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Clinical Practice Guideline for Headache Disorders 2021

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ABSTRACT

The International Headache Society published the International Classification of Headache Disorders, 3rd edition in 2018. In this classification, Chapter 3—previously "Cluster headache and other trigeminal-autonomic cephalalgias"—was renamed "Trigeminal-autonomic cephalalgias (TACs)." Trigeminal-autonomic cephalalgias are a group of disorders characterized by unilateral severe headache and cranial autonomic symptoms, with cluster headache as a representative condition. Several major revisions have also been made regarding the diagnostic criteria for trigeminal-autonomic cephalalgias in terms of ictal symptomatology and the duration of remission period. Moreover, calcitonin gene-related peptide-targeting treatments have enabled significant improvements in migraine management to be made. In Japan, in response to these advances in headache medicine, the Clinical Practice Guideline for Headache Disorders was revised by the Study Group for Headache Clinical Practice Guideline Development. The new guidelines include the latest information and present global standards of management for both primary and secondary headache disorders in consideration of local labelling and regulatory approvals. The guideline comprises eight chapters: "I. Headache: general considerations," "II. Migraine," "III. Tension-type headache," "IV. Trigeminal-autonomic cephalalgias," "V. Other primary headache disorders," "VI. Medication-overuse headache (MOH)," "VII. Headaches in children," and "VIII. Secondary headaches." The GRADE system was adopted to address the clinical question "Are triptans more useful than nonsteroidal anti-inflammatory drugs as acute treatment for migraines?" This paper was prepared to present the core treatment recommendations for primary headache disorders and medication-overuse headache in English.

1 | Introduction

Humans have been afflicted by headache since ancient times; the first descriptions of headache treatment can be traced back to the ritual texts of Mesopotamia, circa 4000 BC [1]. Headache remains a considerable health issue in contemporary society. According to the Global Burden of Disease study 2021, at level 3 (groups of related disorders), headache disorders are ranked the 15th cause of disability-adjusted life years [2, 3]. Primary headache disorders are not life-threatening. Nevertheless, with respect to years lived with disability, which serves as a measure of lost health attributable to nonfatal disease, headache disorders are in third place. At the level of individual disorders, migraine is ranked fourth among young adults and third among young females, imposing a considerable financial burden on society [2]. Treating headache disorders appropriately, both at

the individual and societal levels, is crucial. Clinical guidelines, compatible with local labelling and regulatory approvals, are required to guide physicians in making the right therapeutic decisions [4, 5].

2 | Procedures and Organization

In 2018, the International Headache Society released the International Headache Classification of Headache Disorders, 3rd edition (ICHD-3) [6]. In November of the same year, the ICHD Committee of the Japanese Headache Society published the Japanese version of the ICHD-3 [7]. Globally, monoclonal antibodies targeting calcitonin gene-related peptide (CGRP) or its receptor had been shown to be safe and efficacious for migraine prophylaxis since 2014 [8–15]. These antibodies were approved as a novel prophylactic treatment for migraine in the United States in 2018. Considering these developments in the global headache field, the Japanese Headache Society established a guideline committee to compile an updated set of clinical guidelines for headache disorders. A decision was made that the Japanese Society of Neurology, the Japanese Headache Society, and the Japanese Society of Neurological Therapeutics would supervise the compilation and updating of the guidelines and, in collaboration with the Japanese Neurosurgical Society, appointed committee members. The majority of the committee members attended the first conference of the guideline committee held on February 24, 2019. At this conference, committee members decided to devote a chapter to secondary headaches and transfer the contents of the chapter in the previous edition relevant to the genetics of headaches to "Chapter I. Headache: general considerations." At the conference, contributors were assigned to each clinical question (CQ), and the decision was made to incorporate the four appendix CQs from the previous edition into the main text. The new clinical guideline consists of the following eight chapters.

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

At a subsequent committee meeting, members decided to adopt the GRADE (Grading of Recommendation, Assessment, Development, and Evaluation) system for CQ II-2-3, "Are triptans more useful than nonsteroidal anti-inflammatory drugs (NSAIDs) as acute treatment for migraine?" The committee invited Dr. Eishuu Nango (physician), Ms. Kaori Tabata (nurse), Ms. Mie Kato (pharmacist), and Ms. Chihiro Kida (patient representative) as external members to assist in preparing the recommendations to this CQ.

