-scale studies have been conducted. Furthermore, there is a lack of evidence on the correlation after adjusting for risk factors of ischemic diseases, including smoking and hypertension. A high comorbid rate of patent foramen ovale (PFO) in patients who have migraine with aura has been reported, but concrete evidence on the effect of PFO closure on migraine has not been obtained.<sup>4)-6)</sup>

Many studies have investigated the association between migraine and cerebrovascular disorders, especially ischemic cerebrovascular disorder. This aspect is discussed in detail elsewhere in this guideline: “CQII-1-9 “Is migraine a risk factor of cerebral infarction?” (page 85).

Several studies have examined the relationship between migraine and psychiatric diseases such as major depression, bipolar disorder, and anxiety disorder, and the majority demonstrated no significant correlation.<sup>2)(7)</sup> The relationship with epilepsy has been much debated in terms of etiology,<sup>8)(9)</sup> but consistent data showing a correlation is lacking. The correlation between migraine and other diseases such as restless legs syndrome,<sup>10)-(12)</sup> asthma,<sup>3)(13)</sup> allergic diseases,<sup>3)(14)</sup> autoimmune diseases,<sup>3)</sup> Ménière disease,<sup>14)(15)</sup> endometriosis,<sup>16)(17)</sup> biliary tract disorders,<sup>18)</sup> kidney stone,<sup>3)</sup> thyroid disease,<sup>3)</sup> fibromyalgia,<sup>3)(19)(20)</sup> and chronic fatigue syndrome<sup>21)</sup> has received attention, and further accumulation of data is necessary.

Comorbid disorders are important in understanding the pathology of migraine. On the other hand, understanding comorbid condition is also essential when conducting migraine treatment, especially prophylactic therapy.

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## • Search terms and secondary sources

- Search database: PubMed (2012/1/3)
- migraine and (comorbid or comorbidity) 934

## 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. The diagnosis should be made according to the diagnostic criteria of the International Classification of Headache Disorders 3rd Edition beta version (ICHD-3beta).

Grade A

### Background and Objective

Literature was searched to clarify the diagnosis and epidemiological characteristics of chronic migraine.

### Comments and Evidence

Chronic migraine<sup>Notes 1,2</sup> should be diagnosed according to the diagnostic criteria of the International Classification of Headache Disorders 3rd Edition (ICHD-3beta), as described below.

#### Diagnostic criteria:

- A. Headache (tension-type-like and/or migraine-like) on  $\geq 15$  days per month for  $>3$  months<sup>Note 2</sup> and fulfilling criteria B and C
- B. Occurring in a patient who has had at least five attacks fulfilling criteria B-D for 1.1 *Migraine without aura* and/or criteria B and C for 1.2 *Migraine with aura*
- C. On  $\geq 8$  days per month for  $>3$  months, fulfilling any of the following<sup>Note 3</sup>:
  - 1. criteria C and D for 1.1 *Migraine without aura*
  - 2. criteria B and C for 1.2 *Migraine with aura*
  - 3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
- D. Not better accounted for by another ICHD-3 diagnosis.

#### Notes:

1. The diagnosis of 1.3 *Chronic migraine* excludes the diagnosis of 2. *Tension-type headache* or its subtypes because tension-type-like headache is within the diagnostic criteria for 1.3 *Chronic migraine*.
2. The reason for singling out chronic from episodic migraine is that it is impossible to distinguish the individual episodes of headache in patients with such frequent or continuous headaches. In fact, the characteristics of the headache may change not only from day to day but even within the same day. It is extremely difficult to keep such patients medication-free in order to observe the natural history of the headache. In this situation, attacks with or without aura are both counted, as well as tension-type-like headaches. The most common cause of symptoms suggestive of chronic migraine is medication overuse, as defined under 8.2 *Medication-overuse headache*. Around 50% of patients apparently with 1.3 *Chronic migraine* revert to an episodic migraine subtype after drug withdrawal; such patients are in a sense wrongly diagnosed as 1.3 *Chronic migraine*. Equally, many patients apparently overusing medication do not improve after drug withdrawal, and the diagnosis of 8.2 *Medication-overuse headache* may in a sense be inappropriate (assuming that chronicity induced by drug overuse is always reversible). For these reasons, and because of the general rule, patients meeting criteria for 1.3 *Chronic migraine* and for 8.2 *Medication-overuse headache* should be given both diagnoses. After drug withdrawal, migraine will either revert to the episodic subtype or remain chronic, and be re-diagnosed accordingly; in the latter case, the diagnosis of 8.2 *Medication-overuse headache* may be rescinded. In some countries, it is usual practice to diagnose 8.2 *Medication-overuse headache* only on discharge.
3. Characterization of frequently recurring headache generally requires a headache diary to record information on pain and associated symptoms day-by-day for at least 1 month. Sample diaries are available at <http://www.i-h-s.org>.  
The headache observed in patients with chronic migraine does not necessarily manifest typical properties of migraine, and is known to commonly show the properties of tension-type headache. Even in this type of headache, since headache is often improved by treatment with triptan, it is different from the usual tension-type headache and is interpreted as mild

migraine presenting as tension-type headache-like headache.<sup>2)3)</sup> In addition, patients with chronic migraine often use many acute headache medications, with some in a state of overuse.

The prevalence of chronic migraine differs depending on the diagnostic criteria used, and is estimated to range from 1.4 to 2.2%. Patients with chronic migraine has more severe disability, lower QOL, and higher comorbidity rate of psychiatric disorders such as depression, compared with patients with episodic migraine.<sup>4)</sup> The risk factors for chronification of migraine are described in another section: CQ II-1-6-1: What is the prognosis of migraine (including chronification of migraine)? (page 77).

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## • Search terms and secondary sources

- Search database: PubMed (2011/12/7)  
chronic migraine 3108

## Is migraine a risk factor of 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. Migraine without aura does not increase the risk.

**Grade A**

### Background and Objective

Many analytical epidemiological studies have examined the relationship between migraine and cerebrovascular diseases. In addition, cross-sectional studies using MRI have reported increased rates of cerebral deep white matter lesion and infratentorial lesions in patients with migraine compared with controls.<sup>1,2)</sup>

### Comments and Evidence

According to a systematic review and meta-analysis of 11 case-control studies and 3 cohort studies reported by Etminan et al.<sup>3)</sup> in 2005, the relative risk of ischemic stroke was 2.16 (95% confidence interval: 1.89 to 2.48) in all people with migraine, 2.27 (1.61 to 3.19) in people who had migraine with aura, 1.83 (1.06 to 3.15) in people who had migraine without aura, 8.72 (5.05 to 15.05) in migraine patients using oral contraceptives, 2.36 (1.92 to 2.90) in migraine patients aged below 45 years (male and female), and 2.76 (2.17 to 3.52) in female migraine patients aged below 45 years. In another systematic review and meta-analysis of 13 case-control studies, 10 cohort studies and 2 cross-sectional studies reported by Schürks et al.<sup>4)</sup> in 2009, the relative risk of ischemic stroke was 1.73 (1.31 to 2.29) in all people with migraine, 2.16 (1.53 to 3.03) in people who had migraine with aura, 1.23 (0.90 to 1.69) in people who had migraine without aura, 2.08 (1.13 to 3.84) in female migraine patients (including with and without aura), 1.37 (0.89 to 2.11) in male migraine patients, 2.65 (1.41 to 4.97) in migraine patients aged below 45 years of age, 3.65 (2.21 to 6.04) in female migraine patients aged below 45 years of age, 9.03 (4.22 to 19.34) in smoking migraine patients, 7.02 (1.51 to 32.68) in female migraine patients using oral contraceptives. The relative risk of transient ischemic attack in migraine patients was 2.34 (1.90 to 2.88), and the relative risk of hemorrhagic stroke was 1.18 (0.87 to 1.60). A meta-analysis of 13 case control studies and 8 cohort studies reported by Spector et al.<sup>5)</sup> in 2010 showed that the odds ratio of ischemic stroke was 2.30 (1.91 to 2.76) in all people with migraine, 2.51 (1.52 to 4.14) in people who had migraine with aura, 1.29 (0.81 to 2.06) in people who had migraine without aura, and 2.89 (2.42 to 3.45) in female migraine patients.

The results of the above studies show that the risk of ischemic stroke in people who have migraine with aura is increased approximately two-fold, the risk is further increased in young women, smokers, and oral contraceptive users. However, the absolute annual incidence of ischemic stroke in women younger than 45 years is extremely low at 5 to 10 per 100,000 population.<sup>6)</sup> Further accumulation of studies is necessary to arrive at a conclusion of whether migraine alone is a clinically significant risk factor of cerebrovascular diseases.

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- **Search terms and secondary sources**

- Search database: PubMed (2011/9/14)  
migraine and risk and (stroke or cerebrovascular or infarction or infarct or hemorrhage) 798

## Is it safe for migraine patients to use low-dose oral contraceptives?

### Recommendation

Estrogen-containing oral contraceptives are in principle contraindicated in women who have migraine with aura, and other contraceptive methods are recommended. Although these oral contraceptives are not contraindicated in women who have migraine without aura, caution has to be exercised in administration and observation is necessary.

**Grade B**

### Background and Objective

Hormonal contraception is one of the most effective contraception methods, and include low-dose combined oral contraceptive (OC) containing estrogen and progestogen, 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 gynecological 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 are 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.<sup>1)</sup> 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.<sup>2)</sup> Use of OC may aggravate preexisting headache or induce new onset of headache.<sup>3)</sup> 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.<sup>3)</sup>

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<sup>4)</sup> and estrogen supplementation during the pill-free period have been used.<sup>5)</sup>

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 oral contraceptive 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).<sup>6)</sup> A prospective 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.<sup>7)</sup>

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.<sup>8)-11)</sup>

In a metaanalysis 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.<sup>12)</sup> The current WHO medical eligibility criteria for

contraceptive use (WHOMEA) classifies migraine with local neurological signs as category 4 (unacceptable health risk),<sup>13)</sup> and the UK eligibility criteria for contraceptive use (UKMEC) published by the Faculty of Family Planning and Reproductive Health Care (FFPRHC) also classified migraine with aura as category 4 (unacceptable health risk) and a past history ( $\geq 5$  years ago) of migraine with aura as category 3 (risks outweigh advantages).<sup>14)</sup> In Japan, the package insert of OC also lists migraine with aura as a contraindication.

Other than barrier contraception method, the contraception methods that can be used for patients who have migraine with aura in Japan include copper-bearing IUD [both WHOMEA and UKMEC classify as category 1 (no restriction for use)] and levonorgestrel-releasing IUD [WHOMEA classifies as category 3 (risks outweigh advantages) for continuation, while UKMEC classifies as category 2 (advantages outweigh risks)]. When initiating OC in patients who had migraine without aura, the presence of other risk factors such as smoking, obesity, and ischemic attack has to be investigated. In the case of continuation of OC, attention has to be given to new onset of risk factors. When there is aggravation of attack frequency and intensity or new onset of aura or persistent headache, suspension of OC should be considered. WHOMEA classifies continuation in age  $\geq 35$  years 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.

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- 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  
(migraine TH or migraine AL) and (oral contraceptive TH or pill AL) 14  
(headache TH or headache AL) and (oral contraceptive TH or pill AL) 53

# 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) non-steroidal anti-inflammatory drugs (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) non-steroidal anti-inflammatory drugs (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 1 and 2).<sup>1)-9)</sup> 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 stratified treatment according to the severity of migraine.<sup>10)</sup> 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 three 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 counseling for patients having acute attacks, physicians have to provide tailor-made 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).

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- 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

**Table 1. Summary of evidence for acute treatment**

Drug	Quality of evidence	Scientific evidence	Clinical impression	Adverse effect	Recommendation grade	Efficacy group	Recommended dose
<b>Triptans</b>							
sumatriptan	I	+++	+++	occasional	A	1	50 mg/dose, 200 mg/day
sumatriptan (nasal spray)	I	+++	+++	occasional-frequent	A	1	20 mg/dose, 40 mg/day
sumatriptan (injection ampoule)	I	+++	+++	frequent	A	1	3 mg/dose, 6 mg/day
sumatriptan (self-injection)	I	+++	+++	frequent	A	1	3 mg/dose, 6 mg/day
sumatriptan (suppository)	I	+++	-	-	A**	1	-
sumatriptan (subcutaneous)	II	++	-	-	A**	1	-
zolmitriptan	I	+++	+++	occasional	A	1	2.5 mg/dose, 10 mg/day
zolmitriptan (nasal spray)	I	+++	-	-	A**	1	-
eletriptan	I	+++	+++	occasional	A	1	20 mg/dose, 40 mg/day
rizatriptan	I	+++	+++	occasional	A	1	10 mg/dose, 20 mg/day
naratriptan	I	+++	+++	occasional	A	1	2.5 mg/dose, 5 mg/day
naratriptan (injection)	I	+++	-	-	A**	1	-
almotriptan	I	+++	-	-	A**	1	-
frovatriptan	I	+++	-	-	A**	1	-
<b>Anxiolytics, antipsychotics, anesthetics, antiemetics</b>							
metoclopramide	I	+++	++	occasional	A**	2	5 mg/dose, 30 mg/day
metoclopramide (intramuscular/intravenous)	I	+++	++	occasional	A**	2	10 mg/dose, 20 mg/day
domperidone	II	++	++	occasional	A**	2	5 mg/dose, 30 mg/day
domperidone (suppository)	II	++	-	occasional	B**	4	60 mg/dose
prochlorperazine	I	+++	-	occasional-frequent	B**	4	5 mg/dose
prochlorperazine (intramuscular)	I	+++	-	occasional-frequent	B**	4	5 mg/dose
chlorpromazine	I	+++	-	occasional-frequent	B**	4	30 mg/dose
chlorpromazine (intramuscular)	I	+++	-	occasional-frequent	B**	4	10 mg/dose
droperidol (intramuscular)	II	++	-	occasional-frequent	C**	4	-
propofol (intravenous)	III	+	-	frequent	C**	4	-
diazepam (intramuscular/ intravenous)	III	+	-	frequent	C**	4	-
<b>Acetaminophen/NSAIDs</b>							
acetaminophen	I	+++	++	occasional	A	2	0.5 (-10) g/dose, 1.5 (-4) g/day
aspirin	I	+++	++	occasional	A	2	330 mg/dose, 990 mg/day
ibuprofen	I	+++	++	occasional	A**	2	100-200 mg/dose, 600 mg/day
diclofenac	I	+++	++	occasional	A*	2	25-50 mg/dose, 75-100 mg/day
naproxen	I	+++	++	occasional	A**	2	100-300 mg/dose, 300-600 mg/day
etodolac	II	++	++	occasional	A**	2	100-200 mg/dose, 400 mg/day
celecoxib	II	++	++	rare-occasional	A**	2	100-200 mg/dose, 400 mg/day
mefenamic acid	II	++	++	occasional	A	2	250-500 mg/dose, 1,500 mg/day
zaltoprofen	III	+	++	occasional	A**	2	80-160 mg/dose, 240 mg/day
pranoprofen	III	+	++	occasional	A**	2	75-150 mg/dose, 225 mg/day
loxoprofen	III	+	++	occasional	A*	2	60-120 mg/dose, 240 mg/day
lornoxicam	III	+	++	occasional	A**	2	4-8 mg/dose, 24 mg/day

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/day, up to 10 tablets/week, combined use with triptans contraindicated
dihydroergotamine	II	++	++	frequent	B	4	1 mg/dose, 3 mg/day, combined use with triptans contraindicated
Steroids							
dexamethasone (intravenous)	III	+	++	occasional	C**	3	2–8 mg/dose
hydrocortisone	III	+	++	occasional	C**	3	200–500 mg/dose
Others							
tramadol	III	+	-	occasional-frequent	C**	4	100 mg/dose, 300 mg/day
tramadol-acetaminophen combination	III	+	-	occasional-frequent	C**	4	1 tablet/dose, 4 tablets/day
tramadol (intramuscular)	III	+	-	occasional-frequent	C**	4	
magnesium preparation	III	+	-	rare	C**	2	

### Quality of evidence

I. Evidence from systematic review or meta-analysis, or from at least one randomized controlled trial

II. Evidence from non-randomized 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.

\*Covered by health insurance as off-label use for migraine

\*\*Not covered by health insurance.

Drugs not currently available in Japan are written in italics

**Table 2. Acute medications categorized by efficacy**

Group 1 (effective)	Group 2 (somewhat effective)	Group 3 (empirically effective)	Group 4 (effective, beware of adverse effects)	Group 5 (not effective)
<b>Triptans</b>	<b>Antiemetics</b>	<b>Steroids (intravenous infusion)</b>	<b>Anxiolytics, antipsychotics, anesthetics, antiemetics</b>	
sumatriptan	metoclopramide**	dexamethasone**	domperidone (suppository)**	
sumatriptan (nasal spray)	metoclopramide (intramuscular) **	hydrocortisone**	prochlorperazine**	
sumatriptan (injection ampoule)	metoclopramide (intravenous) **		prochlorperazine (intramuscular) **	
sumatriptan (self-injection)	domperidone**		chlorpromazine**	
<i>sumatriptan (suppository)**</i>	<b>Acetaminophen/NSAIDs</b>		chlorpromazine (intramuscular) **	
<i>sumatriptan (subcutaneous)**</i>	acetaminophen		droperidol (intramuscular) **	
zolmitriptan	aspirin		propofol (intravenous) **	
<i>zolmitriptan (nasal spray)</i>	ibuprofen**		diazepam (intramuscular/ intravenous) **	
eletriptan	diclofenac*		<b>Ergotamines</b>	
rizatriptan	naproxen**		ergotamine-caffeine combination	
naratriptan	etodolac**		ergotamine-caffeine-pyrene combination	
<i>naratriptan (injection)**</i>	celecoxib**		dihydroergotamine	
<i>almotriptan**</i>	mefenamic acid		<b>Others</b>	
<i>frovatriptan**</i>	zaltoprofen**		tramadol**	
	pranoprofen**		tramadol-acetaminophen combination**	
	loxoprofen*		tramadol (intramuscular) **	
	lornoxicam**			
	<b>Others</b>			
	magnesium preparation**			

\*Covered by health insurance as off-label use for migraine

\*\*Not covered by health insurance.

Drugs not currently available in Japan are written in italics

## 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 not be effective.

**Grade A**

### Background and Objective

Regarding the timing of using triptan uses, previous reports and use experience have demonstrate that the maximum effect is obtained generally when taken in the early stage of migraine attack. This section verifies the evidence for this observation. In addition, the effects of triptans when taken during the premonitory phase and aura phase before headache attack occurs are also verified.

### Comments and Evidence

Various studies that examined the use of triptans during migraine attack have reported that triptans are effective when taken as early as possible after the onset of attack.<sup>1)-9)</sup> Among them, the Act when Mild (AwM) study was a randomized controlled trial (RCT) with 491 migraine patients taking almotriptan 12.5 mg when pain intensity was mild and in early headache onset or when pain had become moderate or severe. The results indicate that triptan is most effective if taken when migraine pain is still mild or within one hour of onset. Further analyses indicate that when the timing of taking triptan is missed, allodynia may occur concomitantly, which greatly worsens the effect.<sup>10)-12)</sup>

There are few reports on the effectiveness of oral triptan taken in the premonitory phase or aura phase, and therefore a clear conclusion is yet to be arrived. There are reports showing that use of sumatriptan subcutaneous injection, zolmitriptan tablet, and eletriptan tablet in the aura phase is not effective. While it is generally accepted that triptans should be taken when headache is still mild, the relationship with aura remains clear, and they are anticipated to be ineffective when taken in the aura or premonitory phase.<sup>13)14)</sup>

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- **Search terms and secondary sources**

- Search database: PubMed (2011/11/19)
  - migraine & {triptan} & {early} 74
  - migraine & {timing} & {trial} 11 or {randomized} 0
  - migraine & {treatment} & {triptan} 515
  - migraine & {treatment} & {triptan} & {preference} 22 or {comparison} 27
  - migraine & {treatment} & {triptan} & {aura} 52

## 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**

### Background and Objective

When using triptans in the clinical setting, differences in efficacy among various triptans, and differences in effect among individual patients are often experienced. Given these differences and patients' preference, this section examines whether there are rational selection methods among multiple triptans.

### Comments and Evidence

Triptans are a group of selective serotonin receptor agonists, but the pharmacological characteristics of individual triptans vary (Table 1) and the effects also differ depending on individual patients. Therefore, detailed comparison of various triptans is necessary, which would provide a basis for selecting the best triptan for individual patient. However, to date, few precise studies with adequate numbers of patients have been conducted. Moreover, there is no report comparing all the available triptans. Currently, seven types of triptan are being used in overseas countries, but only five types (only sumatriptan has oral, nasal spray, and subcutaneous injection formulations) are available in Japan. Regarding the pharmacokinetic characteristics of triptans as shown in Table 1, the time to reach maximum blood concentration ( $T_{\max}$ ) is approximately within 1 to 2 hours for all oral triptans, except zolmitriptan and naratriptan. Moreover,  $T_{\max}$  is approximately 0.2 hour for sumatriptan injections (especially, 0.18 hour for self-injection). Sumatriptan injection is effective in patients with status migrainosus or in patients who have missed the timing of taking oral triptan, while sumatriptan nasal spray is useful in patients with nausea or vomiting, who have difficulties taking oral triptan. Most triptans have half-life of elimination ( $T_{1/2}$ ) of 1.5-3 hours, and only naratriptan has a long  $T_{1/2}$  of 5.05 hours. Therefore, this drug can be considered for recurrent migraine attacks and menstrual migraine. Patient preference for certain triptan is experienced clinically, but scientific evidence is limited to small-scale studies.<sup>1)-8)</sup>

**Table 1. Pharmacokinetics of triptans**

Generic name	Formulations	Dose (mg)	$T_{\max}$ (hour)	$T_{1/2}$ (hour)
sumatriptan	tablet	50	1.8	2.2
	nasal spray	20	1.3	1.87
	injection (ampoule)	3	0.21	1.46
	self-injection	3	0.18	1.71
zolmitriptan	tablet	2.5	3.0*	2.4 <sup>†</sup>
	orally fast dissolving tablet	2.5	2.98*	2.9 <sup>†</sup>
eletriptan	tablet	20	1.0	3.2
rizatriptan	tablet	10	1.0	1.6
	orally fast dissolving tablet	10	1.3	1.7
naratriptan	tablet	2.5	2.68	5.05

$T_{\max}$ : time to reach maximum blood concentration;  $T_{1/2}$ : half-life of elimination; \*: median; <sup>†</sup>: mean (Pharmacokinetics of the drugs are extracted from package inserts used in Japan)

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## • Search terms and secondary sources

- Search database: PubMed (2011/10/21)  
migraine & {treatment} & {triptan} 515  
& {preference} 22 OR {comparison} 27

## When and how are non-oral formulations of triptans used for the treatment of migraine?

### Recommendation

As acute treatment for migraine, non-oral 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)

### Background and Objective

Non-oral formulations of triptans (selective serotonin agonists) were developed as specific treatment for acute migraine attacks. Among the non-oral formulations of triptan, the effectiveness differs among injection, nasal spray, suppository and transdermal patch (suppository and transdermal formulation are not marketed in Japan as of March 2013). This section examines the evidence concerning the rational selection method and effects of the non-oral triptans.

### Comments and Evidence

Currently, only two non-oral formulations of triptan are available in Japan: they are sumatriptan injection and sumatriptan nasal spray. In overseas countries, naratriptan injection, zolmitriptan nasal spray, sumatriptan transdermal patch, and sumatriptan suppository are being used.<sup>1)-10)</sup>

Non-oral triptans are effective for severe migraine attacks, and are particularly useful when severe migraine attacks seriously impairs daily and social living, or when frequent vomiting and other symptoms impede oral administration resulting in poor headache control. Especially, injection, nasal spray, transdermal patch and suppository are indicated in patients with severe migraine attacks causing severe disability in daily and social living or patients with frequent vomiting and other gastrointestinal disturbances that render oral administration difficult resulting in poor headache control. Randomized controlled trials (RCT) have been conducted on individual formulations and effectiveness has been proven.<sup>1)-10)</sup> However, for the recently developed transdermal formulations, adequate evidence is not yet available.<sup>1)</sup> (See also CQ in Appendix “Guideline on self-injection of sumatriptan at home”)

**Table 1. Pharmacokinetics of non-oral triptan formulations**

	Dose	T <sub>max</sub> (hour)	T <sub>1/2</sub> (hour)
sumatriptan (nasal spray)	20 mg	1.3	1.87
sumatriptan (subcutaneous)	3 mg	0.21	1.46
sumatriptan (self-injection)	3 mg	0.18	1.71
sumatriptan (suppository)	25 mg	1.5	1.8
sumatriptan (transdermal)	120 mg	1.7	2.9
zolmitriptan (nasal spray)	2.5 mg	2.7–3	2.82–2.9

T<sub>max</sub>: time to reach maximum blood concentration; T<sub>1/2</sub>: half-life of elimination. Sumatriptan suppository and transdermal patch, and zolmitriptan nasal spray are currently not available in Japan.

(Pharmacokinetics of the drugs are extracted and partially modified from package inserts and reference No. 5)

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## • Search terms and secondary sources

- Search database: PubMed (2011/12/21)
- {Migraine & randomized controlled trial 1669}
- & sumatriptan 318
- & injection or subcutaneous 61}
- & nasal or spray 20
- & rectal 17
- & transdermal 4

## 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**

### Background and Objective

Migraine with brainstem aura and hemiplegic migraine are associated with intracranial vasoconstriction, which is assumed to cause aura and the associated symptoms. Literature was searched for the management of the acute phase of these types of migraine.

### Comments and Evidence

There are no specific acute-phase treatments for migraine with brainstem aura and hemiplegic migraine. The main approach is symptomatic treatment, in the same manner as acute treatment for migraine.<sup>1)2)</sup>

However, triptans and ergotamines are considered contraindicated, and their use cannot be supported actively. This is because pathophysiological hypothesis and pharmacological mechanism as well as experimental results suggest that vasoconstriction caused by triptans may exacerbate the clinical symptoms.

A case series reported that episodic use of triptans for migraine with brainstem aura was useful.<sup>3)</sup> In addition, a retrospective study in patients with hemiplegic migraine reported that triptans were a safe and effective treatment.<sup>4)</sup> There are no reports of clinically serious adverse events following actual use of triptans. Further accumulation of evidence is necessary.

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- Search database: PubMed (2011/8/27)
- Basilar migraine 3732
- & treatment 1430
- acute 286
- Hemiplegic migraine
- & Management 21
- Hemiplegic migraine 655
- & treatment 153
- acute 26

## 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**

### Background and Objective

Oral ergotamine-caffeine combination (Cafergot) had long been used as a specific treatment for migraine, but nausea occurs commonly and warning has been raised on the adverse events from long-term overuse. Since the advent of triptans, comparative studies consistently showed inferior effectiveness of Cafergot compared with triptans, and the role of this medication as a specific treatment becomes limited. Currently, the manufacturing and marketing of Cafergot have been discontinued in Japan, and ergotamine-caffeine-isopropylantipyrene combination (Clearmine) and dihydroergotamine are the only ergotamine preparations available in Japan.

### Comments and Evidence

Oral ergotamine and ergotamine-caffeine combination (Cafergot) had been used as an acute treatment for migraine attacks for over thirty years. However, there are few placebo-controlled clinical studies, and the results of effectiveness have been inconsistent.<sup>1)</sup> Randomized controlled trials (excluding injection) comparing with other drugs include 6 studies with triptans,<sup>2)-5)</sup> 6 studies with NSAIDs,<sup>6)-9)</sup> and 2 studies with aspirin.<sup>10)</sup> Compared with ergotamine, triptans improve symptoms more rapidly and are superior in improving associated symptoms. However, relapse within 48 hours was fewer with Cafergot treatment when compared with sumatriptan.<sup>2)</sup> When compared with NSAIDs, Cafergot is equivalent in effectiveness as tolafenamic acid<sup>6)</sup> but is inferior to naproxen,<sup>7)</sup> diclofenac, ketoprofen,<sup>8)</sup> piroprofen,<sup>9)</sup> and aspirin,<sup>10)</sup> while adverse effects were equivalent or more frequent in vomiting. By the time when headache becomes moderate to severe, oral administration of ergotamine combination is no longer effective. Some patients may respond to early treatment; but when treatment fails, triptan cannot be used within 24 hours as a rescue drug. Hence, use of ergotamines is very limited. Since ergotamine has oxytocic and vasoconstriction effects, continued use during pregnancy carries high risk. In the package insert and according to the US FDA, ergotamine is contraindicated during pregnancy. Furthermore, ergotamine-caffeine-isopropylantipyrene combination (Clearmine) is rated a score of 2 or 3 (score 3 for continued use) according to the Toranomon Hospital Drug Teratogenicity Risk Evaluation Criteria (6-point scale from scores 0 to 5).<sup>11)</sup> Ergotamine is contraindicated also during breast-feeding.

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- **Search terms and secondary sources**

- Search database: PubMed (2011/11/4)  
migraine and ergotamine and randomized and controlled 63

## Are acetaminophen and non-steroidal 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**

### Background and Objective

Acetaminophen is one of the frequently used over-the-counter (OTC) medications. Non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin are also commonly used both prescription and OTC medications. This section verifies whether acetaminophen and NSAIDs are effective acute treatments for migraine.

### Comments and Evidence

Acetaminophen and NSAIDs monotherapies are safe and inexpensive, and have been found to be effective for mild to moderate migraine attacks not requiring consultation of a medical facility. However, since migraine patients consult medical facilities when response to OTC drugs is diminished or when headache is severe, early treatment with triptans should be considered for these patients. Many randomized controlled trials (RCTs) and Cochrane reviews on acetaminophen and NSAIDs have been reported, and their effectiveness has been proven (grade A recommendation).

The grade of recommendation for each medication does not indicate the strength of effectiveness. The “quality of evidence” differs depending on the number of RCT reports (see Table 1, page 90).

I: acetaminophen,<sup>1,2)</sup> aspirin,<sup>3)</sup> ibuprofen,<sup>4)</sup> diclofenac,<sup>5)</sup> and naproxen<sup>6)</sup>

II: etodolac,<sup>7)</sup> ketoprofen,<sup>8)</sup> celecoxib,<sup>9)</sup> and mefenamic acid<sup>10)</sup>

III: loxoprofen, zaltoprofen, pranoprofen, lornoxicam, others

Concerning the doses, acetaminophen 600 mg and 1,000 mg, which are the usual doses used overseas,<sup>1,2)</sup> are increasingly being used also in Japan in recent years. On the other hand, since acetaminophen may cause hepatopathy, NSAIDs may cause gastrointestinal bleeding, and overuse of acetaminophen or NSAIDs may induce headache and other effects, it is essential to consider carefully the dosage, use frequency and method of drug taking, and to provide patient guidance.

Aspirin 1,000 mg is an effective acute treatment for migraine, and adding metoclopramide 10 mg attenuates nausea and vomiting.<sup>3)</sup>

Ibuprofen at both doses of 200 mg and 400 mg significantly reduces the severity of headache after 2 hours. Moreover, the 400 mg dose was effective against scintillating scotoma and tinnitus.<sup>4)</sup>

Diclofenac 50 mg was demonstrated to mitigate acute migraine attacks and also the associated symptoms, and the adverse effects were mild or treatable.<sup>5)</sup>

Naproxen 750 mg significantly increased the headache improvement rate after 2 hours compared with placebo, but because various adverse events may occur when used to treat moderate to severe migraine, caution has to be exercised during use.<sup>6)</sup> A comparison of paracetamol (acetaminophen) 1,000 mg, etodolac 400 mg and etodolac 800 mg for the treatment of acute migraine attacks revealed comparable efficacy in the three groups.<sup>7)</sup> A comparison of ketoprofen (75 mg and 150 mg) with placebo and zolmitriptan 2.5 mg reported similar efficacy of ketoprofen and zolmitriptan.<sup>8)</sup> Gastrointestinal symptoms are class adverse effects of NSAIDs, but use of cyclooxygenase-2 inhibitor (celecoxib) is expected to reduce gastrointestinal symptoms.<sup>9)</sup> Mefenamic acid 500 mg monotherapy was reported to be effective against menstrually related migraine, compared to placebo.<sup>10)</sup>

Empirically, the propionic acid derivatives (including loxoprofen, zaltoprofen, and pranoprofen) and oxicam derivatives (including lornoxicam and meloxicam) of NSAIDs are sometimes effective for migraine attacks, but there is no report at RCT level.

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## • Search terms and secondary sources

- Search database: PubMed (2013/1/25)
  - Migraine & randomized controlled trial 1714
  - Migraine & randomized controlled trial & NSAIDs 211
  - Migraine & randomized controlled trial & aspirin 70
  - Migraine & randomized controlled trial & acetaminophen 55
  - Migraine & randomized controlled trial & ibuprofen 34
  - Migraine & randomized controlled trial & naproxen 29
  - Migraine & randomized controlled trial & indomethacin 20
  - Migraine & randomized controlled trial & diclofenac 18
  - Migraine & randomized controlled trial & ketoprofen 6
  - Migraine & randomized controlled trial & mefenamic acid 3
  - Migraine & randomized controlled trial & celecoxib 1
  - Migraine & randomized controlled trial & etodolac 1

## 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 nonsteroidal anti-inflammatory drugs (NSAIDs) is useful.

**Grade B**

### Background and Objective

Nausea, vomiting and delayed gastrointestinal absorption occur in the acute phase of migraine. These associated symptoms, together with headache, are factors that worsen the patients' QOL. In addition, these symptoms also affect the taking and absorption of acute treatment drugs. Treatment of migraine with antiemetics alone has also been attempted. This section reviews the evidence of antiemetics as an acute treatment for migraine.

### Comments and Evidence

Placebo-controlled studies of metoclopramide administered intravenously,<sup>1)</sup> and of prochlorperazine administered intravenously, intramuscularly and transrectally (by suppository)<sup>2)</sup> have demonstrated that these formulations are efficacious. In another study, intramuscular metoclopramide did not differ from placebo in improving migraine, but significantly improved nausea.<sup>3)</sup> Domperidone 30 mg taken orally during the aura phase before migraine attack was significantly superior to placebo in controlling the attack.<sup>4)</sup> In comparative studies between intravenously administered antiemetics, prochlorperazine 10 mg was more effective than metoclopramide 10 mg,<sup>5)</sup> while prochlorperazine 10 mg and metoclopramide 20 mg,<sup>6)</sup> as well as chlorpromazine (0.1 mg/kg) and metoclopramide (0.1 mg/kg) were equivalent in efficacy.<sup>7)</sup> In a comparative study of intramuscular metoclopramide 10 mg versus prochlorperazine 10 mg for acute migraine, prochlorperazine was more effective but the results showed that antiemetics when used as alone are not adequate for pain relief.<sup>8)</sup> When compared with subcutaneous injection of sumatriptan 6 mg, intravenous prochlorperazine 10 mg + diphenhydramine 12.5 mg was more effective,<sup>9)</sup> whereas intravenous metoclopramide 20 mg was similarly effective.<sup>10)</sup> Intramuscular sumatriptan 6 mg and intravenous chlorpromazine 12.5 to 37.5 mg were equally efficacious.<sup>11)</sup> However, intravenous injections of prochlorperazine and chlorpromazine are currently not available in Japan.

In a study of antiemetic combination therapy in migraine patients who failed to achieve adequate relief from sumatriptan 50 mg alone, each patient took additional metoclopramide 10 mg or placebo during two consecutive moderate to severe migraine attacks, and the intensity of headache was compared before and after the oral treatment. Headache was improved in 10 of 16 migraine patients (63%) treated with sumatriptan plus metoclopramide combination compared with 5 (31%) patients treated with sumatriptan plus placebo. There was no difference in adverse effects compared with placebo. Hence, combining metoclopramide with triptan was useful in migraine patients who failed to achieve adequate pain relief from triptan alone.<sup>12)</sup> In addition, combining antiemetic with ergotamine<sup>13)</sup> or with acetaminophen<sup>14)</sup> also improves headache intensity and gastrointestinal symptoms during the acute phase of migraine.

From the above findings, intravenous metoclopramide, which is a central and peripheral antiemetic widely used in Japan, is recommended as the first-choice antiemetic (grade A recommendation). As the second choice, intramuscular prochlorperazine is recommended considering the antiemetics available in Japan (grade B recommendation). All antiemetics have limited efficacy when used alone, and therefore combined use with other acute treatment drugs is recommended.

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## • Search terms and secondary sources

- Search database: PubMed (2012/1/27)  
 {migraine} OR {vascular headache} OR {hemicrania} 69051  
 & metoclopramide 289  
 & prochlorperazine 101  
 & domperidone 46  
 & chlorpromazine 71

## What other acute treatment drugs for migraine are available?

### Recommendation

As acute treatments for 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, magnesium, tramadol, and tramadol-acetaminophen combination: C)

### Background and Objective

Many drugs have been used empirically with the expectation to abort an acute migraine attack. However, the mechanisms of action remain unknown for many of these drugs. On the other hand, clarification of the therapeutic effects of novel agents may contribute to further elucidation of the pathophysiology of migraine. From this field in which establishment of new EBM may be expected, this section focuses on those drugs that can be used by clinical doctors, such as dexamethasone, magnesium, and tramadol.

### Comments and Evidence

Intravenous corticosteroid (dexamethasone)<sup>(1)-5)</sup> is not likely to become the first-choice acute treatment drug for migraine, because there is no adequate evidence at randomized controlled trial (RCT) level and some RCT conducted in recent years reported no significant difference when used as acute treatment for migraine. On the other hand, there are also studies showing a significant difference in preventing recurrence of migraine attack within several days compared to standard treatment,<sup>2)</sup> and a reduction in the rate of recurrence.<sup>5)</sup> Moreover, intravenous magnesium may be considered for use as an acute treatment,<sup>(6,7)</sup> but there is no adequate scientific evidence and its use is not covered by health insurance in Japan.

Intramuscular tramadol (Tramal Injection), tramadol capsule (Tramal Capsule), and oral tramadol-acetaminophen combination (Tramcet Combination Tablet) are useful. However, due to adverse effects of nausea and vertigo (especially for injection) and the issue of medication-overuse headache induced by analgesic combinations, tramadol is not the first-choice drug at the present time. Use of tramadol, a weak opioid, as acute treatment has been reported. To date, a randomized blinded study comparing intramuscular tramadol and intramuscular diclofenac,<sup>8)</sup> a randomized placebo-controlled study of intravenous tramadol,<sup>9)</sup> and a randomized double-blind study of tramadol-acetaminophen combination<sup>10)</sup> have been conducted, and the effectiveness of tramadol has been reported. However, due to adverse reactions such as nausea and vertigo as well as the issue of medication-overuse headache induced by weak opioid and analgesic combinations, there is an opinion that their use for migraine should be limited to patients who cannot use triptans due to ischemic heart diseases or other reasons.<sup>11)</sup> Furthermore, the risk of inducing serotonin syndrome or seizures by combined use with tricyclic antidepressants or selective serotonin reuptake inhibitors (SSRIs) has been reported. Caution has to be exercised when used as prophylactic treatment for migraine.<sup>12)</sup>

Evidence (evidence level: I) has been accumulated for intravenous, intramuscular, suppository, and combination formulations of prochlorperazine (a phenothiazine antipsychotic) based on the experience of use in emergency rooms (ER) overseas.<sup>13)-15)</sup> In Japan, prochlorperazine is indicated for nausea and vomiting before and after surgery, and its use in severe vomiting associated with headache may be considered. Similarly, occasional reports have indicated the effectiveness of the anesthetic propofol,<sup>16)</sup> but propofol for migraine is currently not approved for health insurance coverage in Japan.

Research is on-going to study novel acute treatment drugs currently being developed, including calcitonin gene-related peptide receptor (CGRP) antagonists, transient receptor potential cation channel subfamily V member 1 (TRPV1) antagonists, and serotonin receptor agonists.<sup>17)</sup>

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- Search database: PubMed (2011/12/26)
- Migraine & randomized controlled trial 1668
- Migraine & randomized controlled trial & steroid 43
- Migraine & randomized controlled trial & dexamethasone 9
- Migraine & randomized controlled trial & magnesium 19
- Migraine & randomized controlled trial & prochlorperazine 24
- Migraine & randomized controlled trial & tramadol 17



## 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

### Background and Objective

Status migrainosus is a severe migraine attack lasting for more than 72 hours, occurring in a patient who has “migraine without aura” (International Classification of Headache Disorders 3rd Edition beta version (ICHD-3beta): 1.4.1 *Status migrainosus*). Even when the severity does not reach status migrainosus, many patients with severe migraine attacks present at the emergency outpatient department. Due to the strong headache and vomiting, history taking is often difficult. At presentation, first of all investigations for dangerous secondary headaches such as subarachnoid hemorrhage should be carried out. Treatment can be started after confirming the general condition.