Search for scientific evidence was conducted using a systematic approach. The literature was searched using the public databases of PubMed, Cochrane Library, and Ichushi-web, a database that contains bibliographic citations and abstracts from more than 2500 biomedical journals and other serial publications published in Japan. Based on the data obtained, we determined the strength of the recommendation (strong/weak) and the level of evidence (A: high, B: moderate, C: low) for each CQ. The committee members met repeatedly to refine the content of CQs. We continued working in the virtual setting during the coronavirus disease 2019 pandemic, and all the CQs were completed in February 2021. We then sought feedback from the Evaluation and Coordination Committee members, before granting a public comment period. We finalized the new guidelines by revising the content in the previous version based on all the feedback.

We would like to express gratitude to everyone for their insightful comments. The recommendations in these guidelines were developed after evaluating the current evidence on individual pharmacological and non-pharmacological treatments for headache disorders. Of note, these guidelines are not intended to impose specific treatments uniformly on providers of headache care.

3 | On Publication of the English Edition of the Guidelines

The previous edition of the guidelines, Clinical Practice Guideline for Chronic Headache 2013, was translated into English (to access the full content, visit https://www.neurology-jp.org/guidelinem/ch/index.html) [7]. Similarly, we decided to publish the CQs related to treatments for migraine, tension-type headache, cluster headache, and MOH of the new guidelines in English. We hope that this article provides useful information to all stakeholders in the field of headache medicine worldwide.

4 | Migraine

4.1 | CQ II-2-1. What Options Are Available for Acute Treatment of Migraine, and How Should They Be Used?

4.1.1 | Recommendations

Pharmacotherapy is the mainstay of treatment for acute migraine. The drugs used include (1) acetaminophen, (2) NSAIDs, (3) ergotamines, (4) triptans, and (5) antiemetics. Stratified treatment according to the severity of migraine is recommended: use NSAIDs such as aspirin and naproxen for mild to moderate headache and use triptans for moderate to severe headache, or even mild to moderate headache when NSAIDs were previously ineffective. Patients must be provided with information on how to use medications (timing, dose, and frequency of use) and medication use during pregnancy and breastfeeding, as well as how to deal with acute attacks.

Some individuals are non-responders to triptans and some cannot tolerate the vasoconstrictive actions of triptans. Therefore, selective 5-HT_{1F} receptor agonists (ditans) and CGRP receptor antagonists (gepants)—both of which have no vasoconstrictive effects—are under development. Lasmiditan, a ditan, was shown to be efficacious as acute migraine treatment in two phase III trials and was approved by the Food and Drug Administration (FDA) in October 2019. In Japan, a clinical trial assessing the efficacy and safety of lasmiditan as an acute treatment for migraines was completed in June 2020 *, and the drug was launched in Japan in June 2022. The gepants, ubrogepant and rimegepant, were shown to be efficacious as treatment for acute migraine in phase III trials and were approved by the FDA in December 2019 and February 2020, respectively.

Strong recommendation.

Level of evidence: A–C (Table 1).

4.2 | CQ II-2-2. How Should Clinicians Establish and Implement Goals for Acute Treatment of Migraine?

4.2.1 | Recommendations

The ideal goal of acute treatment for migraine is to ensure rapid resolution of migraine attacks without adverse events and/or reactions, and to restore the patient's functionality. Pharmacotherapy plays a central role in such treatment. Commonly used drugs include (1) acetaminophen, (2) NSAIDs, (3) triptans, (4) ergotamines, and (5) antiemetics. NSAIDs are used for mild to moderate headaches. Triptans are recommended for moderate to severe headaches or for mild to moderate headaches when NSAIDs were previously ineffective. If the effect is still insufficient, concomitantly administering an NSAID and a triptan should be considered. The concomitant use of antiemetics can help improve symptoms during any migraine attack. Acute treatment is generally considered effective if the headache pain is relieved or significantly relieved at 2 h after administering the drug.

Weak recommendation.

Level of evidence: B.

4.3 | CQ II-2-3. Are Triptans More Useful Than Non-Steroidal Anti-Inflammatory Drugs as Acute Treatment for Migraines?

4.3.1 | Recommendations

Administering triptans is recommended over administering NSAIDs as acute treatment in adults experiencing migraine attacks that interfere with daily life.

4.3.1.1 | Additional Remarks. Treating physicians should consider the balance between efficacy and side effects, patients' comorbidities, age, preferences, and cost. The use of triptans is currently not advised for patients with hemiplegic migraine or migraine with brainstem aura.

Weak recommendation.

Level of evidence: B.

GRADE evidence profile (Table 2).

4.4 | CQ II-2-4. What Is the Recommended Timing for Taking a Triptan?

4.4.1 | Recommendations

Triptans are most effective when the headache is mild or when used early in the migraine attack (up to approximately 1 h after onset). Triptans are not harmful, but may be ineffective if used during the aura or premonitory phase of the migraine attack.

Strong recommendation.

Level of evidence: A.

4.5 | CQ II-2-5. How Should Patient Preferences for Different Triptans Be Determined?

4.5.1 | Recommendations

All triptans have shown clear efficacy as acute treatments for migraine attacks. However, slight differences in the characteristics of each triptan exist.

Recommendation grade: Not applicable (N/A).

4.6 | CQ II-2-6. For Which Patients With Migraine, and How, Should Parenteral Triptans Be Administered?

4.6.1 | Recommendations

Parenteral triptans are effective as acute treatment for severe migraine attacks. Injectable, intranasal, suppository, and transdermal preparations are indicated, especially when migraine attacks severely interfere with daily and social life, or when headache control is difficult because of frequent vomiting and other conditions that hinder oral intake. In terms of the speed of onset of therapeutic effect, injectable preparations are fastest, with intranasal and suppository preparations being almost equivalent. The option of preparations is determined depending on the patient's needs.

Injection: Strong recommendation; Level of evidence: A.

Nasal spray: Strong recommendation; Level of evidence: A.

TABLE 1 | Evidence summary of migraine acute medications.

Drug class	Generic name	Level of recommendation	Level of evidence	Frequency of AEs	Efficacy grade	Recommended dose	Maximal daily dose
Triptan	Sumatriptan oral	Strong	A	Occasional	1	50 mg	200 mg
	Sumatriptan, intranasal	Strong	A	Occasional	1	20 mg	40 mg
	Sumatriptan sc[d]	Strong	A	Occasional	1	3 mg	6 mg
	Sumatriptan kit sc	Strong	A	Occasional	1	3 mg	6 mg
	Sumatriptan suppository[c]		A	—	1	—	—
	Sumatriptan transdermal[c]		A	—	1	—	—
	Zolmitriptan oral	Strong	A	Occasional	1	2.5 mg	10 mg
	Zolmitriptan intranasal[c]		A	—	1	—	—
	Eletriptan	Strong	A	Occasional	1	20 mg	40 mg
	Rizatriptan	Strong	A	Occasional	1	10 mg	20 mg
	Naratriptan	Strong	A	Occasional	1	2.5 mg	5 mg
	Almotriptan[c]		A	—	1	—	—
	Frovatriptan[c]		A	—	1	—	—
Ditan	Lasmiditan[e]	Strong	A	Occasional–Frequent		100 mg	200 mg
Gepant	*Ubrogepant*[c]		A	—			
	Rimegepant[c]		A				
Anxiolytic, antipsychotic, anesthetic, antiemetic	Metoclopramide oral[b]	Strong	A	Occasional	2	5 mg	30 mg
	Metclopramide im, iv[b]	Strong	A	Occasional	2	10 mg	20 mg
	Domperidone[b]	Strong	B	Occasional	2	10 mg	30 mg
	Domperidone suppository[b]	Weak	B	Occasional	4	60 mg	
	Prochlorperazine oral[b]	Weak	A	Occasional–Frequent	4	5 mg	
	Prochlorperazine im[b]	Weak	A	Occasional–Frequent	4	5 mg	
	Chlorpromazine oral[b]	Weak	A	Occasional–Frequent	4	30 mg	
	Chlorpromazine im[b]	Weak	A	Occasional–Frequent	4	10 mg	
	Doroperidol im[b]	Weak	B	Occasional–Frequent	4	—	—
	Propofol iv[b]	Weak	C	Frequent	4	—	—
	Diazepam im, iv[b]	Weak	C	Frequent	4	5–10 mg	

(Continues)

TABLE 1 | (Continued)