### Comments and Evidence

Although there are no large-scale or double-blind studies on status migrainosus, various drugs such as dihydroergotamine,<sup>1)</sup> droperidol,<sup>2)</sup> corticosteroids,<sup>3)</sup> lidocaine,<sup>1)</sup> and intravenous valproic acid<sup>4)</sup> have been used as empirical treatments. There are several randomized controlled trials (RCTs) on acute treatment for migraine in the emergency outpatient setting. Placebo-controlled studies of intravenous metoclopramide,<sup>5)</sup> as well as intravenous, intramuscular and transrectal (by suppository)<sup>6)</sup> prochlorperazine have demonstrated that these drugs are efficacious. When compared with subcutaneous injection of sumatriptan 6 mg, intravenous prochlorperazine 10 mg + diphenhydramine 12.5 mg was more effective,<sup>7)</sup> while intravenous metoclopramide 20 mg<sup>8)</sup> was equally effective. Intramuscular sumatriptan 6 mg and intravenous chlorpromazine 12.5 to 37.5 mg were almost equivalent in efficacy.<sup>9)</sup> However, prochlorperazine and chlorpromazine for intravenous injection are currently not available in Japan. When intramuscular droperidol 0.1 mg, 2.75 mg, 5.5 mg and 8.25 mg was compared with placebo, the headache improvement rates after 2 hours were significantly higher with droperidol 2.75 mg, 5.5 mg and 8.25 mg.<sup>10)</sup> Intramuscular droperidol 2.5 mg had the same efficacy as intramuscular pethidine (1.5 mg/kg).<sup>11)</sup> Regarding adverse effects, droperidol does not cause hypotension, but may induce akathisia or sedation, which requires attention. Although rare, droperidol is associated with the risk of dose-dependent QTc prolongation and torsades de pointes, which prompted the US FDA to issue a black-box warning to the label of droperidol.<sup>12)</sup> Use of droperidol should be limited to cases where other drugs are not effective. In European and American countries, dihydroergotamine injection has been evaluated as a highly effective acute treatment for severe migraine. One RCT<sup>13)</sup> showed that dihydroergotamine 1 mg and subcutaneous sumatriptan 6 mg were similarly effective for moderate to severe headache, but the recurrence rate was higher with sumatriptan and the dose may increase in patients with recurring headache. Intravenous valproic acid 500 mg (currently not approved in Japan) was equally effective as intravenous dihydroergotamine 1 mg + intravenous metoclopramide 10 mg,<sup>14)</sup> and was inferior to intravenous prochlorperazine 10 mg.<sup>15)</sup> However, dihydroergotamine and valproic acid for intravenous injection are currently not available in Japan. Pethidine was reported to be effective in a placebo-controlled study,<sup>16)</sup> but in a meta-analysis using 11 studies conducted by Friedman et al.,<sup>17)</sup> pethidine was less effective than dihydroergotamine, tended to be less effective than antiemetics, and was similar to the NSAID ketorolac. When weighing effectiveness against adverse effects such as sedation and vertigo, carefully consideration has to be given when prescribing pethidine. Intravenous dexamethasone

10 to 24 mg has been reported to be effective in one<sup>18)</sup> and ineffective in other studies<sup>19)-22)</sup> for preventing recurrence of migraine. Although the number of cases was small, a meta-analysis of 7 studies with a total of 742 subjects conducted by Singh et al.<sup>23)</sup> found dexamethasone to be effective in preventing recurrence of migraine, with a 9.7% reduction in relative risk after 24 to 72 hours.<sup>23)</sup> A RCT of dexamethasone as acute treatment for migraine in the emergency department suggested that dexamethasone was effective to a certain extent in patients with status migrainosus although there was no significant difference compared with placebo.<sup>20)</sup>

Based on the above findings, in patients with status migrainosus, first rule out secondary headaches while securing the intravenous line and starting fluid replacement. Considering the agents available in Japan, administer subcutaneous injection of sumatriptan together with an antiemetic of intravenous metoclopramide or intramuscular prochlorperazine. When recurrence of migraine is a concern, consider using intravenous dexamethasone.

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- **Search terms and secondary sources**

- Search database: PubMed (2012/4/30)
  1. "status migrainosus" 57  
& treatment 49  
& management 7  
& randomized control trial 0
  2. migraine & (refractory or intractable or "very severe") 496  
& (treatment or management) 450  
& (treatment or management) & randomized control trial 2
  3. migraine & emergency 559  
& randomized control trial 17
- One reference added by manual search (No. 12)

## How should migraine be treated (acute and prophylactic) during pregnancy and breast-feeding?

### 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 use 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**

### Background and Objective

Migraine is prevalent in women of reproductive age. “How should migraine be treated during pregnancy or breast-feeding?” is a frequently asked question from patients.

Literature was searched to identify the characteristics of migraine during pregnancy and breast-feeding, and the usefulness and safety when conducting pharmacotherapy.

### Comments and Evidence

Migraine tends to improve from the first to third trimester of pregnancy. In the third trimester, migraine attacks are alleviated in 60-80% of the patients.<sup>1)-3)</sup> The degree of improvement is lower in patients who have migraine with aura than in those who have migraine without aura.<sup>4)-6)</sup> In over one-half of the patients, migraine recurs within one month postpartum. Some studies indicated no difference in the frequency and severity of headache between breast-feeding and bottle-feeding,<sup>3)</sup> while others suggested possible inhibition of migraine recurrence by breast-feeding.<sup>1)</sup> At least, breast-feeding presumably does not aggravate migraine. An increasing number of reports indicate a higher risk of stroke during pregnancy and pregnancy-related hypertension in migraine patients,<sup>7)-9)</sup> but most are case-control studies and large-scale prospective studies are awaited.

In general, the risk associated with drug use during pregnancy depends on the risk of the drug per se and also the duration of use. Since there is no effect from the first day of the last menstruation to the 27<sup>th</sup> day, taking migraine medications several times during this period does not pose a concern. Because the first trimester, especially during the 4<sup>th</sup> to 11<sup>th</sup> week of pregnancy, is the organogenetic period, use of medications should be avoided if possible. After the 12<sup>th</sup> week, there is no teratogenic risk, but fetal functional disturbance and fetal toxicity are issues. Although the safety of medications for acute migraine attacks in pregnant women has not been established, acetaminophen is widely used empirically and is recommended in published guidelines.<sup>10)11)</sup> Because bleeding tendency in mother and neonate associated with aspirin as well as Botallo ductal constriction or occlusion associated with NSAIDs have been reported, these drugs should be avoided especially during the third trimester.<sup>12)</sup> Due to the oxytocic effect of ergotamine leading to a risk of preterm birth, this drug is contraindicated during pregnancy as stated in the package insert and the US FDA guidelines. Among the antiemetics, metoclopramide is rated as “benefits justify potential risks” and is relatively widely used for hyperemesis in Japan, and adverse effect on the fetus has been ruled out.<sup>13)</sup> For domperidone, teratogenicity has been reported from animal experiments and this drug is described as contraindicated for pregnant women in the package insert. As for the safety of triptans, post-marketing surveys have reported no increase in risk of fetal teratogenicity associated with the use of sumatriptan, naratriptan and rizatriptan during the first trimester of pregnancy.<sup>14)15)</sup> Other than the post-marketing surveys, the largest number of reports was on the use of sumatriptan during pregnancy, and the conclusion is that use of sumatriptan during early-stage pregnancy does not increase the risk of fetal teratogenicity.<sup>16)</sup> For other triptans also, larger cohort studies have indicated no greatly increased risk of fetal teratogenicity from use in early-stage pregnancy, and have reported no serious effect on the outcome of pregnancy.<sup>17)18)</sup>

For prophylactic therapy during pregnancy, the antiepileptic drug valproic acid is the most high-risk drug for the fetus, and caution is always required when used in women of reproductive age. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB) have been reported to cause fetal circulatory disturbance when used in the second and third trimesters of pregnancy.<sup>12)</sup> Calcium channel blockers are also contraindicated in the first trimester of pregnancy. When prophylactic medication is necessary during pregnancy, beta-blocker, especially propranolol, is an option based on experience.<sup>10)</sup>

As for the use of triptans during breast-feeding, after subcutaneous injection of sumatriptan 6 mg, approximately 3.5% of the maternal dose is passed into breast milk. Given that oral bioavailability is 14%, the dose transferred to breast milk is estimated to be around 0.5%.<sup>19)</sup> In a statement of the American Academy of Pediatrics, sumatriptan is considered a drug that is compatible with breast-feeding.<sup>20)</sup> According to a report from the manufacturer, in 8 women given a single dose of eletriptan 80 mg, 0.02% of the mean total dose of eletriptan is transferred to breast milk 24 hours after administration.<sup>21)</sup> According to the drug risk classification in “Medications and Mothers’ Milk 14<sup>th</sup> edition”,<sup>22)</sup> only eletriptan is classified as level 2 (relatively safe), while other triptans are classified as level 3 (moderately safe).<sup>22)</sup> The package inserts contain descriptions that breast-feeding should be avoided for 12 hours after taking sumatriptan and breast-feeding should be avoided after taking other triptans. For the other medications, their use should be considered on an individual basis, referring to specialized books and internet sites where necessary.<sup>12)22)-24)</sup> In Japan, the “Japan Drug Information Institute in Pregnancy” website<sup>25)</sup> of the National Center for Child Health and Development as a project of the Ministry of Health, Labour and Welfare provides useful reference.

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- Search database: PubMed (2011/8/11)
  - 1.Migraine
  - 2.1 & {pregnancy} 626
  - 3.1 & {lactation} or {breast feeding} 52
  - 4.2 & treatment 352
  - 5.3 & treatment 40
  - 6.2 & prophylaxis 73
  - 7.3 & prophylaxis 13
- Search database: Ichushi Web for articles published in Japan  
(migraine/TH or migraine/AL) and (pregnancy/TH) or pregnancy/AL) 45  
(migraine/TH or migraine/AL) and (lactation/TH) or lactation/AL) 13

## The diagnosis and treatment of menstrual migraine

### Recommendation

Menstrual migraine is diagnosed according to the International Classification of Headache Disorders 3rd Edition beta version (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**

### Background and Objective

Approximately one-half of the women with migraine are self-aware that migraine attacks occur in relation to the menstrual cycle. Even in surveys using headache diaries, migraine attacks occur frequently from several days before menstruation to during menstruation. The attacks occurring during this period are more severe and last longer than attacks occurring outside this period, and are often refractory to treatment.

### Comments and Evidence

In the past, menstruation-related headache had various names such as menstrual migraine, premenstrual migraine, and perimenstrual migraine, with no common definition regarding the time of headache occurrence. In the Appendix of ICHD-3beta, migraine is classified into A1.1 *Migraine without aura*, A1.1.1 *Pure menstrual migraine without aura*, A1.1.2 *Menstrually related migraine without aura*, and A1.1.3 *Non-menstrual migraine without aura*.<sup>1)2)</sup>

According to the criteria proposed by MacGregor et al.,<sup>3)</sup> A1.1.1 *Pure menstrual migraine without aura* is defined as attacks occurring exclusively on day 1  $\pm$  2 (*i.e.*, from 2 days before menstruation to day 3 of menstruation) in at least two out of three menstrual cycles and at no other times of the cycle, while A1.1.2. *Menstrually-related migraine without aura* as attacks occurring not only in the period specified in A1.1.1 but also in other times of the cycle. Menstrual migraine tends to be more severe and lasts longer than migraine occurring in other times.<sup>4)5)</sup>

With respect to pharmacotherapy for menstrual migraine, basically both acute treatment and prophylactic therapy are the same as those for general migraine. However, since the attacks are often severe, triptans have been reported to be effective as the acute treatment drug. Randomized controlled trials (RCT) have demonstrated the effectiveness of subcutaneous sumatriptan 6 mg<sup>6)</sup> and oral sumatriptan (50 mg and 100 mg),<sup>7)</sup> oral zolmitriptan (1.25 mg, 2.5 mg and 5 mg)<sup>8)9)</sup> oral rizatriptan (10 mg),<sup>10)</sup> and oral naratriptan (2.5 mg)<sup>11)</sup> for menstrually related migraine. One systematic review and meta-analysis concluded that grade B recommendation can be given for the use of oral sumatriptan (50 mg and 100 mg), mefenamic acid (500 mg every 8 hours from the initial menstrual migraine attack until during menstruation),<sup>12)</sup> and rizatriptan (10 mg) as acute treatments for menstrually related migraine.<sup>13)</sup> Although currently not approved in Japan, oral sumatriptan 85 mg + naproxen 500 mg combination tablet has been proven by RCT to be effective even in dysmenorrhea.<sup>14)</sup> In cases of inadequate response to acute treatment or recurring attacks, prophylactic therapy can be considered for patients who use large quantities of acute medications. When the menstrual cycle is predictable and attacks are mainly associated with menstruation with few attacks in other times, the effectiveness of short-term prophylactic therapy with triptans<sup>15)</sup> or NSAIDs<sup>16)</sup> taken from before menstruation to end of menstruation was verified. Use of other short-term prophylactic therapies including vitamin E,<sup>17)</sup> magnesium,<sup>18)</sup> and phytoestrogen<sup>19)</sup> has been reported. For hormonal therapy, the effectiveness of estradiol was examined in an RCT.<sup>20)</sup> The above-mentioned systematic review and meta-analysis also reported grade B recommendation for transdermal estradiol 1.5 mg/day, oral naratriptan 1 mg twice daily, and oral frovatriptan (currently not approved in Japan) 2.5 mg twice daily as short-term prophylactic therapies.



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## • Search terms and secondary sources

- Search database: PubMed(2011/12/21)
  1. Menstrual migraine 629
  - 2.1 & treatment 396
  - 3.1 & prophylaxis 108
  - 4.1 & prevention 94
- Search database: Ichushi Web for articles published in Japan  
(menstruation/TL or menstruation/AL) and (migraine/TL) or migraine/AL) 63

## 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**

### Background and Objective

Prophylactic therapy is needed if disability in daily living due to migraine is not adequately relieved by acute treatment alone. The goals of prophylactic therapy are to (1) reduce headache frequency, severity, and duration, (2) improve the response to treatment of acute attacks, and (3) improve function and reduce disability.

Since overuse of acute treatment drugs would induce medication-overuse headache, prophylactic therapy is also required in the case of excess use of acute medications.

### Comments and Evidence

Some prophylactic therapies have been used empirically from the past. For some prophylactic therapies, scientific evidence has been obtained from randomized controlled trials (RCT). The effectiveness and usefulness of prophylactic medications are evaluated by the degrees of reduction in frequency, severity and duration of headache, and by the degrees of improvement in functioning and disability in daily living. Evaluation methods include the number of days with headache, duration of headache, quantity of acute medications used, QOL scales, and migraine severity scales. Scientific evaluation is possible, and significance of the difference versus placebo can be analyzed statistically.

However, the evidence regarding the degree of improvement that is deemed adequate is inadequate at present, and this issue has to be studied further.

In the migraine treatment guidelines published to date, expert consensus recommendations for the indication of prophylactic therapy are based on scientific evidence and use experience of prophylactic medications available in individual countries or regions at the time of guideline development.

In the guideline published in 1993 by the Italian Society for the Study of Headache,<sup>1)</sup> prophylactic therapy is recommended when migraine with the same frequency persists after three months of symptomatic treatment in patients with two or more disabling migraine attacks per month or 4 or more days with headache per month.

In the Canadian guidelines,<sup>2)</sup> prophylactic therapy is recommended if migraine attacks are severe enough to impair the patient's QOL or the patient has three or more attacks per month that fail to respond adequately to acute treatment.

In the Danish guideline,<sup>3)</sup> prophylactic therapy is indicated when the patient has two or more attacks per months or persistent attacks that do not respond adequately to acute treatment.

The US Headache Consortium<sup>4)5)</sup> recommends to decide indication of prophylactic therapy based on the needs of individual patients and other migraine characteristics. Prophylactic therapy is indicated when migraine interferes with daily living despite acute treatment; in the case of frequent headache attacks, or contraindication, failure or overuse of acute treatments; and when adverse events occur due to acute treatment. In addition, consideration of the costs of both acute and prophylactic treatments as well as patient preference is necessary. In the presence of uncommon migraine conditions with a risk of causing permanent neurological deficits, such as hemiplegic migraine, migraine with brainstem aura, migraine with prolonged aura, and migrainous infarction, prophylactic therapy for migraine is indicated to prevent neurologic damage.

In Japan, the headache treatment guideline was published in 2002 by the Japanese Society of Neurology.<sup>6)</sup> In this guideline, an indication of prophylactic therapy is considered when migraine attacks occur at high frequency and do not respond adequately to acute treatment alone, when acute medications cannot be used due to contraindications or adverse effects, when abortive medications are not effective, and when overuse of acute medications occurs. Then the indication should be decided considering the health economic aspect (when prophylactic therapy is less costly) and patient's preference. In addition, prophylactic therapy is indicated in the case of special migraine conditions with a risk of causing serious neurological

damage, such as hemiplegic migraine, basilar-type migraine, migraine with prolonged aura, and migrainous infarction.

According to the guideline published in 2002 by the American Society of Internal Medicine,<sup>7)</sup> for patients with two or more disabling attacks (6 or more days) per month, contraindication or no response to acute treatments, use of abortive medication two or more times per week, or the presence of uncommon migraine conditions including hemiplegic migraine, an indication of prophylactic therapy should be decided upon considering the adverse effects of acute treatments, patient preference, and the costs of both acute and prophylactic therapies.

In the French guideline,<sup>8)</sup> prophylactic therapy is recommended when disability in activities of daily living (ADL) occurs due to the frequency and intensity of migraine attacks, and when the patient has taken acute migraine medication 6 to 8 times per month for three months or longer.

In the Taiwanese guideline,<sup>9)</sup> prophylactic therapy is indicated in patients who have more than three to four migraine attacks per month with no response or contraindication to acute medications; in patients with special migraine conditions such as hemiplegic migraine, migraine with prolonged aura, and migrainous infarction; or in patients with migraine attacks that severely impair daily living.

In the 2009 revision of the European Federation of Neurological Societies (EFNS) guideline,<sup>10)</sup> prophylactic therapy is recommended when daily living is severely impaired; when attacks occur two or more times per month; when migraine attacks do not respond to acute medications; and when frequent, prolonged, or uncomfortable auras occur.

A health insurance database analysis conducted in the US by Silberstein et al.<sup>11)</sup> found that implementing prophylactic therapy in migraine patients reduced the use of acute migraine medications, decreased visits to medical facilities, and decreased the frequency of utilization of brain CT and MRI scans. The study concluded that prophylactic therapy is beneficial also from the medico-economic point of view.

Furthermore, research on comorbid conditions in migraine patients has advanced. In patients with comorbid conditions such as cardiovascular diseases including hypertension and neurological disease including depression, selection of medications that are both therapeutic for the comorbid conditions and preventive for migraine is recommended.

If superior acute medications are developed, the scope of indication for prophylactic therapy would decrease. If superior prophylactic therapies with little adverse effects are developed, the scope of indication for prophylactic therapy would expand. Therefore, with future advances in the development of both acute and prophylactic medications, the criteria for indication of prophylactic therapy are likely to change. At this time, the indications arrived by consensus of the guideline committee are recommended.

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- **Search terms and secondary sources**

- Benefit of prophylactic therapy for migraine patient (2012/5/30)
  - migraine
  - & prophylaxis 2631
  - & benefit 154
  - & QOL 9
  - & guideline 71
  - & efficacy 622
  - & preventive 756
  - & benefit 55
  - & QOL 8
  - & guideline 27
  - & efficacy 195

## What kinds of drugs are available for prophylactic therapy?

### Recommendation

The drugs used in prophylactic therapy for migraine are shown in [Table 1](#).

Furthermore, the prophylactic drugs for migraine can be classified into five efficacy groups as shown in [Table 2](#), 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 1](#) (list of prophylactic medications for migraine) and [Table 2](#) (efficacy groups) were constructed by reviewing the guidelines published to date<sup>1)-13)</sup> 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 dihydroergotamine. As of March 2013, verapamil and amitriptyline are approved for off-label use.

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**Table 1. Summary of evidence for prophylactic therapies**

Drug	Quality of evidence <sup>1)</sup>	Scientific evidence	Clinical impression <sup>2)</sup>	Adverse effect	Recommendation grade <sup>3)</sup>	Efficacy group <sup>4)</sup>	Recommended dose
<b>Antiepileptic drugs</b>							
valproic acid	A	+++	+++	occasional-frequent	A	1	400–600 mg/day
topiramate	A	+++	+++	occasional-frequent	A**	1	50–200 mg/day
gabapentin	B	++	++	occasional-frequent		2	
levetiracetam	B	?	?	occasional-frequent		2	
<b>Antidepressants</b>							
amitriptyline	A	+++	+++	frequent	A*	1	10–60 mg/day
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	
sulpiride	C	?	+	rare		3	
duloxetine	C	?	?	occasional		3	
<i>fluoxetine</i>	B	+	+	occasional		2	
<b>Beta-blockers</b>							
propranolol	A	++	+++	rare-occasional	A	1	20–60 mg/day
metoprolol	A	++	+++	rare-occasional	A**	2	40–120 mg/day
atenolol	B	++	++	rare-occasional		2	
nadolol	B	+	+++	rare-occasional		2	
<i>timolol</i>	A	+++	+	rare-occasional		1	
<b>Calcium channel blockers</b>							
lomerizine	B	+	++	rare	B	2	10–20 mg/day
verapamil	B	+	++	rare-occasional	B*	2	80–240 mg/day
diltiazem	C	?	++	rare-occasional		3	
nicardipine	C	+	++	rare-occasional		3	
<i>flunarizine</i>	A	++	+++	frequent		4	
<b>ARB/ACE inhibitors</b>							
candesartan	B	+	+	rare	B**	2	8–12 mg/day
lisinopril	B	+	+	occasional	B**	2	5–20 mg/day
enalapril	C	?	?	occasional		3	
olmesartan	C	?	?	occasional		3	
<b>Others</b>							
dihydroergotamine	A	++	++	occasional	B	4	2–3 mg/day
<i>methysergide</i>	A	+++	+++	frequent		4	
botulinum toxin type A (acute/chronic)	B/A	++	?	rare	C**/A**	2	
<i>feverfew</i>	B	++	+	rare	B	2	
magnesium preparation	B	+	+	rare	B**	2	
vitamin B2		B	+++	++	rare	B**	2
tizanidine	B	+	+	rare		2	
<i>melatonin</i>	C	?	?	rare	C	4	
olanzapine	C	?	?	frequent	C**	4	

<sup>1)</sup> 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

<sup>2)</sup> 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

<sup>3)</sup> 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.

<sup>4)</sup> See Table 2.

<sup>5)</sup> Recommended dose: according to the evidence and consensus obtained in Japan.

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

\*\*Not covered by health insurance in Japan

Drugs not currently available in Japan are written in italics

**Table 2. Prophylactic medications categorized by efficacy**

Group 1 (effective)	Group 2 (somewhat effective)	Group 3 (empirically effective)	Group 4 (effective, beware of adverse effects)	Group 5 (not effective)
<b>Antiepileptic drugs</b> valproic acid topiramate**	<b>Antiepileptic drugs</b> levetiracetam** gabapentin*	<b>Antidepressants</b> fluvoxamine** imipramine** nortriptyline** paroxetine** sulpiride** trazodone** mianserin** duloxetine** clomipramine**	<b>Calcium channel blockers</b> <i>Flunarizine**</i>  <b>Others</b> <i>Methysergide**</i> dihydroergotamine <i>Melatonin**</i> Olanzapine**	<b>Antiepileptic drugs</b> chlonazepam** lamotrigine** carbamazepine  <b>Calcium channel blockers</b> nifedipine**  <b>Beta-blockers</b> acebutolol** pindolol** alprenolol** oxprenolol**  <b>Others</b> clonidine**
<b>Beta-blockers</b> propranolol <i>timolol**</i>	<b>Beta-blockers</b> metoprolol** atenolol** nadolol**	<b>Calcium channel blockers</b> diltiazem** nicardipine**		
<b>Antidepressants</b> amitriptyline*	<b>Antidepressants</b> <i>fluoxetine**</i>  <b>Calcium channel blockers</b> lomerizine verapamil*  <b>ARB/ACE inhibitors</b> candesartan* lisinopril**  <b>Others</b> <i>feverfew**</i> magnesium preparation** vitamin B2** tizanidine** botulinum toxin type A**	<b>ARB/ACE inhibitors</b> enalapril** olmesartan**		

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

\*\*Not covered by health insurance in Japan

Drugs not currently available in Japan are written in italics

## • Search terms and secondary sources

- Benefit of prophylactic therapy for migraine patient (2012/5/30)  
migraine  
& prophylaxis 2631  
& benefit 154  
& QOL 9  
& guideline 71  
& efficacy 622  
& preventive 756  
& benefit 55  
& QOL 8  
& guideline 27  
& efficacy 195



## 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 two to three 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**

### Background and Objective

Prophylactic therapy is selected when acute treatment alone is not adequate. The goals of prophylactic therapy are to (1) reduce headache frequency, severity and duration, (2) improve the response to treatment of acute attacks, and (3) improve function and reduce disability. To achieve these goals, it is necessary to choose the optimal prophylactic medication according to scientific evidence as well as the physical condition and needs of individual patients.

### Comments and Evidence

Although various guidelines published to date<sup>(1)-13)</sup> recommend to choose prophylactic drugs with high safety profile and start from a low dose, there is a lack of clear evidence regarding the criteria of selection, as is also the case for the indication criteria of prophylactic drugs.<sup>14)</sup>

The US Headache Consortium Guideline<sup>(4)(5)</sup> provides the following recommendations for selecting and using prophylactic drugs. A. Initiate prophylactic therapy with a drug that has the highest level of evidence-based efficacy. B. Initiate therapy with the lowest dose and increase dose slowly until adequate clinical efficacy is achieved in the absence of adverse events. C. Give each drug an adequate evaluation, which may take 2 to 3 months to reach clinical efficacy. D. Avoid using interfering medications (for example, overuse of acute medications). E. Use of a long-acting formulation may improve compliance.

In addition, comorbid conditions should be considered in the choice of drugs. Some comorbid/coexisting conditions are commonly found in migraine patients. Some conditions such as stroke, myocardial infarction, Raynaud's phenomenon, epilepsy, affective disorders, and anxiety disorders are associated with both treatment opportunities and limitations. In such cases, it is important to: A. if possible, select a drug that can treat both the comorbid condition and migraine; B. select a migraine medication that is not contraindicated for the comorbid condition; C. select drugs for the treatment of comorbid condition which do not exacerbate migraine; and D. beware of all drug interactions.<sup>(4)(5)</sup>

As a special attention for women who are pregnant or who wish to become pregnant, prophylactic drugs may have teratogenic effects. If prophylactic therapy is absolutely necessary, drugs with the lowest risk to the fetus should be selected.<sup>(4)(5)</sup>

For the evaluation of prophylactic therapy, observing the properties and duration of headache as well as monitoring the amounts of acute drugs used are important, while the use of headache diary is very useful. Although detailed records would provide more information, simply recording the number of days with headache alone is useful.<sup>(1)(10)</sup> Switching of drug for prophylactic therapy is necessary for appropriate evaluation of the effectiveness of prophylactic therapy.

The latest guideline of the American Academy of Neurology (2012)<sup>(12)(13)</sup> lists the following drugs as having proven effectiveness for migraine prevention: *divalproex sodium*, sodium valproate, topiramate, metoprolol, propranolol, and *timolol*. In addition, the guideline recommends frovatriptan, a triptan currently not available in Japan, as short-term prophylactic therapy for menstrually related migraine. Moreover, butterbur (*Petasites hybridus*), a non-pharmaceutical product, has been regarded to be effective for migraine prevention, but due to possible association with hepatotoxicity, the Ministry of Health, Labour and Welfare in Japan has issued a warning against its intake (February 2012).

The 2009 European Federation of Neurological Societies (EFNS) guideline<sup>(10)</sup> recommends metoprolol (50 to 200 mg/day), propranolol (40 to 240 mg/day), *flunarizine* (5 to 10 mg/day), valproic acid (500 to 1,800 mg/day), and topiramate (25 to 100 mg/day) as drugs of first choice; and amitriptyline (50 to 150 mg/day), *venlafaxine* (75 to 150 mg/day), naproxen (2 × 250 to 500 mg/day), *petasites* (2 × 75 mg/day), and bisoprolol (5 to 10 mg/day) as drugs of second choice for prophylactic

therapy of migraine. Since continuous use of NSAIDs may induce medication-overuse headache, long-term use of naproxen as a prophylactic drug is still open to question.

In Taiwan<sup>9)</sup>, propranolol (20 to 160 mg/day) is recommended as the drug of first choice, and valproic acid (300 to 1,800 mg/day), topiramate (50 to 100 mg/day), *flunarizine* (5 to 10 mg/day), and amitriptyline (10 to 75 mg/day) as drugs of second choice for migraine prevention.

In clinical practice in Japan, it is also necessary to consider whether the drugs are covered by health insurance for use as migraine prophylactic therapy.

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- Benefit of prophylactic therapy for migraine patient (2012/5/30)  
migraine  
& prophylaxis 2631  
& benefit 154  
& QOL 9  
& guideline 71  
& efficacy 622  
& preventive 756  
& benefit 55  
& QOL 8  
& guideline 27  
& efficacy 195

## 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 to 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**

### Background and Objective

Prophylactic therapy is implemented when acute treatment alone does not adequately relieve disability in daily living. The goals of prophylactic therapy are to (1) reduce headache frequency, severity and duration, (2) improve the response to treatment of acute attacks, and (3) improve function and reduce disability. When these goals are achieved, tapering and discontinuation of the prophylactic drug should be considered.

### Comments and Evidence

Consideration of the duration of prophylactic therapy as well as tapering and discontinuation of the therapy depends also on the severity of headache-induced disability before the prophylactic therapy, and no uniform criteria can be applied. The guidelines published to date recommend various regimens such as: to continue prophylactic therapy for at least 3 months, and taper and discontinue when a frequency of 1 to 2 headaches or less per month has continued for at least 2 months;<sup>1)</sup> or to continue therapy for several months if the goal of 50% reduction of headache frequency and severity is achieved, followed by gradual tapering;<sup>2)</sup> or to continue therapy for 6-12 months and then assess whether continuation is needed;<sup>3)</sup> or to continue until treatment goal is achieved and stabilized, then taper and discontinue;<sup>4)-6)</sup> or to continue for 6 months to 1 year if prophylactic therapy is effective, then taper over 3 to 6 months, and restart the same therapy if attack frequency increases again.<sup>7)</sup>

Regarding prophylactic therapy for special migraine conditions with a risk of causing serious neurological damage, such as hemiplegic migraine, migraine with brainstem aura, migraine with prolonged aura, and migrainous infarction, evidence for the duration of therapy and the timing of discontinuation is insufficient. Discontinuation has to be conducted with extreme caution.

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### • Search terms and secondary sources

- Benefit of prophylactic therapy for migraine patient (2012/5/30)  
migraine  
& prophylaxis 2631  
& benefit 154  
& QO L9  
& guideline 71  
& efficacy 622  
& preventive 756  
& benefit 55  
& QOL 8  
& guideline 27  
& efficacy 195

## 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 to 30 mg/day followed by 30 to 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**

### Background and Objective

Beta blockers are mainly used as therapeutic agents for hypertension, coronary artery disease and tachyarrhythmia, but these drugs have also been used for migraine prevention from the past.

Although the mechanisms of action and pharmacological evidence remain largely unclear, the effectiveness of beta blockers including propranolol, metoprolol, atenolol and nadolol has been proven. These agents can be used actively provided there are no comorbid conditions in which beta blockers are contraindicated, such as heart failure, asthma, and a depressive state. They are also prophylactic drugs that can be administered relatively safely in pregnant women. However, it should be noted that propranolol increases the blood concentration of rizatriptan, and co-administration of the two is contraindicated.

In Japan, propranolol as a prophylactic drug for migraine has been approved for health insurance coverage in March 2013.

### Comments and Evidence

Over 46 clinical studies have been conducted on propranolol, the representative beta blocker. Placebo-controlled clinical trials have demonstrated the usefulness of propranolol as a migraine prophylactic drug. Moreover, meta-analysis has been conducted. According to a meta-analysis reviewing 53 studies (2,403 patients) conducted by Holroyd et al.,<sup>1)</sup> the typical dose of propranolol was 160 mg/day and the mean response rate of propranolol in double-blind trials was 43.7% which was significantly ( $p < 0.001$ ) higher than 14.3% for placebo. Propranolol reduced migraine attacks by 44% when headache diaries were used to assess treatment outcome. Propranolol achieved 65% improvement when subjective scales or clinical ratings of effectiveness were used. On the other hand, the improvement rate for placebo remained at around 14% for all the evaluation methods. Because of the variation in dose among studies, the dose-response relationship (dose versus migraine prophylactic effect) could not be established. Propranolol is well tolerated.

From the above results, the effectiveness of propranolol as a prophylactic drug for migraine is established. The usefulness of metoprolol has been demonstrated in more than four placebo-controlled clinical trials.<sup>2)3)</sup> Although the quality of evidence is slightly inferior, metoprolol may be considered to have similar prophylactic effect as propranolol.

Three clinical trials of timolol have been reported, and the effectiveness has been demonstrated.<sup>4)</sup> However, only timolol ophthalmic solution is available in Japan, and the oral formulation is currently not available.

Three placebo-controlled clinical studies have proven the effectiveness of atenolol.<sup>5)</sup> The usefulness of nadolol has also been demonstrated in more than two placebo-controlled studies. In addition, a randomized control trial (RCT) comparing nadolol and propranolol was conducted in 48 migraine patients taking nadolol 80 mg/day or 160 mg/day or propranolol 160 mg/day for 12 weeks.<sup>6)</sup> Headache frequency was reduced from 6.13 to 2.74 per month with nadolol 80 mg/day, from 5.56 to 2.93 per month with nadolol 160 mg/day, and from 7.42 to 4.54 per month with propranolol. While improvement was observed in all three groups, the improvement was the greatest with nadolol 80 mg/day. One RCT comparing nebivolol with metoprolol reported equivalent efficacy of the two drugs,<sup>7)</sup> but nebivolol is currently not available in Japan.

Based on the above findings, beta blockers including propranolol, metoprolol, timolol, atenolol, and nadolol have proven prophylactic effect against migraine and few serious adverse reactions. Active use of these agents as prophylactic drugs for migraine is recommended.

Among beta blockers, those with intrinsic sympathomimetic activity (ISA) such as acebutolol,<sup>8)</sup> pindolol, alprenolol,<sup>9)</sup> and oxprenolol<sup>10)</sup> have been investigated in clinical trials, but no prophylactic effect on migraine was observed. Therefore beta blockers with ISA cannot be expected to be effective in preventing migraine, but the reason is unknown.

Based on the sufficient evidence for propranolol, the US Headache Consortium Guideline<sup>11)-13)</sup> recommends propranolol at a dose of 120 to 240 mg/day for prophylactic therapy. In the Japanese chronic headache guidelines published in 2006, a dose range of 20 to 60 mg/day was recommended, which was based on the experience of use in Japan and lower than that based on overseas evidence. Following this recommendation, the experience of use in Japan has accumulated, and propranolol for migraine treatment was approved for health insurance coverage in March 2013.

In addition, the guidelines published to date state that when prophylactic therapy is necessary in pregnant women, beta blockers including propranolol are relatively safe.

Since the major metabolic pathway for both propranolol and rizatriptan is oxidative deamination catalyzed by monoamine oxidase type A, there is a possibility that propranolol use may increase the blood level of rizatriptan and augment the effects. Therefore combined use of the two is contraindicated.<sup>14)</sup>

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## • Search terms and secondary sources

- Search database: PubMed (2011/12/13)
- {migraine} OR {vascular headache} OR {hemicrania} 68566
- & propranolol 614
- & metoprolol 146
- & timolol 58
- & pindolol 32
- & nadolol 39
- & nebivolol 17
- & atenolol 101
- & acebutolol 11
- & alprenolol 7
- & acebutolol 11
- & bisoprolol 16
- & practolol 7
- & labetalol 33
- & carteolol 4
- & oxprenolol 10
- & prindolol 32
- 447 articles excluded due to duplication or out of scope
- 10 articles adopted upon perusing abstract and text
- Secondary source, 4 references added by manual search (Nos. 11-14)

## 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**

### Background and Objective

Calcium channel blockers are a class of drugs widely used as antihypertensive agents. They have also been used as prophylactic drug for migraine from the past. Flunarizine is being used overseas as a migraine prophylactic drug, but is currently not available in Japan. As a similar diphenylpiperazine calcium channel blocker, lomerizine was developed in Japan and approved for health insurance coverage as migraine prophylaxis, and has been used since 1999. Literature was searched for evidence concerning the prophylactic effect of various calcium channel blockers for migraine.

### Comments and Evidence

Over 45 clinical trials of calcium channel blockers for migraine prevention have been reported.

Among the calcium channel blockers, the quality of evidence for flunarizine is the highest, with effectiveness reported by more than 6 randomized placebo-controlled double-blind trials (RCT).<sup>1)-7)</sup> Furthermore, a meta-analysis using four of these reports also demonstrated its effectiveness, but sale of this drug was discontinued in Japan. For a similar compound lomerizine, one open-label study reported effectiveness<sup>8)</sup> and one randomized placebo-controlled double-blind trial demonstrated effectiveness and usefulness.<sup>9)</sup> In an RCT of lomerizine compared with dimetotiazine, while the two drugs showed similar prophylactic effect for migraine, lomerizine was superior in safety. Although attention has to be given to adverse events such as Parkinsonism and depression (which are issues associated with flunarizine) when using lomerizine, clinical trials have found that adverse events of lomerizine are comparable to placebo. Despite being an open-label study, one trial has reported a 55.2% reduction in migraine attacks and absence of flunarizine-associated adverse effects even after prolonged use of flunarizine for 6 months, indicating the safety of this agent.<sup>10)</sup> For the phenylalkylamine calcium channel blocker verapamil, two randomized placebo-controlled double-blind trials<sup>11)-12)</sup> have demonstrated its usefulness. After migraine patients were treated with verapamil 320 mg (divided into 4 doses) for three months, migraine frequency decreased from 6.7 to 3.8 per month.<sup>11)</sup> In a cross-over study of verapamil 240 mg administered for 8 weeks, headache frequency was reduced significantly from 3.4 per month during placebo administration to 2.8 per month during verapamil administration, and the use of acute medications was also significantly reduced.<sup>12)</sup> According to the Notification from the Director of Medical Economics Division, Health Insurance Bureau, Ministry of Health, Labour and Welfare (Ho-I-Hatsu 0928 No. 1) "Health Insurance Handling Related to Off-Label Use of Pharmaceuticals" dated September 28, 2011, off-label use of verapamil for migraine and cluster headache was approved for health insurance coverage. For diltiazem, a benzothiazepine compound, one open-label study has shown its usefulness.<sup>13)</sup> For the dihydropyridine calcium channel blocker nimodipine, randomized placebo-controlled double-blind studies reported both effective<sup>14)-16)</sup> and ineffective<sup>17)-19)</sup> findings. This drug is currently not available in Japan. Another dihydropyridine compound nifedipine was considered to have no or very weak prophylactic effect,<sup>20)-21)</sup> but one randomized placebo-controlled double-blind study on nifedipine has shown its usefulness.<sup>22)</sup>

Based on the above findings, lomerizine is recommended as the first choice calcium channel blocker that can be expected to exhibit prophylactic effect for migraine; although the number of clinical trials is small and evidence is slightly weak, this drug has been used for approximately 10 years in Japan and is covered by health insurance. Verapamil is recommended as the second choice, because there is evidence and the drug is covered by health insurance for off-label use.



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## • Search terms and secondary sources

- Search database: PubMed (2011/12/13)
- {migraine} or {vascular headache} or {hemicrania} 68566
- & {calcium antagonists} or {Ca antagonists} 7587
- & flunarizine 337
- & diltiazem 103
- & nifedipine 293
- & verapamil 305
- & nimodipine 120
- & nicardipine 60
- & lomerizine 23
- & cinnarizine 66
- & dotarizine 7
- & amlodipine 115
- & azelnidipine 3
- & aranidipine 1
- & efonidipine 0
- & cilnidipine 1
- & nisoldipine 16
- & nitrendipine 53
- & barnidipine 4
- & felodipine 65
- & benidipine 1
- & manidipine 7
- & nilvadipine 6
- & cyclandelate 14

→ For 403 articles excluded due to duplication or out of scope, the abstracts were perused.

Although important articles focusing on placebo-controlled RCT and meta-analysis were adopted, some open studies and comparative studies with other drug groups were also adopted (22 references).



## 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**

### Background and Objective

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II blockers (ARB) are widely used as antihypertensive agents with few adverse effects. Accumulated experience that patients taking ACE inhibitors for hypertension tended to show reduced migraine frequency and severity had led to the report of several small-scale case series, which was followed by a randomized placebo-controlled cross-over trial on the ACE inhibitor lisinopril, demonstrating its prophylactic effect against migraine. Randomized studies have also been conducted on ARB (candesartan), and demonstrated its usefulness. Both migraine and hypertension are diseases with high prevalence, and the two coexist in many patients. ACE inhibitors and ARB are a group of drugs with few adverse effects and good tolerability, and the possibility of these drugs to become one of the prophylactic agents to improve the QOL of migraine patients is anticipated.

### Comments and Evidence

A report published in 1995 demonstrated the prophylactic effect of ACE inhibitors for migraine in 17 patients with migraine diagnosed according to the criteria of the International Headache Society.<sup>1)</sup> The subjects aged 18 to 59 years had moderate to severe migraine with at least two migraine attacks per month, and were treated with ACE inhibitors for a duration ranging from 3 months to 3 years. Most were given enalapril, and some used lisinopril. The mean dose was 16.4 mg (10 to 25 mg)/day. Ten patients showed marked response, 6 achieved moderate improvement, and 1 slight improvement. The major adverse event was cough; 3 patients discontinued treatment because of coughing and 1 continued treatment despite coughing. A RCT has proven the prophylactic effect of lisinopril 20 mg/day for migraine.<sup>2)</sup> Lisinopril 20 mg/day reduced the hours with headache, days with headache, and days with migraine by 20% (95% confidence interval: 5 to 36%), 17% (5 to 30%) and 21% (9 to 34%), respectively, compared with placebo. Moreover, lisinopril reduced the days with migraine by at least 50% compared with placebo in 14 participants (14/60, 23.3%). Other studies on lisinopril include a relatively well designed case series,<sup>1)</sup> research using patient database,<sup>3,4)</sup> and an open-label study suggested the effectiveness of lisinopril 5 mg/day.<sup>5)</sup> For enalapril also, evidence exists even though it is inadequate.<sup>16)</sup> There is no evidence for migraine for the other ACE inhibitors. For ARB, the prophylactic effect of candesartan for migraine has been examined.<sup>7)</sup> In an intention-to-treat (ITT) analysis of 57 patients, the mean number of days with headache for 12 weeks (primary end point) was 18.5 for placebo versus 13.6 for candesartan, showing a significant ( $P = .001$ ) decrease with candesartan. Furthermore, when candesartan responder was defined as at least 50% improvement compared with placebo, the responder rate was 18/57 (31.6%) when assessed by days with headache, and 23/57 (40.4%) when assessed by days with migraine. For other ARB, the prophylactic effect of olmesartan 10 to 40 mg/day in patients with coexisting migraine and hypertension was investigated in an open-label study, which showed usefulness and good tolerability of olmesartan.<sup>8)</sup> The migraine prophylactic effect of telmisartan 80 mg/day was evaluated in a RCT, which suggested the usefulness of the drug, but with no significant difference.<sup>9)</sup>

In Japan, one case in which ACE inhibitor enalapril was effective was reported,<sup>10)</sup> and several cases in which ARB (candesartan and telmisartan) were effective<sup>11)-13)</sup> were also reported.

From the above findings, the ACE inhibitor lisinopril and the ARB candesartan are recommended as prophylactic drugs for migraine. Start lisinopril from 5 mg/day, and if reduction in migraine attacks is inadequate, increase stepwise up to 20 mg/day. For candesartan, overseas evidence indicates a dose of 16 mg/day, and the European Federation of Neurological Societies migraine treatment guideline<sup>14)</sup> lists candesartan 16 mg/day as the drug of third choice. In Japan, the dosing regimen of candesartan for hypertension is “4 to 8 mg/day orally, and increase up to 12 mg as necessary”. In Japan, an open-

label study using 8 mg/day has been reported. Considering the use experience in Japan and safety, candesartan 8 mg/day is recommended for migraine prevention. For enalapril and olmesartan, while the evidence is not strong, their usefulness has been suggested, and these agents may be options. ACE inhibitors and ARB are a group of anti-hypertensive drugs with high quality evidence. Active use of these agents is recommended in patients with migraine and coexisting hypertension, and dosing should take into account the dose for hypertension treatment. Although the usefulness of ARB in patients with migraine but no hypertension has been reported, further accumulation of evidence is necessary.

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- Search database: PubMed (2012/1/9)
  - Migraine & prophylaxis 2568
  - Migraine & (angiotensin-converting enzyme inhibitors) 41
  - Migraine & (angiotensin receptor blockers) 37
  - Migraine & losartan 2
  - Migraine & Valsartan 2
  - Migraine & candesartan 19
  - Migraine & telmisartan 2
  - Migraine & Irbesartan 1
  - Migraine & olmesartan 2
  - 11 articles adopted
- Search database: Ichushi (2012/1/9)
  - (Migraine/TH or Migraine/AL) and prophylaxis/AL 451
  - (Migraine/TH or Migraine/AL) and ("Peptidyl-Dipeptidase A"/TH or ACE/AL) 154
  - (Migraine/TH or Migraine/AL) and ("Angiotensin II Type 1 Receptor Blockers"/TH or ARB/AL) 97
  - 3 articles adopted

## 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 to 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**

### Background and Objective

Valproic acid increases the GABA level in the brain by activating glutamic acid decarboxylase and inhibiting GABA aminotransferase, and suppresses neuron excitability. Therefore, the effect of valproic acid on migraine and refractory chronic headache has been investigated. As a migraine treatment, some 20 years of use experience has been accumulated, and in European and American countries, valproic acid together with beta blockers and amitriptyline are listed among the first choice drugs for migraine prevention. In Japan also, valproic acid has been covered by health insurance since 2010. Topiramate is evaluated favorably overseas as a prophylactic drug for migraine, but is not covered by health insurance in Japan.

### Comments and Evidence

Prospective studies of valproic acid for migraine prevention consist of two studies on sodium valproate and four on divalproex sodium (compound of valproic acid and valproate in 1:1 ratio). From these results, a Cochrane review concludes that valproic acid reduces the frequency of headache attacks and increases the number of patients for whom migraine frequency is reduced by 50% or more.<sup>1)</sup> In addition, some reports indicate that valproic acid reduces headache frequency as well as decreases headache intensity and shortens headache duration.<sup>2,3)</sup> On the contrary, other report shows that valproic acid reduces headache frequency but does not improve headache intensity or headache duration.<sup>4)</sup> When compared with other drugs, valproic acid shows similar effectiveness as flunarizine,<sup>5)</sup> propranolol,<sup>6)</sup> and topiramate.

In overseas countries, the European Federation of Neurological Science (EFNS) migraine treatment guideline recommends valproic acid at level A.<sup>7)</sup> The American Academy of Neurology migraine guideline recommends valproic acid at grade A,<sup>8)</sup> and describes its indication under the following conditions: (1) two or more disabling attacks (6 or more days) per month, (2) contraindication or no response to acute treatments, (3) use of abortive medication two or more times per week, and (4) uncommon migraine conditions including hemiplegic migraine.

The dose range showing effectiveness in overseas studies was 400 to 2,000 mg/day.<sup>9)</sup> In the US, use of divalproex sodium 500 to 1,000 mg/day is approved for migraine prevention. The EFNS guideline recommends 500 to 1,800 mg/day.<sup>7)</sup> In Japan, a dose of 800 mg/day was used in a trial (open-label study) of valproic acid for migraine prevention,<sup>10)</sup> and doses ranging from 200 to 1,000 mg/day have been reported when case reports are included. In one study, the group with blood level lower than 50 µg/mL had less adverse effects than the group with 50 µg/mL or higher, while showing significant decreases in headache frequency and number of days with headache. This report thus recommended low-dose valproic acid of 500 to 600 mg/day for migraine prevention.<sup>11)</sup> Furthermore, another report indicated that in migraine patients who did not respond to low-dose valproic acid, dose increase did not improve response.<sup>12)</sup> From the above findings, the recommended dose of sodium valproate is 400 to 600 mg/day. Reports that measured blood levels<sup>13,14)</sup> also recommended a target blood level less than 50 µg/mL.

According to a survey on the use of valproic acid in Japanese, adverse effects include somnolence, hyperammonemia, dizziness, hepatic function impairment, elevated creatine phosphokinase, and anemia.<sup>15)</sup>

Special attention has to be given when administering valproic acid to women of child-bearing potential. Regarding malformations associated with valproic acid, combined data of eight cohort studies showed 118 malformations among a total

of 1,565 pregnancies in which women took valproic acid, and the incidence was significantly higher compared to controls not exposed to valproic acid or with chromosomal malformations.<sup>16)</sup> The rate of teratogenicity increases when the dose of valproic acid exceeds 1,000 to 1,500 mg/day,<sup>17)-20)</sup> suggesting a dose- and blood level-dependent increase in teratogenicity rate. In a prospective study of pregnant women with epilepsy receiving monotherapy of antiepileptic drug (carbamazepine, lamotrigine, or valproic acid), cognitive function test conducted in three year-old children showed significantly lower IQ in children exposed to valproic acid treatment exceeding 1,000 mg/day in the fetal stage compared with other antiepileptic drugs.<sup>21)</sup> From the above data, it was concluded that taking valproic acid during pregnancy is associated with teratogenicity and impaired cognitive function in fetus. In May 2013, FDA advised that unlike epilepsy treatment, use of valproic acid for the prevention of migraine is contraindicated in pregnant women and women who may be pregnant, because the risk outweighs the benefit. When used in women of child-bearing potential, the patients should be given prior explanations of adverse effects and teratogenicity and sustained release formulation should be chosen so that blood level increases gradually. Since the frequency of teratogenicity is increased when using multidrug antiepileptic therapy,<sup>17)18)</sup> combined use with other antiepileptic drugs should be avoided. Patients should be advised to check the menstrual cycle and basal temperature, and to stop taking valproic acid and contact the attending doctor when pregnancy is suspected. To reduce the risk of neural tube defect, patients should be advised to take folic acid supplement 0.4 mg/day.<sup>22)</sup>

Use of other antiepileptic drugs for migraine prevention is currently not covered by health insurance.

The usefulness of topiramate in migraine prevention has been confirmed by RCT.<sup>23)24)</sup> In a relatively large-scale placebo-controlled study, the monthly headache frequency was reduced by 1.1 days with placebo versus 2.1 days with topiramate 100 mg/day ( $p = .008$ ), and 2.4 days with 200 mg/day ( $p < .001$ ).<sup>24)</sup> The American Academy of Neurology guideline published in 2012<sup>25)</sup> gives grade A recommendation for topiramate, as for valproic acid.

For gabapentin, a study comparing gabapentin 2,400 mg/day with placebo reported a significant decrease in monthly frequency of attack, and the presence of adverse effects of moderate somnolence and dizziness.<sup>26)</sup>

On the other hand, there are few reports indicating the effectiveness of lamotrigine for migraine. A study comparing lamotrigine 50 mg/day with placebo failed to demonstrate the effectiveness for the primary end point.<sup>27)</sup> For carbamazepine and chlonazepam, there is a lack of evidence and effectiveness has not been demonstrated.

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## • Search terms and secondary sources

- Search database: PubMed (2010/12/30)  
(migraine) and ((preventive) or (prophylactic) or (prophylaxis)) and ((valproate) or (valproic acid))225
- Search database: PubMed (2011/1/23)  
valproate  
and migraine 349  
and pregnancy and malformation 502  
and pregnancy and malformation and polytherapy 48  
and folic acid 134
- Search database: Ichushi Web for articles published in Japan (2006-2011) (2011/1/23)  
Valproic acid and migraine 68

## 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 to 10 mg/day before bedtime), and titrate upward while confirming the effect. A dose of 10 to 60 mg/day is recommended.

**Grade A**

### Background and Objective

Chronic headache may coexist with a depressive state. Use of antidepressants is known not only to improve the depression state but also to reduce headache. Antidepressants are also considered to be useful in patients with migraine not accompanied by a depressive state. The pathophysiology of migraine has been associated with neurotransmitters such as serotonin. Many antidepressants are considered to exhibit anti-depressive effect by increasing the extraneuronal serotonin and norepinephrine concentrations in the central nervous system. Although the mechanisms of action by which antidepressants prevent migraine remain unknown, these drugs have long been used in various countries.

### Comments and Evidence

Amitriptyline, a tricyclic antidepressant, is the most studied and clinically the most widely used drug in this class. Three randomized placebo-controlled trials on amitriptyline have been conducted.<sup>1)-4)</sup> Using headache index and frequency of migraine attacks as outcome measures, the doses and treatment durations of 50 to 150 mg/day for 8 weeks,<sup>4)</sup> 50 to 100 mg/day for 4 weeks,<sup>2)</sup> and 30 to 60 mg/day for 27 weeks<sup>3)</sup> have consistently showed effectiveness, and a metaanalysis<sup>5)</sup> has also demonstrated its usefulness.

Two studies compared amitriptyline and propranolol. The evaluations of amitriptyline 50 to 150 mg/day and propranolol 80 to 240 mg/day for a treatment period of 8 weeks yielded almost equivalent prophylactic effect for migraine.<sup>4)</sup> In a report comparing amitriptyline 25 to 75 mg/day and propranolol 60 to 160 mg/day for 6 months or longer,<sup>6)</sup> both agents were effective, but the efficacy of amitriptyline was higher than that of propranolol in patients with migraine and coexisting tension-type headache. Regarding the dose of amitriptyline used in Japan, the starting dose is recommended to be 5 to 10 mg/day based on experience.

Whether the anti-migraine effect of amitriptyline and other antidepressants is mediated via the antidepressant effect or is an independent action remains inconclusive. However, clinically the prophylactic effect of amitriptyline for chronic headache is definitive irrespective of whether or not a depressive state exists.<sup>5)</sup>

Two placebo-controlled studies of clomipramine have been reported, but its usefulness is not yet proven. Although combined use of nortriptyline and topiramate<sup>7)</sup> or propranolol<sup>8)</sup> has been reported to be effective, the prophylactic effect of nortriptyline alone has not been proven. No placebo-controlled clinical study on imipramine has been conducted.

For tetracyclic antidepressants, mianserin has been studied in one RCT.<sup>9)</sup> Treatment with mianserin 60 mg/day significantly reduced the intensity and frequency of headache compared to the observation period but the effect was not significant compared with placebo. Trazodone has been shown to be useful in children with migraine.<sup>10)</sup> There is no evidence for maprotiline and setipiline.

Among the selective serotonin reuptake inhibitors (SSRI), fluoxetine was studied in three RCT,<sup>11)</sup> two of which showed usefulness. Fluvoxamine which is available in Japan has been suggested to have the same effectiveness as amitriptyline,<sup>12)</sup> but no placebo-controlled study has been conducted. Although cases responsive to paroxetine have been reported, evidence is insufficient. The effectiveness of sertraline has not been reported.

For serotonin norepinephrine reuptake inhibitors (SNRI), reports have suggested the effectiveness of venlafaxine<sup>13)</sup> (currently not available in Japan) and duloxetine<sup>14)-16)</sup> (available in Japan), but no placebo-controlled clinical trials have been reported. There is no report on the migraine prophylactic effect for milnacipran. Further studies on SSRI and SNRI are required in the future.

Mirtazapine, a noradrenergic and specific serotonergic antidepressant (NaSSA), has been suggested to be effective for migraine prevention in some case reports,<sup>17)18)</sup> but large-scale clinical trials have not been reported.



As for other antidepressants, some reports have suggested the usefulness of sulpiride, but evidence is unclear.

Tricyclic antidepressants have well known adverse effects (such as somnolence and thirst) due to the anticholinergic action. Although these adverse events occur at high frequencies, they can be reduced by starting from low doses.<sup>3)</sup>

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## • Search terms and secondary sources

- Search database: PubMed (2012/1/16)
- migraine and antidepressant 723
- migraine and antidepressant and {(randomized and controlled) or double-blind} 122
- migraine and amitriptyline and {(randomized and controlled) or double-blind} 44
- migraine and imipramine and {(randomized and controlled) or double-blind} 0
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- migraine and lofepramine and {(randomized and controlled) or double-blind} 0
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- migraine and setipiline and {(randomized and controlled) or double-blind} 0
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- migraine and sertraline and {(randomized and controlled) or double-blind} 1
- migraine and SNRI and {(randomized and controlled) or double-blind} 0
- migraine and milnacipran and {(randomized and controlled) or double-blind} 0
- migraine and sulpiride and {(randomized and controlled) or double-blind} 1
- migraine and duloxetine 8
- migraine and mirtazapine 5



## 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**

### Background and Objective

Migraine occurs coincidentally with depressive disorder/depressive state at high frequency. In migraine patients, serotonergic drugs such as serotonin selective reuptake inhibitors (SSRI) and serotonin noradrenalin reuptake inhibitors (SNRI) are used frequently as prophylaxis for migraine or treatment for depressive disorder/depressive state. The potential risk of developing serotonin syndrome by combined use of triptans (serotonin receptor agonist) and SSRI/SNRI is a concern. The evidence concerning safety of their use is commented below.

### Comments and Evidence

Serotonin syndrome is caused by excessive serotonergic activities, and manifests nervous and muscular symptoms (such as increased tendon reflex, myoclonus, and muscle rigidity), autonomic symptoms (such as fever, tachycardia, sweating, tremor, diarrhea, and rubeosis), and psychiatric symptoms (such as anxiety, agitation, confusion, and hypomania). The SSRI/SNRI, tricyclic antidepressants, monoamine oxidase (MAO) inhibitors, lithium carbonate, analgesics, antitussives, and supplements (St. John's wort) are known to be associated with serotonin syndrome.<sup>1)</sup> Hunter Serotonin Toxicity Criteria<sup>2)</sup> and Sternbach criteria<sup>3)</sup> are used as diagnostic criteria.

In 2006, the US Food and Drug Administration (FDA) issued an alert to the effect that the risk of serotonin syndrome may increase by combined use of triptan and SSRI/SNRI, based on a report of 29 cases of serotonin syndrome occurring in patients treated with triptans and SSRIs/SNRIs.<sup>4)</sup> In 2008, Soldin and Tonning<sup>5)</sup> reported that of over 100 million persons worldwide using triptans since 1991, there were 11 cases of serotonin syndrome associated with the use of triptan alone. Additionally, a one-year prospective study showed that of 12,339 persons using subcutaneous sumatriptan, 1,784 also used SSRI in combination and there was no report of serotonin syndrome.<sup>5)</sup>

In 2010, the American Headache Society re-evaluated the 29 cases that formed the basis of the FDA alert and the 11 cases reported by Soldin and Tonning.<sup>5)</sup> Among the 29 cases, 10 cases fulfilled the Sternbach criteria but none of the cases satisfied the Hunter Serotonin Toxicity Criteria. Regarding the 11 cases reported by Soldin and Tonning,<sup>5)</sup> detailed evidence for a diagnosis of serotonin syndrome was not provided. From the above findings, the American Headache Society currently concludes that there is inadequate evidence to support an increase in risk of serotonin syndrome with triptan monotherapy or combined triptan and SSRI/SNRI therapy. Moreover, triptan has high affinity for 5-HT<sub>1B/1D/1F</sub> but low affinity for 5-HT<sub>1A</sub> receptors. On the other hand, serotonin syndrome is associated with 5-HT<sub>2A</sub> receptor stimulation in animals models; therefore the skepticism about the speculated association with 5-HT<sub>1A</sub> stimulation is also supported from the pharmacological viewpoint.

Nevertheless, given the seriousness of the condition, clinicians should pay attention when using these drugs and ensure appropriate treatment in the remote event that serotonin syndrome occurs.<sup>6)</sup>

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- Search database: PubMed (2011/12/21)
  - {triptans} and {(SSRI) or (SNRI)} 397
  - {triptans} and {(SSRI) or (SNRI)} and {serotonin syndrome} 40
  - {triptans} and {serotonin syndrome} 2661
  - {triptans} and {serotonin syndrome} and {migraine} 86

## 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. NSAIDs 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.

**Grades B and C** (magnesium, vitamin B2 and feverfew: B; NSAID short-term prophylaxis: C)

### Background and Objective

Some organic foods and ingredients used in supplements, represented by magnesium, vitamin B2 (riboflavin) and feverfew, have been suggested to have prophylactic effect for migraine. Some migraine patients who do not favor prophylactic therapy with prescription drugs prefer to take these supplements. In addition, NSAIDs that are used as acute treatment are commonly used as short-term prophylactic therapy for menstrual migraine and menstrually related migraine. A literature search was conducted to examine the migraine prophylactic effects of these compounds.

### Comments and Evidence

The blood magnesium level and intrathecal magnesium level have been reported to be lowered in migraine patients, and magnesium supplementation has been attempted for migraine prevention. There are five reports of randomized control trial (RCT) on migraine prophylaxis with oral magnesium, four of which reported effectiveness<sup>(1)-4)</sup> and one study reported no efficacy.<sup>5)</sup> Therefore, magnesium is considered to be effective for the prevention of migraine (grade B recommendation). There are three reports of RCT on acute treatment of migraine with intravenous magnesium. One study using 2 g reported no effect.<sup>6)</sup> Another study using 1 g reported that the treatment was effective and safe.<sup>7)</sup> The third study found that while 2 g was useful in alleviating headache, there was no significant difference compared with metoclopramide or placebo.<sup>8)</sup>

From the hypothesis of an association between mitochondrial dysfunction and migraine, RCT have been conducted on its migraine prophylactic effect. In a study of 55 migraine patients treated with oral vitamin B2 400 mg/day or placebo for three months, vitamin B2 significantly decreased headache frequency and shortened the number of days with headache in migraine patients.<sup>9)</sup> Two RCT on children have been reported. Studies using 200 mg/day and using 50 mg/day both demonstrated no effectiveness.<sup>10)11)</sup> Because of its high efficacy, good tolerability, and low cost, vitamin B2 is a promising option for migraine prophylaxis in adults (grade B recommendation). One RCT using coenzyme Q10, another useful agent that improves mitochondrial function, also reported its effectiveness.<sup>12)</sup>

Feverfew is a herb and has been considered to be effective in preventing migraine from the past. There are three reports of RCT on feverfew, two of which indicated its effectiveness<sup>13)14)</sup> while one observed effectiveness only in intention-to-treat (ITT) analysis. Adverse effects were similar to placebo, with no dose-dependent difference (grade B recommendation).<sup>15)</sup> An RCT using the feverfew CO<sub>2</sub>-extract (MIG-99) also reported its effectiveness.<sup>16)</sup>

In 2004, a study investigating the effectiveness of a compound containing the three above-mentioned agents was reported.<sup>17)</sup> Forty-nine migraine patients were treated with a combination of magnesium 300 mg, vitamin B2 400 mg and feverfew 100 mg, or placebo containing vitamin B2 25 mg for three months. There were no significant differences in the frequency and intensity of headache between two groups, but significant headache improvement compared to before treatment was observed in both groups, which may suggest that the effect observed with the combination could reflect the migraine prevention effect of vitamin B2 25 mg alone. Although the number of clinical trials for magnesium, vitamin B2 and feverfew remains small, their effectiveness for migraine prevention is being proven gradually.

Among analgesics such as NSAIDs, naproxen has been shown in at least five RCT to have significant prophylactic effect for migraine compared with placebo, and although gastrointestinal events are thought to be common, adverse effects did not

differ compared to placebo.<sup>18)19)</sup> Aspirin taken orally at a dose of 1,300 mg/day is known to be effective for migraine prevention.<sup>20)21)</sup> Among the selective cyclooxygenase (COX)-2 inhibitors, rofecoxib has been reported to be an effective short-term prophylactic therapy for menstrually related migraine, but evidence remains insufficient.<sup>22)</sup> There is no evidence for migraine prevention with loxoprofen, diclofenac, selective COX-2 inhibitors, meloxicam, etodolac and nabumetone, which are currently available in Japan. Since some analgesics including NSAIDs exhibit prophylactic effect for migraine, they may be considered as options not only as acute treatment but also as prophylactic drugs. However, due to the issue of medication-overuse headache, these agents are not suitable for long-term prophylactic therapy. There is one report on RCT of short-term prophylactic therapy for menstrual migraine. In this study, subjects took naproxen 500 mg twice daily for 13 days during each menstrual cycle, for three cycles, and naproxen significantly reduced headache frequency and intensity compared to placebo.<sup>23)</sup> Evidence for menstrually related migraine is insufficient,<sup>24)</sup> and generally 5 to 7-day treatment is considered. Although there is no report of RCT for status migrainosus, drugs are administered empirically for 3 to 7 days. From the above findings, their use should be limited to short-term prophylactic therapy for menstrual migraine, menstrually related migraine, and status migrainosus (grade C recommendation).

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- Search database: PubMed (2012/6/4)  
migraine OR vascular headache OR hemicranias 68389  
& magnesium 271  
& vitamin B 271  
& riboflavin 78  
& feverfew 75  
& naproxen 95  
& flurbiprofen 22  
& ketoprofen 41  
& tolfenamic acid 34  
& aspirin 735  
& fenoprofen 8  
& ibuprofen 228  
& indomethacin 575  
& lornoxicam 6  
& rofecoxib 30  
& meloxicam 3  
& etodolac 8  
& nabumetone 4  
& loxoprofen 7  
& diclofenac 102  
& mefenamic acid 31  
& tramadol 117
- Search database: Ichushi Web for articles published in Japan (2011/11/21)  
(migraine/TH or migraine/AL) and (magnesium/TH or magnesium/AL) 21  
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(migraine/TH or migraine/AL) and (riboflavin/TH or vitamin B2/AL) 11  
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(migraine/TH or migraine/AL) and (diclofenac/TH or diclofenac/AL) 11  
(migraine/TH or migraine/AL) and ("mefenamic acid"/TH or mefenamic acid/AL) 5  
flurbiprofen, tolfenamic acid, fenoprofen, lornoxicam, Etodolac Nabumetone, tramadol, tramadol-acetaminophen 0

## 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)

### Background and Objective

A literature search was conducted on the prophylactic effect of dihydroergotamine for migraine attacks, focusing on large-scale trials. Regarding melatonin, since control of migraine attacks has been reported occasionally, a search for evidence of its usefulness was conducted. The antipsychotic olanzapine has been used empirically for refractory headache. Accordingly, literature was searched for evidence of the prophylactic effect of olanzapine. In addition, evidence for the migraine prophylactic effect of butterbur (*Petasites hybridus*) was also searched.

### Comments and Evidence

Several randomized controlled trials (RCT) on dihydroergotamine have been reported. The PROMISE study [PROphylaxis of Migraine with SEglor (dihydroergotamine mesilate)] conducted in France included 363 migraine patients treated with dihydroergotamine or placebo for 5 months after a 1-month placebo run-in period.<sup>1)</sup> In this study, oral dihydroergotamine was effective in preventing migraine attacks and in improving quality of life. The administration method is 1 mg three times daily. Several other clinical studies have been conducted, and reports that dihydroergotamine is generally effective in preventing migraine attacks are encountered. However, in Japan, while dihydroergotamine is sometimes used also in children, it is not frequently used as the first-choice drug in adult patients.

Melatonin secreted from the pineal gland affects hypothalamic function and is known to be closely associated with the pathophysiology of migraine. In migraine patients, impaired melatonin secretion has been reported to cause abnormal release of calcitonin gene-related peptide (CGRP). Therefore, from the mechanism of action, melatonin has strong potential as one of the migraine prophylactic drugs. While melatonin 3 mg/day was reported to be effective in preventing migraine attacks, an RCT of 48 migraine patients found no significant difference between patients taking melatonin 2 mg orally one hour before bedtime and patients taking placebo.<sup>2)3)</sup> In any case, both studies included small numbers of subjects, and further large-scale RCT is needed.

In the clinical setting, olanzapine has been used in cases of refractory headache, but the number of reports on olanzapine remains small. The report of Silberstein et al.<sup>4)</sup> showed effectiveness in a small series. In this study, 50 patients with refractory migraine were treated with olanzapine for at least 3 months, and oral olanzapine 5 mg/day or 10 mg/day was markedly effective in improving headache attacks. The report concluded that olanzapine is very effective for patients with headache not responding to other available prophylactic drugs, or patients who have coexisting psychiatric diseases such as depressive disorder and bipolar disorder. However, it should be noted that weight gain as an adverse event is observed in 38% of the patients, and olanzapine is therefore contraindicated in patients with impaired consciousness and diabetes.

There are two RCT on butterbur (*Petasites hybridus*). A total of 293 migraine patients were randomized to butterbur (Petadolex) 150 mg/day, Petadolex 100 mg/day or placebo, and the three groups were compared. After treatment for 3 to 4 months with butterbur, the frequency of attacks was reduced significantly and over 50% of the patients showed symptomatic

improvement. Furthermore, adverse reactions are primarily gastrointestinal symptoms (such as burping), and few serious reactions are observed. Impaired liver function and malignant tumor have been reported.<sup>5)-8)</sup>

In January 27, 2012, the UK Medicines and Healthcare Products Regulatory Agency (MHRA) issued an alert that butterbur is associated with liver toxicity and advised consumers not to use products containing butterbur (*Petasites hybridus*). Accompanying this move, the Japanese Ministry of Health, Labour and Welfare also issued a warning advising not to take these products (February 8, 2012).

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- Search database: PubMed (2011/11/18)  
migraine & {melatonin} 61  
& {olanzapine} 5  
& {butterbur} 35  
& {dihydroergotamine} 391& {prevention} 76  
& {prophylaxis} 88



## 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**

### Background

Botulinum neurotoxin (BoNT) is a zinc metalloprotease produced by *Clostridium botulinum*. In nerve endings, BoNT binds receptors and are taken up into the nerve cells, where it cleaves the SNARE (soluble N-ethylmaleimide-sensitive fusion protein attachment protein receptor) protein and blocks exocytosis. As a result, secretion of neurotransmitters and expression of cell membrane receptors are affected. BoNT is classified into types A to G. Type A (BoNT-A) is used clinically for the treatment of migraine. BoNT-A has proven efficacy not only for dystonia but also for pain disorders and autonomic dysfunctions. Although the mechanism by which BoNT-A exhibits therapeutic effect against migraine remains unclear, inhibition of calcitonin gene-related protein (CGRP) release and inhibition of muscle contraction may be involved.<sup>1)</sup>

### Comments and Evidence

Botulinum neurotoxin type A (BoNT) is marketed worldwide as products brand named Botox or Dysport. The former is used clinically in Japan mainly for the treatment of dystonia. From around 2000, the prophylactic effect of BoNT-A for paroxysmal migraine began to be investigated by randomized placebo-controlled double-blind trials. Using the change from baseline in number of headache attacks as the primary end point, no significant difference was observed compared to placebo.<sup>2)</sup> Due to the difficulties in interpreting some results such as that the effect of BoNT-A 25 U is superior to that of 75 U,<sup>3)</sup> Evers et al.<sup>4)</sup> concluded that the prophylactic effect of BoNT-A for paroxysmal migraine is not certain. However, a recent double-blind randomized placebo-controlled trial of Dysport showed superiority of Dysport compared to placebo at some secondary end points.<sup>5)</sup> In addition, since some open-label studies have reported the effectiveness of BoNT-A, the prophylactic effect of BoNT-A for paroxysmal migraine cannot be totally excluded.

On the other hand, the effect of BoNT-A on chronic daily headache (CDH) and chronic migraine has attracted attention in North America. Mathew et al.<sup>6)</sup> randomized CDH patients to placebo- and BoNT-A-treated groups, and examined the therapeutic effect during treatment for 180 days. During this period, the majority of the CDH patients had chronic migraine. For the primary end point, which was the change from baseline in frequency of headache-free days in a 30-day period, there was no difference between BoNT-A- and placebo-treated groups. However, significant differences were observed in secondary end points including the percentage of patients with a decrease in headache frequency of 50% or greater. Furthermore, a subanalysis of patients not receiving other prophylactic medications revealed significant improvement in headache symptoms for many outcome measures in BoNT-A-treated group compared to placebo-treated group.<sup>7)</sup> With this background, multiple centers in North America and Europe jointly planned a phase III clinical trial called PREEMPT (the Phase III Research Evaluating Migraine Prophylaxis Therapy) to investigate the efficacy of BoNT-A for chronic migraine. Eventually PREEMPT 1 was conducted in North America and PREEMPT 2 in Europe in parallel. In this trial, a total of 1,384 patients with chronic migraine participated and the BoNT-A-treated group was administered doses of 155 to 195 U. The double-blind trial period was planned for a relatively long period of 24 weeks. In PREEMPT 1, no significant difference was observed between BoNT-A- and placebo-treated groups with respect to the primary end point, which was mean change from baseline in number of headaches per 28 days.<sup>8)</sup> However, in PREEMPT 2, a significant difference was detected between two groups for the primary end point of change from baseline in number of days with headache per 28 days.<sup>9)</sup> An analysis of the pooled data of PREEMPT 1 and 2 concluded that BoNT-A significantly improves headache symptom compared with placebo in chronic

migraine patients.<sup>10)</sup> Regarding the symptom reduction effect for chronic migraine, BoNT-A demonstrated equivalent efficacy as topiramate in comparative studies.<sup>11)12)</sup> Many clinical studies have evaluated BoNT-A as having few serious adverse reactions and high tolerability. Based on the results of PREEMPT, BoNT-A is approved for the treatment of chronic migraine in American and European countries.

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## • Search terms and secondary sources

- Search database: PubMed (2011/12/21)
- Botulinum neurotoxin and migraine 198

## 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**

### Background and Objective

The ICHD-II defined visual, sensory or speech symptoms as aura of migraine, and visual aura is the most frequently encountered. Visual aura without headache is observed especially in the elderly. In this section, literature was searched on the diagnosis and the relevance of treatment for typical aura without headache.

### Comments and Evidence

#### 1. Diagnosis

According to the International Classification of Headache Disorders 2nd Edition (ICHD-II),<sup>1)2)</sup> the diagnostic criteria for typical aura without headache are as follows.

A. At least 2 attacks fulfilling criteria B to D

B. Aura consisting of at least one of the following, with or without speech disturbance, but no motor weakness:

1. fully reversible visual symptoms including positive features (such as flickering lights, spots or lines) and/or negative features (loss of vision)
2. fully reversible sensory symptoms including positive features (pins and needles) and/or negative features (numbness)

C. At least two of the following:

1. homonymous visual symptoms or unilateral sensory symptoms (or both)
2. at least one aura symptom develops gradually over  $\geq 5$  minutes, and/or different aura symptoms occur in succession over  $\geq 5$  minutes
3. each symptom lasts  $\geq 5$  and  $\leq 60$  minutes
4. not aggravated by routine physical activity such as walking or climbing stairs

D. Headache does not occur during aura or within 60 minutes following aura

E. Not attributed to another disorder

In the Framingham study including 2,110 subjects, visual aura without headache was reported by 26 subjects (1.23%), 77% of whom started having the symptoms after age 50 years, 42% had no history of migraine, and 58% never had accompanying headache.<sup>3)</sup> In another study of 100 women with migraine and 245 healthy women, The prevalence of visual aura without headache was 37% in migraine patients and 13% in the general population.<sup>4)</sup> In a study that observed patients who had migraine with aura for 10 to 20 years, 11% of the patients evolved to visual aura without headache.<sup>5)</sup> Therefore, it may be concluded that typical aura without headache is relatively common in elderly persons, and patients who have migraine with aura tend to evolve to only visual aura with advancing age.

It is important to differentiate from other diseases such as transient ischemic attack, recurrent cerebral embolism, epileptic seizure, and retinal disease. Special attention has to be given to cases of elderly onset without a history of migraine. In these cases, head MRI, magnetic resonance angiography (MRA) and electroencephalography should be conducted actively.

## 2. Treatment

There is no clear evidence concerning the necessity of treatment for typical aura without headache. The Framingham study reported no relationship between visual aura per se and increased risk of stroke.<sup>3)</sup> On the other hand, studies have demonstrated that cerebral infarction is more frequent in patients who have migraine with aura.<sup>3)</sup> A meta-analysis of eight studies that stratified the risk of cerebral infarction by the presence or absence of aura in migraine patients reported that the risk was significantly higher in patients who had migraine with aura [2.16 (1.53 to 3.03)] compared to patients who had migraine without aura [1.23 (0.90 to 2.11)], but the absolute number was very small.<sup>6)</sup> Furthermore, in a population-based cross-sectional study of 780 subjects, patients who had migraine with aura had significantly high odds ratio of 12.4 for deep white matter lesion and 3.4 for cerebral infarction, but there was no association with cognitive impairment.<sup>7)</sup>

The above findings thus indicate that for typical aura without headache that is common seen in the elderly, active acute treatment or prophylactic therapy is not necessary. However, in the case that the symptoms occur frequently or last a long duration, or when they cause disability in daily living, use of prophylactic drugs for migraine may be considered. Although the evidence so far is limited to case reports, valproic acid, gabapentin, topiramate, propranolol, and lomerizine are being used for prophylactic therapy. Among them, valproic acid and lomerizine that are covered by health insurance in Japan are recommended.<sup>8)</sup> In a randomized double-blind, placebo-controlled cross-over study of tonabersat, a gap junction inhibitor, although the frequency of headache per se did not decrease, aura was significantly reduced from a mean of 3.2 episodes to 1 episode per 12 weeks. This agent may become a new treatment option in the future.<sup>9)</sup> Since triptans do not reduce aura, use of triptans for typical aura without headache has no clinical relevance.<sup>10)11)</sup>

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- Search database: PubMed (2012/6/4)  
Typical migraine aura without headache 228  
Typical aura without headache 3665  
& stroke 442  
& brain infarction 114
- Search database: Ichushi Web for articles published in Japan (2012/6/4)  
Typical aura without headache 5  
Typical migraine aura without headache 0

## How should chronic migraine be treated?

### Recommendation

When migraine becomes chronic, implement appropriate prophylactic therapy (initiate prophylactic drug for migraine, or increase the dose, or change prophylactic drug, or add prophylactic drug) as early as possible. Investigate the reason for chronification, and simultaneously treat comorbid conditions if present.

**Grade B**

### Background and Objective

The goals of treating chronic migraine are to reduce headache frequency and severity, and duration of chronic migraine, and at the same time to limit the use of acute treatment drugs, prevent transformation to medication-overuse headache, and improve the functions and activities of daily living.<sup>1)</sup> In recent years, the pathophysiology of chronification and organic changes in the brain have been elucidated gradually [see CQ II-1-6-1 What is the prognosis of migraine (including chronification of migraine)? (page 77)]. Also, compared to episodic migraine, chronic migraine results in more severe functional impairment, lower quality of life, anxiety and depression, and higher rate of medical facility consultation.<sup>2)</sup> Therefore treatment for chronic migraine is very important. Literature was searched focusing on double-blind placebo-controlled trials of pharmacotherapy (excluding botulinum neurotoxin type A) for chronic migraine, especially chronic daily headache.

### Comments and Evidence

Literature in English language from 1993 to 2011 was searched. Double-blind randomized controlled trials (RCT) of prophylactic therapies for chronic migraine (CM) and chronic daily headache (CDH) with drugs currently used in Japan (including those not covered by health insurance) were identified. The drugs comprise antiepileptic drugs of gabapentin (GBP), valproic acid (VPA), topiramate (TPM) and levetiracetam (LEV); the antidepressant amitriptyline; and the central muscle relaxant tizanidine.

In a GBP–placebo cross-over study reported in 2003 in which GBP 2,400 mg/day was administered for 6 weeks, percent headache-free days was 9.1% more with GBP.<sup>3)</sup> Adverse effects were observed in 31% of subjects taking GBP, mainly vertigo, somnolence, deconditioning and nausea.

In a study of VPA 1,000 mg/day given for 3 months compared with placebo, patients with CM showed significant decreases in scores for the maximum pain scale (visual analog scale: VAS) and the usual VAS, together with a significant decrease in headache frequency.<sup>4)</sup> The adverse effects of VPA were rare.

A large volume of evidence is available for TPM.<sup>5)-7)</sup> Treatment with approximately 100 mg/day for 3 months significantly reduced the number of days with headache per month. However, regarding whether TPM prevents the progression of frequent episodic migraine to CDH, there was no significant difference compared with placebo. Major adverse effects were paresthesia, fatigue, dizziness, and nausea, but there were no serious adverse effects.

A placebo-controlled study of LEV 3 g/day reported that LEV did not significantly reduce the number of days with headache, but significantly improved VAS score.<sup>8)</sup>

A study on amitriptyline conducted in 1976-79 was reported in 2011.<sup>9)</sup> At 8 and 16 weeks after amitriptyline (25 to 100 mg/day) treatment was started, headache frequency in CDH patients was reduced significantly. The adverse effects of amitriptyline included thirst, constipation, urinary retention, and dizziness.

In a placebo-controlled study of tizanidine, an A2 adrenergic receptor agonist, tizanidine (mean 18 mg/day) was effective in reducing the number of days with headache, headache intensity and headache duration.<sup>10)</sup> However, tizanidine and placebo did not differ in the MIDAS score.

According to the above findings, valproic acid, topiramate (currently not covered by health insurance), and amitriptyline (off-label use for migraine) may be recommended for the treatment of CM and CDH in Japan. Considering the experience gained until now, lomerizine may also be added to this list.

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## • Search terms and secondary sources

- Search database: PubMed (2011/12/21)
- chronic daily headache treatment 17966
- & chronic migraine 1641
- & therapy 1468
- chronic daily headache double-blind placebo-controlled study 764
- chronic migraine & treatment 2029
- & therapy 1764
- & double-blind placebo-controlled study 47

# III

## Tension-type headache



## How is tension-type headache classified?

### Recommendation

Since 1962, various classifications for tension-type headache have been proposed. Currently, classification according to the International Classification of Headache Disorders 3rd Edition (beta version) (ICHD-3beta) published in 2013 is recommended.

Grade A

### Background and Objective

Diagnostic classification that forms the basis of guidelines is certainly important for formulating clinical care and treatment policies. The ICHD-3beta is not simply a document based on classification, it also addresses diagnosis and treatment scientifically and practically from all aspects.

### Comments and Evidence

The classification of tension-type headache (TTH) is provided by the International Classification of Headache Disorders 3rd edition beta version (ICHD-3beta).<sup>1)2)</sup>

The division of tension-type headache into episodic and chronic types adopted by the first edition of the International Classification of Headache Disorders (1988)<sup>3)</sup> is extremely useful. The International Classification of Headache Disorders 2nd edition (ICHD-II) further subdivides the episodic type according to frequency, and states that this is based on the difference in pathophysiology. The former *episodic tension-type headache* (ETTH) is further classified into 2.1 *infrequent episodic tension-type headache* (IETTH) with headache episodes less than once per month (<12 days/year), and 2.2 *frequent episodic tension-type headache* (FETTH) with higher frequency and longer duration (<15 days/month). The infrequent subtype has little impact on the individual, and to a certain extent, is understood to be within the range of physiological response to stress in daily life. However, frequent episodes may cause disability that sometimes requires expensive drugs and prophylactic medication. Headache classified as 2.3 *chronic tension-type headache* (CTTH) with 15 or more headache episodes per month (≥15 days/month) significantly impacts quality of life (QOL) and causes severe disability in daily living, accompanied by high personal and socio-economic costs.

The classification of tension-type headache excerpted from the ICHD-3beta is shown below.

#### 2. Tension-type headache

##### 2.1 Infrequent episodic tension-type headache

2.1.1 Infrequent episodic tension-type headache associated with pericranial tenderness

2.1.2 Infrequent episodic tension-type headache not associated with pericranial tenderness

##### 2.2 Frequent episodic tension-type headache

2.2.1 Frequent episodic tension-type headache associated with pericranial tenderness

2.2.2 Frequent episodic tension-type headache not associated with pericranial tenderness

##### 2.3 Chronic tension-type headache

2.3.1 Chronic tension-type headache associated with pericranial tenderness

2.3.2 Chronic tension-type headache not associated with pericranial tenderness

##### 2.4 Probable tension-type headache

2.4.1 Probable infrequent episodic tension-type headache

2.4.2 Probable frequent episodic tension-type headache

2.4.3 Probable chronic tension-type headache

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- 3) Headache Classification Committee of the International Headache Society: Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. of headache. Headache Classification Committee of the International Headache Society. Cephalalgia 1988; 8(Suppl 7): 1-96.

- **Search terms and secondary sources**

- Search database: PubMed (2011/12/14)  
tension type headache 2458  
& classification 519  
& history 95  
(However, no useful references were identified)

## How is tension-type headache diagnosed?

### Recommendation

Tension-type headache is diagnosed according to the diagnostic criteria of the International Classification of Headache Disorders 3rd Edition (beta version) (ICHD-3beta).

**Grade A**

### Background and Objective

Diagnostic criteria should address diagnosis and treatment scientifically and practically from all aspects. As with other diseases, it is necessary to diagnose tension-type headache based on diagnostic criteria that fulfill the above requirements. Comments concerning the diagnosis of tension-type headache as well as the diagnostic criteria of the ICHD-3beta<sup>1)</sup> are given below.

### Comments and Evidence

The diagnostic criteria for tension-type headache are shown below.

Subtypes of tension-type headache are mainly diagnosed by their respective frequencies of headache (criterion A) as well as by fulfilling the following criteria (B to E).

B. Headache lasting from 30 minutes to 7 days

C. Headache has at least two of the following characteristics:

1. bilateral location
2. pressing or tightening (non-pulsating) quality
3. mild to moderate intensity
4. not aggravated by routine physical activity such as walking or climbing stairs

D. Both of the following:

1. no nausea or vomiting (anorexia may occur)
2. no more than one of photophobia or phonophobia

However, for chronic tension-type headache

1. no more than one of photophobia, phonophobia or mild nausea
2. neither moderate or severe nausea nor vomiting

E. Not better accounted for by another ICHD-3 diagnosis.

A.

2.1 For *infrequent episodic tension-type headache*, headache occurring on <1 day per month (<12 days per year)

2.2 For *frequent episodic tension-type headache*, headache occurring on 1 to 14 days per month (≥12 days and <180 days per year)

2.3 For *chronic episodic tension-type headache*, headache occurring on ≥15 days per month (≥180 days per year)

2.4 In *probable tension-type headache*, fulfilling one of the diagnostic criteria for tension-type headache, but not meeting criteria for migraine.