Drug class	Generic name	Level of recommendation	Level of evidence	Frequency of AEs	Efficacy grade	Recommended dose	Maximal daily dose
Simple analgesic, NSAID	Acetaminophen oral	Strong	A	Occasional	2	300–1000 mg	4000 mg
	Acetaminophen div[b]	Strong	A	Occasional	2	300–1000 mg	4000 mg
	Aspirin	Strong	A	Occasional	2	0.5–1.5 g	1–4.5 g
	Ibuprofen[b]	Strong	A	Occasional	2	200 mg	600 mg
	Diclofenac[a]	Strong	A	Occasional		25–50 mg	75–100 mg
	Naproxen[b]	Strong	A	Occasional		200–300 mg	300–600 mg
	Indometacin oral (discontinued in Japan)[c]						
	Indometacin suppository[b]	Strong	B	Occasional		25–50 mg	50–100 mg
	Indometacin farnesil[a]	Strong	B	Occasional		200 mg	400 mg
	Acemetacin[b]	Weak	C	Occasional		30 mg	90–180 mg
	Celecoxib[b]	Strong	B	Rare–Occasional		100–200 mg	400 mg
	Etodolac[b]	Strong	B	Occasional		100–200 mg	400 mg
	Mefenamic acid	Strong	B	Occasional		250–500 mg	1500 mg
	Loxoprofen[a]	Strong	C	Occasional		60–120 mg	240 mg
	Pranoprofen[b]	Weak	C	Occasional		75–150 mg	225 mg
	Zaltoprofen[b]	Weak	C	Occasional		80–160 mg	240 mg
	Lornoxicam[b]	Weak	C	Occasioanl		4–8 mg	24 mg
Ergotamine	Ergotamine tartrate + anhydrous caffeine + isopropylantipyrine	Weak	B	Frequent		1 Tablet	3 Tablets (up to 10 Tablets/week)
	Ergotamine tartrate + caffeine (discontinued in Japan)[c]		B	Frequent			
	Dihydergotamine (discontined in Japan)[c]		B	Frequent			
Steroid	Dexamethasone div[b]	Weak	C	Occasional		2–8 mg	
	Hydrocortisone div[b]	Weak	C	Occasional		200–500 mg	
	Methylprednisolone div[b]	Weak	C	Occasional		40–125 mg	

(Continues)

TABLE 1 | (Continued)

Drug class	Generic name	Level of recommendation	Level of evidence	Frequency of AEs	Efficacy grade	Recommended dose	Maximal daily dose
Others	Tramadol oral[b]	Weak	C	Occasioal–Frequent		100 mg	300 mg
	Tramadol im[b]	Weak	C	Occasioal–Frequent		—	—
	Tramadol + acetaminophen[b]	Weak	C	Occasioal–Frequent		1 Tablet	4 Tablets
	Magnesium iv[b]	Weak	C	Rare		—	—

Note: Levels of recommendation and evidence were determined according to the descriptions in the main text of this guideline. Recommended doses are based on evidence and consensus in Japan for adults. Minus signs denote that the dose is currently difficult to evaluate. Efficacy grade: Group 1 (effective), Group 2 (somowhat effective), Group 3 (empirically effective), Group 4 (effective, though caution for adverse effects is required.), Group 5 (not effective). Those that have never been approved for any formulation or indication in Japan are indicated in italics.

Abbreviations: AE, adverse effect; div, drip intravenous; im, intramuscular; iv, intravenous; sc, subcutaneous.

[a]Covered by health insurance in Japan for off-label use for migraine.

[b]Not covered by health insurance in Japan for migraine.

[c]Not available in Japan.

[d]Discontinued in December 2021 in Japan.

[e]Launched in Japan in May 2022.

4.7 | CQ II-2-7. Which Patients With Migraine Should Use Sumatriptan Self-Injection at Home, and What Are the Indications, Side Effects, and Contraindications Associated With Its Use?

4.7.1 | Recommendations

Sumatriptan self-injection at home is indicated for patients diagnosed with cluster headache or migraine. Cluster headaches are considered the most suitable indication for sumatriptan self-injection at home, which conveniently confers immediate effectiveness. This treatment is also indicated for migraines, especially those that severely impair daily and social life, or render oral treatment challenging due to frequent vomiting.