According to the opinions of general clinicians, migraine and tension-type headache often cannot be differentiated by severity and the presence or absence of nausea, vomiting, photophobia and phonophobia. Furthermore, the existence of transitional form or intermediate form of tension-type headache and migraine is also a problem.<sup>2)3)</sup> In addition, the diagnosis of chronic headache is associated with the issue of medication overuse, and hence differentiation is often difficult. These problems have not been completely solved (see CQ III-5, page 158).

On the other hand, it was criticized that the diagnostic criteria for tension-type headache in the first edition of the International Classification of Headache Disorders (1988)<sup>4)</sup> adopted many negative features, which might be picked up by other headache disorders. To address the shortcoming of the first edition, the International Classification of Headache Disorders 2nd Edition (ICHD-II)<sup>5)</sup> has incorporated items of “*probable chronic migraine*” and “*probable tension-type headache*”, which have almost solved the issues. The essential feature of the diagnostic criteria may be considered a reverse of the diagnosis of migraine. Furthermore, in ICHD-II,<sup>5)</sup> episodic tension-type headache is subdivided into an infrequent subtype with headache episodes less than once per month and a frequent subtype. The infrequent subtype has relatively little

impact on the individual and does not draw much attention from the medical profession. However, frequent occurring tension-type headache may be associated with disability that sometimes necessitates treatment with expensive drugs or prophylactic medications. Moreover, headache classified as the chronic subtype is a serious disease, having great impact on quality of life (QOL) and causing severe disability.

The ICDH-3beta<sup>1)</sup> is not simply a document based on classification, but involves careful scrutiny of almost all the available articles with high level of evidence. Its use for diagnosis is highly recommended.

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- 5) Headache Classification Subcommittee of the International Headache Society: The International Classification of Headache Disorders, 2nd edition. *Cephalalgia* 2004; 24(Suppl 1): 9-160.

## • Search terms and secondary sources

- Search database: PubMed (2011/12/14)  
tension type headache 2458  
& classification 519  
& history 95  
(However, no useful references were identified)

## How big is the population of tension-type headache patients?

## 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**

### Background and Objective

Tension-type headache is the most common primary headache, but is also the least studied. Identifying the risk factors and triggers and knowing the prognosis are important in the treatment of tension-type headache.

### Comments and Evidence

Headache societies including the International Headache Society (IHS) in collaboration with the World Health Organization (WHO) started the initiative 'Lifting The Burden: The Global Campaign to Reduce the Burden of Headache Worldwide'. As a part of the initiative, Stovner et al.<sup>1)</sup> calculated the global prevalence of headache by reviewing the results of headache epidemiological surveys conducted worldwide. According to their study, the percentage of the global population with tension-type headache was 38%, and 46% when adult population was calculated. However, only 12 epidemiological studies on adults with tension-type headache were used in their estimation, and the number was extremely small compared to migraine. Moreover, the prevalence reported in different studies varied greatly: ranging from 21.7% to 86.5% in 1-year prevalence, and 12.9% to 78% in life-time prevalence. In Japan, the epidemiological study conducted by Takeshima et al.<sup>2)</sup> in Daisen reported 1-year prevalence of 21.7%. This figure was also used in the above-mentioned estimation of global prevalence. Following the report of Stovner et al., several epidemiological studies have been conducted, also showing great variation in prevalence. However, most of the studies do share two common findings: tension-type headache has the highest prevalence among the primary headaches, and the prevalence is higher in women than in men. Although some studies reported significant differences in prevalence depending on factors such as educational level and place of domicile (urban or rural), the results were not consistent among studies. Because the prevalence is high in Europe and low in Africa, a report emphasized the correlation between latitude and prevalence.<sup>3)</sup> The discrepancy in prevalence has been attributed to survey methodology (personal interview, telephone interview, questionnaire, others).<sup>1)</sup> To obtain the correct prevalence, apart from establishing appropriate survey methods, it is necessary to address the diagnostic issues such as dual diagnosis of chronic migraine and chronic tension-type headache as well as the differentiation between transformed migraine and chronic tension-type headache.<sup>4)</sup>

There are few studies on risk factors and triggers of tension-type headache, and these factors have not been established. Obesity, insufficient exercise and smoking have been reported to be independent risk factors.<sup>5)</sup> On the other hand, there is also report that while obesity is a risk factor for chronification of episodic migraine, it is not a risk factor for tension-type headache.<sup>6)</sup>

The prevalence of tension-type headache decreases with age, but the decrease is not as marked as for migraine. Although rare, first onset after age 50 has been reported, and the prevalence remains high even among the elderly.<sup>7)</sup> Although the prognosis is generally favorable for episodic tension-type headache, transition to chronic tension-type headache is found in some cases. Lyngberg et al.<sup>8)</sup> reported that factors associated with poor outcome for tension-type headache include chronic headache at baseline, coexisting migraine, being single, and sleeping problems.

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## • Search terms and secondary sources

- Search database: PubMed (2011/3/10)
  - tension type headache 2347
  - & prevalence 652
  - & risk factor 205
  - & prognosis 311

## 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**

### Background and Objective

Tension-type headache is the most common headache among the primary headaches. However, the precise pathogenetic mechanism is still unclear, and tension-type headache is also one of the least studied primary headaches regarding the pathophysiology.

In the past, tension-type headache was considered to be primarily psychogenic. After publication of the first edition of the International Classification of Headache Disorders (1988), many studies were published strongly suggesting a neurobiological basis, at least for the severe subtypes of tension-type headache. This section reviews the evidence for the pathophysiology of tension-type headache.

### Comments and Evidence

#### 1. Peripheral elements

A high prevalence of pericranial muscle tenderness in tension-type headache patients than in healthy persons has been proven. Moreover, the degree of tenderness is known to correlate with the frequency and intensity of tension-type headache.<sup>1)</sup> This tendency has been reported to be strong in women.<sup>2)</sup> On the other hand, muscle tenderness in pericranial and neck-shoulder regions has been reported to be normal in children with tension-type headache.<sup>3)</sup> However, evaluation of severity of tenderness varies among investigators, and objective assessment is difficult to achieve. For the evaluation of tenderness in tension-type headache, the usefulness of total tenderness score (TTS) and objective assessment using muscle hardness meter has been proven.<sup>4)-6)</sup> Electromyography also has been used to measure muscle tone in tension-type headache.<sup>4)</sup>

In a study that examined the effect of administration of botulinum toxin on chronic tension-type headache, although electromyographic improvement in the temporal muscle was observed, headache did not improve.<sup>7)</sup> Other studies also reported no difference in interstitial lactate concentration in the trapezius muscle at rest and during exercise in patients with chronic tension-type headache compared to healthy controls,<sup>8)</sup> and also no increase in inflammatory mediators at tender points of the trapezius muscle.<sup>9)</sup> These findings thus suggest that the pathophysiology of chronic tension-type headache is not associated with hyperactivity, inflammation or metabolic disturbance of pericranial muscles.<sup>10)</sup>

#### 2. Central elements

Because exercise-induced increase in trapezius muscle blood flow is blunted in patients with chronic tension-type headache, involvement of sympathetic vasoconstriction due to over-excitation of the central nervous system is possible.<sup>11)</sup> Moreover, increased pain perception was observed in both single and repetitive 2-Hz electrical stimulations, suggesting abnormality in pain control mechanism in the central nervous system.<sup>12)</sup>

Administration of nitroglycerin that generates nitric oxide in the body is known to induce typical tension-type headache after several hours,<sup>13)</sup> suggesting that central hypersensitivity to nitric oxide may also be involved in chronic tension-type headache, as in migraine.<sup>10)</sup> In addition, administration of L-N(G)-methylarginine hydrochloride that inhibits nitric oxide has been shown to reduce muscle tenderness and attenuate headache clinically.<sup>14)15)</sup> These findings may provide evidence supporting the hypothesis that sensitization of the trigeminal nerve may also be a central element involved in tension-type headache.<sup>13)</sup>

In normal persons, when the trigeminal nerve is stimulated as an afferent pathway, a muscle contraction inhibitory mechanism mediated by interneurons in the lateral pontine tegmentum connecting with the spinal trigeminal nucleus is known to exist. In some types of tension-type headache, this central muscle contraction inhibitory mechanism has been



reported to be deficient.<sup>15)16)</sup> In chronic tension-type headache, the possibility of secondary involvement of nociceptors in the trigeminal system has been suggested.<sup>17)</sup>

On the other hand, in episodic tension-type headache, peripheral sensitization of myofascial afferent sensory nerves has been suggested to be a cause of hypersensibility.<sup>18)</sup>

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## • Search terms and secondary sources

- Search database: PubMed (2011/12/21)  
tension type headache & pathophysiology 745

## 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 International Classification of Headache Disorders 3<sup>rd</sup> Edition (beta version) includes the concept of transformed migraine.

**Grade B**

### Background and Objective

Although transformed migraine is not described in the International Classification of Headache Disorders 2nd Edition (ICHD-II), it is an important headache disorder encountered in the routine clinical setting. While differentiation between transformed migraine and chronic tension-type headache may be difficult, discrimination of the two is important in the treatment of chronic headaches.

### Comments and Evidence

“Transformed migraine” as proposed by Mathew<sup>1)</sup> is not included in the International Classification of Headache Disorders 2nd Edition (ICHD-II), but this headache disorder is widely accepted in routine clinical practice. A large number of patients present with a pattern consisting of infrequent but severe migraine attacks at younger ages, evolving to more frequent but less severe headaches as age advances, with a gradual loss of migraine characteristics. Transformed migraine is generally diagnosed according to the Silberstein-Lipton diagnostic criteria.<sup>2,3)</sup> These diagnostic criteria include the item of “a history of migraine”, while the current headache diagnostic criteria only specify the frequency and duration of headache attacks. With the Silberstein-Lipton diagnostic criteria, if the headache fulfilled the criteria for migraine in the past, then transformed migraine can be diagnosed even though the present headache has lost all the elements of migraine. In other words, transformed migraine is not diagnosed as a point at one headache episode, but as a line including the past history of headache.

The ICHD-II<sup>4)</sup> basically diagnoses headache episodes individually, and diagnosis criteria including also the past history are not compatible with ICHD-II. This constitutes the difference in concept between *chronic migraine* in ICHD-II published in 2004 and *transformed migraine*.<sup>2)</sup> The 2004 diagnostic criteria for chronic migraine require that individual headache episodes fulfill the characteristics of migraine. Therefore, for patients who satisfy the Silberstein-Lipton criteria for transformed migraine, if their present headaches have lost all the features of migraine, they are most probably not diagnosed with chronic migraine but with chronic tension-type headache if there is no medication overuse. However, to address the criticism that very few patients fit into the 2004 diagnostic criteria for chronic migraine, the International Headache Society published revised diagnostic criteria for chronic migraine in 2006, to be included in the appendix of ICHD-II.<sup>5)</sup> According to these criteria, a headache can be diagnosed as chronic migraine if headaches fulfilling the diagnostic criteria for migraine occur on more than 8 days per month, even in the presence of other headaches. Furthermore, in the case that the present headache has no characteristics of migraine but progression to migraine attack is suggested, the criterion “treated and relieved by triptans or ergot before the expected development of migraine symptoms” was added to allow a diagnosis of chronic migraine. Using these criteria, a considerable number of cases of transformed migraine without medication overuse would be diagnosed as chronic migraine. However, if triptan or ergotamine is not effective, then the headache will not be classified as chronic migraine. Eventually, transformed migraine and chronic migraine are not the same entity. In the International Classification of Headache Disorders 3<sup>rd</sup> Edition (beta version) published in 2013,<sup>6)</sup> *chronic migraine* includes the concept of transformed migraine.

In conclusion, when headache episodes are diagnosed individually, differentiation between chronic tension-type headache and transformed migraine is difficult, but the two can be discriminated if past history is considered.<sup>7)</sup> The general treatment strategy for chronic tension-type headache that has evolved from episodic tension-type headache may differ from that for transformed migraine that has lost the migraine features and resembles chronic tension-type headache. When making a

diagnosis of chronic tension-type headache, the possibility of transformed migraine has to be borne in mind and a careful clinical interview including past history of headache has to be conducted.

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- Search database: PubMed (2011/3/10)  
tension type headache 2347  
& transformed migraine 84

## 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 non-pharmacotherapy. 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**

### Background and Objective

Tension-type headache is the most common headache among the primary headaches. Among the various types, frequent tension-type headache and chronic tension-type headache cause severe disability in daily living, and are conventionally treated with acute and prophylactic therapies. Comments on the evidence for the necessity and options of these treatments are given in this section.

### Comments and Evidence

The International Classification of Headache Disorders 3rd Edition (beta version) (ICHD-3beta)<sup>1)</sup> subdivides episodic tension-type headache into an infrequent subtype with headache episodes less than once per month and a frequent subtype. Tension-type headaches that occur infrequently and improve with over-the-counter (OTC) drugs usually do not require consultation of medical facility, except for the patient's own reassurance. On the other hand, when headache restricts daily life or when headache frequency and intensity increase, then treatment is required. Furthermore, patients who are taking OTC drugs more than necessary may develop medication-overuse headache or rebound headache, and these patients also require appropriate treatment<sup>2)3)</sup> (grade A recommendation).

In general, patients who need treatment are those who have frequent episodic tension-type headache or chronic tension-type headache. While central pain mechanisms (including stress, depressed mood, central pain processing abnormality, and central sensitization) play more important roles in chronic tension-type headache, peripheral pain mechanisms (including muscle strain, myofascial factor, and peripheral sensitization) are most likely involved in infrequent episodic tension-type headache. Treatments for central mechanisms such as tricyclic antidepressants, stress management, relaxation training, and acupuncture; and therapies for peripheral mechanisms such as relaxation training and physical therapy have been investigated<sup>4)</sup> (grade C recommendation).

Therapies for tension-type headache are divided into acute (abortive) treatment and prophylactic treatment. Each consists of pharmacotherapy and non-pharmacotherapy<sup>4)5)</sup> (grade A recommendation).

For acute treatment by pharmacotherapy, medication-overuse headache that results in treatment failure should always be borne in mind, and use for more than 2 to 3 days per week should be avoided<sup>1)-3)</sup> (grade A recommendation).

Prophylactic therapy should be considered for patients with frequent episodic tension-type headache and patients who do not respond adequately to acute treatment. Especially, for patients who have headaches two or more times per month, prompt initiation of prophylactic therapy should be considered because headache may subsequently increase exponentially<sup>6)</sup> and the effectiveness of prophylactic therapy may be reduced by frequent use of acute medications.<sup>2)</sup> However, whether treatment can prevent or delay the progression of infrequent tension-type headache to chronic tension-type headache remains unclear.<sup>2)</sup> Furthermore, a review reported no prophylactic effect of antidepressants.<sup>7)</sup> For this reason and considering also adverse effects, if there is no response, a decision has to be made on whether to continue medication for three months (6 months the longest) or discontinue treatment<sup>4)5)</sup> (grade A recommendation).

On the other hand, stress and mental strain are risk factors of tension-type headache,<sup>8)9)</sup> while depressive and anxiety disorders are risk factors of progression to chronic headache.<sup>10)</sup> Moreover, compared to headache-free subjects, patients with migraine and chronic tension-type headache are 2 to 5 times more likely to have depressive and anxiety disorders as comorbidities.<sup>11)-14)</sup> These psychiatric disorders also require treatment (grade C recommendation).

Regarding treatment for oromandibular dysfunction, since headache-free subjects may also have oromandibular

dysfunction, this aspect has not been analyzed adequately. However, since oromandibular dysfunction is a risk factor of tension-type headache, treatment should be considered<sup>15)-17)</sup> (grade C recommendation).

Other factors that may induce tension-type headache include inadequate exercise and prone posture, and basic treatment should be considered (grade C recommendation).

When encountering cases in which diagnosis of headache type is difficult or treatment effect is inadequate, referral to an expert is recommended.<sup>2)</sup>

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- Search database: PubMed (2011/12/21)  
tension headache & treatment 646  
tension (type) headache & treatment 1215

## 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 non-steroidal anti-inflammatory drugs (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 2 to 3 times per week should be avoided.

**Grade A-C**

### Background and Objective

Tension-type headache is the most commonly encountered headache in routine clinical care, and occupies the largest fraction of functional headache. Various pharmacotherapies are the mainstay of acute treatment for tension-type headache. However, acute pharmacotherapy should be used with caution so as not to induce medication-overuse headache.

### Comments and Evidence

Pharmacotherapy using analgesics and NSAIDs is the main acute treatment for tension-type headache.<sup>1)-7)</sup> The representative analgesic is acetaminophen, and the representative NSAIDs aspirin, mefenamic acid, and ibuprofen are recommended (grade A recommendation). However, since adverse effects such as gastrointestinal disturbance and hematopoietic disturbance may occur, caution has to be exercised during administration. For pregnant women with onset of tension-type headache, acetaminophen is selected also from the safety viewpoint.

Combination therapy with caffeine, which is known to be an effective acute medication, is fast-acting but can cause dependence, with a risk of inducing medication-overuse headache.<sup>8)</sup> A recent report has indicated the effectiveness of selective cyclooxygenase (COX)-2 inhibitor for the treatment of episodic tension-type headache.<sup>9)</sup>

Representative drugs and the recommendation grades are listed below.

#### 1. Analgesics and NSAIDs (grade A recommendation)

- (1) acetaminophen 500 mg
- (2) aspirin 500 to 1,000 mg
- (3) ibuprofen 200 to 800 mg
- (4) ketoprofen 25 mg
- (5) naproxen 200 to 600 mg
- (6) diclofenac 12.5 to 50 mg
- (7) loxoprofen 60 mg

All taken as needed

#### 2. Caffeine 65 to 200 mg taken as needed (useful when used in combination) (grade B recommendation)

#### 3. Selective COX-2 inhibitors (grade C recommendation)

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- **Search terms and secondary sources**

- Search database: PubMed (2011/12/21)
  - tension headache & treatment 654
  - tension (type) headache & treatment 1208



## How should prophylactic therapy for tension-type headache be conducted?

### Recommendation

Prophylactic therapy for tension-type headache can be broadly divided into pharmacotherapy and non-pharmacotherapy. Pharmacotherapy using mainly antidepressants, and non-pharmacotherapies 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 non-pharmacotherapies have not been established.

**Grade A-C**

### Background and Objective

Prophylactic therapies for tension-type headache comprise pharmacotherapy and non-pharmacotherapy. Pharmacotherapy is conducted mainly using antidepressants. In contrast, non-pharmacotherapy attempts to reduce headache utilizing combinations of various modalities such as electromyographic biofeedback therapy, physical therapy, acupuncture, exercise therapy (exercise to relax neck and occipital muscles), psychotherapy, and lifestyle guidance.

### Comments and Evidence

Among the different types of tension-type headache, prophylactic therapy is used for episodic tension-type headache (especially the frequent subtype) and chronic tension-type headache. In episodic tension-type headache, since not only increased craniocervical muscle tension induces pain but central pain mechanisms are also involved,<sup>1)2)</sup> pain processing dysfunction caused by psychological stress or emotional disturbance is presumed to be the fundamental problem. From this point of view, treatment with oral antidepressants is most frequently used as a treatment with high level of evidence.<sup>3)-8)</sup> Especially, prophylactic therapy using tricyclic antidepressants such as amitriptyline is recommended (grade B recommendation). Tetracyclic antidepressants are also sometimes selected because they can be used in combination with muscle relaxants such as tizanidine and eperison, with also the merit of few adverse effects.

For chronic tension-type headache also, first a history should be taken on whether there is medication overuse; and in the case of overuse, in principle medication is discontinued or tapered. Pharmacotherapy for chronic tension-type headache also mainly uses muscle relaxants and antidepressants. Since chronic tension-type headache is often evolved from episodic tension-type headache, the tricyclic antidepressant amitriptyline is especially effective as a prophylactic medication. For treatment, start from a low dose of 5 to 10 mg/day, and titrate up to around 30 mg/day, but pay attention to adverse effects such as thirst and constipation. In chronic tension-type headache, headache per se is a stressor, and tends to cause secondary depression or anxiety. And, these psychological factors may further exacerbate headache, leading to refractory headache. For patients who have developed refractory headache, explain to the patients about the relationship between psychological stress and headache. At the same time, in addition to tricyclic or tetracyclic antidepressants for the treatment of depression as for episodic tension-type headache, selection and use of appropriate serotonin-noradrenaline reuptake inhibitor (SNRI) or noradrenergic and specific serotonergic antidepressant (NaSSA) is recommended. For patients who complain of strong anxiety, use of anxiolytic in treatment provides prompt relief. The effectiveness of anxiolytic was investigated in a randomized controlled trial (RCT) of etizolam and mefenamic acid combination therapy in 144 patients with frequent or infrequent tension-type headache. While no overall significant difference for etizolam was detected, headache and shoulder pain were improved significantly in female and young patients treated with etizolam and mefenamic acid combination compared to mefenamic acid alone.<sup>9)</sup>

Studies in recent years have found that among patients with chronic tension-type headache, some manifest headache as a somatic symptom of psychiatric disorder,<sup>10)</sup> and the prevalence of such cases is high. The majority are somatoform disorders such as somatization disorder and pain disorder, emotional disorders such as major depression and dysthymia, and anxiety

disorders such as panic disorder and generalized anxiety disorder. These are secondary headaches [International Classification of Headache Disorders, 3rd edition (beta version); A12. *Headache attributed to psychiatric disorder*], and treatment in corroboration with psychosomatic specialist or psychiatrist is recommended.

No evidence can be found for the therapeutic effect of greater occipital nerve block that has long been used for the treatment of chronic tension-type headache. Several studies investigating the effectiveness of botulinum toxin<sup>11)-14)</sup> reported no therapeutic effect for episodic tension-type headache, and therapeutic effect for chronic tension-type headache only when relatively large doses were injected at specific sites. It should be noted that when botulinum toxin is chosen to treat tension-type headache, fast-acting effect should not be expected. Other non-pharmacotherapies<sup>7)</sup>, used for prophylactic therapy<sup>15)-17)</sup> include electromyographic biofeedback therapy (grade A recommendation) and exercise for headache relief (grade B recommendation), as well as cognitive behavioral therapy, neck acupressure, acupuncture, Tiger Balm, percutaneous electrical nerve stimulation (PENS), and hypnotherapy, all of which are grade C recommendation.

Representative drugs used in prophylactic therapy are shown below.

#### 1. Antidepressants/antiepileptic drugs

##### 1) Tricyclic antidepressants

- (1) amitriptyline 5 to 75 mg/day (grade A recommendation)
- (2) clomipramine 75 to 150 mg/day (grade B recommendation)

##### 2) Tetracyclic antidepressants (grade B recommendation)

- (1) maprotiline 75 mg/day
- (2) mianserin 30 to 60 mg/day

##### 3) NaSSA

- mirtazapine 30 mg/day (grade B recommendation)

##### 4) Antiepileptic drug

- topiramate (grade C recommendation)

#### 2. Anxiolytics

- (1) alprazolam 0.4 to 1.2 mg/day (grade B recommendation)
- (2) etizolam 0.5 to 1 mg/day (grade B-C recommendation for combination therapy)
- (for both, avoid continuous use)

#### 3. Muscle relaxants

- (1) tizanidine 3 to 6 mg/day (grade B recommendation)
- (2) eperison 150 mg/day (grade C recommendation)

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- **Search terms and secondary sources**

- Search database: PubMed (2011/12/21)  
tension headache & treatment654  
tension (type) headache & treatment1208

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

### Recommendation

Non-pharmacotherapies for tension-type headache include psycho-behavioral therapy, physical therapy, acupuncture, and Tiger Balm<sup>®</sup>, and those with proven usefulness warrant recommendation as treatment method. Among them, combined use of electromyographic biofeedback (psycho-behavioral therapy) and relaxation training is recommended.

**Grade A**

### Background and Objective

Non-pharmacotherapies for tension-type headache include psycho-behavioral therapy, physical therapy, acupuncture, and Tiger Balm<sup>®</sup>, and only those that are proven useful would warrant recommendation. The evidence for the effectiveness of non-pharmacotherapy for tension-type headache is reviewed and commented.

### Comments and Evidence

Non-pharmacotherapies comprise the following:

- A. Psycho-behavioral therapy (grade A or C recommendation)
  - (1) electromyographic biofeedback (grade A recommendation)
  - (2) cognitive behavioral therapy (grade C recommendation)
  - (3) relaxation training (grade C recommendation)
  - (4) hypnotherapy (grade C recommendation)
- B. Physical therapy (grade C recommendation)
  - (1) exercise program
    - \*Exercise for relief of headache (grade B recommendation)
  - (2) massage, neck acupressure
  - (3) ultrasound and electrical stimulation
  - (4) improvement of posture
  - (5) oromandibular treatment
  - (6) hot and cold packs
- C. Acupuncture (grade C recommendation)
- D. Tiger Balm<sup>®</sup> (grade C recommendation)

Psycho-behavioral therapies consist of electromyographic (EMG) biofeedback, cognitive behavioral therapy, relaxation training and hypnotherapy.

In EMG biofeedback, an electromyograph is used to present the action potential of muscles to the patient, so that the patient becomes aware of the muscle tension and try to control it. This method is considered effective. Active use of EMG biofeedback combined with relaxation training achieves long-term efficacy more easily.<sup>1)</sup> However, it is not clear whether the effect differs depending on the subtype of tension-type headache.

Cognitive behavioral therapy is an approach to enable patient to recognize the relationship between stress and headache. Various exercises are used. The method is considered effective, but clear evidence is lacking at present.<sup>2)3)</sup>

Relaxation training includes breathing exercise and meditation. Evidence for effectiveness is inconclusive.<sup>2)</sup>

The effectiveness of hypnotherapy is unknown.<sup>2)4)</sup>

Many of the physical therapies are difficult to evaluate precisely, but study has suggested the effectiveness of exercise program, and this approach is recommended also because of low cost.<sup>5)</sup> Exercise for relief of headache has level 4 evidence, based on expert opinion and experience. However, because of few adverse effects and low cost, exercise for relief of headache is given grade B recommendation. In addition, combined use with massage, relaxation and exercise program is effective.<sup>6)7)</sup> Other treatments are also widely used, but there are no report clearly showing effectiveness. Spinal manipulation has been

used, but no effectiveness is demonstrated and this method is not recommended.

Acupuncture is effective for short-term outcome (up to three months), and is speculated to be more effective in the long term.<sup>8)9)</sup> However, further study is needed.

Topical application of Tiger Balm® or peppermint oil on the forehead is reported to be superior to placebo.<sup>10)</sup>

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## • Search terms and secondary sources

- Search database: PubMed (2011/12/21)
  - tension headache & treatment 646
  - tension (type) headache & treatment 1215

## 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**

### Background and Objective

The pathogenetic mechanisms of tension-type headache remain unclear. Several hypotheses have been proposed. (1) Hypersensitivity to pain in craniocervical tissues (especially increased muscle tone) has been proposed as the peripheral factor. (2) Changes in central pain sensitivity (especially lowering of pain threshold and amplification of normal central nociceptive input) due to continuous excessive nociceptive input from the periphery have been proposed as the central factor. The latter is considered to occur more commonly in chronic tension-type headache.

In tension-type headache, the major action of BTX, which is reducing muscle tone, is expected to improve the peripheral factor. In addition, inhibition of input from muscle spindle may also improve the central factor. Since these effects persist for several months (usually 3-4 months), BTX can be expected to be useful as a prophylactic therapy, but not as a fast-acting agent.

In this section, the effectiveness of BTX in tension-type headache is evaluated.

### Comments and Evidence

Since Zwart et al.<sup>1)</sup> first reported the effect of BTX on tension-type headache in 1994, a large number of reports have appeared. The earlier reports were mostly open-label studies. Recently, randomized placebo-controlled double-blind studies have been conducted.<sup>2)-7)</sup> Among them, two reports corresponding to level I evidence have been published.<sup>2),3)</sup>

A study of BTX treatment in 112 patients with chronic tension-type headache comparing headache at 6 weeks before treatment and 12 weeks after treatment found no significant difference between BTX (500 mouse unit) and placebo.<sup>2)</sup> A study in 300 patients with chronic tension-type headache reported no difference in headache improvement at day 60 after treatment between all BTX doses and placebo, but less decrease in days with headache with 150 U BTX compared to placebo.<sup>3)</sup> However, this study reported 50% reduction in headaches at day 90 in the other dose groups.

Other studies suggested a tendency of symptom improvement up to 12 weeks but no significant difference,<sup>4),5)</sup> and a reduction in headache after a prolonged observation period of 240 days.<sup>6)</sup>

Based on the above reports, the conclusion in American and European countries is that BTX is not effective for chronic tension-type headache, at least by short-term treatment.<sup>8)</sup>

However, there are issues regarding the evaluation of effectiveness of BTX therapy; differences in total dose and site of injection among studies. On one hand, increasing the dose does not achieve effectiveness. On the other hand, two methods of administration are used: injection at a specified site (fixed method), and injection at the site of pain (follow the pain method). In the future, comparative studies including control subjects and using a fixed injection method should be conducted to examine the usefulness of BTX for tension-type headache.

Adverse effects were reported in 2.5 to 25% of subjects treated with BTX, mainly as transient or mild muscular weakness. Safety is rated as tolerable.<sup>8)</sup>

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- Search database: PubMed (2011/12/21)  
Headache & botulinum 379  
{tension type headache} & botulinum 114



# IV

## Trigeminal autonomic cephalalgias

## How are trigeminal autonomic cephalalgias classified and typed?

### Recommendation

The International Classification of Headache Disorders 3rd Edition (beta version; ICHD-3 beta) 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**

### Background and Objective

The objective of this section is to classify “*Trigeminal autonomic cephalalgias*” according to the International Classification of Headache Disorders 3rd Edition (beta version; ICHD-3 beta).<sup>1)2)</sup>

### Comments and Evidence

Cluster headache and related diseases are characterized by short-lasting, unilateral headache attacks accompanied by cranial parasympathetic autonomic symptoms including conjunctival injection, lacrimation, and rhinorrhea. These syndromes support the involvement of trigeminal-parasympathetic reflex activation, and ICHD-3 beta introduces the concept of trigeminal autonomic cephalalgias (TACs) (Table 1). TACs comprise the following subtypes: 3.1 *cluster headache*, 3.2 *paroxysmal hemicrania*, 3.3 *short-lasting unilateral neuralgiform headache attacks*, 3.4 *hemicrania continua*, and 3.5 *probable trigeminal-autonomic cephalalgia*.

**Table 1. Classification of “3. Trigeminal autonomic cephalalgias”**

3.1 Cluster headache
3.1.1 Episodic cluster headache
3.1.2 Chronic cluster headache
3.2 Paroxysmal hemicrania
3.2.1 Episodic paroxysmal hemicrania
3.2.2 Chronic paroxysmal hemicrania (CPH)
3.3 Short-lasting unilateral neuralgiform headache attacks
3.3.1 Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)
3.3.1.1 Episodic SUNCT
3.3.1.2 Chronic SUNCT
3.3.2 Short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA)
3.3.2.1 Episodic SUNA
3.3.2.2 Chronic SUNA
3.4 Hemicrania continua
3.4.1 Hemicrania continua, remitting subtype
3.4.2 Hemicrania continua, unremitting subtype
3.5 Probable trigeminal autonomic cephalalgia
3.5.1 Probable cluster headache

### References

- 1) Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013; 33: 629-808.
- 2) International Headache Classification Promotion Committee of Japanese Headache Society (translator): International Classification of Headache Disorders 3rd Edition (beta version). Igakushoin, 2014. (In Japanese)

### Search terms and secondary sources

- Search database: Ichushi Web for articles published in Japan (2011/12/21)  
Cluster headache 585  
Cluster headache and classification 98
- Search database: PubMed (2011/12/21)  
Cluster headache 2865  
Cluster headache and classification 307

## How are trigeminal autonomic cephalalgias diagnosed?

### Recommendation

Trigeminal autonomic cephalalgias are diagnosed according to the International Classification of Headache Disorders 3rd Edition (beta version; ICHD-3 beta).

**Grade A**

### Background and Objective

This section describes the diagnostic criteria of the various diseases included in “*trigeminal autonomic cephalalgias*” as provided by the International Classification of Headache Disorders 3rd edition (beta version; ICHD-3 beta).

### Comments and Evidence

The International Classification of Headache Disorders 3rd edition (beta version; ICHD-3 beta)<sup>1,2)</sup> provides the diagnostic criteria for the headache types included in “3. *Trigeminal autonomic cephalalgias*” as follows:

#### 3.1 *Cluster headache*

##### • Diagnostic criteria

- A. At least five attacks fulfilling criteria B-D
- B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 min (when untreated)<sup>1)</sup>
- C. Either or both of the following:
  - 1. at least one of the following symptoms or signs, ipsilateral to the headache:
    - a) conjunctival injection and/or lacrimation
    - b) nasal congestion and/or rhinorrhoea
    - c) eyelid oedema
    - d) forehead and facial sweating
    - e) forehead and facial flushing
    - f) sensation of fullness in the ear
    - g) miosis and/or ptosis
  - 2. a sense of restlessness or agitation
- D. Attacks have a frequency between one every other day and 8 per day for more than half of the time when the disorder is active
- E. Not better accounted for by another ICHD-3 diagnosis.

Note:

- 1. During part (but less than half) of the time-course of 3.1 *Cluster headache*, attacks may be less severe and/or of shorter or longer duration.

#### 3.1.1 *Episodic cluster headache*

##### • Diagnostic criteria

- A. Attacks fulfilling criteria for 3.1 *Cluster headache* and occurring in bouts (cluster periods)
- B. At least two cluster periods lasting from 7 days to 1 year (when untreated) and separated by pain-free remission periods of  $\geq 1$  month.

#### 3.1.2 *Chronic cluster headache*

##### • Diagnostic criteria

- A. Attacks fulfilling criteria for 3.1 *Cluster headache*, and criterion B below
- B. Occurring without a remission period or with remissions lasting  $< 1$  month, for at least 1 year.

### 3.2 *Paroxysmal hemicrania*

- Diagnostic criteria

- A. At least 20 attacks fulfilling criteria B-E
- B. Severe unilateral orbital, supraorbital and/or temporal pain lasting 2-30 min
- C. At least one of the following symptoms or signs, ipsilateral to the pain:
  - 1. conjunctival injection and/or lacrimation
  - 2. nasal congestion and/or rhinorrhea
  - 3. eyelid edema
  - 4. forehead and facial sweating
  - 5. forehead and facial flushing
  - 6. sensation of fullness in the ear
  - 7. miosis and/or ptosis
- D. Attacks have a frequency above five per day for more than half of the time
- E. Attacks are prevented absolutely by therapeutic doses of indomethacin<sup>1)</sup>
- F. Not better accounted for by another ICHD-3 diagnosis.

- Note:

- 1. In an adult, oral indomethacin should be used initially in a dose of at least 150 mg daily and increased if necessary up to 225 mg daily. The dose by injection is 100-200 mg. Smaller maintenance doses are often employed.  
[In Japan, oral indomethacin is used up to a dose of 75 mg and the rectal formulation (suppository) up to 100 mg. Therefore, for differentiating indomethacin-responsive headache, if no response is observed when the oral formulation is used up to the highest dose of 75 mg and the rectal formulation (suppository) up to the highest dose of 100 mg, then the case can be evaluated as nonresponsive.]

### 3.3 *Short-lasting unilateral neuralgiform headache attacks*

- Diagnostic criteria

- A. At least 20 attacks fulfilling criteria B-D
- B. Moderate or severe unilateral head pain, with orbital, supraorbital, temporal and/or other trigeminal distribution, lasting for 1-600 seconds and occurring as single stabs, series of stabs or in a saw-tooth pattern
- C. At least one of the following cranial autonomic symptoms or signs, ipsilateral to the pain:
  - 1. conjunctival injection and/or lacrimation
  - 2. nasal congestion and/or rhinorrhoea
  - 3. eyelid edema
  - 4. forehead and facial sweating
  - 5. forehead and facial flushing
  - 6. sensation of fullness in the ear
  - 7. miosis and/or ptosis
- D. Attacks have a frequency of at least one a day for more than half of the time when the disorder is active
- E. Not better accounted for by another ICHD-3 diagnosis.

#### 3.3.1 *Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)*

- Diagnostic criteria

- A. Attacks fulfilling criteria for 3.3 *Short-lasting unilateral neuralgiform headache attacks*
- B. Both of conjunctival injection and lacrimation (tearing).

#### 3.3.2 *Short lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA)*

- Diagnostic criteria

- A. Attacks fulfilling criteria for 3.3 *Short-lasting unilateral neuralgiform headache attacks*, and criterion B below
- B. Only one or neither of conjunctival injection and lacrimation (tearing).

### 3.4 *Hemicrania continua*

- Diagnostic criteria:

- A. Unilateral headache fulfilling criteria B-D
- B. Present for >3months, with exacerbations of moderate or greater intensity

- C. Either or both of the following:
  - 1. at least one of the following symptoms or signs, ipsilateral to the headache:
    - a) conjunctival injection and/or lacrimation
    - b) nasal congestion and/or rhinorrhoea
    - c) eyelid edema
    - d) forehead and facial sweating
    - e) forehead and facial flushing
    - f) sensation of fullness in the ear
    - g) miosis and/or ptosis
  - 2. a sense of restlessness or agitation, or aggravation of the pain by movement
- D. Responds absolutely to therapeutic doses of indomethacin<sup>1)</sup>
- E. Not better accounted for by another ICHD-3 diagnosis.

Note:

- 1. In an adult, oral indomethacin should be used initially in a dose of at least 150 mg daily and increased if necessary up to 225 mg daily. The dose by injection is 100-200 mg. Smaller maintenance doses are often employed.  
 [In Japan, oral indomethacin is used up to a dose of 75 mg and the rectal formulation (suppository) up to 100 mg. Therefore, for differentiating indomethacin-responsive headache, if no response is observed when the oral formulation is used up to the highest dose of 75 mg and the rectal formulation (suppository) up to the highest dose of 100 mg, then the case can be evaluated as nonresponsive.]

### 3.5 Probable trigeminal autonomic cephalalgia

- Diagnostic criteria:
  - A. Headache attacks fulfilling all but one of criteria A-D for 3.1 *Cluster headache*, criteria A-E for 3.2 *Paroxysmal hemicrania*, criteria A-D for 3.3 *Short-lasting unilateral neuralgiform headache attacks* or criteria A-D for 3.4 *Hemicrania continua*
  - B. Not fulfilling ICHD-3 criteria for any other headache disorder
  - C. Not better accounted for by another ICHD-3 diagnosis.

## • References

- 1) Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013; 33: 629-808.
- 2) International Headache Classification Promotion Committee of Japanese Headache Society (translator): International Classification of Headache Disorders 3rd Edition (beta version). Igakushoin, 2014.

## • Search terms and secondary sources

- Search database: Ichushi for articles published in Japan (2011/12/21)
  - Cluster headache 585
  - Cluster headache and classification 23
- Search database: PubMed (2011/12/21)
  - Cluster headache 2865
  - Cluster headache and classification 1469

## How big is the population of patients with 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 to 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 3 to 5 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**

### Background and Objective

Cluster headache is characterized by severe headache from the periorbital region spreading to the frontal and temporal regions, occurring in clusters lasting several weeks to several months. Headache attacks occur commonly at nighttime and during sleep. Male preponderance has been reported. It usually takes a long time before a diagnosis of cluster headache is finally made. Describing its clinical characteristic is important.

### Comments and Evidence

The incidence of cluster headache varies among reports, and range from 56 to 401 per 100,000 population ([Table 1](#)).<sup>1)-9)</sup>

Previous studies have reported a male: female ratio of 5-6.7 : 1, showing male preponderance. However, Manzoni<sup>10)</sup> investigated the time of onset of cluster headache by decade and found a gradual decrease in male preponderance (male to female ratio of 6.2 : 1 in patients with onset before 1960, and 3.5 : 1 in patients with onset in 1990-1995). This report also showed a relationship with change in lifestyle, especially smoking. Likewise, Ekbom et al.<sup>11)</sup> also reported a trend of decreasing male preponderance as the year of onset became more recent.

The age of onset is commonly between 20 to 40 years. A report from Japan indicated mean onset ages of 29-40 years in men and 24-40 years in women, with no significant difference.<sup>12)</sup>

Various triggering and aggravating factors have been reported, including alcoholic drink, nitroglycerin, and histamine. Cluster headache has been reported to be common in heavy alcohol drinkers and heavy smokers.<sup>13)</sup>

Sjöstrand et al.<sup>14)</sup> conducted long-term follow-up of 60 patients, and reported that 26.5% had only one cluster period during follow-up. This report also showed that 83% had a second period of cluster headache within 3 years. In another study that followed 189 patients for over 10 years, 13% of the patients with an initial diagnosis of episodic cluster headache shifted to chronic cluster headache, while 33% of the patients with an initial diagnosis of chronic cluster headache shifted to episodic cluster headache.<sup>15)</sup>

**Table 1. Studies on the prevalence of cluster headache**

	Age of subjects	Prevalence per 100,000 population (95% confidence interval)
Sweden <sup>1)</sup>	18 year	92 (42-174)
San Marino <sup>2)</sup>	All ages	69 (39-114)
USA <sup>3)</sup>	All ages	401 (262-588)
San Marino <sup>4)</sup>	All ages	56 (31-92)
Norway <sup>5)</sup>	18-65 years	381 (153-254)
Italy <sup>6)</sup>	18-65 years	200 (146-254)
Sweden <sup>7)</sup>	All ages (twins)	151 (108-194)
Italy <sup>8)</sup>	≥14 years	279 (173-427)
Georgia <sup>9)</sup>	≥18 years	87 (no data-258)

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## • Search terms and secondary sources

- Search database: PubMed (2011/12/29)
  - Cluster headache 2614
  - and prevalence 297
  - and gender 38
  - and clinical findings 473
  - and prognosis 205



## 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**

### Background and Objective

Studies to elucidate the pathophysiology of cluster headache have proposed the hypothesis of headache arising from around the internal carotid artery and the hypothesis of headache originating from a hypothalamic generator based on the abnormal circadian rhythm in patients. Furthermore, it has also been hypothesized that cluster headache is caused by parasympathetic activation due to hyperexcitation of trigeminal nerve, and this is included in the category of trigeminal autonomic cephalalgias (TACs).

### Comments and Evidence

The hypotheses of the pathophysiology for trigeminal autonomic cephalalgias are classified as follows:

#### 1. Generator in the hypothalamus

Observation of changes in melatonin related to circadian rhythm in cluster headache patients has suggested a possibility that central changes in circadian rhythm may be involved in cluster headache.<sup>1)</sup> In addition, PET study has demonstrated that the posterior hypothalamus is activated during cluster headache attacks.<sup>2)</sup> Also, MRI (T1-weighted image) with voxel-based morphometry has demonstrated high cell density in posterior hypothalamus gray matter.<sup>3)</sup> Moreover, studies using MR spectroscopy (MRS) in patients with cluster headache have shown a decrease in N-acetylaspartate (NAA)/creatinine ratio, an indicator of neuronal damage, suggesting the presence of organic abnormalities in the hypothalamus.<sup>4)5)</sup> Other reports have suggested a possible association of neural orexin (hypocretin) distributed in the lateral hypothalamus area with the onset of cluster headache.<sup>6)7)</sup>

#### 2. Explanation by the association of trigeminal nerve activity with vascular response based on changes in serum neuropeptide concentrations

During headache attacks in cluster headache patients, external jugular vein blood levels of calcitonin gene-related peptide (CGRP) and vasoactive intestinal peptide (VIP) are increased while substance P (SP) and neuropeptide Y are unchanged. In addition, oxygen inhalation and subcutaneous injection of sumatriptan reduce the augmented CGRP levels to those of normal subjects. These findings thus provide *in vivo* evidence for trigeminovascular activation during cluster headache attacks in patients.<sup>8)</sup> Another study has reported that levels of nitric oxide (NO) metabolites in cerebrospinal fluid are increased during attacks compared to remission, and that NO metabolite levels are increased during remission in cluster headache patients compared to healthy controls.<sup>9)</sup> These findings suggest that changes in neuropeptides in the trigeminovascular system may trigger cluster headache.

#### 3. Pain generation around the internal carotid artery

At present, three candidate culprit lesions have been proposed for the generation of pain and diverse autonomic symptoms.

### (1) Cavernous sinus

This is the hypothesis that dilatation of the internal carotid artery inside the cavernous sinus increases blood flow to the orbit and increases venous inflow to the sinus, but dilatation of the internal carotid artery also reduces the venous outflow from the sinus causing congestion in the sinus, resulting in unilateral periorbital pain and associated symptoms.<sup>10)</sup>

### (2) Proximity to cavernous sinus

Parasympathetic fibers from the sphenopalatine ganglion, pain fibers from the trigeminal nerve, and sympathetic fibers from the superior cervical ganglion join in the cavernous sinus. It has been hypothesized that when these fibers are excited, dilatation of the internal carotid artery occurs in addition to autonomic symptoms.<sup>11)</sup>

### (3) Proximity to foramen lacerum

When the internal carotid artery inside the carotid canal in the temporal bone is dilated for some reason, the compression may inhibit sympathetic functions and at the same time induce inflammation in the surrounding area to stimulate the parasympathetic nerves, thereby causing autonomic symptoms characteristic of cluster headache. Especially, the presence of a small ganglion (internal carotid ganglion), located where the greater superficial petrosal nerve (parasympathetic nerve) joins the internal carotid nerve (cervical sympathetic nerve) on the wall of the internal carotid artery, has been demonstrated in humans. This ganglion, which contains parasympathetic and sensory neurotransmitters, has been suggested to be associated with the onset of cluster headache.<sup>12)</sup>

## 4. Parasympathetic activation due to hyperexcitation of trigeminal nerve

Because cluster headache is characterized by severe unilateral headache (first and second branches of the trigeminal nerve) accompanied by ipsilateral autonomic symptoms including Horner sign, lacrimation, conjunctival injection, nasal congestion and rhinorrhea, this headache belongs to the category of trigeminal-autonomic cephalgias (TACs).<sup>13)</sup> Regarding the mechanism of how over-excitation of the trigeminal nerve causes parasympathetic activation, the following hypothesis has been proposed. When the trigeminal system becomes highly activated, the excitation spreads to the superior salivary nucleus, resulting in excitation from the sphenopalatine ganglion to parasympathetic nerves of intracranial large blood vessels, lacrimal glands and nasal mucosa. As a result, autonomic symptoms such as lacrimation and nasal congestion are manifested.<sup>13)-15)</sup> Furthermore, Goadsby et al.<sup>13)</sup> have shown that stimulation of the trigeminal ganglion leads to release of CGRP, SP and VIP from trigeminal nerve endings in cats, and increases in CGRP and VIP in blood of jugular vein during attacks in patients with cluster headache and paroxysmal hemicrania.<sup>13)</sup> In addition to the above proposed pathophysiology, there is also a possibility that hypothalamus in the central nervous system acts as the generator, inducing cluster headache and the associated autonomic symptoms.<sup>14)</sup>

## 5. Others

Other reports have suggested the involvement of hormonal abnormalities such as estrogen,<sup>16)</sup> polymorphism of the orexin (hypocretin) receptor (present in hypothalamus) gene,<sup>17)</sup> and genetic background, but these factors have not been studied as much as in migraine.

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- **Search terms and secondary sources**

- Search database: PubMed (2011/12/29)  
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## 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 to 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, general analgesics [nonsteroidal anti-inflammatory drugs (NSAIDs)] have no effect.

**Grades 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)

### Background and Objective

Before the development of triptans, there was no effective treatment for acute attacks of cluster headache, and various treatment methods were used based on experience. The section aims to consolidate the evidence-based acute treatments for cluster headache and to develop guidelines.

### Comments and Evidence

#### 1. Triptans

Studies conducted overseas have reported that subcutaneous sumatriptan 6 mg has few adverse effects and shows no decline in efficacy on long-term use.<sup>1,2)</sup> Reports showed that headache was improved at 15 min after subcutaneous injection in 74% of the patients, and was completely relieved at 30 min in 77% of the patients, and the effectiveness was also demonstrated in Japan.<sup>3-5)</sup> A study overseas has reported that subcutaneous sumatriptan at doses lower than 6 mg is also effective (headache improvement rate was 98% with 6 mg subcutaneous injection, 74% with 3 mg, and 8% with 2 mg)<sup>6)</sup> (grade A recommendation).

Randomized controlled double-blind trials have reported that intranasal sumatriptan (20 mg/dose) using nasal spray is effective, with headache improvement rate of 57% at 30 min,<sup>7-9)</sup> but this formulation is currently not available in Japan (grade B recommendation).

Oral zolmitriptan has been reported to be highly effective,<sup>10)</sup> but this drug is currently not covered by health insurance in Japan (grade B recommendation). Recently zolmitriptan nasal spray has been developed overseas and is being used as an acute treatment for cluster headache. Randomized controlled double-blind trials have reported that intranasal zolmitriptan nasal spray 5 mg and 10 mg significantly improved headache compared to placebo.<sup>11-13)</sup> The European Federation of Neurological Societies (EFNS) guidelines for cluster headache and other trigeminal autonomic headaches rates zolmitriptan 5 and 10 mg/dose as grade A/B recommendation.<sup>14)</sup>

#### 2. Oxygen inhalation<sup>15)</sup>

Randomized double-blind trials comparing pure oxygen inhalation and room air inhalation have found approximately 8% improvement with pure oxygen inhalation. In a recent randomized controlled double-blind trial on high-flow oxygen (12 L/min), approximately 78% of the patients inhaling oxygen became pain free, compared to 20% of the patients inhaling room air<sup>16)</sup> (grade A recommendation).

#### 3. Others

Use of lidocaine,<sup>17)</sup> cocaine, ergotamine,<sup>18)</sup> and NSAIDs has been reported but effectiveness has not been confirmed (grade

C recommendation). Somatostatin was reported in the past to be effective,<sup>19)</sup> and a recent randomized placebo-controlled double-blind trial has reported the effectiveness of octreotide, a somatostatin analog<sup>20)</sup> (grade C recommendation).

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## • Search terms and secondary sources

“Cluster Headache/therapy” [MeSH] 875

“cluster”“headache”“acute”“treatment” 173

“cluster”“headache”“acute”“treatment”, Limits Activated: Clinical Trial, Randomized Controlled Trial 30

## 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 to 2 mg) taken orally before bedtime may be effective as prophylaxis.

(3) Civamide (a structural analog of capsaicin) nasal spray has been reported overseas to be effective, but clinical trial has not been conducted in Japan.

(4) Corticosteroids are considered effective, but there is no clear evidence.

(5) The prophylactic effects of triptans and melatonin are not known.

#### 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.

#### Grades 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) civamide; 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]

### Background and Objective

Because there are few therapies that are effective for the prevention of cluster headache, this section aims to consolidate the prophylactic therapies for cluster headache based on evidence and develop guidelines.

### Comments and Evidence

#### 1. Prophylaxis for episodic cluster headache

##### (1) Calcium channel blockers

The prophylactic effect of verapamil 360 mg/day has been proven overseas in placebo-controlled double-blind trials, but attention is required regarding the adverse event of cardiac conduction delay causing bradycardia and heart failure.<sup>1)</sup> In Japan, verapamil was approved for off-label use for migraine and cluster headache from September 28, 2011 ([http://www.hospital.or.jp/pdf/14\\_20110928\\_01.pdf](http://www.hospital.or.jp/pdf/14_20110928_01.pdf)) (grade B recommendation). Lomerizine is expected to have some prophylactic effect in the clinical trial stage (currently not covered by health insurance in Japan (grade C recommendation).

##### (2) Ergotamine tartrate

Many cases responding to prophylactic therapy with oral ergotamine tartrate have been reported, but stringent placebo-controlled double-blind trials have not been conducted (grade C recommendation).

### (3) Civamide

Civamide is a structural analog of capsaicin. Use of civamide nasal spray [100 µL of 0.025% civamide (25 µg)] for 7 consecutive days reduces the frequency of headache<sup>2)</sup> (grade C recommendation)

### (4) Corticosteroids

For corticosteroids, although a report has indicated the effectiveness of intravenous bolus of high-dose methylprednisolone,<sup>3)</sup> randomized controlled double-blind trials have not been conducted. On the other hand, another open-label study suggests that methylprednisolone alone does not provide any advantage above prednisone.<sup>4)</sup> Use of prednisolone 40 to 60 mg/day or dexamethasone 8 mg has also been reported.<sup>5)</sup> The 2006 European Federation of Neurological Societies (EFNS) guideline recommends a protocol to start with 60-100 mg of prednisone once daily for at least 5 days, then taper by 10 mg/day.<sup>6)</sup> In this guideline, steroids are ranked grade A even though appropriate randomized controlled double-blind trials have not been conducted.<sup>6)</sup> In Japan, steroids have been approved for off-label use for cluster headache on September 28, 2011 (grade B recommendation).

### (5) Others

Beta blockers are usually not effective for cluster headache, and they are not used. Among triptans, a study has concluded that sumatriptan 300 mg/day is not effective as prophylactic treatment.<sup>7)</sup> More recently, eletriptan (80 mg/day) has been reported to be effective,<sup>8)</sup> but controlled double-blind studies have not been conducted. Melatonin 10 mg was reported to be effective,<sup>9)</sup> but a recent controlled double-blind study has reported no difference compared to placebo.<sup>10)</sup> (grade C recommendation).

## 2. Prophylactic therapy for chronic cluster headache

Lithium carbonate was reported to be effective in approximately 40% of the patients with chronic cluster headache,<sup>11)</sup> but recent reports raise doubt about its effectiveness. The effectiveness of valproic acid,<sup>12)</sup> gabapentin,<sup>13)14)</sup> topiramate,<sup>15)</sup> baclofen,<sup>16)</sup> and divalproex sodium<sup>17)</sup> has been reported, but controlled double-blind trials have not been conducted and the effects are yet to be established (grade C recommendation).

## 3. Treatments other than pharmacotherapy

Nerve block therapies including trigeminal nerve block, stellate ganglion block, greater occipital nerve block,<sup>18)</sup> and sphenopalatine ganglion block<sup>19)</sup>; trigeminal rhizotomy; and sphenopalatine ganglion resection have been conducted. Gamma knife treatment<sup>20)</sup> and deep brain stimulation<sup>21)22)</sup> have also been attempted, and reported to be effective in some patients. Because of the high rate of failure and adverse effects associated with gamma knife treatment, recent reports conclude that this modality cannot be recommended actively.<sup>23)24)</sup> Furthermore, greater occipital nerve electrical stimulation<sup>25)</sup> and suboccipital steroid injection<sup>26)</sup> have been reported to be effective in some patients. (grade C recommendation).

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## • Search terms and secondary sources

“Cluster Headache/prevention and control” [MeSH] 95

Cluster Headache prevention treatment 180

“prevention”“cluster headache”Limits: Clinical Trial, Randomized Controlled Trial 27

## 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, nonsteroidal anti-inflammatory drugs (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)

### Background and Objective

Paroxysmal hemicrania manifests pain and associated symptoms similar to those of cluster headache. However the duration of attack is 2 to 30 min, which is shorter than that of cluster headache, and the frequency of headache attack is high. Paroxysmal hemicrania occurs more commonly in women than in men, and responds absolutely to indomethacin. This section reviews the literature on indomethacin and other drugs for the treatment of paroxysmal hemicrania.

### Comments and Evidence

Based on the International Classification of Headache Disorders, 3rd Edition (beta version) (ICHD-3 beta),<sup>1)</sup> the diagnostic criteria for paroxysmal hemicrania are as follows:

Diagnostic criteria:

- A. At least 20 attacks fulfilling criteria B-E
- B. Severe unilateral orbital, supraorbital and/or temporal pain lasting 2-30 minutes
- C. At least one of the following symptoms or signs, ipsilateral to the pain:
  - 1. conjunctival injection and/or lacrimation
  - 2. nasal congestion and/or rhinorrhea
  - 3. eyelid oedema
  - 4. forehead and facial sweating
  - 5. forehead and facial flushing
  - 6. sensation of fullness in the ear
  - 7. miosis and/or ptosis
- D. Attacks have a frequency above five per day for more than half of the time
- E. Attacks are prevented absolutely by therapeutic doses of indomethacin
- F. Not better accounted for by another ICHD-3 diagnosis.

The ICHD-3 $\beta$  provides the above diagnostic criteria. Among them, criterion “E. Attacks are prevented absolutely by therapeutic doses of indomethacin” clearly states the absolute therapeutic effect of indomethacin (grade A recommendation). The 2006 European Federation of Neurological Societies (EFNS) guideline<sup>2)</sup> also describes the treatment for paroxysmal hemicrania, noting that indomethacin is the most effective prophylactic drug according to many reports.<sup>3)-6)</sup> Furthermore, in a prospective study reported in 2008 on the administration of indomethacin in 31 patients with paroxysmal hemicrania, all patients responded to indomethacin.<sup>7)</sup> Regarding the dose of indomethacin, *Note 1* of the ICHD-II diagnostic criteria states “In order to rule out incomplete response, indomethacin should be used in a dose of  $\geq 150$  mg daily orally or rectally, or  $\geq 100$  mg by injection, but for maintenance, smaller doses are often sufficient.” On the other hand, the Japanese Edition of the International Classification of Headache Disorders 3rd edition (beta version)<sup>8)</sup> gives the dose of indomethacin that can be used in Japan as follows.

“In Japan, oral indomethacin is used up to a dose of 75 mg and the rectal formulation (suppository) up to 100 mg. Therefore, for differentiating indomethacin-responsive headache, if no response is observed when the oral formulation is used up to the highest dose of 75 mg and the rectal formulation (suppository) up to the highest dose of 100 mg, then the case

can be evaluated as nonresponsive”.

Other drugs such as verapamil, NSAIDs and topiramate have been reported to be effective,<sup>9)-13)</sup> but clear evidence is yet to be established (grade C recommendation).

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## • Search terms and secondary sources

- Search database: PubMed (2011/12/21)  
Paroxysmal hemicrania & treatment & Clinical trial Results 14

## 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**

### Background and Objective

Short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) is characterized by short-lasting attacks of unilateral pain accompanied by ipsilateral lacrimation and congestion in the eye. On the other hand, short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA) is accompanied by either conjunctival injection or lacrimation, and SUNCT is considered possibly a subform of SUNA. This section reviews the literature on the treatments SUNCT and SUNA.

### Comments and Evidence

Few headache guidelines in European and American countries describe the treatments for SUNCT and SUNA. The 2006 European Federation of Neurological Societies (EFNS) guideline has the following description, “No controlled trials have been published, and the rareness of the syndrome makes this a difficult task”.<sup>1)</sup> Among the treatments tried, lamotrigine is considered the most effective from case reports, while gabapentin and topiramate are also regarded to be effective. For headaches that severely impact daily living, intravenous lidocaine has been reported to be effective. A small-scale prospective study on treatments of SUNCT reported that SUNCT attacks did not respond to oxygen inhalation or intramuscular indomethacin in all patients.<sup>2)</sup> This report also indicated that lamotrigine (up to 400 mg/day) was effective in 68% of SUNCT and 25% of SUNA patients, topiramate (up to 400 mg/day) was effective in 52% of SUNCT patients, and gabapentin (up to 3,600 mg/day) was effective in 45% of SUNCT and 60% of SUNA patients.<sup>2)</sup>

A review on case reports of treatment of SUNCT by lamotrigine was reported.<sup>3)</sup> While the doses used were variable, in 5 patients started with 25 mg/day and titrated at 25 mg/week to a maintenance dose of 125 to 200 mg/day, 3 patients achieved complete remission and 2 patients showed 80% or greater reduction in attack frequency.<sup>4)</sup>

For gabapentin, among 8 patients who received a starting dose of 600 mg/day divided in 2 doses, increasing when attack occurred in one week up to a dose of 900 mg/day divided in 3 doses, 5 patients (62.5%) achieved complete relief and 3 patients showed marked improvement in headache duration, frequency and severity.<sup>5)</sup> In Japan, there is a case report of SUNCT in which gabapentin 800 mg/day achieved resolution of headache attack and autonomic symptoms.<sup>6)</sup>

In a prospective study of lidocaine used with lamotrigine, intravenous or subcutaneous infusion of lidocaine (2 g dissolved in 100 mL of saline) at a rate of 6 mL/hour (2 mg/min) for 5 to 14 days was effective in 11 of 14 patients.<sup>7)</sup>

In a case report, oral zonisamide was started at 100 mg/day and titrated from day 3 to a dose of 300 mg/day. Since attack did not occur, zonisamide was tapered and discontinued. Attack recurred on day 3 after discontinuation, and the drug was restarted with no more attack thereafter.<sup>8)</sup>

In addition to pharmacotherapy, cases of response to deep brain stimulation and gamma knife radiosurgery have been reported.<sup>9)10)</sup> However, cases showing no response to gamma knife radiosurgery of the trigeminal nerve, but occurrence of adverse effects including anesthesia dolorosa, deafness, vertigo, and dysequilibrium were also reported,<sup>11)</sup> indicating that gamma knife radiosurgery of the trigeminal nerve is not necessarily an appropriate treatment for SUNCT.

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SUNCT and treatment Limits Activated: Clinical Trial Results 6

SUNCT and treatment Limits Activated: meta-analysis Results 1

SUNCT and radiosurgery Results 2

## 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**

### Background and Objective

This section reviews the literature and discusses the degree of disability in daily living caused by pain during the attack period in patients with cluster headache.

### Comments and Evidence

Various instruments such as Short Form-36 (SF-36) and Migraine Specific Quality of Life Questionnaire version 2.1 (MSQ 2.1) have been used to investigate the degree of disability in daily life of patients with cluster headache. The SF-36 is a scientific scale used to assess health-related quality of life (QOL). It consists of a number of questions, and the responses are scored and calculated to measure eight health concepts: (1) physical functioning, (2) role physical, (3) bodily pain, (4) general health, (5) vitality, (6) social functioning, (7) role emotional, and (8) mental health. In the MSQ, patients are asked to provide response to questions related to headache-related impact on daily and social life during the past 4 weeks, rated on a six-point scale from “none of the time” to “all of the time”, and the total score is used to measure the degree of QOL impairment.

A study comparing SF-36 scores between 56 patients with cluster headache and 1,636 healthy persons found significant differences in six items, and a study comparing SF-36 and MSQ 2.1 scores between 35 patients with cluster headache and 62 healthy persons also reported significant differences in both scores.<sup>1)2)</sup> Furthermore, comparison between cluster headache patients and migraine patients revealed significant differences in the SF-36 subscales of “physical pain” and “social functioning”, indicating that the degree of disability in daily living caused by cluster headache is as severe as or more severe than that caused by migraine.<sup>2)</sup> In addition, a study comparing 13 patients with cluster headache and 79 patients with migraine using SF-20 reported significantly higher pain score as well as poorer health associated with social functioning in cluster headache patients compared to migraine patients.<sup>3)</sup>

Regarding the consumption habits, cigarette-smoking has been reported to be significantly more frequent in cluster headache patients than in the general population, suggesting an issue in lifestyle among cluster headache patients.<sup>4)</sup> Regarding the economic loss for cluster headache patients, a study comparing the treatment costs due to healthcare utilization (direct costs) and loss due to headache-related absence from work (indirect costs) over a 6-month period between 72 patients with chronic cluster headache and 107 patients with episodic cluster headache reported direct/indirect economic loss of €5,963 per person.<sup>5)</sup>

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- **Search terms and secondary sources**

- Search database: PubMed (2011/12/21)  
(Cluster Headache) & (Quality of Life) 53  
(Cluster Headache) & (burden) 18



# V

## **Other primary headache disorders**

## Apart from migraine, tension-type headache and cluster headache, what are the other types of primary headache disorders?

### Recommendation

In the International Classification of Headache Disorders, 3rd Edition (beta version) (ICHD-3beta),<sup>1,2)</sup> 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**

### Background and Objective

In the first edition of the International Classification of Headache Disorders published in 1988 by the Headache Classification Committee (Chairman, Jes Olsen) of the International Headache Society,<sup>3)</sup> these headaches were grouped under “*Miscellaneous headaches unassociated with structural lesion*”.

The headaches were classified into the following types: idiopathic stabbing headache, external compression headache, cold stimulus headache, benign cough headache, benign exertional headache, and headache associated with sexual activity. Cold stimulus headache was further divided into two subtypes: external application of a cold stimulus, and ingestion of a cold stimulus. Headache associated with sexual activity was classified into dull type, explosive type, and postural type.

When the first edition of the International Classification of Headache Disorders was undergoing complete revision, the Japanese Headache Society (International Classification Promotion Committee) in collaboration with the Ministry of Health, Labour and Welfare Study Group (Study Group for Chronic Headache Clinical Guideline) translated the revised guidelines<sup>4)</sup> and published the Japanese Edition of the International Classification of Headache Disorders 2nd Edition.<sup>5)</sup> In the second edition, headache disorders other than migraine, tension-type headache and cluster headache have been classified under the new term “*Other primary headaches*”.

### Comments and Evidence

Headache disorders are classified according to the International Classification of Headache Disorders 3rd Edition (beta version) (ICHD-3beta), published in 2013.<sup>2)</sup> In the ICHD-3beta, primary headache disorders other than migraine, tension-type headache and cluster headache are grouped under “*Other primary headaches disorders*”, and classified into ten types as follows: 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.

Primary stabbing headache is transient and localized stab-like headache that occurs spontaneously in the absence of organic disease in local structures or in the cranial nerves.

Primary cough headache is headache triggered by coughing or straining, in the absence of intracranial diseases.

Primary exercise headache is headache triggered by exercise (regardless of type). Subforms such as “weight-lifters’ headache” are recognized.

Primary headache associated with sexual activity is headache precipitated by sexual activity, usually starting as a bilateral dull ache as sexual excitement increases and suddenly intensifies at orgasm, in the absence of intracranial diseases.

Hypnic headache manifests as dull headache attacks that always awaken the patient from asleep.

Primary thunderclap headache is high-intensity headache of abrupt onset mimicking that of ruptured cerebral aneurysm.

Hemicrania continua is persistent, strictly unilateral headache responsive to indomethacin.

Hemicrania continua, originally grouped under “*Other primary headaches disorders*” in International Classification of Headache Disorders 2nd Edition (ICHD-II), is moved to “*Trigeminal autonomic cephalalgias: TACs*” in ICHD-3beta.

New daily persistent headache is headache that is daily and unremitting from very early after onset. The pain is typically

bilateral, pressing or tightening in quality, and of mild to moderate intensity. Photophobia, phonophobia or mild nausea may occur.

Some of these headaches are symptomatic. Careful evaluations using neuroradiological imaging such as MRI, and other tests are necessary.

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## • Search terms and secondary sources

- Search database: Ovid (2011/12/21)  
Headache and Headache disorders 560  
{Headache and Headache disorders} and Classification 87
- Search database: Ichushi Web for articles published in Japan (2011/12/21)  
Headache 5576  
Headache and classification 166  
Headache and classification and clinical guideline 9

## 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 International Classification of Headache Disorders, 3rd Edition (beta version) (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**

### Background and Objective

Primary stabbing headache, primary cough headache, and primary exercise headache are included in primary headaches other than migraine, tension-type headache, and cluster headache. The objective of this section is to review the reports on the diagnosis and treatment of these disorders.

### Comments and Evidence

#### 1. Diagnosis

##### (1) Primary stabbing headache<sup>1,2)</sup>

- A. Head pain occurring spontaneously as a single stab or series of stabs and fulfilling criteria B-D
- B. Each stab lasts for up to a few seconds
- C. Stabs recur with irregular frequency, from one to many per day
- D. No cranial autonomic symptoms
- E. Not better accounted for by another ICHD-3 diagnosis

##### (2) Primary cough headache<sup>1,2)</sup>

- A. At least two headache episodes fulfilling criteria B-D
- B. Brought on by and occurring only in association with coughing, straining and/or other Valsalva maneuver
- C. Sudden onset
- D. Lasting between 1 second and 2 hours
- E. Not better accounted for by another ICHD-3 diagnosis

##### (3) Primary exercise headache<sup>1,2)</sup>

- A. At least two headache episodes fulfilling criteria B and C
- B. Brought on by and occurring only during or after strenuous physical exercise
- C. Lasting <48 hours
- D. Not better accounted for by another ICHD-3 diagnosis

#### 2. Treatment

##### (1) Primary stabbing headache

Several uncontrolled studies have reported response to indomethacin,<sup>3,4)</sup> but there are also reports of partial or even no response. Mathew<sup>5)</sup> treated 5 patients with 50 mg indomethacin 3 times a day and reported drastic reduction in mean headache frequency in a week compared to aspirin and placebo. On the other hand, Pareja et al.<sup>6)</sup> studied the clinical features of 38 patients, and reported that among 17 patients treated with 75 mg/day indomethacin for 15 days, 6 patients (35%) achieved complete remission and 5 patients had partial remission, while 6 patients (35) were refractory to treatment. Several case reports are available for drugs other than indomethacin. They include a report of a 71 year-old woman responding to

nifedipine sustained release tablet 90 mg/day;<sup>7)</sup> a report of 3 cases recommending a treatment regimen of melatonin starting at a dose of 3 mg/day and increasing gradually;<sup>8)</sup> a report of 4 young onset cases responding to gabapentin 400 mg/day;<sup>9)</sup> and 3 cases responding to celecoxib, a cyclooxygenase-2 inhibitor.<sup>10)</sup>

## (2) Primary cough headache

This headache usually responds to indomethacin. Mathew<sup>5)</sup> conducted a double-blind study in 2 patients, and reported the effectiveness of indomethacin 150 mg/day. Raskin<sup>11)</sup> treated 16 patients with indomethacin 50 to 200 mg (mean 78 mg) per day, and observed complete remission in 10 patients, moderate improvement in 4 patients and no response in 2 patients. In the report of Pascual et al.,<sup>12)</sup> response was observed in 6 of 13 patients treated with indomethacin 75 mg/day. Indomethacin is considered to be the most effective drug for symptomatic relief.<sup>13)</sup> As for the other treatments, Calandre et al.<sup>14)</sup> reported cases responding to propranolol 120 mg and also cases responding to methysergide. In one case reported by Mateo and Pascual,<sup>15)</sup> naproxen 550 mg given every 12 hours achieved partial relief. Wang et al.<sup>16)</sup> studied the usefulness of acetazolamide in 5 indomethacin responsive patients. Acetazolamide was started at a dose of 125 mg three times a day and titrated until maximum effect was obtained, up to a maximum of 2,000 mg/day. The outcome was complete response in 2 patients, favorable response in 2 patients and no response in 1 patient. Raskin<sup>11)</sup> treated 14 patients by performing lumbar puncture to remove 40 mL of cerebrospinal fluid, and reported response in 6 patients; with response observed immediately after the procedure in 3 patients, and 2 days or longer later in the other 3 patients.

## 3. Primary exercise headache

Indomethacin has long been used as the drug of choice for prophylactic treatment of exertional headache. Diamond<sup>17)</sup> treated 15 patients with indomethacin starting from 25 mg/day and titrating to a maximum dose of 150 mg. Response was obtained in 13 patients (87%). After headache was controlled, indomethacin was discontinued and headache recurred within 7 days in 12 of 13 patients. As for the other drugs, Pascual et al.<sup>12)</sup> tried ergotamine tartrate in 16 patients who took the drug before exertion started, and 4 patients reported subjective response showing potential prophylactic effect. They also treated 5 patients with propranolol prophylactically; 3 patients had irregular attacks, 1 patient showed clear response, while 1 patient did not respond but improved with indomethacin. A study in Japan also reported the usefulness of propranolol as a prophylactic drug.<sup>18)</sup> Furthermore, flunarizine was administered to 2 patients, and response was obtained in 1 patient.<sup>12)</sup>

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- **Search terms and secondary sources**

1. Diagnosis

- Search database: PubMed (2012/1/30)  
{Headache and Headache disorders} and Classification 170

2. Treatment

- Search database: PubMed (2012/1/30)  
{Stabbing headache} 60  
{Primary cough headache} or {Benign cough headache} or {Valsalva manoeuvre headache} 119  
{Exertional headache} 68

## 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 International Classification of Headache Disorders, 3rd Edition (beta version) (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**

### Background and Objective

Statistical data from headache clinics suggest that primary headache associated with sexual activity is rare. However, potential patients probable exist in relatively large numbers. Appropriate approach to this disorder is necessary.

### Comments and Evidence

#### 1. Diagnosis

The diagnostic criteria for primary headache associated with sexual activity are as follows<sup>1)</sup>:

- A. At least two episodes of pain in the head and/or neck fulfilling criteria B-D
- B. Brought on by and occurring only during sexual activity
- C. Either or both of the following:
  - 1. increasing in intensity with increasing sexual excitement
  - 2. abrupt explosive intensity just before or with orgasm
- D. Lasting from 1 minute to 24 hours with severe intensity and/or up to 72 hours with mild intensity
- E. Not better accounted for by another ICHD-3 diagnosis

When occurring at the first time, it is mandatory to exclude subarachnoid hemorrhage and internal carotid artery or vertebral artery dissection. Differential diagnosis also includes intracerebral hemorrhage, subdural hematoma, unruptured aneurysm, cerebral venous sinus thrombosis, Arnold-Chiari I malformation, posterior fossa neoplasm, increased intracranial pressure, decreased intracranial pressure, and cervical spinal cord disease.<sup>2)</sup> Reversible cerebral vasoconstriction syndrome (RCVS) has also been reported, emphasizing the necessity of diagnostic imaging study.<sup>3)</sup> Headache clinic surveys reported that patients with primary headache associated with sexual activity occupied 0.2 to 1.3% of all headache patients.<sup>4)</sup> A more recent case-control study estimated a prevalence of 0.9% in the general population.<sup>5)</sup> It is possible that the headache is underdiagnosed because patients are embarrassed to describe the circumstances in detail, and that the true prevalence may be considerably higher. The prevalence is 3 to 4 times higher in men than in women. The age at onset has two peaks, one in the early twenties and the other around 40 years of age.<sup>4,6)</sup> Type 1 and type 2 in the first edition of the International Classification of Headache Disorders are equivalent to preorgasmic headache (dull type, approximately 20%) and orgasmic headache (explosive type, approximately 80%), respectively, in the International Classification of Headache Disorders 2nd Edition (ICHD-II). Type 3 in the first edition, which is positional headache, is caused by cerebrospinal fluid leak and is coded as "headache attributed to spontaneous low CSF pressure" in ICHD-II.<sup>7)</sup> The pathogenetic mechanism has not been fully elucidated, but onset of preorgasmic headache is associated with tension-type headache and muscular contraction mainly in the neck,<sup>8)</sup> while orgasmic headache is associated with increased intracranial pressure accompanying an abrupt increase in blood pressure or heart rate.<sup>2)</sup> Patients' blood pressure increases markedly during sexual activity, and the existence of metabolism-related impaired cerebrovascular autoregulation is speculated.<sup>9)</sup> Headache is bilateral and commonly occur in



the occipital region. The pain lasts from several minutes to several hours or one day, and headache is severe usually during the first 5 to 15 minutes. The headache duration is longer in orgasmic headache than in preorgasmic headache. Headache occurs during coitus with the usual partner and also during masturbation. Comorbidity with migraine, tension-type headache, and primary exertional headache has been reported.<sup>2)(6)</sup>

## 2. Treatment

To treat primary headache associated with sexual activity, the patient's and partner's understanding of the disorder is necessary.<sup>10)</sup> In preorgasmic headache, headache is usually relieved by discontinuing sexual activity. Therefore patients are advised to remain sexually inactive as much as possible until they are completely free of headache.<sup>4)</sup> The usefulness of taking indomethacin (50 to 100 mg) 1 to 2 hours before coitus,<sup>4)</sup> and the use of triptans (such as naratriptan) have been reported. Treatment with ergotamine and benzodiazepine compounds has also been used.<sup>11)(12)</sup> For patients with prolonged headache duration, prophylactic therapy using propranolol, metoprolol, and diltiazem has been attempted.<sup>2)(8)</sup> A report has shown the usefulness of greater occipital nerve blockade by injection of a steroid and local anesthetic combination.<sup>13)</sup> The prognosis of headache associated with sexual activity is relatively good. In the majority, the headache appears in a bout and remits, but 25% of patients have a chronic course.<sup>10)</sup>

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Headache  
& {Sexual activity} 134  
& {Migraine} 27  
Sexual Headache 649  
& {Migraine} 474  
& {Treatment} 21
- Search database: PubMed (2011/12/5)  
Sexual headache 340  
& {Migraine} & {Treatment} 9
- Search database: Ichushi Web for articles published in Japan (2011/11/11)  
Sexual headache 5

## How is hypnic headache diagnosed and treated?

### Recommendation

#### 1. Diagnosis

Hypnic headache is diagnosed according to the International Classification of Headache Disorders, 3rd Edition (beta version) (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**

### Background and Objective

Although hypnic headache is a rare headache disorder, over 170 cases have been reported. Reported for the first time by Raskin in 1988, this headache is also called “alarm clock headache” because it awakens the patient from sleep. In the International Classification of Headache Disorders, 3rd Edition (beta version) (ICHD-3 beta), hypnic headache is classified in the group “*Other primary headache disorders*”.<sup>1)</sup> The pathophysiology has not been fully elucidated.

### Comments and Evidence

#### 1. Diagnosis

The diagnostic criteria of hypnic headache are as follows<sup>1)</sup>:

- A. Recurrent headache attacks fulfilling criteria B-E
- B. Developing only during sleep, and causing wakening
- C. Occurring on  $\geq 10$  days per month for  $>3$  months
- D. Lasting  $\geq 15$  minutes and for up to 4 hours after waking
- E. No cranial autonomic symptoms or restlessness
- F. Not better accounted for by another ICHD-3 diagnosis

Hypnic headache is a rare headache, and is estimated to occupy 0.07 to 0.35% of headache patients.<sup>2)3)</sup> The male to female ratio is 1: 1.2 to 1: 1.7, with a female preponderance. The mean age of onset is around 60 years. although hypnic headache occurs typically in older persons,<sup>4)-8)</sup> pediatric cases have also been reported.<sup>3)</sup> Only a small number of cases have been reported in Japan.<sup>9)</sup> Headache is typically mild to moderate in intensity, dull and bilateral, but one-third is pulsating with severe intensity. The duration ranges from 15 to 180 minutes (mean 80 minutes), although headache may last 6 hours. The frequency of attack is 1 to 2 times per night, and the mean frequency of headache episodes is 23 per month. When patients are woken up by the headache at night, they read books, watch television, drink or eat, or walk inside the room. These characteristics are in contrast to the excited and restless states in cluster headache.<sup>5)-8)</sup> Polysomnographic studies have reported that headache arises during REM sleep,<sup>10)-13)</sup> but recent research contradicts the association between hypnic headache and sleep stage.<sup>7)14)</sup> A MRI study with voxel-based morphometry (VBM) has reported a decrease in posterior hypothalamus gray matter.<sup>15)</sup> The characteristic clinical picture of chronobiological abnormality in addition to pain suggests impairments of pain sensation and sleep rhythm at the trigeminal nerve in the hypothalamo-pituitary system. It is important to conduct imaging studies to differentiate from secondary headaches such as posterior fossa tumor, pontine infarction and pituitary tumor. Other headache disorders that should be differentiated include cluster headache, trigeminal-autonomic cephalalgias, and hemicrania continua.

#### 2. Treatment

Caffeine is used not only as an acute treatment but also as a prophylactic drug.<sup>3)16)17)</sup> Drinking a cup of coffee when awoken by pain or before going to sleep is effective. As prophylactic drugs, lithium is usually effective, while topiramate, indomethacin, melatonin, and amitriptyline have also been used. Some cases remit spontaneously, while others remit upon treatment but relapse later.

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Hypnic headache 118
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Hypnic headache 4

## How is primary thunderclap headache diagnosed and treated?

### Recommendation

#### 1. Diagnosis

Primary thunderclap headache is diagnosed according to the International Classification of Headache Disorders, 3rd Edition (beta version) (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**

### Background and Objective

In the diagnosis of thunderclap headache, the first and foremost step is to exclude a wide variety of secondary headaches. Accurate diagnosis and treatment by headache specialists are important.

### Comments and Evidence

#### 1. Diagnostic criteria

The diagnostic criteria of primary thunderclap headache are as follows.<sup>1)</sup>

- A. Severe head pain fulfilling criteria B and C
- B. Abrupt onset, reaching maximum intensity in <1 minute
- C. Lasting for ≥5 minutes
- D. Not better accounted for by another ICHD-3 diagnosis

The most important step in diagnosis is to differentiate from disorders that may cause secondary thunderclap headache. It is mandatory to exclude subarachnoid hemorrhage due to ruptured cerebral aneurysm,<sup>2)</sup> unruptured saccular cerebral aneurysm,<sup>3,4)</sup> carotid or vertebral artery dissection,<sup>5)</sup> intracerebral hemorrhage,<sup>6)</sup> cerebral infarction,<sup>7)</sup> cerebral venous sinus thrombosis,<sup>8)</sup> and pituitary apoplexy.<sup>9)</sup> Other disorders that require differentiation include central nervous system angitis, colloid cyst of the third ventricle, cerebrospinal fluid hypotension, acute sinusitis (especially barotrauma), retroclival hematoma, primary cough headache, primary exertional headache, primary headache associated with sexual activity,<sup>10)</sup> and bath-related headache.<sup>11)</sup> In recent years, reversible cerebral vasoconstriction syndrome (RCVS)<sup>12,13)</sup> as a cause of secondary thunderclap headache has drawn attention. For the diagnosis of headaches associated with subarachnoid hemorrhage, dissecting aneurysm and pituitary apoplexy, see the CQs for “Headache: General Considerations”.

Primary thunderclap headache is known to occur commonly in female adults, and is diagnosed only after all organic underlying diseases have been excluded. Secondary thunderclap headaches are treated according to the treatments for the underlying diseases, while treatment for primary thunderclap headache has not been established. The pathophysiology of primary thunderclap headache remains largely unclear, although failure of the afferent sympathetic nerve system that modulates intracranial vascular tone causing acute vasoconstriction or alteration in vascular tone has been suggested to cause the headache.<sup>10)</sup>

#### 2. Treatment

Nimodipine has been reported to be effective,<sup>14)</sup> but there is no established treatment.

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thunderclap headache215
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thunderclap headache 948

## How is hemicrania continua diagnosed and treated?

### Recommendation

#### 1. Diagnosis

Hemicrania continua is diagnosed according to the International Classification of Headache Disorders, 3rd Edition (beta version) (ICHD-3 beta).

**Grade A**

#### 2. Treatment

Complete remission is obtained by treatment with indomethacin.

**Grade A**

### Background and Objective

Hemicrania continua is a rare disorder.<sup>1,2)</sup> Since the disorder was first described by Sjaastad in 1984, over 150 cases have been reported.<sup>3)-11)</sup> Although hemicrania continua is characterized by association with autonomic symptoms and marked response to indomethacin, the pathophysiology, clinical picture, treatment and prognosis remain undefined.

### Comments and Evidence

#### 1. Diagnostic criteria

The diagnostic criteria of hemicrania continua are as follows.<sup>1,2)</sup>

- A. Unilateral headache fulfilling criteria B-D
- B. Present for >3 months, with exacerbations of moderate or greater intensity
- C. Either or both of the following:
  - 1. at least one of the following symptoms or signs, ipsilateral to the headache:
    - a) conjunctival injection and/or lacrimation
    - b) nasal congestion and/or rhinorrhoea
    - c) eyelid edema
    - d) forehead and facial sweating
    - e) forehead and facial flushing
    - f) sensation of fullness in the ear
    - g) miosis and/or ptosis
  - 2. a sense of restlessness or agitation, or aggravation of the pain by movement
- D. Responds absolutely to therapeutic doses of indomethacin<sup>Note 1</sup>
- E. Not better accounted for by another ICHD-3 diagnosis

#### Note:

1. In an adult, oral indomethacin should be used initially in a dose of at least 150 mg daily and increased if necessary up to 225 mg daily. The dose by injection is 100-200 mg. Smaller maintenance doses are often employed.

Hemicrania continua is a rare disorder and evidence is limited to case series.<sup>3)-11)</sup> In summary, the male to female ratio is approximately 1: 2, with a female preponderance. The mean onset age is in the thirties. Headache is unilateral and does not shift to the other side, and is lasting pain with mild to moderate intensity. The sites of headache are mainly in the frontal, temporal, orbital and occipital regions. Exacerbation of headache occurs sometimes and intense pain greatly impairs daily living. During exacerbation, ipsilateral autonomic symptoms including lacrimation and conjunctival injection often occur. Headache may be accompanied by the associated symptoms seen in migraine. Hemicrania continua is characterized by chronically persistent pain. When recurrence occurs after a remission, the pain usually takes a chronic course thereafter. Complete remission is obtained by indomethacin. Only a few cases of hemicrania continua have been reported in Japan.<sup>12)-13)</sup> However, cases of pain shifting to the other side, cases not responsive to indomethacin, cases with no autonomic symptoms, and cases manifesting autonomic symptoms not listed in the diagnostic criteria of ICHD-3beta have been reported. Although PET examination demonstrated activation in contralateral posterior hypothalamus and ipsilateral dorsal rostral pons, the

exact pathophysiology remains unknown.<sup>14)</sup> Both hemicrania continua and paroxysmal hemicrania exhibit indomethacin responsiveness and autonomic symptoms, thereby raising a possibility that they share a common pathophysiological basis.<sup>8)10)</sup>

Differential diagnosis includes unilateral localized chronic migraine, new daily persistent headache, cervicogenic headache, trigeminal-autonomic cephalgias, chronic post-traumatic headache, headache attributed to arterial dissection, and headache attributed to brainstem infarction.