The main side effects of subcutaneous sumatriptan injection include nausea, chest discomfort, palpitations, bleeding at the injection site, fatigue, and drowsiness. Its safety for administration to children has not been established. Sumatriptan injection should be administered with caution in older patients. It should not be administered to patients with familial hemiplegic migraine, sporadic hemiplegic migraine, migraine with brainstem aura, a history of heart disease, cerebrovascular disorders, peripheral circulation disorders, uncontrolled hypertension, or severe liver impairment, or those currently using or having used any monoamine oxidase inhibitor within the last 2 weeks. When prescribing sumatriptan self-injection at home to patients already taking ergotamine-based products or an oral triptan other than sumatriptan, patients should be instructed to maintain a minimal interval of 24 h between each dose of medication.

Strong recommendation.

Level of evidence: A.

4.8 | CQ II-2-8. Are Triptans Effective in the Acute Phase of Hemiplegic Migraine?

4.8.1 | Recommendations

Administering triptans in the acute phase of hemiplegic migraine is not advised.

Weak recommendation.

Level of evidence: C.

4.9 | CQ II-2-9. Are Acetaminophen and Non-Steroidal Anti-Inflammatory Drugs Effective in Treating Migraines?

4.9.1 | Recommendations

Monotherapy with acetaminophen or an NSAID is safe and cost-effective. This therapy is recommended as the first option for mild to moderate migraine attacks. However, these medications have limited effectiveness compared with triptans. Early switching to triptans should be considered for patients with migraine that is nonresponsive to acetaminophen or NSAIDs.

TABLE 2 | GRADE evidence profile comparing triptans and NSAIDs as acute treatment for migraines.

Certainty assessment							Summary of results					
							No of patients		Effect			
No of studies	Study design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Triptan	NSAIDs	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain free at 2 h												
6	RCT	Not serious	Not serious	Not serious	Serious[a]	None	353/1376 (25.7%)	338/1612 (21.0%)	RR 1.30 (1.14–1.48)	63 more per 1000 (29 to 101)	⊕⊕⊕◯ Moderate (B)	Critical
Nausea free at 2 h												
4	RCT	Not serious	Not serious	Not serious	Not serious[b]	None	671/1058 (63.4%)	823/1186 (69.3%)	RR 0.92 (0.86–0.97)	56 fewer per 1000 (−97 to −21)	⊕⊕⊕⊕ High (A)	Critical
Photophobia free at 2 h												
4	RCT	Not serious	Serious[c]	Not serious	Serious[a]	None	511/1058 (48.3%)	626/1186 (52.8%)	RR 0.95 (0.87–1.03)	26 fewer per 1000 (−69 to 16)	⊕⊕⊕◯ Low (C)	Important
Phonophobia free at 2 h												
4	RCT	Not serious	Not serious	Not serious	Serious[a]	None	558/1058 (52.7%)	645/1186 (54.4%)	RR 1.00 (0.92–1.08)	0 fewer per 1000 (−44 to 44)	⊕⊕⊕⊕ Moderate (B)	Important
Adverse events at 24 h												
7	RCT	Not serious	Not serious	Not serious	Not serious[b]	None	365/1508 (24.2%)	276/1868 (14.8%)	RR 1.65 (1.43–1.90)	96 more per 1000 (64 to 133)	⊕⊕⊕⊕ High (A)	Critical
Drug-related adverse events at 24 h												
4	RCT	Not serious	Not serious	Not serious	Not serious[b]	None	103/552 (18.7%)	87/706 (12.3%)	RR 1.64 (1.27–2.12)	79 more per 1000 (33 to 138)	⊕⊕⊕⊕ High (A)	Critical
Pain free at 24 h												
3	RCT	Not serious	Not serious	Not serious	Not serious[b]	None	135/949 (14.2%)	104/967 (10.8%)	RR 1.32 (1.04–1.68)	34 more per 1000 (4 to 73)	⊕⊕⊕⊕ High (A)	Critical

(Continues)

TABLE 2 | (Continued)

Certainty assessment							Summary of results				
							No of patients		Effect		
No of studies	Study design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Triptan	NSAIDs	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain relief at 24h												
5	RCT	Not serious	Not serious	Not serious	Not serious[b]	None	449/1273 (35.3%)	382/1291 (29.6%)	RR 1.19 (1.07–1.33)	56 more per 1000 (21 to 98)	⊕⊕⊕⊕ High (A)	Critical
Use of rescue medication within 24h												
6	RCT	Not serious	Not serious	Not serious	Serious[a]	None	526/1361 (38.6%)	680/1600 (42.5%)	RR 0.92 (0.84–1.00)	34 fewer per 1000 (−68 to 0)	⊕⊕⊕⊕ Moderate (B)	Critical

[a]The confidence interval crosses the threshold for clinical decision-making.
[b]The confidence interval does not cross the threshold for clinical decision-making, and the event numbers exceed the optimal information size (OIS).
[c]$I^2 = 82\%$.