In ICHD-3 beta, hemicrania continua is classified as one of the trigeminal-autonomic cephalgias.

## 2. Treatment

Headache responds absolutely to therapeutic doses of indomethacin. In Japan, the maximum dose is 75 mg/day for oral formulation, and 100 mg/day for rectal administration.<sup>2)</sup> In overseas countries, however, indomethacin is used at a starting dose of 25 to 75 mg/day, increasing gradually if there is no response, and the responsive dose has been reported to range from 50 to 300 mg/day.<sup>3)-7)10)</sup> Oral indomethacin has to be taken for long term, and adverse effects including vertigo and gastrointestinal symptoms are an issue. To reduce gastrointestinal adverse effects, the use of indomethacin farnesil, a prodrug of indomethacin, is sometimes effective from experience. Most of the other analgesics are not effective. Ibuprofen, naproxen, and aspirin have been tried, but results are inconsistent.<sup>5)</sup> Supraorbital nerve or greater occipital nerve block has been reported to be effective in patients with tenderness.<sup>15)</sup> In a crossover study of occipital nerve stimulation therapy in 6 patients, good result was reported<sup>16)</sup> but the method has not been established for general use.

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Hemicrania continua 254  
& Indomethacin 138  
Indomethacin farnesyl 13
- Search database: Ichushi Web for articles published in Japan (2012/6/4)  
Hemicrania continua 9  
Hemicrania continua (Japanese) 5  
Hemicrania continua9



## How is new daily persistent headache diagnosed and treated?

### Recommendation

#### 1. Diagnosis

New daily persistent headache is diagnosed according to the International Classification of Headache Disorders, 3rd Edition (beta version) (ICHD-3 beta).

**Grade A**

#### 2. Treatment

There are no clearly established treatment criteria, and also no treatments with established efficacy. There are two types; a type that resolves spontaneously, and a refractory type that is resistant to aggressive treatments.

**Grade C**

### Background and Objective

The International Classification of Headache Disorders 2nd Edition (ICHD-II) recognizes *New daily persistent headache* (NDPH) as a new separate entity. However, details of the headache properties, treatment effects and prognosis are not known. The mode of onset is important in diagnosis, and excluding secondary headaches is important.

### Comments and Evidence

#### 1. Diagnostic criteria

The diagnostic criteria of new daily persistent headache described in the ICHD-3beta are as follows.<sup>1)2)</sup>

A. Persistent headache fulfilling criteria B and C

B. Distinct and clearly remembered onset, with pain becoming continuous and unremitting within 24 hours

C. Present for >3 months

D. Not better accounted for by another ICHD-3 diagnosis

New daily persistent headache is a relatively rare disorder, and evidence is limited to case series.<sup>3)-5)</sup> This headache has also been reported in Japanese, but the number of cases is relatively small.<sup>4)6)</sup> In summary, the male to female ratio is slightly higher in female. The mean age of onset is in the thirties. The day of headache onset is usually clearly remembered by the patient. While the headache often has features resembling those of tension-type headache, it may also manifest characteristics of migraine such as nausea, photophobia and phonophobia. The headache may remit, or recur and remit repeatedly, or persist, but many patients follow a chronic course. Robbin et al.<sup>5)</sup> divided new daily persistent headache according to headache properties into two groups: a group with migraine-like headache that has a female preponderance and frequently a history of anxiety or depressive disorder, and a group with features of tension-type headache in which patients recall accurately the day of headache onset. Their report emphasizes that new daily persistent headache may manifest migraine-like headache. In a Norwegian population-based study of a sample aged 30 to 40 years, the 1-year prevalence was 0.03%.<sup>7)</sup> Among children and adolescents who are less likely to overuse medications than adults, onset of new daily persistent headache is typically secondary to infection and trauma.<sup>8)9)</sup>

Differential diagnosis includes chronic migraine, chronic tension-type headache, hemicrania continua, headache attributed to low cerebrospinal fluid pressure, headache attributed to increased cerebrospinal fluid pressure, headache attributed to head and/or neck trauma, and headache attributed to infection. Although many symptoms resemble those of chronic tension-type headache, the unique features are that headache is not evolved from episodic tension-type headache and that headache is daily and unremitting from the day of onset.

#### 2. Treatment

No prospective placebo-controlled trial has been reported, and clear treatment criteria have not been established.<sup>3)-5)</sup> New daily persistent headache has two types: a self-limiting type that resolves spontaneously, and a refractory subtype that is resistant to aggressive treatment. In line with tension-type headache and migraine, abortive drugs and prophylactic drugs such as gabapentin and topiramate have been tried, with no consistent results.

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- Search database: PubMed (2012/6/4)  
New daily persistent headache 144
- Search database: Ichushi Web for articles published in Japan (2012/6/4)  
New daily persistent headache 7

## How is chronic daily headache diagnosed?

### Recommendation

Chronic daily headache is a headache classification proposed by Silberstein, Lipton and colleagues,<sup>1,2)</sup> and is defined as headache that lasts 4 or more hours per day and occurs on 15 or more days per month. This disorder is classified into four types: transformed migraine, chronic tension-type headache, new daily persistent headache, and hemicrania continua. There is no clear evidence. With the International Classification of Headache Disorders, 3rd Edition (beta version) (ICHD-3beta) now being established, each headache type and medication-overuse headache should be diagnosed according to ICHD-3 beta, and chronic daily headache should be used as an umbrella term that includes various types of chronic headache.

**Grade C**

### Background and Objective

Since the International Headache Society first published the diagnostic criteria for headache disorders in 1988, the debate on how to diagnose and classify headaches that occur daily has continued. Chronic daily headache is a headache classification proposed by Silberstein, Lipton and colleagues<sup>1,2)</sup> in 1994. It is defined as headache that lasts 4 or more hours per day and occurs on 15 or more days per month, and is classified into four types. The International Classification of Headache Disorders, 3rd Edition (beta version) (ICHD-3 beta) published in 2013<sup>3-6)</sup> does not recognize chronic daily headache as a separate entity. However, the name is still used due to the convenience of allowing evaluation of all the headaches that occur on a daily basis.

### Comments and Evidence

In 1994, Silberstein, Lipton and colleagues<sup>1,2)</sup> defined chronic daily headache as headache that lasts 4 or more hours per day and occurs on 15 or more days per month. They classified this group into four types and set out diagnostic criteria. The four types are:

1. Transformed migraine (TM)
2. Chronic tension-type headache (CTTH)
3. New daily persistent headache (NDPH)
4. Hemicrania continua (HC)

The above classification is currently used worldwide. The criterion of at least 4 hours a day excludes cluster headache. Regarding the duration of headache, various articles have described durations ranging from 1 month to 1 year. In accordance with the diagnostic criteria of the International Classification of Headache Disorders, 3rd Edition (beta version) (ICHD-3beta) for chronic migraine, new daily persistent headache and hemicrania continua,<sup>3-6)</sup> a duration of over 3 months is generally accepted.<sup>7-9)</sup> The prevalence of chronic daily headache in the general population has been reported to be approximately 3 to 4%, while a prevalence of approximately 1.5% has been reported among subjects aged 12 to 14 years in population-based studies.<sup>7,9)-13)</sup> In a study comparing 638 adults aged 18 years or older and 170 adolescents aged 13 to 17 years, transformed migraine associated with medication overuse was significantly more frequent in adults while transformed migraine without medication overuse and chronic tension-type headache were significantly more common in adolescents.<sup>12)</sup> In a prospective cohort 8-year follow-up study of 122 adolescents aged 12 to 14 years, one-fourth of the patients continued to have disability in daily living due to chronic daily headache.<sup>14)</sup>

In the ICHD-3beta, chronic daily headache is not recognized as a separate entity, and transformed migraine is handled as chronic migraine and classified as various types in the group of primary headaches, differentiated from medication-overuse headache. Compared with the Silberstein-Lipton diagnostic criteria, the criteria in the ICHD-3beta are stricter. Transformed migraine with increased headache frequency due to medication overuse is considered almost equivalent to the ICHD-3beta codes of “migraine” + “medication-overuse headache”, while transformed migraine with no medication overuse or no increased headache frequency even though there is medication overuse is considered similar to the ICHD-3beta code of “chronic migraine”. Likewise, chronic tension-type headache with increased headache frequency due to medication overuse is considered to be “tension-type headache” + “medication-overuse headache”, while chronic tension-type headache with no

medication overuse or no increased headache frequency even though there is medication overuse to be “*chronic tension-type headache*”. Furthermore, the ICHD-3beta places importance on the presence of autonomic symptoms in hemicrania continua, and the elements of tension-type headache in new daily persistent headache. With the ICHD-3beta being well established, it has been recommended to discontinue using the term chronic daily headache and to diagnose according to ICHD-3beta. However, the term continues to be used currently, because when individual headaches cannot be classified accurately, it offers the convenience to evaluate these headaches under the umbrella term of chronic daily headache.

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- Search database: PubMed (2012/6/4)  
Daily headache 4502  
chronic daily headache 31338  
& definition 224  
& diagnostic criteria 2155  
& prevalence 4655  
& frequency 6238
- Search database: Ichushi Web for article published in Japan (2012/6/4)  
Chronic daily headache 14  
Chronic daily headache (Japanese) 5329

# VI

## Medication-overuse headache

## 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 International Classification of Headache Disorders, 3rd edition (beta version), which was published in Cephalgia in 2013.

**Grade A**

### Background and Objective

The diagnostic criteria for medication-overuse headache described in the International Classification of Headache Disorders 2nd Edition (ICHD-II)<sup>1)</sup> published in 2004 were revised in 2005<sup>2)</sup> and 2006.<sup>3)</sup> This section discusses the changes as well as the issues concerning the diagnostic criteria for medication-overuse headache.

### Comments and Evidence

In the International Classification of Headache Disorders 2nd Edition (ICHD-II) published in 2004,<sup>1)</sup> medication-overuse headache (MOH) is classified within the group of secondary headaches, under 8. *Headache attributed to a substance or its withdrawal*. MOH is characterized by: headache present on at least 15 days of a month, regular overuse of medications for over 3 months, headache developing or exacerbating markedly during medication overuse, and resolution of pain or returning to the previous pattern within 2 months after overuse is stopped. The subforms consist of headaches caused by individual medications: intake of ergotamine, triptan, opioid or combination analgesics on 10 or more days per month for over 3 months; or intake of simple analgesic on 15 or more days per month for over 3 months.

The criteria for medication-overuse headache in ICDH-II were discussed at the International Research Seminar held in March 2004. As a result, a revision (ICHD-II R1) was published in 2005, in which the characteristics of headache were removed and a new subform of headache due to intake of combination of acute medications for 15 days or more (8.2.6 *Medication-overuse headache attributed to combination of acute medications*) was added.<sup>2)</sup> The Japanese Headache Society promptly incorporated the revisions in time for publication of the Japanese edition of ICHD-II. Therefore the Japanese edition essentially corresponds in the contents of the 2005 revision (R1).<sup>4)</sup>

In ICHD-II R1, the criterion “D. Headache resolves or reverts to its previous pattern within 2 months after discontinuation of overused medication” remains. Therefore resolution of pain or reversion to the previous pattern within 2 months after stopping overuse is mandatory. This means that (1) a period of 2 months after cessation of overuse is stipulated, (2) during this period, the diagnosis of probable MOH should be applied, and (3) MOH can be diagnosed only when improvement occurs after cessation of overused medication. However, at that time point, MOH is actually resolved, and the diagnosis would revert to the previous one. Due to the above and other issues, the above-mentioned sentence was eliminated in the 2006 revision,<sup>4)</sup> allowing a diagnosis of MOH to be made before cessation of the overused medication.

Even after the second revision, issues still exist. For example, it is difficult to prove whether medication overuse is caused by frequent headaches, or whether headaches appear or worsen because of medication overuse.<sup>5)6)</sup> Therefore, in the latest revision, the ICHD 3<sup>rd</sup> edition (beta version) (ICHD-3beta),<sup>7)</sup> the criterion “headache has developed or markedly worsened during medication overuse” was omitted.

The diagnostic criteria described in ICHD-3beta are shown below.

#### 8.2 *Medication-overuse headache*

##### • Diagnostic criteria

- A. Headache occurring on  $\geq 15$  days per month in a patient with a pre-existing headache disorder.
- B. Regular overuse for  $> 3$  months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache.
- C. Not better accounted for by another ICHD-3 diagnosis.

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- Search database: PubMed (2011/12/21)  
Medication overuse 825  
Medication overuse headache 529  
& criteria 141  
& diagnosis 267
- Search database: Ichushi Web for articles published in Japan (2011/12/21)  
Medication-overuse headache 115  
& diagnostic criteria 9



## How big is the population of medication-overuse headache patients?

### Recommendation

In overseas countries, the 1-year prevalence of medication-overuse headache in the general population is approximately 1 to 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**

### Background and Objective

In Japan, no epidemiological study has been conducted to investigate the 1-year prevalence of medication-overuse headache in the general population. This section summarizes the prevalence of medication-overuse headache of overseas countries.

### Comments and Evidence

In a review of studies on the prevalence of headache in Europe, which included 49 studies comprising a total of 205,000 adult participants, headache occurred in 54% of the adults and the prevalence of medication-overuse headache (MOH) in the general population was estimated to be 1 to 2%.<sup>1)</sup> In Brazil, of 1,631 persons who participated in an interview survey, 23 persons had MOH or probable MOH and the prevalence was 1.4%.<sup>2)</sup> In a population (1,533 persons) of elderly persons (65 years or older) in Taiwan, the prevalence of MOH was approximately 1%.<sup>3)</sup> There are no great differences in prevalence of MOH in the general population among various overseas countries.

Regarding the gender difference of MOH, women occupied 73% in Denmark,<sup>4)</sup> 93% in Spain,<sup>5)</sup> and 76% in the United States,<sup>6)</sup> showing an overwhelming female preponderance. Mean ages of MOH were reported to be 48 years,<sup>4)</sup> 56 years,<sup>5)</sup> and 42.8 years.<sup>6)</sup> The percentage of MOH in headache clinics and headache centers was up to 30% in Europe and more than 50% in the United States.<sup>7)</sup> The percentage of MOH was 14.6% in a headache center in Japan,<sup>8)</sup> indicating the importance of diagnosis and treatment of MOH in headache centers. A report from Turkey suggests low income and low educational level to be potential risk factors of MOH.<sup>9)</sup>

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- Medication-overuse headache 529
- & epidemiology 157
- & prevalence 176
- Drug-induced headache 347
- & epidemiology 26
- & prevalence 33

## What are the treatment methods and prognosis of medication-overuse headache?

### Recommendation

The treatment principles for medication-overuse headache are: (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 abrupt discontinuation on an inpatient basis is recommended for 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**

### Background and Objective

Even though treatment is important for the frequent headaches in patients with medication-overuse headache, the quality of evidence is low because no randomized controlled trial has been reported. Although there is currently no established treatment, research data is accumulating. This section describes the treatment methods and prognosis.

### Comments and Evidence

Regarding the methods of discontinuing the drugs causing medication-overuse headache (MOH), no prospective study has compared abrupt discontinuation of the overused medication and tapering. Clinical studies conducted in Japan reported more relapses of MOH after tapering compared to abrupt discontinuation.<sup>1,2)</sup>

A prospective randomized open-label study that compared inpatient versus outpatient withdrawal therapies found no difference in response rate at 2 years after withdrawal.<sup>3)</sup> From the above findings, an outpatient abrupt withdrawal program appears to be the best approach. In patients with severe medication-overuse headache in whom withdrawal symptoms were a concern or who require closer psychological observation, inpatient withdrawal program should be considered.

In the International Classification of Headache Disorders 2nd Edition (ICHD-II),<sup>4)</sup> withdrawal headache attributed to overuse of acute medications for headache is defined as headache that develops within 48 hours after last intake of the overused medication and resolves within 7 days after withdrawal. Improvement is observed after a shorter duration in patients overusing triptans than in patients overusing ergotamine or NSAIDs.<sup>5)</sup> Treatment of withdrawal headache using triptans, naproxen, prochlorperazine, steroids and other drugs have been reported, but they were open-label studies with small numbers of cases. A double-blind study of oral prednisolone given for 6 days (starting with 60 mg/day, increasing by 20 mg every 2 days) reported no difference compared to placebo.<sup>6)</sup> In severe cases, hospitalization and management with hydration, antiemetics, sedatives and steroids should be considered.<sup>7)</sup>

Early initiation of prophylactic therapy has been shown to be effective to reduce the number of days with headache by 7.2 days at 3 months and by 10.3 days at 12 months.<sup>8)</sup> Therefore, initiation of prophylactic medications at the time of withdrawal or even before withdrawal of overused medications is recommended. Since most of the MOH patients have migraine prior to MOH, valproic acid, lomerizine, propranolol, amitriptyline (off-label use approved in Japan) and topiramate (currently not covered by health insurance in Japan) may be considered as prophylactic medications.

Evidence for treatment of MOH at the level of randomized controlled trial (RCT) is available for topiramate. In a study conducted in the US comparing topiramate (n = 153) and placebo (n = 153), the change in number of days with headache after withdrawal was -5.6 days in the topiramate group versus -4.1 days in the placebo group, showing a significant improvement in the topiramate group compared to placebo.<sup>9)</sup> In a study conducted in EU, the change in number of days with headache was -3.5 days in the topiramate group (n = 27) versus -0.2 days in the placebo group (n = 32), showing greater decrease in the topiramate group.<sup>10)</sup> For amitriptyline also, a double-blind placebo (trihexyphenidyl)-controlled trial showed a significant reduction in headache frequency in the amitriptyline-treated group.<sup>11)</sup> Moreover, treatment with amitriptyline

in patients who did not respond to withdrawal of misused drugs alone reduced the number of days with headache in 36% of the patients.<sup>12)</sup> These studies suggest the usefulness of amitriptyline in the treatment of MOH.

The relapse rate of MOH after withdrawal therapy is approximately 30% (14-21%).<sup>13)</sup> Therefore, even after discontinuation, use of headache diary to regularly monitor drug intake as well as patient education are important.

The factors predicting poor prognosis for MOH are long duration of migraine, frequent migraine attacks after discontinuation, intake of combination analgesics after withdrawal therapy, frequent drug taking, alcohol consumption, smoking, and taking the former medication again after withdrawal therapy.<sup>13)14)</sup>

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- Search database: PubMed (2011/12/21)  
Medication overuse 825  
Medication overuse headache 529  
& withdrawal 118  
& advice 4  
& risk factor 69  
& detoxification 29  
& treatment 395  
& prognosis 96  
& outcome 100  
Drug-induced headache 347  
& treatment 280
- Search database: Ichushi Web for articles published in Japan (2011/12/21)  
Medication-overuse headache 115  
& treatment 97

# VII

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## Headaches in Children

## 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 to 13.5% and the prevalence in school-based (number of students) surveys is 1.7 to 21.3%, while the prevalence of tension-type headache is 17.4% and 0.7 to 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**

### Background and Objective

Most of the reports on headache prevalence in children were on migraine, but since 2005, the number of reports on headaches other than migraine has increased. Most of them reported prevalence of headaches diagnosed according to the diagnostic criteria of the first edition of the International Classification of Headache Disorders (IHS classification, 1988) or the International Classification of Headache Disorders 2nd Edition (ICHD-II, 2004). Some studies are based on population, some are based on the number of students in schools, and some are based on the number of outpatients attending headache clinics. The Japanese data are from two articles only,<sup>19)23)</sup> and further accumulation of research data is anticipated.

### Comments and Evidence

The prevalence and the basic data of statistical analyses extracted from the references are shown in **Tables 1 to 3**. **Table 1** lists the population-based studies;<sup>1)-7)</sup> **Table 2** shows the school (number of students)-based studies;<sup>8)-25)</sup> and **Table 3** presents the outpatient-based studies.<sup>26)-29)</sup>

The numbers and ages of subjects included in the statistical data and countries of the studies are shown below (the numbers refer to the numbers in the reference list).

1. Review: 50 articles, ages below 20 years
2. Review: 36,000 subjects for migraine (children and youth), 25,000 subjects for tension-type headache (children and youth)
3. 30,636 subjects (3-17 years) (Serbia)
4. 1,679 subjects (11-18 years) (Nigeria)
5. 1,856 subjects (5-11 years) (Brazil)
6. 1,994 subjects (5-12 years) (Brazil)
7. 2,114 subjects (12-14 years) (Denmark)
8. Review: 13 articles
9. 1,385 subjects (11-18 years) (Turkey)
10. 953 subjects (mean 13.2 years) (Thailand)
11. 3,963 subjects (13-15 years) (Taiwan)
12. 2,235 subjects (grades 9-12) (India)
13. 2,669 subjects (mean 8.2±2.4 years) (Turkey)
14. 2,384 subjects (14-18 years) (Turkey)
15. 1,789 subjects (12-15 years) (Thailand)
16. 76,333 subjects (9-17 years) (Turkey)
17. 3,324 subjects (12-15 years) (Germany)
18. Unknown, 8 schools randomly selected from 9 districts (Turkey)
19. 6,472 subjects (12-15 years) (Japan)
20. 1,259 subjects (7-12 years) (Serbia)
21. 2,226 subjects (6-13 years) (Iran)

22. 1,270 subjects (12-14 years), 1,117 subjects (15-17 years) (Turkey)
23. 2,462 subjects (senior high school) (Japan)
24. 13,426 subjects (13-15 years) (Taiwan)
25. 5,777 subjects (grades 2-5) (Turkey)
26. 87 subjects (12-17 years, selected after interview at school) (Turkey)
27. 375 subjects (Thailand)
28. 124 subjects ( $\leq 18$  years) (Hong Kong)
29. 105 subjects ( $\leq 6$  years) (Italy)

**Table 1. Population-based studies on prevalence of headache in children.**

Author	Year	Country	Age (yr)	Prevalence of migraine (%)			Prevalence of tension-type headache (%)		
				Boy	Girl	Total	Boy	Girl	Total
Knezevic-Pogancev et al	2010	Serbia	3-17	8.0	9.6	8.6			—
			3-7	4.2	3.6	3.9			—
Ofove et al	2010	Nigeria	11-18			13.5			—
Arruda et al	2010	Brazil	5-12	3.9	3.6	3.8	17.0	17.7	17.4
Russell et al*	2006	Denmark	12-14	7.0	8.2	7.6	78.6	84.5	79.5
Abu-Arafeh et al	2010	review	3-19	6.0	9.7	7.7			—
Stovner et al	2010	review	5-21	5.6	8.2	8.3	10.9	16.1	14.0

\*Since data are those for adolescents (12-14 years) from a large-scale study of 33,764 twins aged 12-41 years, we excluded the data of this article from calculation of average age.

**Table 2. School (number of students)-based studies on prevalence of headache in children.**

Author	Year	Country	Age (yr)	Prevalence of migraine (%)			Prevalence of tension-type headache (%)		
				Boy	Girl	Total	Boy	Girl	Total
Alp et al*		Turkey	11-18			14.3	4.4	4.2	8.6
Including probable migraine				23.0	29.5	25.5			
Visudtibhan et al	2010	Thailand	12-14			12.1			0.7
Fuh et al	2010	Taiwan	13-15			12.2			27.6
Gupta et al	2010	India	16-18			17.2			11.0
Igik et al	2009	Turkey	5-10			3.4			—
Unalp et al	2009	Turkey	14-18			21.3			5.1
Visudtibhan et al	2006	Thailand	12-15	11.7	16.2	13.8			—
Akyol et al	2007	Turkey	9-17	7.8	11.7	9.7			—
Fendrich et al	2007	Germany	12-15	4.4	9.3	6.9	19.1	21.2	20.2
Ando et al	2007	Japan	12-15	3.3	6.5	4.8			—
Milovanovi. et al	2007	Serbia	7-12	2.1	4.6	3.3	0.9	1.7	1.3
Ayatollahi et al	2007	Iran	6-13			1.7	5.5		—
Karli et al	2006	Turkey	12-17			14.5			—
Suzuki et al	2006	Japan	16-18	13.7	17.5	15.6	23.0	30.6	26.8
Wang et al	2005	Taiwan	13-15			5.9			6.3
Bugdayci et al	2005	Turkey	8-16			10.4			24.7
Lewis	2007	Review					Preschool; 3%, primary school; 4-11%, senior high school; 8-23%		

**Table 3. Outpatient-based studies on prevalence of headache in children.**

Author	Year	Country	Age (yr)	Prevalence of migraine (%)	Prevalence of tension-type headache (%)
Karli et al	2010	Turkey	12-17	57.5	27.6
Ruangsuwan et al	2007	Thailand	3-16	35.2	12.5
Chan et al	2006	Hong Kong	$\leq 18$	5.6	24.2
Raieli et al	2005	Italy	$\leq 6$	35.2	18.0
Mean				33.4	20.6

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## • Search terms and secondary sources

- Search database: PubMed (2011/10/12) The number of articles is shown in parentheses.  
 #6Search #4 or #5 Limits: Humans, English, Japanese, All Child: 0-18 years, Publication Date from 2005 to 2011 (476)  
 #5Search headache disorders/epidemiology Limits: Humans, English, Japanese, All Child: 0-18 years, Publication Date from 2005 to 2011 (429)  
 #4Search Headache Disorders/classification Limits: Humans, English, Japanese, All Child: 0-18 years, Publication Date from 2005 to 2011 (87)  
 #3Search Headache Disorders/classification Limits: Humans, English, Japanese, All Child: 0-18 years (241)  
 #2Search Headache Disorders/classification (866)  
 #1Search Headache Disorders



## How is migraine in children diagnosed?

### Recommendation

Migraine and tension-type headache, which are representative primary headaches in children, are diagnosed according to the International Classification of Headache Disorders, 3rd edition (beta version).

**Grade A**

### Background and Objective

In the past, migraine in children was diagnosed mainly according to the Vahlquist criteria. Since the publication of the first edition of the International Classification of Headache Disorders (IHS classification, 1988), the diagnostic criteria of the IHS classification began to be used. However, the IHS classification was developed mainly for headaches in adults. Reports appeared pointing out that the migraine duration and headache location provided by the IHS classification could not be applied directly to diagnose migraine in children. In the International Classification of Headache Disorders 2nd Edition (ICHD-II),<sup>1,2)</sup> the criteria for diagnosing migraine in children, which are different from those used in adults, were added. Then, in the International Classification of Headache Disorders, 3rd edition (beta version)<sup>3)</sup> the headache duration for migraine in children has been changed.

### Comments and Evidence

According to the International Classification of Headache Disorders, 3rd edition (beta version) (ICHD-3beta), migraine in children is under “1.1 *migraine without aura*” and “1.2 *migraine with aura*”. The diagnostic criteria for “1.2 *migraine with aura*” are not different between adults and children, and hence are not described here. The diagnostic criteria for “1.1 *migraine without aura*” are shown below. However, there are differences when these criteria are applied to children, and these are described in Note 3.

#### 1.1 *Migraine without aura*

- A. At least five attacks<sup>Note 1</sup> fulfilling criteria B-D
- B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)<sup>Notes 2,3</sup>
- C. Headache has at least two of the following four characteristics:
  1. unilateral location
  2. pulsating quality
  3. moderate or severe pain intensity
  4. aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
- D. During headache at least one of the following:
  1. nausea and/or vomiting
  2. photophobia and phonophobia
- E. Not better accounted for by another ICHD-3 diagnosis

#### • Notes

1. One or a few migraine attacks may be difficult to distinguish from symptomatic migraine-like attacks. Furthermore, the nature of a single or a few attacks may be difficult to understand. Therefore, at least five attacks are required. Individuals who otherwise meet criteria for 1.1 Migraine without aura but have had fewer than five attacks, should be coded 1.5.1 *Probable migraine without aura*.
2. When the patient falls asleep during a migraine attack and wakes up without it, duration of the attack is reckoned until the time of awakening.
3. In children and adolescents (aged under 18 years), attacks may last 2-72 hours (the evidence for untreated durations of less than 2 hours in children has not been substantiated).

#### • Comments

Migraine headache in children and adolescents (aged under 18 years) is more often bilateral than is the case in adults; unilateral pain usually emerges in late adolescence or early adult life. Migraine headache is usually frontotemporal. Occipital

headache in children is rare and calls for diagnostic caution. In young children, photophobia and phonophobia may be inferred from their behavior.

In ICHD-3beta, “1.6 *Episodic syndromes that may be associated with migraine*” has been added. This group of disorders occurs in patients who also have 1.1 *migraine without aura* or 1.2 *migraine with aura*, or who have an increased likelihood to develop either of these disorders. Although historically noted to occur in childhood, they may also occur in adults.

#### 1.6.1.1 *Cyclic vomiting syndrome*

- A. At least five attacks of intense nausea and vomiting, fulfilling criteria B and C
- B. Stereotypical in the individual patient and recurring with predictable periodicity
- C. All of the following:
  - 1. nausea and vomiting occur at least four times per hour
  - 2. attacks last  $\geq 1$  hour and up to 10 days
  - 3. attacks occur  $\geq 1$  week apart
- D. Complete freedom from symptoms between attacks
- E. Not attributed to another disorder<sup>Note 1</sup>
- Note
  - 1. In particular, history and physical examination do not show signs of gastrointestinal disease.

#### 1.6.1.2 *Abdominal migraine*

- A. At least five attacks of abdominal pain, fulfilling criteria B-D
- B. Pain has at least two of the following three characteristics:
  - 1. midline location, periumbilical or poorly localized
  - 2. dull or ‘just sore’ quality
  - 3. moderate or severe intensity
- C. During attacks, at least two of the following:
  - 1. anorexia
  - 2. nausea
  - 3. vomiting
  - 4. pallor
- D. Attacks last 2-72 hours when untreated or unsuccessfully treated
- E. Complete freedom from symptoms between attacks
- F. Not attributed to another disorder<sup>Note 1</sup>
- Note:
  - 1. In particular, history and physical examination do not show signs of gastrointestinal or renal disease, or such disease has been ruled out by appropriate investigations.

#### 1.6.2 *Benign paroxysmal vertigo*

- A. At least five attacks fulfilling criteria B and C
- B. Vertigo<sup>Note 1</sup> occurring without warning, maximal at onset and resolving spontaneously after minutes to hours without loss of consciousness
- C. At least one of the following associated symptoms or signs:
  - 1. nystagmus
  - 2. ataxia
  - 3. vomiting
  - 4. pallor
  - 5. fearfulness
- D. Normal neurological examination and audiometric and vestibular functions between attacks
- E. Not attributed to another disorder
- Note:
  - 1. Young children with vertigo may not be able to describe vertiginous symptoms. Parental observation of episodic periods of unsteadiness may be interpreted as vertigo in young children.

### 1.6.3 *Benign paroxysmal torticollis*

- A. Recurrent attacks<sup>Note 1</sup> in a young child, fulfilling criteria B and C
  - B. Tilt of the head to either side, with or without slight rotation, remitting spontaneously after minutes to days
  - C. At least one of the following associated symptoms or signs:
    - 1. pallor
    - 2. irritability
    - 3. malaise
    - 4. vomiting
    - 5. ataxia<sup>Note 2</sup>
  - D. Normal neurological examination between attacks
  - E. Not attributed to another disorder.
- Notes:
    - 1. Attacks tend to recur monthly.
    - 2. Ataxia is more likely in older children within the affected age group.

## Appendix

### A1.6.4 *Infantile colic*

- A. Recurrent episodes of irritability, fussing or crying from birth to 4 months of age, fulfilling criterion B
- B. Both of the following:
  - 1. episodes last for  $\geq 3$  hours per day
  - 2. episodes occur on  $\geq$  days per week for  $\geq 3$  weeks
- C. Not attributed to another disorder.

### A1.6.5 *Alternating hemiplegia of childhood*

- A. Recurrent attacks of hemiplegia alternating between the two sides of the body and fulfilling criteria B and C
- B. Onset before the age of 18 months
- C. At least one other paroxysmal phenomenon is associated with the bouts of hemiplegia or occurs independently, such as tonic spells, dystonic posturing, choreoathetoid movements, nystagmus or other ocular motor abnormalities and/or autonomic disturbances
- D. Evidence of mental and/or neurological deficit(s)
- E. Not attributed to another disorder.

In ICHD-II, the diagnostic criteria have been modified to include headache duration from 1 hour and bilateral headache if frontotemporal in location for the diagnosis of migraine in children. Several reports indicated that use of the ICDH-II criteria improved the diagnostic sensitivity of migraine in children.<sup>4)-7)</sup> On the other hand, some reports also pointed out that the sensitivity of 73.9% (53% for migraine without aura and 71.0% for migraine with aura) remained unsatisfactory.<sup>4)5)</sup> Regarding associated symptoms, the proposed revision of considering photophobia and phonophobia as independent diagnostic criteria is regarded not useful at this time.<sup>7)</sup> In ICHD-3beta, the headache duration for migraine in children has been changed from one hour or longer to two hours or longer.

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- **Search terms and secondary sources**

- Search database: PubMed (2011/10/7)
  - migraine & children 2679
  - & diagnosis 1538 & ICHD 39
  - & ICHD- 217
  - pediatric migraine 737
  - & ICHD 18
  - & diagnosis 494
  - cyclical vomiting 61
  - & diagnosis 32
  - cyclic vomiting 394
  - & diagnosis 190
  - abdominal migraine 17167 & children 2298
  - & diagnosis 1322
  - & criteria 378
  - benign paroxysmal vertigo & children 100
  - & diagnosis 78
  - & criteria 9
- Search database: Ichushi Web for articles published in Japan (2011/10/7)
  - Children & headache 1491
  - & migraine 276
  - & secondary 13
  - & diagnosis 1061
  - & classification 80

## 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**

### Background and Objective

There are few reports on the prevalence of secondary headaches in children. Irrespective of general pediatricians, pediatric neurologists and pediatric emergency physicians, diagnosing secondary headaches appropriately is important also from the viewpoint of making an accurate diagnosis of primary headaches (migraine and tension-type headache).

### Comments and Evidence

In a population-based study of 2,165 schoolchildren (aged 5 to 15 years) in the community, the prevalence of secondary headache among all children with headache was 42.9%, including infection 30.9%, trauma 5.1%, special illness 2.3%, and poor eyesight 1.3%.<sup>1)</sup>

In a study of 437 patients (aged 3 to 19 years) attending a headache clinic of a university hospital, secondary headache was found in 26 patients (6%). According to the first edition of the International Classification of Headache Disorders (1988), 9 patients were diagnosed with “5. Headache associated with head trauma”, 1 patient with “6. Headache associated with vascular disorders”, 1 patient with “7. Headache associated with non-vascular intracranial disorder”, 8 patients with “9. Headache associated with non-cephalic infection”, and 7 patients with “11. Headache or facial pain associated with disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cranial structures”.<sup>2)</sup>

In a study of 243 patients at the pediatric headache clinic of a university hospital using the International Classification of Headache Disorders 2nd Edition (ICHD-II), 3 patients had “6. Headache attributed to cranial or cervical vascular disorder”, 1 patient had “7. Headache attributed to non-vascular intracranial disorder”, 1 patient had “8. Headache attributed to a substance or its withdrawal”, 4 patients had “11. Headache or facial pain attributed to disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cranial structures”, 2 patients had “12. Headache attributed to psychiatric disorder”, and 17 patients were unclassifiable.<sup>3)</sup>

In a study of 478 patients (aged 2 to 15 years) with chronic and recurrent headache attending the pediatric outpatient clinic of a general hospital, 13 patients (3%) had secondary headaches. According to the IHS classification (1988), 3 patients had “6. Headache associated with vascular disorders” (1 patient each with intracranial hemorrhage, moyamoya disease, and hypertension due to renin-producing tumor) and 6 patients had “7. Headache associated with non-vascular intracranial disorder” (3 patients with intracranial neoplasm, 1 with high cerebrospinal fluid pressure/hydrocephalus, and 2 with headache associated with other intracranial disorder). In addition, 4 patients had “11. Headache or facial pain associated with disorder of facial or cranial structures” (1 patient with eosinophilic granuloma of cranial bone, 1 with hyperopic astigmatism, and 2 with acute sinusitis).<sup>4)</sup>

A total of six articles on secondary headaches in pediatric emergency department were identified.<sup>5)-10)</sup> The most common secondary headache is headache attributed to infection, represented by viral diseases, with frequencies of 14.8 to 61.0%.<sup>5)-10)</sup> This was followed by headache attributed to head and/or neck trauma with frequencies of 6.6 to 20.0%,<sup>5)6)9)10)</sup> and headache attributed to sinusitis with frequencies of 9.0 to 16.7%.<sup>5)6)10)</sup> The frequencies of headache attributed to viral meningitis were 0.4 to 9.0%,<sup>5)-10)</sup> and the frequencies of headache attributed to VP shunt problem were 0.3 to 11.5%.<sup>5)-10)</sup> The frequencies of headache attributed to intracranial neoplasm were 0.4 to 2.6%.<sup>6)8)-10)</sup> Although there are no reports of prevalence according to age, approximately 70% of secondary headaches are attributed to infections especially in young children aged 2 to 5 years<sup>9)</sup> (Table 1).

Head CT should be performed in patients who have recent onset headache with unexplained etiology and in patients who

have underlying diseases.<sup>7)</sup> On the other hand, for young children presenting with headache but no abnormal neurological findings and no remarkable history, head CT seldom contributed to diagnosis and early intervention.<sup>9)</sup> In another study, when neuroimaging was performed upon requests from patients or their parents or when there were changes in headache properties, none of those patients required surgical treatment.<sup>11)</sup>

**Table 1. Etiologies of secondary headaches**

	Burton <sup>5)</sup> (1997)	Lewis <sup>6)</sup> (2000)	Kan <sup>7)</sup> (2000)	Scagni <sup>8)</sup> (2008)	Lateef <sup>9)</sup> (2009)	Conicella <sup>10)</sup> (2008)
Age (yr.)	2-18	2-18	0-18	0-16	2-5	2-18
No. of patients	288	150	130	526	364	432
% secondary headaches				42.0	84.3	55.0
Viral disease	39.2	39.0	28.5	38.0	61.0	14.8
Sinusitis	16.0	9.0				16.7
Traumatic head injury	6.6	20.0		—*	13.0	8.7
Beta hemolytic streptococcal pharyngitis	4.9	9.0				
Viral meningitis	5.2	9.0	2.3	0.4	1.1**	2.5
VP shunt problem	0.3	2.0	11.5	0.4	3.8	1.8
Brain tumor		2.6		0.4	1.9	1.1
Post-convulsion		1.3		0.9	0.5	
Cerebrovascular disease				0.5	0.3***	

Data are percentage relative to all headaches.

\*: Excluding headache attributed to head trauma and headache attributed to bacterial meningitis

\*\*: Bacterial meningitis or viral meningitis

\*\*\*: Cerebral infarction or ADEM

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## • Search terms and secondary sources

- Search database: PubMed (2011/10/7)
- Headache & Children (6566)
- & Secondary (392)
- & emergency (277)
- & infection (770) & emergency (39)
- & meningitis (343) & emergency (30)
- & head trauma (277) & emergency (61)
- & brain tumor (561) & emergency (17)
- & brain hematoma (73) & emergency (13)
- & brain hemorrhage (317) & emergency (30)
- & VP shunt (13) & emergency (1)
- Secondary headache (2895)
- & prevalence (412)
- & children (393) & epidemiology (99)
- & children (393) & prevalence (107)

- Search database: Ichushi Web for articles published in Japan (2011/10/7)  
Children & headache 1491  
& migraine 276  
& secondary 13  
& diagnosis 1061  
& classification 80



## 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 effective 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**

### Background and Objective

In children also, pharmacotherapy is necessary when migraine causes a high degree of disability in daily living. This section examines whether ibuprofen and acetaminophen are superior acute medications for migraine in children, and whether triptans are effective and tolerable for children. In children with frequent severe migraine attacks, prophylactic therapy should be considered. This section also investigates the types, efficacy and safety of prophylactic medications.

### Comments and Evidence

The recommended management of migraine in children is first to identify and avoid factors that trigger headache, and to use non-pharmacologic biobehavioral treatments such as regular sleep, dietary modification, exercise, biofeedback and stress management.<sup>1)</sup>

#### 1. Acute medications

Ibuprofen and acetaminophen are effective and safe acute medications for migraine in children.<sup>1)-3)</sup> The recommended strategy is to start treatment at an adequate dose as early as possible after onset of headache.<sup>1)2)</sup> Among the triptans, sumatriptan and zolmitriptan (currently not available in Japan) in nasal spray form, and rizatriptan and almotriptan (currently not available in Japan) in tablet form have been reported to be safe and efficacious.<sup>1)</sup> Three randomized controlled trials (RCT) have demonstrated the efficacy and safety of sumatriptan nasal spray.<sup>2)</sup> It is recommended for children aged 12 years and older, although one RCT in children aged 6 years and older showed no adverse effects except bad taste.<sup>1)2)</sup> In a small-scale Japanese study of sumatriptan nasal spray in 20 patients aged 12 to 17 years with migraine, treatment was effective in 75% of the patients ( $p = 0.002$ ), but only 55% wished to continue the prescription in the future mainly because of the adverse effect of bad taste.<sup>4)</sup> For oral triptan, an RCT studied rizatriptan in 96 children with migraine aged 6 to 17 years using a dose of 5 mg for those weighed 20 to 39 kg, and 10 mg for those weighing 40 kg or more.<sup>5)</sup> In this trial, the primary end point at 2 hours revealed effective rates of 74% after the first dose and 73% after the second dose; both were significantly higher ( $p < 0.001$ ) compared to placebo (36%), with no serious adverse effects. In a large-scale multicenter study of zolmitriptan tablet for migraine in 850 adolescents aged 12 to 17 years, there was no significant improvement between zolmitriptan and placebo. Examination of the study method suggested the high placebo response rate in adolescents.<sup>6)</sup> On the other hand, an RCT of zolmitriptan tablet in an European headache clinic recruiting 29 children with migraine aged 6 to 18 years reported significantly higher ( $p < 0.05$ ) effective rate for zolmitriptan (62%) compared to placebo (28%).<sup>3)</sup> A multicenter RCT of eletriptan in 380 adolescents with migraine aged 12 to 17 years demonstrated no significant difference in response rate between eletriptan and placebo, but eletriptan was significantly superior ( $p = 0.028$ ) to placebo with respect to the reduction of headache recurrence within 24 hours.<sup>7)</sup>

#### 2. Prophylactic medications

For children younger than 10 years of age who have no obesity problem, cyproheptadine at 2 to 4 mg as a single bedtime dose is a simple and safe strategy.<sup>1)</sup> The dose may be increased, but children become sedated at doses higher than 4 to 8 mg/day.

Attention is necessary, because in children with a history of convulsion and/or with fever, cyproheptadine may induce convulsion. Although amitriptyline has not been evaluated by RCT, it is the most widely used medication.<sup>112)</sup> The starting dose is 5 to 10 mg at bedtime, and may gradually be increased to 1 mg/kg/day. Since the publication of guideline on treatment of migraine in children in 2004,<sup>2)</sup> the antiepileptic drug topiramate has been shown to achieve good outcome in RCT, and has become the recommended drug. In a multicenter RCT recruiting 32 adolescents with migraine aged 12 to 17 years, treatment with topiramate 50, 100, and 200 mg/day for 26 weeks reduced monthly migraine frequency by 46% ( $P = 0.07$ ), 63% ( $P = 0.02$ ), and 65% ( $P = 0.04$ ), respectively, compared to placebo (16%).<sup>8)</sup> In an RCT conducted at the pediatric outpatient department of a university hospital, the group treated with topiramate 100 mg/day had significantly greater reduction in headache frequency per month compared to the group treated with placebo ( $p = 0.025$ ), and significantly reduced school absenteeism ( $p = 0.002$ ).<sup>9)</sup> In a multicenter RCT, topiramate at 100 mg/day, but not 50 mg/day, resulted in a significant reduction in monthly migraine attack rate and a significant decrease in number of days with migraine compared to placebo.<sup>10)</sup> In all these trials, no serious adverse events were observed, but weight loss, lowered concentration, somnolence, and dizziness were found in topiramate-treated patients. The recommended regimen for topiramate is to start from 15 to 25 mg once a day at bedtime, and increase gradually to 50 mg twice a day.<sup>1)</sup>

For divalproex sodium, an RCT on migraine prophylaxis conducted in adolescents aged 12 to 17 years was available.<sup>11)</sup> No significant difference in migraine prophylactic effect was observed between any dose of divalproex sodium (250 mg/day, 500 mg/day or 1,000 mg/day) and placebo, but the drug was well-tolerated. In a single-center open-label study, after 4 months treatment with divalproex sodium, 50% headache reduction was achieved in 78.5% of patients, 75% reduction in 14.2% of patients, and 9.5% of patients became headache-free.<sup>12)</sup> Two open-label studies of levetiracetam showed some efficacy of levetiracetam for migraine prevention, and concluded that this drug seemed to be a promising candidate. In a small-scale open-label study of zonisamide, reduction in headache frequency was observed.<sup>1)</sup>

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## • Search terms and secondary sources

- Search database: PubMed (2011/11/17)  
Migraine treatment 13921  
& children 1602 & adolescents 2376  
& children adolescents 1002  
OR analgesics 236 OR triptan 23 OR acetaminophen 31 OR ibuprofen 28  
OR preventive 60 OR prophylactic 106 OR antiepileptic 145
- Search database: Ichushi Web for articles published in Japan (20/11/17)  
migraine treatment (excluding proceedings) 1832  
& children 189 OR adolescent 11  
& children adolescent 9

## What is the prevalence of chronic daily headache in children, and how is the headache diagnosed and treated?

### Recommendation

According to population-based surveys, the prevalence of chronic daily headache (CDH) was 1.68% in children aged 5 to 12-years, 1.5% in those aged 12 to 14 years, and 3.5% in those aged 12 to 17 years. The prevalence of CDH in headache centers was variable, ranging from 5.9 to 38.0% in patients aged 6 to 18 years. The diagnostic criteria of CDH require the presence of headache on 15 or more days per month, for a duration of 1 month in two sets of population-based survey and more than 3 months in the data of all headache centers. The duration of headache per day was often not included in the diagnostic criteria. There is no randomized controlled trial on the treatment of CDH in children, and is an issue for future study.

**Grades B and C**

(prevalence and diagnosis: B, treatment: C)

### Background and Objective

In headache clinics, children and adolescent sometimes present with chronic daily headache (CDH) that impairs daily living. The CDH in this age group does not respond well to analgesics and often becomes refractory to treatment. To find out the prevalence of CDH in children and adolescents and how this headache is diagnosed and treated, this section reviews population-based studies and data from various headache clinics to identify the prevalence and appropriate diagnosis and treatment of CDH in children and adolescents.

### Comments and Evidence

#### 1. Prevalence of CDH in children (using the International Classification of Headache Disorders 2nd Edition: ICHD-II)

##### (1) Population-based prevalence and headache types

The prevalence of CDH among adolescents age 12 to 17 years was 3.5%, and the prevalence by headache type was chronic migraine (CM) 20.9% and chronic tension-type headache (CTTH) 2.8%. Consequently, 76.3% of the cases could not be diagnosed as CM or CTTH, 27.5% of which fulfilled the diagnostic criteria for medication overuse headache (MOH). In a US study of adolescents aged 12 to 17 years, the prevalence of CM without MOH was 0.79% and that of CM with MOH was 1.75%, and was higher in females than in males.<sup>1)</sup> In a Brazilian study, the prevalence of CDH among children aged 5 to 12 years was 1.68% (girls 2.09%, boys 1.33%), and was significantly higher in girls.<sup>2)</sup> In a report from Taiwan, the prevalence of CDH in adolescents aged 12 to 14 years was 1.5% (girls 2.4%, boys 0.8%), and was significantly higher in girls. By type of CDH, the prevalence of CM was 6.6% and that of CTTH was 65.5%, and was significantly higher for CTTH. Twenty percent of the cases were suspected of medication overuse (Taiwan).<sup>3)</sup> In summary, CDH was more prevalent in girls among primary school and also junior and senior high school students, and medication overuse or suspected overuse was found in more than 20% of senior high school students with CDH.

##### (2) Prevalence in pediatric headache center or outpatient clinic and headache types

The prevalence of CDH among children with headache attending pediatric headache outpatient departments reported from various countries was: 24% (mean age: 11.8 years, 70% girls) from Japan,<sup>4)</sup> 31.7% (6 to 18 years, 68.6% girls) from Canada,<sup>5)</sup> 16.5% (mean age: 10.5 years, 61.8% girls) from France,<sup>6)</sup> prevalence unknown due to no data of total number (mean age: 12.8 years, 70% girls) from the United States,<sup>7)</sup> 5.9% (mean age: 13.5 years, 69.6% girls) from Italy,<sup>8)</sup> 38.0% (mean age: 10, 59.5% girls) from Holland,<sup>9)</sup> and 18.9% (mean age: 11.2 years, 62.7% girls) from Italy.<sup>10)</sup> From these studies, the prevalence varied between 5.9 and 38.0%, but it was higher in girls than in boys.

The prevalence of subtypes of CDH was 6%,<sup>5,9)</sup> 10%,<sup>7)</sup> 17.9%,<sup>8)</sup> and 50%<sup>6)</sup> for CM; 16%,<sup>5)</sup> 22%,<sup>9)</sup> 30%,<sup>7)</sup> 34% (IHS),<sup>10)</sup> and 64.3%,<sup>8)</sup> for CTTH; and 47% (IHS)<sup>10)</sup> and 53%<sup>5)</sup> for concurrent CM and CTTH. The prevalence of CDH with school phobia was 5% for CM, 46% for CTTH, and 50% for co-occurrence of CM and CTTH.<sup>4)</sup> Analgesic overuse was found in 22.8%,<sup>9)</sup> 52.9%,<sup>6)</sup> and 60% (36% with suspected CM, 24% with CTTH).<sup>7)</sup> Some reported no overuse,<sup>4,8)</sup> while one report mentioned that analgesic overuse is not involved in the chronicization process.<sup>10)</sup>

## 2. Diagnosis of CDH in children

As for the diagnostic criteria of CDH, the required headache frequency was more than 15 days per month in most references,<sup>1)-10)</sup> or more than 8 days per month according to the ICHD-II diagnostic criteria for migraine in children; the required duration was 3 months or longer<sup>3)-10)</sup> or for the past one month.<sup>1)-2)</sup> The duration of a headache episode was variable: more than 4 hours,<sup>5)-9)</sup> more than 2 hours,<sup>3)</sup> more than 1 hour,<sup>4)</sup> or not stated.<sup>1)-2)-6)-8)-10)</sup> The headache types were diagnosed according to the ICHD-II,<sup>1)-9)</sup> or the first edition of International Classification of Headache Disorders (IHS classification 1988). New criteria for the diagnosis of CDH in children have been proposed.<sup>11)</sup>

## 3. Disability and comorbidities of CDH in children

**(1) In children, CDH causes a high degree of disability in daily living, and should be considered.**<sup>1)-10)</sup>

### (2) Coexistence of psychiatric disorders

In the literature, CDH coexisted with psychiatric disorders (anxiety disorders,<sup>4)-5)-7)-10)</sup> mood disorders,<sup>5)-7)</sup> adjustment disorders,<sup>4)</sup> somatoform disorders,<sup>4)-5)</sup> sleep disorders<sup>9)-10)</sup>), stressors,<sup>5)-6)</sup> and school absenteeism.<sup>4)-9)</sup>

## 4. Treatment of CDH in children

There is no randomized controlled trial for the treatment of CDH in children.<sup>11)-12)</sup> The information presented here are extracted from two review articles published by pediatric headache experts.<sup>11)-12)</sup> Both articles described that control of CDH takes several months.

### (1) Non-pharmacotherapy<sup>11)</sup>

Relaxation training, biofeedback, and counseling for mood disorders and anxiety disorders provided by clinical psychologists, as well as exercises such as aerobic exercise (starting from 10 minutes a day) are recommended. Environmental factors play an important role in CDH. Many children are well during summer holiday and deteriorate as school starts. Factors such as stress, lack of sleep, bright light in school, decreased access to exercise, less time for relaxation, and a tendency to skip breakfast may be associated. School absenteeism is a significant problem. Once children have been out of school, it is difficult for them to return to school schedule. Many of these children have sleep disturbances, and find it difficult to start off with early morning classes. Therefore, starting with one or two class periods around lunch time should be considered.

### (2) Pharmacotherapy<sup>11)</sup>

The goals of pharmacotherapy for CDH are to reduce the frequency of migraine headache and to reduce the severity of the headache that persists all day. The following prophylactic medications have been proven by RCT in adults.

- Amitriptyline (decrease in headache frequency)
- Topiramate (decrease in headache days)
- Gabapentin (increase in headache-free days)
- Valproic acid (reduction in maximal pain levels and frequency)

However, there are limitations to use valproic acid in adolescent females due to the potential for weight gain, possible risk of polycystic ovary syndrome and teratogenicity.<sup>12)</sup>

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## • Search terms and secondary sources

- Search database: PubMed (2011/10/6)  
Chronic daily headache 30373  
& {Children} 4096  
& (Children and adolescents) 2709 & {Prevalence} 815  
OR {epidemiology} 719 OR {diagnosis} 1664 OR (treatment) 1357  
OR {psychological factor} 375 OR {anxiety disorders} 154  
OR {depression} 168 OR {mood disorders} 94  
OR {somatoform disorders} 37 OR {phobia} 14  
OR {conversion} 8  
Articles with large number of cases and using ICHD-II criteria were selected.
- Search database: Ichushi Web for articles published in Japan (2011/10/29)  
Chronic daily headache 3135 (excluding proceedings)  
& children 259  
& children adolescents 9  
All were case reports with only comments. There were no high quality original articles

# VIII

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## Genetics

## 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.

**Grade B**

### Background and Objective

Many studies have been conducted with the aim to identify the causative genes and susceptibility genes of migraine. Three causative genes have been identified for familial hemiplegic migraine, but the association of these genes with “normal” migraine has been ruled out. Many association analyses using the candidate gene approach have also been conducted, and some of the findings have been subjected to meta-analysis. In addition, linkage analyses and large-scale genome-wide association studies (GWAS) are ongoing, and multiple chromosomal loci and genes have been reported. However, the detailed pathophysiological mechanisms remain unclear.

### Comments and Evidence

Although it has long been noted that migraine commonly occurs within the family, whether this phenomenon is based on genetic factors or environmental factors, or simply due to coincidence because of the high prevalence of migraine has been much debated.

More recently, pedigree analysis<sup>1)</sup> and twin analyses<sup>2,3)</sup> suggested that migraine is a multi-factorial genetic disease likely to be associated with a combination of multiple genetic factors and environmental factors. It has been reported that both genetic and environmental factors are involved in migraine without aura, while genetic factors are more strongly associated with migraine with aura, but some reports showed no difference between migraine with and without aura.<sup>4,5)</sup>

Since the first report of a causative gene found in some families with familial hemiplegic migraine (FHM, a special type of migraine with aura),<sup>6)</sup> several genes; *FHMI*, *FHM2* and *FHM3*, have so far been identified (for details, see Comments and Evidence of CQ VIII-4, page 239). All the genes are related to membrane channel function, suggesting a relationship between the excitability of neurons and pathophysiology of migraine.<sup>7)</sup> These findings were the driving force that promoted the great advances in genetic research on migraine. However, association analyses have ruled out the association between the causative genes of FHM and “normal” migraine.<sup>8)</sup>

A pedigree analysis focusing on the K<sup>+</sup> channel in patients with familial migraine other than FHM reported new finding of a significant relationship with mutation in *KCNK18*.<sup>9)</sup>

As for the migraine susceptibility genes, many investigations and verification studies using a candidate gene approach have been conducted, but most yielded inconsistent results. Some of the reports have been subjected to meta-analysis, and a significant relationship has been reported for multiple genes including *ACE*,<sup>10)</sup> *MTHFR*,<sup>10,11)</sup> *ESR-1*<sup>12)</sup> and *5-HTT*.<sup>13)</sup>

Linkage analyses have reported multiple chromosomal loci, but the exact genes have not been identified.

Genome-wide association study has revealed associations of *PRDM16*, *TRPM8* and *LRP1* with migraine,<sup>14)</sup> but the contribution of individual genes was low, and the detailed pathophysiology mechanisms remain unclear.

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## • Search terms and secondary sources

- Search database: PubMed (2011/10/07)

Search was conducted using the same search terms as for Chronic Headache VIII-1 in the Clinical Practice Guidelines 1<sup>st</sup> edition, narrowed to after 2004 only.

migraine

& association 877

& genetics 897

& polymorphisms 213

& (genetic factor OR genetic factors) 287

& genetic influence 44

& familial occurrence 239

& inheritance 59

& twin 48

& segregation 6

& adoption 3

& linkage 108

## 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**

### Background and Objective

Family-based and twin studies have reported the involvement of genetic factors in cluster headache, but the mode of inheritance and other details remain unclear. Some reports have indicated the involvement of gene polymorphism, but analysis is difficult due to the clinical diversity and the low prevalence of cluster headache.

### Comments and Evidence

Summarizing reports of genetic epidemiological surveys on cluster headache, first-degree relatives of patients with cluster headache are 5 to 18 times, and second-degree relatives are 1 to 3 times more likely to have cluster headache than the general population, suggesting that in addition to environmental factors, genetic predispositions are involved in the development of cluster headache.<sup>1)</sup>

Many studies have investigated the causative genes and susceptible genes of cluster headache.

In relation to the pathophysiological hypothesis of cluster headache, research has focused on orexin (hypocretin), a physiologically active peptide closely associated with the hypothalamus. It has been shown that patients with cluster headache have a significantly higher frequency of GG genotype of 1246G>A polymorphism [rs2653349] in the hypocretin receptor 2 gene (HCRT2: MIM ID 602393). A meta-analysis of two reports that confirmed such association<sup>2)</sup> and one report that found no such association<sup>3)</sup> verified an association between cluster headache and *HCRT2*.<sup>4)</sup>

A genetic study also reported two-fold higher frequency of GG genotype of 925A>G polymorphism [rs1126671] in exon 7 of the alcohol dehydrogenase 4 gene (ADH4: MIM ID 103740) in patients with cluster headache.<sup>5)</sup>

In relation to treatment, carriers of CT genotype of 825C>T polymorphism [rs5443] in the guanine nucleotide-binding protein  $\beta 3$  gene (GNB3: MIM ID 139130) was three times more responsive to triptan compared to carriers of CC genotype.<sup>6)</sup>

Further clinical genetic data have to be accumulated to determine whether these genes are the causative genes or susceptibility genes of cluster headache. One genome-wide association study of cluster headache was conducted, and found no significant genes associated with cluster headache.<sup>3)</sup>

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### Search terms and secondary sources

- Search database: PubMed (2011/10/11)

Search was conducted using the same search terms as for Chronic Headache VIII-2 in the Clinical Practice Guidelines 1<sup>st</sup> edition, narrowed to after 2004 only.

cluster headache

- & association 73
- & genetics 60
- & polymorphisms 14
- & (genetic factor OR genetic factors) 21
- & genetic influence 4
- & familial occurrence 24
- & inheritance 4
- & twin 9
- & segregation 0
- & adoption 0
- & linkage 7

## 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**

### Background and Objective

There is less research on the genetic factors for tension-type headache compared to migraine and cluster headache. Reports are limited to some twin studies. Although environmental factors are mainly involved in the development of tension-type headache, the involvement of genetic predisposition has been reported for frequent episodic tension-type headache.

### Comments and Evidence

A study using the New Danish Twin Register of 5,360 twins found no significant difference in concordance of tension-type headache in both monozygotic and dizygotic twin pairs.<sup>1)</sup> The report concluded that genetic factor, if it exists, has minor effect.

In a subsequent study using the same Register, of 11,199 twin pairs with tension-type headache and no migraine, the concordance rate of frequent episodic tension-type headache was higher in monozygotic than in dizygotic twin pairs.<sup>2)</sup> The concordance rate of infrequent episodic tension-type headache was significantly higher in monozygotic than in dizygotic twin pairs in women only, and the difference was small in men. The report concluded that genetic factors play a role in frequent episodic tension-type headache, while infrequent episodic tension-type headache is caused primarily by environmental factors, and that no firm conclusion could be drawn for chronic tension-type headache.

Further accumulation of clinical genetic data for different regions and various races is required to elucidate whether genetic element is involved in tension-type headache.

### • References

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### • Search terms and secondary sources

- Search database: PubMed (2011/10/11)

Search was conducted using the same search terms as for Chronic Headache VIII-3 in the Clinical Practice Guidelines 1<sup>st</sup> edition, narrowed to after 2004 only.

tension-type headache

& association 102

& genetics 30

& polymorphisms 11

& (genetic factor OR genetic factors) 27

& genetic influence 2

& familial occurrence 42

& inheritance 1

& twin 9

& segregation 0

& adoption 1

& linkage 2

## Does familial (hereditary) migraine caused by single gene mutations exist?

### Recommendation

Familial hemiplegic migraine type 1, type 2 and type 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 (**RVCL**), 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

### Background and Objective

Genetic diseases causing migraine due to single gene mutations exist, and the causative genes have been identified in recent years.

### Comments and Evidence

#### 1. Familial migraine caused by single gene mutations

##### (1) Familial hemiplegic migraine type 1 (FHM1; MIM ID 141500)

The causative gene of FHM1, *CACNA1A*, is located on chromosome 19p13 and encodes  $\text{Ca}_v2.1$ , the  $\alpha 1$  subunit of P/Q type voltage-gated calcium channel.<sup>1)</sup> *CACNA1A* is also known to be the causative gene of spinocerebellar ataxia type 6 (SCA6), episodic ataxia type 2 (EA2) and progressive cerebellar ataxia (PCA). FHM1 is complicated with diverse symptoms including disturbance of consciousness, fever, and cerebella ataxia. Among the mutations, the frequency of p.T666M point mutation (substituting methionine for threonine at codon 666) is high.

##### (2) Familial hemiplegic migraine type 2 (FHM2; MIM ID 602481)

The causative gene of FHM, *ATP1A2*, is located on chromosome 1q21-23 and encodes the  $\alpha 2$  subunit of ATP-dependent Na,K-ATPase.<sup>2)</sup> Unlike FHM1, most of the FHM2 patients manifest a clinical picture of pure hemiplegic migraine, although some cases are complicated with cerebellar ataxia, epilepsy and mental retardation.

##### (3) Familial hemiplegic migraine type 3 (FHM3; MIM ID 609634)

The causative gene of FHM3, *SCN1A*, is located on chromosome 2q24 and encodes  $\text{Na}_v1.1$ , the  $\alpha 1$  subunit of voltage-gated sodium channel.<sup>3)</sup> *SCN1A* is also known to be the causative gene of generalized epilepsy febrile seizures plus (GEFS+) or Dravet syndrome. Apart from pure familial hemiplegic migraine, cases of FHM3 are complicated with epilepsy and elicited repetitive transient daily blindness (ERDB) have been reported.

#### 2. Genetic diseases with concurrent migraine

##### (1) Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL; MIM ID 125310)

The causative gene of CADASIL is *NOTCH3* located on chromosome 19p13.<sup>4)</sup> Twenty to 30% of CADASIL patients manifest migraine with aura concurrently. With onset at 30 to 50 years of age, CADASIL is characterized by recurrent subcortical infarction and transient ischemic attack, as well as diverse symptoms including impaired cognitive function, psychiatric symptoms, and pseudobulbar palsy. CADASIL is an autosomal dominant disease. On brain MRI, characteristic hyperintense signals in external capsule and temporal pole white matter on T2-weighted and FLAIR images are observed.

##### (2) Retinal vasculopathy with cerebral leukodystrophy (RVCL, MIM ID 192315)

The causative gene of RVCL is *TREX1*, located on chromosome 19p13.<sup>5)</sup> RVCL is an autosomal dominant disorder. With

onset symptoms of retinal vasculopathy and progressive visual disturbance at 30 to 40 years of age, migraine is added to the clinical picture together with diverse neurological symptoms including cognitive decline due to multiple infarcts in cerebral cortex, convulsion, spastic paralysis and dysarthria, as well as systemic symptoms including Raynaud symptom, renal disease and cirrhosis. On brain MRI, multiple contrast-enhancing lesions in cerebral subcortical white matter and surrounding edema are observed.

### (3) Hereditary hemorrhagic telangiectasia (HHT)

So far four genetic loci (HHT1 to 4) have been reported, and the causative genes for HHT1 and HHT2 have been identified. Approximately 40% of patients with HHT1 manifest migraine concurrently. The causative gene of HHT1 (MIM ID 187300) is *ENG*, located on chromosome 9q34.<sup>6)</sup> HHT1 is an autosomal dominant disease previously known as Osler-Rendu-Weber disease. The disorder is characterized by arteriovenous malformations in the lung, brain, liver and spinal cord, as well as multiple telangiectases and hemorrhages in the skin, mucous and internal organs.

### (4) Mitochondrial disorder

Migraine has been reported to occur concurrently with subtypes of mitochondrial disorder: MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes) characterized by episodic vomiting, headache, convulsion and stroke-like symptoms, and MERRF (myoclonic epilepsy associated with ragged-red fibers) with myoclonus, cerebellar ataxia and myopathy as main symptoms. Eighty percent of MELAS cases are caused by A3243G mutation of *MTTL1* that encodes mitochondrial tRNA-leucine.<sup>7)</sup> Mutations of *ND5* that encodes the subunit 5 of electron transport complex 1 are also known. On the other hand, the major causative mutation in MERRF is A8344G mutation of *MTTK* that encodes mitochondrial tRNA-lysine.

## 3. Other genes associated with familial migraine

Using candidate gene approach or pedigree analysis, mutations in various other genes such as *EAAT1*,<sup>8)</sup> *SLC4A4*,<sup>9)</sup> and *KCNK18*<sup>10)</sup> have been reported in pedigrees with familial migraine. To determine whether these genes are causative genes of migraine, further accumulation of clinical genetic data is necessary.

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- **Search terms and secondary sources**

- Search database: PubMed (2011/12/21)
  - Migraine & CACNA1A 253
  - Migraine & ATP1A2 115
  - Migraine & SCN1A 41
  - Migraine & Notch 3104
  - TREX 168
  - Migraine & HHT 10
  - Migraine & MELAS 70
  - Migraine & MERRF 7
  - Migraine & genome-wide association study 29



## 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 genome-wide association study, the contribution of individual gene is low and not useful for genetic diagnosis.

**Grade B**

### Background and Objective

With advances made in the identification of causative genes for familial hemiplegic migraine, genetic diagnosis of this disorder has become possible. For common migraine also, susceptibility genes are gradually being identified.

### Comments and Evidence

In general, for conducting genetic diagnosis, detailed explanations and various supports such as genetic counseling have to be provided to the subjects, according to the guideline for genetic diagnosis of neurological diseases (2009). In addition, since the causative genes of hemiplegic migraine; *CACNA1A*, *ATP1A2* and *SCN1A*<sup>(1)(2)</sup> are relatively large genes, it is inefficient to conduct genetic diagnosis on all the cases. Careful consideration of the indication for genetic diagnosis is recommended, by reviewing genetic epidemiological and clinical information including frequency of disease, age of onset and associated symptoms.

Among the causative genes for hemiplegic migraine, the mutation frequencies of *CACNA1A* and *ATP1A2* are high, and that of *SCN1A* is low. Therefore, in conducting genetic diagnosis, analyzing *CACNA1A* and *ATP1A2* first, and then proceeding to *SCN1A* is recommended.

In a large-scale epidemiological survey of the whole Danish population of 5.2 million people, a total of 44 families with familial hemiplegic migraine (FHM) were identified.<sup>(3)</sup> When mutation analyses of all exons of *CACNA1A* and *ATP1A2* as well as p.Q1489K mutation of *SCN1A* were conducted in 43 families, 14% of the families were positive for these mutations. The mutation frequencies for *CACNA1A* and *ATP1A2* were similar, and no *SCN1A* mutation was detected. In the same population, 105 individuals with sporadic hemiplegic migraine were identified.<sup>(4)</sup> Mutation analysis was conducted in 100 individuals, and causative gene mutations were found in only 2 individuals.

Therefore, FHM is a genetically heterogeneous disease, and so far genetic diagnosis has not identified mutations in the majority of the affected families. This point has to be explained when obtaining informed consent for genetic diagnosis.

Causative mutations identified in FHM are rarely detected in patients with SHM. However, when analysis was conducted in early-onset SHM only, *de novo* mutation was identified in 19 of 25 (76%) SHM patients aged 16 years or younger.<sup>(5)</sup> Therefore genetic diagnosis has clinical significance in early-onset SHM. However, whether amino acid substitutions identified in SHM represent true causative mutations has to be examined carefully.

No large-scale genetic epidemiological study on hemiplegic migraine has been conducted in Japan, and the frequency of mutation in Japanese remains unknown. As of November 2011, reports of mutations in hemiplegic migraine among Japanese included two families with p.T666M mutation in *CACNA1A*, one family with p.S218L mutation in *CACNA1A*, and one family with p.H916L mutation in *ATP1A2*.

Regarding the involvement of FHM-related causative mutations in common migraine, linkage analysis, association study and direct sequencing analysis yielded negative results.<sup>(6)</sup> Therefore analysis of FHM-related genes in common migraine has no relevance. As for migraine susceptibility genes, candidate gene approach suggested an association with *MTHFR*<sup>(7)</sup> and *5-HTT*.<sup>(8)</sup> Genome-wide association study reported an association with *TRPM8* and *LRP1*.<sup>(9)</sup> However, the odds ratios were 1.3 to 1.5 at the highest, not sufficiently accounting for the heritability of migraine. Therefore, at this time, they are not useful for genetic diagnosis.

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## • Search terms and secondary sources

- Search database: PubMed (2011/12/21)
  - hemiplegic migraine AND epidemiology 38
  - (hemiplegic migraine) AND Japanese 24
  - familial hemiplegic migraine AND sporadic 77
  - (common migraine) AND (CACNA1A OR ATP1A2 OR SCN1A) 206
  - (migraine) AND (susceptibility gene) 294
- Japanese Society of Neurology (ed.): Guideline for Genetic Diagnosis of Neurological Diseases 2009. Igakushoin 2009.

# **Appendix I**

## **Guideline for Self-injection of Sumatriptan at Home**

## 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**

### Background and Objective

Subcutaneous injection of sumatriptan is an effective treatment for cluster headache attacks. However, attacks occur frequently at night, when seeking treatment at a medical facility is difficult. Moreover, the headache duration is relatively short. Even if a patient visits a medical facility during attack, often the headache has improved by the time the patient is seen by a doctor. Also, visiting a medical facility is difficult in the case of severe migraine attack, especially when accompanied by vomiting. During severe headache attack, self-injection of sumatriptan at home is a fast acting and convenient treatment modality. This section examines what kind of patients can use sumatriptan self-injection at home safely.

### Comments and Evidence

Since cluster headache attacks are accompanied by severe pain of relatively short duration (50 to 180 min) compared to migraine, self-injection of sumatriptan at home that can stop the pain as soon as attack occurs is an effective treatment. To make a definitive diagnosis of cluster headache, it is important to differentiate from secondary headache caused by paranasal sinus, pituitary and other disorders.

For migraine, the best indication for self-injection of sumatriptan at home is patients who have very severe attacks, such as those who have a history of being transported to emergency department, and who respond to sumatriptan injection. The treatment is especially indicated for patients who have associated symptom of repeated vomiting, making oral administration difficult. However, before deciding whether to prescribe self-injection of sumatriptan at home, ensure that adequate treatments including conventional oral medications and other concomitant medications have been implemented, and confirm in a medical institution that the patient responds to sumatriptan injection.

According to the experience of clinical use of 7000 cases in Japan, sumatriptan injection is as highly effective as the tablet and nasal spray formulations, and is safe.<sup>1)</sup> In a postmarketing surveillance of sumatriptan self-injection (Imigran Kit Subcutaneous Injection 3 mg) conducted in Japan, the treatment was effective in 92 of 103 patients (89.3%) with migraine and in 60 of 60 patients (100%) with cluster headache, showing high response rates. Adverse reactions were observed in 28 of 173 patients (16.2%), and the major adverse reactions were nausea (3.5%), chest discomfort (2.9%), palpitation (2.3%), bleeding at injection site (1.7%), malaise (1.7%) and somnolence (1.7%). None of the events were serious. These result confirmed high effectiveness and safety of this product.<sup>2)</sup>

No case-control study on sumatriptan subcutaneous injection in children has been reported. In an open-study of

sumatriptan subcutaneous injection in children and adolescents with migraine, response was observed in 64 to 78% of the patients, but adverse reactions occurred in approximately 80% of the patients.<sup>3)</sup> In children, due to the predicted difficulties in identifying symptoms and handling the subcutaneous injection kit, self-injection is not recommended.

Regarding the risk of heart disease after sumatriptan administration, sumatriptan is a vasoactive drug and theoretically is predicted to cause vasoconstriction. In a study on chest oppression and electrocardiographic changes after sumatriptan injection, no ST changes were observed.<sup>4)</sup> A report indicates that use of triptans in patients with no coronary disease does not increase the risk of serious cardiovascular events.<sup>5)</sup> A literature review of 32 cases in which vascular events occurred after triptan administration identified few cases with a definite causal relationship with triptan.<sup>6)</sup> The above findings thus suggest a very low risk of cardiovascular or cerebrovascular events caused by triptan. However, triptans should be used with caution in patients with risk factors.

#### • Precautions in prescription

- (1) First of all, exclude secondary headaches, and perform a definitive diagnosis for cluster headache or migraine.
- (2) Only prescribe to patients who can judge that they have migraine or cluster headache.
- (3) Prescribe to patients who have a good understanding of self-injection at home.
- (4) In principle, there is no need to switch to this treatment if headache is controlled by the medications already prescribed.
- (5) For migraine patients who do not respond adequately to oral or nasal spray formulations, there is a possibility that they are missing the timing of using the medication early after onset. Before switching to sumatriptan self-injection, the patients should be given thorough guidance on early use of medications.
- (6) When prescribing, bearing in mind that due to the characteristic of the formulation, blood level increases rapidly during administration and adverse reactions not seen with oral or nasal spray formulations may appear.
- (7) In principle, do not prescribe to patients who feels resistance or anxiety toward “injections”.
- (8) In many Western countries, this treatment is not recommended for children (aged 18 or younger) and elderly patients (aged 65 or above). In Japan, the package insert states that “safety is not established” for children, and “use with caution” for elderly patients. Greater caution is needed.

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#### • Search terms and secondary sources

- Search database: PubMed  
sumatriptan & injection 407, sumatriptan & injection & self 34
- Search database: Ichushi Web for articles published in Japan  
sumatriptan & subcutaneous injection 94  
sumatriptan & self injection 24

## 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 (4 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 7 kits (14 ampoules).

**Grade A**

### Background and Objective

In order that self-injection of sumatriptan at home is used safely and properly, it is important to provide detailed and accurate guidance and explanations at the time of initiation.

Some patients with migraine or cluster headache do not obtain satisfactory result with oral medications alone. These patients can be prescribed self-injection drugs for the purpose of treatment. When using this treatment, it is important to accurately predict the effectiveness and safety in order to accomplish the goal. Prescription should be decided upon considering concomitant use with existing treatments and the general health insurance rules.

### Comments and Evidence

#### Initiation of self-injection and explanation to patients

There are few reports on the initiation of self-injection of sumatriptan at home and explanations to patients. In a study comparing the practicality of a pen-type injector included in the sumatriptan injection kit and the conventional autoinjector for sumatriptan, 80% of the responders rated the pen-type injector as “very easy” or “easy” to use.<sup>1)</sup> Furthermore, 75% of the patients already using autoinjector reported that explanation of the pen injector took less than 5 minutes. The report concluded that subcutaneous injection can be done even during severe migraine attacks. Although the above report indicates that self-injection of sumatriptan at home is easy to use, it is necessary to conduct adequate patient education before initiating treatment.

#### 1. Method of explanation to patient using the training set

A doctor or a nurse who has good understanding of the safety and effectiveness of self-injection of sumatriptan at home, and is capable of giving sufficient guidance on the use of this treatment to the patients should provide appropriate guidance and explanations.

Use the “Imigran® Kit Subcutaneous Injection 3 mg Training Set”<sup>2)</sup> when giving guidance or explanation to patients.<sup>2)</sup> Following the “Start Manual”, and explain based on “Instructions for Practice”. If necessary, use the “Use Instruction DVD” and “Points for Explaining to Patients”.

Make sure to check how much the patient has learned using the “Training Checklist for Use in Medical Institution”. When team care is practiced, decide the roles of team members; such as, the nurse explains the process of self-injection of

this drug and the doctor checks whether the patient can use the drug properly. This will also allow double checking and reduce the burden on doctors.

In addition, various approaches have to be used to increase patient's understanding, such as asking the patient to practice by him/herself using kits for practice.

## **2. Method of initiation training**

Initiation training for patient should be conducted repeatedly during each visit or admission, until the patient is judged to have acquired the competence of self-injecting sumatriptan at home. The number of training sessions required varies depending on the patient's degree of understanding. Since it may take some time from prescription to actually using the drug, give a starter pack to the patient at the time of prescription, and instruct him/her to practice at home.

## **3. Method of disposal of used cartridge packs**

At the time of prescription, instruct the patient on the method of disposal of used cartridge packs. The disposal method differs depending on the rules of the municipality in which the patient lives. Instruct the patient to make inquiries at the municipality. Inquiry should be made to the department that handles waste disposal and recycling, at the municipality nearest to the patient's residence.

There are mainly three methods of waste disposal:

- (1) If disposal as general waste (combustible waste or non-combustible waste for landfill) is possible, the patient can dispose at their own home
- (2) If disposal as general waste (as above) is not possible, bring back to the medical institution that prescribed the drug.
- (3) If disposal method is not known or cannot be confirmed even after inquiring to the municipality, bring back to the medical institution that prescribed the drug.

## **The amount to be prescribed**

For migraine, common attacks are often controlled by oral or nasal spray triptans, and sumatriptan self-injection is usually used when oral medication is difficult due to severe vomiting, when attack starts during sleep at night and the patient is awoken by the pain, or when oral or nasal spray administration is delayed and attack becomes severe. As long as the patient is receiving appropriate treatment, an increase in number of self-injection is not expected. A study investigating the migraine attack frequency reported that 52% had an attack frequency of around once a month.<sup>3)</sup> The proportions of patients with headache frequency of 1 to 7 days a year were reported to be 52.6% for migraine with aura,<sup>4)</sup> and 37.9%<sup>4)</sup> or 40%<sup>5)</sup> for migraine without aura. Therefore, considering also consecutive days off, one prescription of 2 kits (4 ampules) may be appropriate. However, since patients may have difficulties visiting hospitals, one prescription from 2 kits (4 ampules) up to 5 kits (10 ampules) is recommended. In patients with frequent severe attacks, prescription of an amount deemed appropriate to the patient is possible.

For cluster headache, the attack frequency is once every other day to eight times a day according to the ICHD-II diagnostic criteria. A study investigating the attack frequency reported that the most common frequency was 4 or 5 times a day.<sup>6)</sup> Another study reported a mean attack frequency of 1.67 times a day, while most patients had attacks once to 4 times a day.<sup>7)</sup> Based on the above findings, assuming an attack frequency of 2 times per day and conforming to the number of prescription days for other as-needed medications, a prescription for 7 days seems suitable. Hence, prescribing a maximum of 7 kits (14 ampules) is considered appropriate. Moreover, the cluster period for cluster headache has been reported to be 8.6 weeks on average,<sup>6)</sup> and usually continues for 1 to 2 months. Therefore, a maximum of four prescriptions a month is required.

The explanatory leaflet and confirmation leaflet are shown in **Figures 1 and 2**, respectively.

## **General principle for guidance and management fees for home care**

- (1) "Guidance and management fees for home care" is computed in the case of the following: for a patient in whom a doctor has judged that the above-mentioned guidance and management are necessary and appropriate, the above-mentioned doctor gives guidance and appropriate advice to the patient or the person who cares for the patient; provides adequate medical management of the patient; conducts guidance regarding the methods of home care, matters requiring attention, and measures during emergency; and supplies necessary and adequate amounts of hygienic materials or insurance-covered medical materials.
- (2) The above-mentioned medical institution (authorized to treat patients under health insurance coverage) should supply the patients with materials for disinfection (such as alcohol cotton swab) needed to conduct self-injection, in an amount deemed necessary and appropriate, and calculated as part of the guidance and management fees for home care



\*Imigran Kit Subcutaneous Injection 3 mg is a triptan product that can be “injected on the spot” when migraine or cluster headache attacks occur.

\*To prescribe Imigran Kit Subcutaneous Injection 3 mg, it is necessary to have a definitive diagnosis of “migraine without aura”, “migraine with aura” or “cluster headache” according to the International Headache Society diagnostic criteria for migraine and cluster headache.

\*Imigran Kit Subcutaneous Injection 3 mg is prescribed to patients who have been judged by the doctor to be capable of using it properly.

\*Imigran Kit Subcutaneous Injection 3 mg does not require dose adjustment: it contains a cartridge pack that holds 2 cartridges each holding one dose of the drug. The cartridge holder and a pen-type injector are fitted in a carrying case for easy portability.

#### [Action]

1. For both migraine and cluster headache, headache is improved within 10 minutes of injection (33 cases)

Migraine	after 10 min → 30.3%	Cluster headache	after 10 min → 63.6%
	after 20 min → 51.5%		after 20 min → 78.8%
	after 30 min → 75.8%		after 30 min → 93.9%
	after 60 min → 93.9%		

2. Associated symptoms of migraine (nausea, vomiting, photophobia, phonophobia) improve over 20 to 60 minutes after injection.

3. The half-life of Imigran Kit Subcutaneous Injection 3 mg is approximately 2 hours.

#### [Adverse reactions]

1. Major adverse reactions

Malaise, pressure (chest, throat, etc.), weakness, drowsiness, nausea, heat sensation, vertigo, flickering, transient blood pressure increase, tachycardia, bradycardia, palpitation, numbness, injection site pain, etc.

\*The drug may induce drowsiness. While using the drug, do not drive a car or use machinery or do anything that may involve danger.

2. Serious adverse reactions

(1) Anaphylactic shock, anaphylactoid symptoms (less than 1%)

• Serious allergic symptoms; urticarial, breathing difficulty, diarrhea, hypotension and other potentially life-threatening symptoms

(2) Arrhythmia, angina pectoris, ischemic heart disease-like symptoms including myocardial infarction (less than 1%)

(3) Epilepsy-like symptoms (rare)

#### [Dosage and Administration]

1. A single dose of 3 mg is injected during attack of migraine or cluster headache. Use 3 mg for each injection. Do not exceed 6 mg a day.

2. For one attack of migraine headache, if headache is reduced after the first injection, an additional dose can be injected for the attack that occurs within 24 hours. Inject the second dose separated by an interval of one hour after the first dose.

3. For cluster headache, two doses can be injected in one day. Inject the second dose separated by an interval of one hour after the first dose.

4. Intervals between administration of Imigran preparations:

Initial dose	Additional dose	Interval
Imigran Kit Subcutaneous Injection 3 mg	Imigran Kit Subcutaneous Injection 3 mg/Tablet 50/Nasal Spray 20	1 hour or longer
Imigran Tablet 50	Imigran Kit Subcutaneous Injection 3 mg/Injection 3/Tablet 50/Nasal Spray 20	2 hours or longer
Imigran Nasal Spray 20	Imigran Kit Subcutaneous Injection 3 mg/Injection 3/Tablet 50/Nasal Spray 20	2 hours or longer

5. Intervals between Imigran preparations and other triptan preparations or ergotamine preparations

Initial dose	Additional dose	Interval
Imigran preparation	Other triptan preparations or ergotamine preparations	24 hours or longer
Other triptan preparations or ergotamine preparations	Imigran preparation	24 hours or longer

6. Drugs that should not be used in combination with Imigran Kit Subcutaneous Injection 3 mg

(1) Ergotamine preparations: Cleamine A, Cleamine S, Dihidergot, Ergometrine F, Methergin

(2) Triptan preparations: Zomig, Zomig RM, Relpax, Maxalt, Maxalt RPD, Amerge

#### [Administer with Caution to the Following Persons]

1. Person with a possibility of ischemic heart disease

2. Person with history of epileptic seizure or person with risk factors that may precipitate epileptiform seizure

3. Person with impaired liver function

4. Elderly person

5. Person with controlled hypertension

6. Person with a possibility of cerebrovascular disease

7. Person with hypersensitivity to sulfonamide (sulfa drugs)

8. Person who is pregnant or with a possibility of being pregnant

#### [Basic Precautions]

1. Before prescribing self-injection, it is necessary to receive guidance until the doctor, nurse, and the person involved have confirmed that the injection can be used appropriately.