Strong recommendation.

Level of evidence: A.

4.10 | CQ II-2-10. Are Antiemetics Beneficial in Acute Treatment of Migraine?

4.10.1 | Recommendations

Antiemetics are effective for nausea and vomiting, which are symptoms that accompany migraines. Intravenous injection of metoclopramide is moderately effective in relieving migraine headache pain and is recommended for use in the acute phase of migraine attacks. Oral metoclopramide or domperidone should be administered concomitantly with analgesics.

Weak recommendation.

Level of evidence: B.

4.11 | CQ II-2-11. What Other Drugs Are Available for Acute Treatment of Migraine?

4.11.1 | Recommendations

- Use of intravenous prochlorperazine is effective for treating nausea and vomiting during the acute phase of migraine, but the drug is not covered by insurance in Japan. (Weak recommendation; Level of evidence: B)
- Intravenous dexamethasone is a therapeutic option for status migrainosus or acute attacks of chronic migraine. (Weak recommendation; Level of evidence: C)
- Intravenous chlorpromazine or intravenous magnesium may be considered for acute treatment of migraine attacks; however, scientific evidence supporting their effectiveness is lacking. Moreover, these treatments are not covered by insurance in Japan. (Weak recommendation; Level of evidence: C)
- The tramadol and acetaminophen combination is not recommended because it has the potential to induce central sensitization and MOH. (Weak recommendation; Level of evidence: C)
- Other therapeutic options include the as-needed use of Chinese herbal medicines such as goshuyuto, goreisan, and keishininjinto. Complementary and alternative therapies include acupuncture, feverfew, and caffeine; however, these must be used with caution to avoid side effects and interactions with other medications in use. (Weak recommendation; Level of evidence: C)

4.12 | CQ II-2-12. What Acute Treatments Can Be Used for Severe Migraine Attacks and Status Migrainosus?

4.12.1 | Recommendations

Treatment for severe migraine attacks and status migrainosus should be offered as follows.

- Exclusion of secondary headaches. (Strong recommendation; Level of evidence: B)
- Fluid replacement via a secure intravenous route: To improve dehydration caused by vomiting and prepare for side effects such as hypotension caused by therapeutic drugs. (Strong recommendation; Level of evidence: B)
- Subcutaneous injection of sumatriptan (3 mg): The total dose within 24 h and headache recurrence should be monitored. (Weak recommendation; Level of evidence: B)
- Injection of antiemetics: Including intravenous metoclopramide (10 mg) or intramuscular prochlorperazine (5 mg). (Weak recommendation; Level of evidence: C)
- Administration of intravenous propofol. (Weak recommendation; Level of evidence: C)
- Administration of intravenous haloperidol. (Weak recommendation; Level of evidence: C)
- Administration of intravenous dexamethasone or oral prednisolone. (Weak recommendation; Level of evidence: C)

4.13 | CQ II-2-13. How Should Clinicians Manage Migraine During Pregnancy and Breastfeeding, Including What Therapeutic Options Are Available for Both the Acute Phase and Prevention?

4.13.1 | Recommendations

- If attacks are so severe that acute treatment is required, acetaminophen is recommended. (Weak recommendation; Level of evidence: B)
- The safety of triptans for use during pregnancy has not been established. However, no increased risk of teratogenicity has been reported with their use during early pregnancy. Triptans may be administered for severe attacks, but the risks and benefits should be carefully considered. (Weak recommendation; Level of evidence: B)
- Preferred practice is to not use prophylactic drugs during pregnancy. However, if necessary, β blockers and low-dose amitriptyline should be considered as therapeutic options. (Weak recommendation; Level of evidence: B)
- For acute treatment during breastfeeding, a safer option from among the NSAIDs and triptans should be selected. Other drugs and preventive therapies require individual consideration. (Strong recommendation; Level of evidence: B)

4.14 | CQ II-2-14. How Should Clinicians Diagnose and Treat Menstrual Migraine?

4.14.1 | Recommendations

- The diagnosis of menstrual migraine should be made according to the ICHD-3 criteria. A headache diary, including records for three menstrual cycles, should be maintained to clarify the relationship between the menstrual cycle and migraine attacks. (Strong recommendation; Level of evidence: A)
- Migraine without aura attacks related to the menstrual cycle are often severe. Therefore, the administration of triptans is recommended for acute management if NSAIDs have not been effective for previous attacks. (Strong recommendation; Level of evidence: B)
- Although preventive therapy should follow standard protocols, if the occurrence of attacks is closely related to menstruation, short-term prevention therapy may be a therapeutic option. (Weak recommendation; Level of evidence: C)

4.15 | CQ II-3-1. Which Patients With Migraine Require Prophylactic Treatment?

4.15.1 | Recommendations

Prophylactic treatment should be considered for patients who have two or more migraine attacks per month or three or more days of disabling headache per month. Prophylactic treatment is recommended when migraine attacks interfere with daily life with acute treatment alone, when acute medication cannot be used, or when—in special subtypes of migraine—a risk of permanent neurological damage exists.

Weak recommendation.

Level of evidence: B.

4.16 | CQ II-3-2. What Drugs Are Available for Migraine Prophylaxis?

4.16.1 | Recommendations

Table 3 lists the drugs used for prophylactic treatment of migraine.

Prophylactic drugs for migraine can be divided into different groups, based on evidence of their efficacy and risk of adverse events (Table 4).

Strong recommendation.

Level of evidence: A.

4.17 | CQ II-3-3. How Are Goals for Migraine Prophylaxis Established and Implemented?

4.17.1 | Recommendations

The goals of migraine prophylaxis are to reduce the frequency, severity, and headache duration of migraine attacks; improve the response to acute therapy; enhance individual functionality; and reduce impairment in daily living.

Major preventive drugs for migraine include:

TABLE 3 | Evidence summary of migraine prophylactic drugs.

Drug class	Generic name	Level of recommendation	Level of evidence	Frequency of AEs	Efficacy grade	Recommended dose
Anti-CGRP Ab	Galcanezumab	Strong	A	Rare	1	120 mg/month (loading dose: 240 mg)
	Fremanezumab	Strong	A	Rare	1	225 mg/4 weeks, 675 ng/12 weeks
	Eptinezumab[c]		A	Rare	1	
Anti-CGRP receptor Ab	Erenumab	Strong	A	Rare	1	70 mg/4 weeks
CGRP receptor antagonist	*Rimegepant*[c]		A	Rare	1	
	Atogepant[c]		A	Rare	1	
Antiepileptic drug (Antiseizure medication)	Valproate	Strong	A	Occasional–Frequent	1	400–600 mg/day[d]
	Topiramate[b]	Strong	A	Occasional–Frequent	1	50–200 mg/day
	Gabapentin[b]	Weak	B	Occasional–Frequent	2	
	Levetiracetam[b]	Weak	B	Occasional–Frequent	2	
Antidepressant	Amitriptyline[a]	Strong	B	Frequent	1	10–60 mg/day
	Nortriptyline[b]	Weak	C	Frequent	3	
	Imipramine[b]	Weak	C	Frequent	3	
	Clomipramine[b]	Weak	C	Frequent	3	
	Torazodone[b]	Weak	C	Occasional–Frequent	3	
	Mianserin[b]	Weak	C	Occasional–Frequent	3	
	Fluvoxamine[b]	Weak	C	Occasional	3	
	Paroxetine[b]	Weak	C	Occasional	3	
	Sulpiride[b]	Weak	C	Rare	3	
	Duloxetine[b]	Weak	C	Occasional	3	
	Fluoxetine[c]		B	Occasional	2	
β blocker	Propranolol	Strong	A	Rare–Occasional	1	20–60 mg/day
	Timolol[b]		A	Rare–Occasional	1	
	Metoprolol[b]	Strong	B	Rare–Occasional	2	40–120 mg/day
	Atenolol[b]	Weak	B	Rare–Occasional	2	
	Nadolol[b]	Weak	B	Rare–Occasional	2	

(Continues)

TABLE 3 | (Continued)