2. It is possible for a family member to administer the injection to the person prescribed the drug. In that case, the family member should also receive guidance.

3. The drug can only be used by the person prescribed the drug. It should not be used by another other persons.

4. Use only during /migraine or cluster headache attacks. Do not use for the purpose of prevention.

5. Do not use for headaches that are different from the habitual migraine or cluster headache (secondary headaches = headache arises as a symptom of another disease).

(1) Sudden headache

(2) Headache never experienced before

(3) Headache different from usual

(4) Headache that increases in frequency and severity

(5) Headache with neurological deficit (numbness, gait disturbance, speech disturbance, sight disturbance, etc.)

(6) Fever, inflammation, headache with convulsion, etc.

• subarachnoid hemorrhage, brain tumor, meningitis, cerebral hemorrhage, hypertension, sinusitis, etc.

• including headache due to cold or hangover, etc.

6. Combined use with some drugs requires special caution. Report to the doctor if you are taking other medications, or when you use new medications

**Figure 1. Self-injection of Imigran® Kit Subcutaneous Injection 3 mg (to be continued)**

7. In the case of any abnormality after self-injection, contact the medical institution immediately.
8. Be sure to read the package insert.

[Precautions in Use]

1. Use only for subcutaneous injection. Do not inject intravenously.
2. In the case that there is absolutely no response after injection, the headache may be due to other reasons. Do not inject another dose.
3. Even if the first injection is missed, count as the first injection. Additional injection of Imigran Kit Subcutaneous Injection 3 mg should be made after an interval of at least one hour.
4. If you have no experience of Imigran subcutaneous injection but is prescribed this drug by doctor's decision, it is advisable to have an observer nearby during self-injection in the case of emergency due to shock.
5. Use the pen autoinjector provided.
6. If the seal covering the cartridge containing the drug is broken, do not use the syringe.
7. Imigran Kit Subcutaneous Injection 3 mg has been sterilized. Use promptly after removing from the cartridge pack.
8. Pay attention not to reuse a used Imigran Kit Subcutaneous Injection 3 mg by mistake.
9. Imigran Kit Subcutaneous Injection 3 mg contains a needle. Take care to avoid accidental injection or infection. Dispose according to the instructions given by the medical institution.
10. Do not use a product after the validity date has expired.
11. Store at room temperature. Do not store in the refrigerator.
12. Keep out of reach of children.
13. If you feel anxious about injecting yourself, visit the doctor during consultation hours.

**Figure 1. Self-injection of Imigran® Kit Subcutaneous Injection 3 mg**

Contents		Understanding	
1. Do you understand about self-injection?		Yes	No
2. Do you understand that adverse reactions may occur during use of Imigran Kit Subcutaneous Injection 3 mg (malaise, tightness, weakness, nausea, drowsiness, heat sensation, palpitation, arrhythmia, angina pectoris, myocardial infarction, transient blood pressure increase, flickering, vertigo, etc.)?		Yes	No
3. Do you understand how to use and how to store Imigran Kit Subcutaneous Injection 3 mg?		Yes	No
4. Do you understand the timing of using Imigran Kit Subcutaneous Injection 3 mg?		Yes	No
5. Do you understand the interval separating the first and the second injection of this drug during headache attack, and the interval separating use of this drug and use of combined medications?		Yes	No
6. Do you understand the necessity of being always aware that headache may start any time, and that you need to practice self-injection so that you are ready to inject calmly during an attack?		Yes	No
7. Do you understand that you need to record the date when cartridges are prescribed and also the expiry date in the notebook?		Yes	No
8. Do you understand that you need to record the date of receiving the carrying case and the pen autoinjector, and also the expiry date in the notebook?		Yes	No
9. Do you understand that you have to return the used cartridge packs to the medical institution that you are visiting?		Yes	No
10. Do you understand that in order to prescribe Imigran Kit Subcutaneous Injection 3 mg, you need to receive guidance until the doctor, the nurse and yourself have confirmed that you can use it properly?		Yes	No
11. Do you understand that Imigran Kit Subcutaneous Injection 3 mg is to be used by yourself (prescribed person) only?		Yes	No
12. Do you understand that your family member can inject Imigran Kit Subcutaneous Injection 3 mg for you, but in that case, your family member must also receive guidance?		Yes	No
13. Do you understand that Imigran Kit Subcutaneous Injection 3 mg should not be used for headaches that are not migraine or cluster headache (not the usual headache)?		Yes	No
14. Do you understand that Imigran Kit Subcutaneous Injection 3 mg is a drug to be used when a migraine or cluster headache attack occurs, and should not be used for prevention purpose?		Yes	No

\*Circle one of the two

Imigran Kit Subcutaneous Injection 3 mg Self-injection: Proper Use Agreement

Prescribing doctor's signature	Patient's signature
<p>I have provided explanations and guidance regarding the above-mentioned contents for the purpose of prescribing Imigran Kit Subcutaneous Injection 3 mg.</p> <p style="text-align: right;">Date: _____</p> <p>Name of medical institution _____</p> <p>Doctor's signature _____</p>	<p>I have read explanations and watched DVD regarding self-injection of Imigran Kit Subcutaneous Injection 3 mg, and received the above-mentioned explanation and guidance, and understand the contents. I will conform to the precautions and use this drug appropriately on my own responsibility.</p> <p style="text-align: right;">Date: _____</p> <p>Patient's signature _____</p> <p>Guardian's signature _____</p>

\*Emergency contact

Name of medical institution: \_\_\_\_\_

Doctor in charge: \_\_\_\_\_

Address: \_\_\_\_\_

Tel: \_\_\_\_\_ Fax: \_\_\_\_\_

\*In case of emergency, please visit the local emergency medical institution.

**Figure 2. Items to confirm proper use of Imigran® Kit Subcutaneous Injection 3 mg self-injection.**

## • References

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## • Search terms and secondary sources

- Search database: PubMed (2011/12/22)
  - “sumatriptan” “self administration” Limits Activated: Clinical Trial 29
  - “migraine” “attack” “frequency” 431
  - “cluster headache” “attack” “frequency” 75

## 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**

### Background and Objective

Serious adverse events of sumatriptan subcutaneous injection are very rare, but anaphylactic shock and myocardial infarction have been reported.<sup>1)</sup> When a patient self-injects sumatriptan at home for the first time, anxiety over the technique and adverse events is anticipated. Therefore, this section verifies the desirable approach for first time use. Other emergencies may occur, such as when sumatriptan is used by mistake for secondary headaches or other conditions. This section also examines the measures to be taken in emergency situations (when serious adverse events occur) and precautions to take foreseeing the occurrence of emergencies, and presents the recommended methods.

### Comments and Evidence

Some articles from overseas have reported serious adverse events associated with sumatriptan 6 mg subcutaneous injection, such as myocardial infarction, cerebrovascular disorder, and allergic reactions, but at a very low incidence of less than 1% for anaphylactic shock or anaphylactoid symptoms, and less than 1% for arrhythmia, angina pectoris or ischemic heart disease-like symptoms such as myocardial infarction.<sup>1)-3)</sup> For sumatriptan 3 mg subcutaneous injection that became available in Japan since 2000, serious adverse events are extremely rare.<sup>4)</sup> In a clinical trial of sumatriptan self-injection conducted in Japan, the incidence of adverse reactions was 11 of 66 subjects (16.7%), and the major adverse reactions included malaise 4.5%, asthenia 3.0%, and chest discomfort 3.0%.<sup>5)</sup> According to the post-marketing surveillance conducted in Japan, adverse reactions were found in 28 of 173 patients (16.2%), and the major reactions included nausea, chest discomfort, and palpitation, none of which were serious. Among 173 patients, only 2 of 110 migraine patients and 2 of 63 cluster headache patients had used sumatriptan before being prescribed the kit product, while the vast majority of the patients had no experience of use. These results suggest that even in patients with no experience of using sumatriptan injection, there is a low risk of serious adverse reactions.<sup>6,7)</sup> Evaluation of proper usage showed high rates of proper usage in both migraine patients (99.1%) and in cluster headache patients (98.4%).<sup>6)</sup> In a study on the practicality of a kit product by Gobel et al.<sup>8)</sup>, 80% of the patients evaluated the kit to be easy to use or very easy to use. With adequate prior explanations and practice, there seems to be little technical problem.

When a patient self-injects sumatriptan for the first time, anxiety over the technique and adverse events is anticipated. In Japan, a randomized controlled trial (RCT) of self-injection kit used at home was conducted recruiting migraine patients who had received sumatriptan injection for migraine attacks within one year, and cluster headache patients irrespective of treatment history. After receiving adequate guidance on self-injection and undergoing mock injection, these patients self-injected at home for the RCT.<sup>9)</sup>

In overseas clinical trials of self-injection kits, patients with no experience of using sumatriptan self-injected at home after giving detailed instructions.<sup>9,10)</sup> Since serious adverse events such as anaphylactic shock and myocardial infarction occur not only during the first injection, constant attention is necessary. For the first injection at home, detailed instructions should be given beforehand, and it is advisable to perform the injection in the presence of an observer in case of emergency. For patients with strong anxiety toward the technique or adverse events and patients with a history of allergy, a recommended option to

initiate self-injection is to admit the patients into hospitals or let patients self-inject under supervision of medical personnel in outpatient or emergency department.

Headache attacks that differ in severity from the usual migraine or cluster headache may be secondary headaches such as subarachnoid hemorrhage, intracerebral hemorrhage, and cerebral infarction, and appropriate measures have to be taken. Before prescription, patients should be given instructions and information to seek emergency care at a medical institution when serious adverse events occur or when secondary headache that differs from the usual headache is suspected.

Medical institutions that have 24-hour emergency service should give information and instructions to patients self-injecting at home to seek emergency care when emergency situation occurs, and should clearly state in the medical records that the patients are self-injecting sumatriptan at home. Medical institutions that cannot provide immediate care during night time or emergency (such as clinics and medical institutions located far from the patients' residence) should collaborate with medical institutions that can accept emergency cases, and should explain this to the patients. Since emergency may occur during travelling or in work locations, patients should be instructed to bring along a sumatriptan kit together with a referral letter to the attending doctor or a card recording relevant information as an aid to provide information when the patients visit the nearest medical institution in case of emergency.

## • References

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## • Search terms and secondary sources

- Search database: PubMed (2011/12/22)  
Sumatriptan  
& ({subcutaneous} OR {injection} OR {self-}) 549  
84 articles adopted from screening title and abstract  
6 articles adopted after reviewing abstract and text
- Search database: Ichushi Web for articles published in Japan (2011/12/22)  
Sumatriptan & injection 127  
16 articles adopted from screening title and abstract  
3 articles adopted after reviewing abstract and text

# **Appendix II**

**Guideline for Migraine Treatment  
by Valproic Acid (Provisional Edition)**

# Introduction

The Japanese Headache Society together with the Japanese Society of Neurology requested the Ministry of Health, Labour and Welfare to develop the use of sodium valproate for migraine. This issue was considered to qualify as medical and pharmaceutical data in the public domain at the “The Fifth Review Meeting on Non-approved Drugs and Off-label Drugs with High Need” held on October 6, 2010, and was accepted at the “Meeting of the First Committee on Drugs of the Pharmaceutical Affairs and Food Sanitation Council” on October 29, 2010. As a result, Depakene® for migraine was approved for health insurance coverage from October 29, 2010.

Regarding this health insurance coverage, attention has been called to the effect that users should be knowledgeable about the contents of the “Report Concerning the Qualification as Application Based on Public Domain Data”, and use the drug with caution by adjusting dosage according to the conditions of individual patients.

Furthermore, instruction has been issued to publicize the following:

- (1) Be well aware of the precautions for use of this drug. Strive to give prior explanations to patients regarding the treatment contents and possible adverse reactions, and obtain their informed consent.
- (2) When a serious adverse effect is known, report to the relevant company or to the Ministry of Health, Labour and Welfare. Strive to obtain information of the cases in case of off-label use.

With this background, Board Director Sakai instructed the Treatment Promotion Committee to produce a guideline (provisional edition) urgently, in order that “migraine treatment by valproic acid” can be used effectively and safely. The guideline was produced jointly with the Committee for the Development of Diagnostic and Treatment Guidelines for Chronic Headache (Chairman: Nobuo Araki) which was inaugurated around the same time.

## Committee for Guideline for Migraine Treatment by Valproic Acid (Provisional Edition):

The committee is composed of chairman: Kiyomi Yamane; vice-chairmen: Nobuo Araki and Takao Takeshima; members: Naoki Ando, Hisaka Igarashi, Keiko Imamura, Yasuo Ito, Yuji Kato, Kentaro Kuwabara, Tomokazu Shimazu, Hikaru Doi, Mitsue Fujita, Naoto Fujiki and Yuka Watanabe.

## Production process and contents of guideline

The guideline was produced based on evidence and according to the “Diagnostic and Treatment Guidelines for Chronic Headache” compiled by the Japanese Headache Society. When there is insufficient evidence, the recommendation may be made according to expert opinion. The present guideline is provisional. The principle policy was to gather opinions from members of the Japanese Headache Society after publication of this provisional guideline and reflect the opinions in a subsequent revised edition.

The guideline contains the following clinical questions (CQ):

- CQ 1. Is valproic acid effective for migraine prevention?  
Is there international consensus for valproic acid as prophylactic medication for migraine?
- CQ 2. What kinds of migraine patients are treated by valproic acid?
- CQ 3. What doses of valproic acid are used for the treatment of migraine?  
What are the precautions during administration of valproic acid?
- CQ 4. What is the significance of measuring blood levels of valproic acid in the treatment of migraine?
- CQ 5. Is valproic acid safe and effective in preventing migraine in children?

## Conclusion

Hereafter, validation of the efficacy and safety of using valproic acid as prophylactic treatment for migraine attacks mainly by members of the Japanese Headache Society is necessary. Generation of new evidence is anticipated through this validation process.

On behalf of the authors of Guideline for Migraine Treatment by Valproic Acid (Provisional Edition)

Fumihiko Sakai, Board Director of the Japanese Headache Society

Nobuo Araki, Chair of Guideline Committee

Kiyomi Yamane, Chair of Guideline for Migraine Treatment by Valproic Acid (Provisional Edition) Committee

\*This guideline was first published in Japanese Journal of Headache 2012; 38(3): 269-274.



## 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**

### Background and Objective

Valproic acid increases GABA level in the brain by activating glutamic acid decarboxylase and inhibiting GABA aminotransferase, and suppresses neuron excitability. Therefore, the effect of valproic acid on migraine and refractory chronic headache has been investigated. Approximately 20 years of use experience for migraine has been accumulated, and in European and American countries, valproic acid together with beta blockers and amitriptyline are listed among the first-choice drugs for migraine prevention.

### Comments and Evidence

Prospective studies of valproic acid for migraine prevention include two studies on sodium valproate and four on divalproex sodium (compound of valproic acid and sodium valproate in 1:1 ratio). The results of these studies were subjected to systematic review in a Cochrane review, which concludes that sodium valproate/divalproex sodium reduces the frequency of headache attacks and increases the number of patients in whom migraine frequency is reduced by 50% or more.<sup>1)</sup>

Shaygannejad et al.<sup>2)</sup> reported that by taking oral sodium valproate 400 mg/day for 8 weeks, the frequency of headache attacks was reduced from 5.4 to 4.0 per month, headache severity from visual analog scale (VAS) score 7.7 to 5.8, and headache duration from 21.3 hours to 12.3 hours. While some reports indicate that valproic acid reduces headache frequency as well as attenuates headache intensity and shortens headache duration,<sup>2,3)</sup> other reports show that valproic acid reduces headache frequency but does not improve headache intensity or headache duration.<sup>4)</sup>

When compared with other drugs, valproic acid shows equivalent effectiveness as flunarizine,<sup>5)</sup> propranolol,<sup>6)</sup> and topiramate.

In overseas countries, the European Federation of Neurological Science (EFNS) migraine treatment guideline recommends valproic acid 500 to 1,800 mg/day for migraine prophylaxis at level A.<sup>7)</sup> The American Academy of Neurology migraine guideline also recommends valproic acid at grade A.<sup>8)</sup> Therefore, international consensus has been obtained for valproic acid as a prophylactic medication for migraine.

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- **Search terms**

- PubMed search (2010/12/30)

(migraine) and ((preventive) or (prophylactic) or (prophylaxis)) and ((valproate) or (valproic acid)) 225

## 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**

### Background and Objective

The effect of valproic acid was investigated in patients with migraine or refractory chronic headache. Valproic acid significantly improved migraine compared with placebo, and the clinical trial results consistently showed that valproic acid is an effective prophylactic drug for migraine.<sup>1)-5)</sup>

The goals of valproic acid prophylactic therapy are:

- (1) to reduce headache frequency, severity and duration
- (2) to improve response to acute treatment
- (3) to improve function and reduce disability in daily living.

### Comments and Evidence

In a clinical trial conducted in migraine patients with a disease duration of two years or longer and migraine attacks of 4 times or more per month, attacks were reduced significantly during valproic acid treatment period compared with placebo period ( $p < 0.001$ ). Valproic acid has been reported to be especially effective in treating refractory migraine.<sup>6)-7)</sup> Even compared with other drugs, valproic acid shows equivalent effectiveness as propranolol<sup>3)</sup> and flunarizine.<sup>8)</sup>

The American College of Physician guideline, U.S. Headache Consortium guideline,<sup>9)</sup> and American Academy of Neurology guideline<sup>10)</sup> recommend valproic acid as one of the first-choice prophylactic therapies for migraine with the following indications:

- (1) two or more disabling attacks (6 or more days) per month,
- (2) contraindication or no response to acute treatments,
- (3) use of acute medications two or more times per week,
- (4) uncommon migraine conditions including hemiplegic migraine.

The guidelines also recommend to consider the adverse effects of acute treatments, patient preference, and the costs of both acute and prophylactic therapies.

Moreover, valproic acid is recommended as the first-choice medication especially in patients with comorbid conditions of epilepsy, mania, or bipolar disorder.<sup>11)-12)</sup>

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- PubMed search (2011/1/26)
  - {migraine} 24041
  - & {treat} 11630
  - & {(preventive) or (prophylactic) or (prophylaxis)} 2888
  - & {(valproate) or (valproic acid)} 210
  - & {patient} 132

## 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 to 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**

### Background and Objective

Valproic acid preparations include sodium valproate used in Japan, and divalproex sodium (preparation of valproic acid and sodium valproate in 1:1 ratio, valproic acid content is almost equivalent to sodium valproate) used in overseas countries. In Japan, the use of Depakene<sup>®</sup> for migraine was approved for health insurance coverage on October 29, 2010, and was officially approved in September 2011. Since migraine commonly occurs in women of child-bearing potential, and because there is a possibility of pregnancy during treatment, it is important to know about adverse reactions and precautions in use, and administer with caution. The safe and effective dose for use in Japan has to be proposed.

### Comments and Evidence

Double-blind parallel-group controlled study and double-blind cross-over controlled study conducted overseas have proven that valproic acid is effective for migraine prevention, and the doses used in those studies ranged from 400 to 2,000 mg/day.<sup>1)</sup> In Japan, the reported doses were 800 mg/day according to a study on migraine prevention (open study) conducted by Oana et al.,<sup>2)</sup> and ranged from 200 to 1,000 mg/day when case reports were included. In the US, use of divalproex sodium at 500 to 1,000 mg/day was approved. The European Federation of Neurological Societies (EFNS) guideline recommends doses of 500 to 1,800 mg/day.<sup>3)</sup>

Regarding the relationship between dose and prophylactic effect, one study reported that compared with blood valproic acid level of 50 µg/mL or higher, blood level lower than 50 µg/mL was associated with less adverse effects, significant decreases in headache frequency and number of days with headache. This report thus recommended low-dose valproic acid of 500 to 600 mg/day for migraine prevention.<sup>4)</sup> Furthermore, another report indicated that in migraine patients who did not respond to low-dose valproic acid, dose increase did not improve response.<sup>5)</sup> From the above findings, the recommended dose range of sodium valproate is 400 to 600 mg/day.

According to a survey on the use of valproic acid in Japanese patients with mania or with a manic state of bipolar disease, the major adverse effects include drowsiness, hyperammonemia, vertigo, hepatic function impairment, elevated creatine phosphokinase, and anemia.<sup>6)</sup> Special attention is required when using valproic acid in women of child-bearing age. Regarding the relationship of valproic acid with congenital malformation, combined data from 8 cohort studies identified 118 cases of malformations in a total of 1565 pregnancies in which the women were exposed to valproic acid, showing a significantly higher incidence than in women not exposed to the drug.<sup>7)</sup> In addition, the rate of malformation increased as the dose of valproic acid exceeded 1,000 to 1,500 mg/day,<sup>8)-11)</sup> suggesting that the rate of teratogenicity increases depending on the dose and blood level. In a prospective study of pregnant women with epilepsy receiving monotherapy with anti-epileptic drug (carbamazepine, lamotrigine, phenytoin or valproic acid), cognitive function test conducted in three year-old children showed significantly lower IQ in children exposed to valproic acid treatment exceeding 1,000 mg/day in the fetal stage compared with other antiepileptic drugs.<sup>12)</sup> From the above data, it was concluded that taking valproic acid during

pregnancy is associated with teratogenicity and impaired cognitive function in fetus. In May 2013, FDA advised that different from epilepsy treatment, use of valproic acid for migraine prevention is contraindicated in pregnant women and women who may be pregnant, because the risk outweighs the benefit. When used in women of child-bearing potential, the patients should be given prior explanations of adverse effects and teratogenicity, and sustained release formulation should be chosen so that blood level increases gradually. Since the frequency of teratogenicity is increased with multi-drug antiepileptic therapy,<sup>8)9)</sup> combined use of valproic acid with other antiepileptic drugs should be avoided. Patients should be instructed to check the menstrual cycle and basal temperature, and to stop taking valproic acid and contact the attending doctor when pregnancy is suspected. To reduce the risk of neural tube defect, patients should be advised to take folic acid 0.4 mg/day.<sup>13)</sup>

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- Search database: PubMed (2011/1/23)  
valproate  
and migraine 349  
and pregnancy and malformation 502  
and pregnancy and malformation and polytherapy 48  
and folic acid 134
- Search database: Ichushi Web for articles published in Japan (2006-2011) (2011/1/23)  
Valproate and migraine 68

## 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**

### Background and Objective

Although valproic acid has been reported to be effective for the prevention of migraine, there are large individual differences in absorption, and elevated blood level may cause serious adverse reactions such as disturbance of consciousness. Valproic acid is mainly used for the treatment of epilepsy, and the effective blood concentration range is considered to be 50 to 100 µg/mL. However, it remains unknown whether the same optimal blood level applies to migraine that has different pathophysiology from epilepsy. Therefore, setting the optimal effective blood level of valproic acid is desirable, also from the viewpoint of reducing adverse reactions.

### Comments and Evidence

In general, due to the great individual differences in absorption of valproic acid and wide intraday variation of blood level, it is difficult to estimate the time to reach peak level. Therefore, trough level that is not affected by absorption is usually measured. When blood level exceeds 120 µg/mL, impaired blood coagulation, drowsiness, tremor, sedation, aggressiveness, hyperammonemia, and hyperglycemia appear. Drugs that increase blood valproic acid level include amitriptyline that is used as a prophylactic drug for migraine, and salicylic acid agents that are used during headache attacks. Long-term use of these drugs in combination with valproic acid requires caution.<sup>1)</sup> In elderly persons who have reduced albumin level, there is a risk of increase in blood level of the free drug.

In migraine, adverse reactions occur less readily when the blood valproic acid level is maintained below 50 µg/mL, while significant reductions of headache frequency and days of attack are achieved. Consequently, a lower blood level goal is recommended when valproic acid is used for migraine prevention.<sup>2)</sup> Furthermore, in patients who do not respond to low doses of valproic acid, increasing the dose does not achieve response.<sup>3)</sup> The mean (SD) blood valproic acid level was 38.9 (37.3) µg/mL in an open-label extension trial administering divalproex sodium (a preparation of valproic acid and sodium valproate in 1:1 ratio) to migraine patients aged 12 to 17 years<sup>4)</sup> and was 44.8 (35.5) µg/mL in an open-label multicenter study,<sup>5)</sup> with significant decrease in migraine attacks. From the evidence so far, the recommended dosing regimen is oral administration of extended release sodium valproate preparation aiming at a blood level of 21 to 50 µg/mL.

In rat experiments, oral administration of sodium valproate immediately followed by oral administration of rizatriptan or sumatriptan resulted in significantly lower plasma levels of valproic acid compared with controls.<sup>6,7)</sup> This result suggests a possibility that even in humans, when valproic acid and triptan are used in combination in patients with coexisting epilepsy and migraine, epilepsy may be less well controlled (for migraine, since triptan is already being used, transient decrease in blood level of valproic acid may not affect migraine).

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- **Search terms**

- Search database: PubMed (2010/12/26)  
Migraine and Valproate 349
- Search database: Ichushi Web for articles published in Japan (2010/12/26)  
Migraine and Valproate 57

## 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**

### Background and Objective

Although valproic acid is also used in children as an anti-epileptic drug, adverse reactions such as liver dysfunction and hematocytopenia are sometimes encountered. Precautions are being undertaken, such as performing blood count and biochemical tests including ammonia level before starting treatment, and regularly performing blood test during treatment. In addition, the risk of teratogenicity in pregnant women has been reported. Therefore valproic acid is not the first choice as migraine prophylaxis for children including adolescent girls.

### Comments and Evidence

Reports have shown different results of oral valproic acid therapy for preventing migraine in children. While one article showed no difference compared to placebo<sup>1)</sup> and another article showed equivalent effect as propranolol,<sup>2)</sup> many articles reported its effectiveness.<sup>3)-7)</sup>

The drugs of first choice for preventing migraine in children are cyproheptadine, amitriptyline,<sup>8)9)</sup> and lomerizine (but all should be avoided for pregnant women and women who may be pregnant, and constant attention has to be given to the possibility of pregnancy). Use of valproic acid as a prophylactic medication for migraine in children is restricted to either I or II as shown below.

#### I. When disability is severe and patient does not respond to prophylactic drugs other than valproic acid:

Severe disability is indicated by:

- 1) although frequency is not high, each attack is accompanied by vomiting and severe headache requiring bed rest
- 2) high frequency (10 times or more a month, necessitating analgesic)

#### II. Migraine showing epileptic discharge on EEG (or epilepsy-related headache)

When using valproic acid for migraine in children, perform blood tests (blood count and biochemistry including ammonia level) before starting oral treatment, and perform the above tests and measure blood level of valproic acid at around 2 weeks after starting treatment. To assess the degree of improvement of migraine attacks by valproic acid, advise the patient to use a headache diary and always make an appointment for the next visit. Do not use aimlessly. Explain to adolescent female patient that use of the drug should be avoided if pregnancy is possible. Consider prescribing folic acid in combination with valproic acid as necessary.

When valproic acid is used for epilepsy in children, the maintenance dose is 15 to 50 mg/kg, dose escalation is 5 to 10 mg/kg for each step, and the blood level range is 50 to 100 µg/mL.<sup>10)</sup> When used for preventing migraine in children, response may be obtained with lower doses than above.

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## • Search terms

#1 migraine

#2 valproic

#3 valproic acid

#4 #2 OR #3

#5 #1 AND #2

#6 #1 AND #2 Limits: All Infant: birth-23 months, All Child: 0-18 years, Newborn: birth-1 month, Infant: 1-23 months, Preschool Child: 2-5 years, Child: 6-12 years, Adolescent: 13-18 years

#7 #1 AND #2 Limits: Clinical Trial, Meta-Analysis, Practice Guideline, Randomized Controlled Trial, Review, All Infant: birth-23 months, All Child: 0-18 years, Newborn: birth-1 month, Infant: 1-23 months, Preschool Child: 2-5 years, Child: 6-12 years, Adolescent: 13-18 years

# **Appendix III**

**Guideline for Migraine Treatment  
by Propranolol (Provisional Edition)**

# Introduction

The Japanese Headache Society together with the Japanese Society of Neurology requested the Ministry of Health, Labour and Welfare to approve health insurance coverage of propranolol for the treatment of migraine. This issue was considered to qualify as medical and pharmaceutical data in the public domain at the Meeting of the First Committee on Drugs of the Pharmaceutical Affairs and Food Sanitation Council held on August 31, 2012. As a result, treatment of migraine by propranolol (Inderal<sup>®</sup>) was approved for health insurance coverage from August 31, 2012.

Regarding this health insurance coverage, attention has been called to the effect that users should be knowledgeable about the contents of the “Report Concerning the Qualification as Application Based on Public Domain Data”, and use the drug with caution by adjusting dosage according to the conditions of individual patients.

Furthermore, instruction has been issued to publicize the following:

- (1) Be well aware of the precautions for use of this drug. Strive to give prior explanations to patients regarding the treatment contents and possible adverse reactions, and obtain their informed consent.
- (2) When a serious adverse effect becomes known, report to the relevant company or to the Ministry of Health, Labour and Welfare. Strive to obtain information of the cases in the case of off-label use

With this background, Board Director Sakai instructed the Treatment Promotion Committee to produce a guideline (provisional edition) urgently in order that “migraine treatment by propranolol” can be used effectively and safely.

## Guideline Committee:

The Guideline Committee was inaugurated in September 2012. The Committee is composed of chairman: Kiyomi Yamane; vice-chairmen: Takao Takeshima, Nobuo Araki; members: Hisaka Igarashi, Shoji Kikui, Tomokazu Shimazu, Naoto Fujiki; assessor: Fumihiko Sakai

## Production process and contents of guideline

The guideline was produced based on evidence and according to the “Diagnostic and Treatment Guidelines for Chronic Headache” compiled by the Japanese Headache Society.

The guideline contains the following clinical questions (CQ):

- CQ 1. Is propranolol effective for migraine prevention?  
Is there international consensus for propranolol as prophylactic medication for migraine?
- CQ 2. What kinds of migraine patients are treated by propranolol?
- CQ 3. What doses of propranolol are used for the treatment of migraine?
- CQ 4. What precautions have to be taken during administration of propranolol (adverse reactions, interactions)?

## Conclusion

Hereafter, validation of the efficacy and safety of using propranolol as prophylactic treatment for migraine attacks led by members of the Japanese Headache Society is necessary. Generation of new evidence is anticipated through this validation process.

On behalf of the authors, November 6, 2012

Fumihiko Sakai, Board Director of the Japanese Headache Society

Kiyomi Yamane, Chair of Guideline for Migraine Treatment by Propranolol (Provisional Edition)  
Committee

\*This guideline was first published in Japanese Journal of Headache 2013; 39(3): 297-302.

## 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**

### Background and Objective

Propranolol is a beta-blocker used mainly for the treatment of hypertension, coronary arterial diseases and tachyarrhythmia, but it is also used as a prophylactic drug for migraine. Many good quality clinical trials with placebo control have demonstrated the effectiveness of propranolol, and meta-analysis has also been conducted. Although many aspects of the mechanism of action and pharmacological evidence remain unclear, studies suggest that the actions involve not only peripheral blood vessels and beta blockade of autonomic nerves but also central neurotransmission.<sup>1)</sup> In American and European countries, propranolol together with another beta blocker metoprolol, the antiepileptic drugs valproic acid and topiramate, as well as the antidepressant amitriptyline are listed as first-choice drugs for migraine prevention.

### Comments and Evidence

At least 46 studies on propranolol have been conducted, and placebo-controlled clinical trials have proven the effectiveness of propranolol as a prophylactic drug for migraine. In addition, meta-analysis has been conducted. In a meta-analysis of 53 studies (2,403 subjects) reported by Holroyd et al.,<sup>2)</sup> the modal dose of propranolol was 160 mg/day. Double-blind studies showed a mean effective rate of 43.7% for propranolol and was significantly ( $p < 0.001$ ) higher than the rate of 14.3% for placebo. Propranolol yielded a 44% reduction in migraine attacks when headache diary was used to assess treatment outcome, and a 65% improvement when clinical or subjective ratings of improvement were used, whereas placebo gave approximately 14% improvement for both assessment methods. While the doses used varied among studies, the dose–response relationship for migraine prevention is not clear. Propranolol is well tolerated. Apart from propranolol, other drugs that exhibit migraine prophylactic effect include metoprolol,<sup>3,4)</sup> timolol,<sup>5)</sup> atenolol,<sup>6)</sup> and nadolol.<sup>7)</sup> In general, beta blockers that stimulate intrinsic sympathomimetic activity lack effectiveness in migraine prevention, although the reason is unknown.

When compared with other drugs, propranolol has almost equivalent effectiveness as flunarizine,<sup>8)</sup> valproic acid,<sup>9)</sup> topiramate,<sup>10)</sup> and amitriptyline.<sup>11)</sup>

In overseas countries, the European Federation of Neurological Science (EFNS) migraine treatment guideline recommends propranolol 40 to 240 mg/day for migraine prophylaxis at level A.<sup>12)</sup> The American Academy of Neurology migraine guideline also recommends propranolol at grade A.<sup>13)14)</sup> Therefore, international consensus has been obtained for propranolol as a prophylactic medication for migraine.

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## • Search terms

- Search database: PubMed (2012/8/31)
- 1. {migraine} OR {vascular headache} OR {hemicrania} 71380
  - & propranolol 633
  - & metoprolol 149
  - & timolol 62
  - & nadolol 41
  - & atenolol 102
- 2. {migraine} OR {vascular headache} OR {hemicrania} & {propranolol}
  - & flunarizine 72
  - & valproate 61
  - & topiramate 63
  - & amitriptyline 84
- Secondary source, 3 references added by manual search (Nos. 12-14)



## 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**

### Background and Objective

Propranolol is one of the therapeutic agents for hypertension, coronary artery disease and tachyarrhythmia, but has also been shown to be useful for migraine prevention. Propranolol can be used as long as the patients have no comorbidities that are contraindications for propranolol, such as heart failure and asthma, and is a relatively safe prophylactic drug for pregnant women.

### Comments and Evidence

Placebo-controlled clinical trial has shown that propranolol is useful as a prophylactic drug against migraine for patients who have migraine attacks two or more times a month and disability in daily living not resolved by acute treatment alone.<sup>1)</sup> In American and European countries, propranolol together with another beta blocker metoprolol, the antiepileptic drugs valproic acid and topiramate, as well as the antidepressants amitriptyline are listed as first-choice drugs for migraine prevention.<sup>2)-9)</sup>

The US Headache Consortium<sup>3)-5)</sup> recommends that choice of prophylactic medication should consider the comorbidities. Several comorbid conditions are present in migraine patients, and are associated with both opportunity and limitation for treatment. Hence, it is important to choose medications that can treat both the comorbidities and migraine, and at the same time are not contraindications or do not aggravate the comorbid conditions. Therefore, in patients who have co-existing hypertension, coronary artery disease or tachyarrhythmia for which propranolol is a therapeutic agent, propranolol is recommended as the first choice in such patients. On the other hand, propranolol cannot be used in patients with heart failure, asthma or other comorbid conditions for which propranolol is contraindicated. In addition, since propranolol may increase the blood level of rizatriptan, co-administration of the two is contraindicated. Furthermore, attention has to be given to the possibility of occurrence of depressive state as an adverse reaction.

Guidelines published so far state that when prophylactic therapy is unavoidable in pregnant women, beta blockers including propranolol are relatively safe.<sup>2)-12)</sup>

Although study has indicated that valproic acid and propranolol have equivalent efficacy in children,<sup>13)</sup> evidence is inadequate. Overseas guidelines do not recommend propranolol for use in pediatric cases.

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## • Search terms

- Search database: PubMed (2012/9/10)
  - migraine & propranolol 521
  - & guideline 14
  - & benefit 25
  - & prophylaxis 258
  - & preventive 44

## What doses of propranolol are used for the treatment of migraine?

### Recommendation

For adults, start with propranolol 20 to 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**

### Background and Objective

Since August 31, 2012, Inderal has been approved for health insurance coverage in Japan, through an application based on public domain data. The use of this drug is expected to increase in the future. The approved doses of propranolol as prophylactic therapy for migraine are 80 to 240 mg in the United States and 80 to 160 mg/day in the United Kingdom. In Japan, the approved doses for cardiovascular diseases such as hypertension are much lower, at 30 to 60 mg/day. There is a need to recommend the safe and effective doses of propranolol as prophylactic therapy for migraine.

### Comments and Evidence

Propranolol is mainly used as therapeutic agents for hypertension, coronary artery disease and tachyarrhythmia, but this drug has also been used for migraine prevention from the past. According to a meta-analysis reviewing 53 studies (2,403 patients) conducted by Holroyd et al.,<sup>1)</sup> the modal dose of propranolol was 160 mg/day and the mean response rate of propranolol in double-blind trials was 43.7% which was significantly ( $p < 0.001$ ) higher than 14.3% for placebo. Propranolol reduced migraine attacks by 44% when headache diaries were used to assess treatment outcome, and achieved 65% improvement when subjective scales or clinical ratings of effectiveness were used. The improvement rate for placebo remained at around 14% for both evaluation methods. While the doses used vary among studies, the dose-response relationship for migraine prophylactic effect is unclear. Propranolol is well tolerated.

In overseas countries, the European Federation of Neurological Science (EFNS) migraine treatment guideline recommends propranolol 40 to 240 mg/day for migraine prophylaxis at level A.<sup>2)</sup> The American Academy of Neurology migraine guideline recommends propranolol 120 to 240 mg/day.<sup>3)-5)</sup> In Japan, the approved doses for cardiovascular diseases such as hypertension are much lower, at 30 to 60 mg/day. With this background, the doses used as prophylactic therapy for migraine in Japan are lower than those used overseas, and open studies have indicated that those doses are effective and safe.<sup>6)-8)</sup> In the chronic headache guidelines published in 2006, doses of 20 to 60 mg/day were recommended based on the experience of use in Japan although there was little evidence, and this dose range was lower than that based on overseas evidence. Following this recommendation, the experience of use in Japan has accumulated.<sup>9)10)</sup> Kikui et al.<sup>10)</sup> treated 16 Japanese patients requiring prophylactic therapy with propranolol 20 to 40 mg/day (mean  $29.4 \pm 4.4$  mg/day), and reported a significant decrease in number of days with migraine from one month of treatment, with a reduction of 36.8% at two months compared to before treatment, and continuation of the effect even after six months. They concluded that low dose propranolol is an effective prophylactic therapy for migraine.

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- Search database: PubMed (2012/8/31)  
{migraine} OR {vascular headache} OR {hemicrania} 71380  
& propranolol 633
- Search database: Ichushi Web for articles published in Japan (2012/8/31)  
(migraine) & (propranolol) 67
- Secondary source: 4 articles added by manual search (Nos. 3-5, 6)

## What precautions have to be taken during administration of propranolol (adverse reactions, interactions)?

### Recommendation

Propranolol has been used as a therapeutic agent for hypertension, angina pectoris, and arrhythmia since 1966, and data of adverse reactions have been accumulated adequately. As a prophylactic drug for migraine, 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**

### Background and Objective

In Japan, since the approval of the application based on public domain data for the use of propranolol as a prophylactic drug for migraine, this drug is expected to be increasingly prescribed in the future. This section examines the adverse reactions and drug interactions that require special attention when propranolol is administered.

### Comments and Evidence

Propranolol has been used as a therapeutic agent for hypertension, angina pectoris, and tachyarrhythmia since 1966, and adequate data on adverse reactions and drug interactions has been accumulated.<sup>1)</sup> As a prophylactic drug for migraine, dozens of clinical trials have been conducted overseas,<sup>2)</sup> and meta-analysis has also been conducted.<sup>3)</sup> According to the meta-analysis conducted by Holroyd et al.<sup>3)</sup> on 2,403 subjects, propranolol is well tolerated and no severe adverse effects have been reported. When propranolol is used as a prophylactic drug for migraine, the ages of the target patients in general are conceivably younger than those treated for hypertension and heart diseases, and the doses used would not exceed those for hypertension and heart disease patients (dose approved in Application Based on Public Domain Data: up to 60 mg/day). Therefore when prescribing for migraine patients in Japan, it is sufficient to pay attention to the adverse reactions accumulated so far for the indicated diseases.

The package insert of propranolol lists heart failure, bradycardia, orthostatic hypotension, and bronchial spasm as “serious adverse reactions”, and bronchial asthma, metabolic acidosis, severe bradycardia, atrioventricular or sinoatrial block, congestive heart failure, hypotension, severe periphery circulatory disturbance, and variant angina as “contraindications for propranolol administration”. Therefore, when prescribing migraine prophylactic drugs for patients with the above comorbid conditions, drugs other than propranolol should be chosen.

As for weight gain that often constitutes a problem in prescribing migraine prophylaxis, while this adverse effect also occurs with propranolol, the rate is extremely low compared to amitriptyline and valproic acid.<sup>4)</sup> In the package insert of propranolol, weight gain is not listed as an adverse effect.

Propranolol has been reported to interact with many drugs. Among them, co-administration with thioridazine and with rizatriptan is contraindicated. Since rizatriptan is an acute medication for migraine, special attention has to be paid to ensure that this drug is not co-administered.<sup>1)5)</sup> When healthy adults taking repeated oral doses of propranolol were administered a single dose of rizatriptan benzoate, the area under the curve (AUC) was 1.67 times, and the maximum drug concentration ( $C_{\max}$ ) was 1.75 times higher compared to when propranolol was not taken in combination,<sup>6)</sup> suggesting a possibility that the effect of rizatriptan may be augmented. Although the mechanism of this interaction has not been elucidated, propranolol is suspected to inhibit rizatriptan metabolism via monoamine oxidase A. The same phenomenon has been confirmed for propranolol and zolmitriptan,<sup>7)</sup> but the changes in AUC and  $C_{\max}$  are relatively small compared to rizatriptan and the effects on the cardiovascular system is not related to whether propranolol is taken. Therefore, co-administration of zolmitriptan and propranolol is not a contraindication and dose reduction is not required. The same interaction is not observed with sumatriptan.<sup>8)</sup>

Caution is needed when propranolol is co-administered with many other drugs.<sup>1)</sup> Most of these drugs are used for treating cardiovascular diseases and their actions are augmented by the interaction. Note that the list of drugs requiring caution for

co-administration also includes calcium channel blocker such as verapamil that may be used as migraine prophylactic medication, ergot alkaloids such as ergotamine that may be used as acute treatment for migraine, and nonsteroidal anti-inflammatory drugs such as indomethacin.

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## • Search terms

- Search database: PubMed (2012/9/3)
  - Migraine & propranolol & side effect 26
  - Migraine & propranolol & interaction 19