Drug class	Generic name	Level of recommendation	Level of evidence	Frequency of AEs	Efficacy grade	Recommended dose
Calcium channel blocker	Lomerizine	Weak	B	Rare	2	10–20 mg
	Verapamil[a]	Weak	B	Rare–Occasional	2	80–240 mg
	Diltiazem[b]	Weak	B	Rare–Occasional	3	
	Nicardipine[b]	Weak	B	Rare–Occasional	3	
	Flunarizine (withdrawn in Japan)[c]		A	Frequent	4	
ARB/ACE-I	Candesartan[b]	Weak	B	Rare	2	8–12 mg
	Lisinopril[b]	Weak	B	Occasional	2	5–20 mg
	Enarapril[b]	Weak	C	Occasional	3	
	Olmesartan[b]	Weak	C	Occasional	3	
Others	Dihydergotamine (discontinued in Japan)[c]		A	Occasional	4	2–3 mg
	Methysergide[c]		A	Frequent	4	
	Onabotulinumtoxin A[b] (for CM)	Strong	A	Rare	1	
	Dimetotiazine	Weak	C	Rare	2	
	Feverfew	Weak	C	Rare	2	
	Magnesium preparetion[b]	Weak	C	Rare	2	
	Vitamin B2[b]	Weak	C	Rare	2	
	Tizanidine[b]	Weak	C	Rare	2	
	Melatonin[c]	Weak	C	Rare	4	
	Olanzapine[b]	Weak	C	Frequent	4	

Note: Levels of recommendation and evidence were determined according to the descriptions in the main text of this guideline. Recommended doses are based on evidence and consensus in Japan for adults. Efficacy grade: Group 1 (effective), Group 2 (somowhat effective), Group 3 (empirically effective), Group 4 (effective, though caution for adverse effects is required.), Group 5 (not effective). Those that have never been approved for any formulation or indication in Japan are indicated in italic.

Abbreviations: Ab, antibody; ACE-I, angiotensin-converting enzyme inhibitor; AE, adverse effect; ARB, angiotensin II receptor blocker; CM, chronic migraine; div, drip intraneous; im, intramuscular; iv, intravenous; sc, subcutaneous.

[a]Covered by health insurance in Japan for off-label use for migraine.

[b]Not covered by health insurance in Japan for migraine.

[c]Not available in Japan.

[d]Although the recommended dose in the attached document is 400–800 mg/day, this guideline recommends a dose of 400–600 mg/day as described in CQ3 of the preliminary version of the therapeutic guideline for the use of valproate in migraine treatment (https://www.jsnet.net/guideline_GL2023.html).

TABLE 4 | Efficacy grade grouping of migraine prophylactic drugs.

Group 1	Group 2	Group 3	Group 4	Group 5
Anti-CGRP Ab	**Antielipetitic drug**	**Antidepressant**	**Calcium channel blocker**	**Antiepileptic drug**
Galcanezumab	Gabapentin[b]	Nortriptyline[b]	Flunarizine[c] (withdrawn in Japan)	Clonazepam[b]
Fremanezumab	Levetiracetam[b]	Imipramine[b]	**Others**	Lamotrigine[b]
Eptinezumab[c]	**βblocker**	Clomipramine[b]	Dihydergotamine[c] (discontinued in Japan)	Carbamazepine[b]
Anti-CGRP receptor Ab	Metoprolol[b]	Torazodon[b]	*Methysergide*[c]	**Calcium channel blocker**
Erenumab	Atenolol[b]	Mianserin[b]	Melatonin[b]	Nifedipine[b]
CGRP receptor antagonist	Nadolol[b]	Fluvoxamine[b]	Olanzapine[b]	**βblocker**
Rimegepant[c]	**Antidepressant**	Paroxetine[b]		Acebutolol[b]
Atogepant[c]	*Fluoxetine*[c]	Sulpiride[b]		Pindolol[b]
Antiepileptic drug	**Calcium channel blocker**	Duloxetine[b]		Alprenolol[c]
Valproate	Lomerizine	**Calcium channel blocker**		Oxprenolol[c]
Topiramate[b]	Verapamil[a]	Diltiazem[b]		**Others**
βblocker	**ARB/ACE-I**	Nicardipine[b]		Clonidine[b]
Propranolol	Candesartan[b]	**ARB/ACE-I**		
Timolol[b]	Lisinopril[b]	Enarapril[b]		
Antidepressant	**Others**	Olmesartan[b]		
Amitriptyline[a]	Dimetotiazine			
Others	Feverfew			
Onabolinumtoxin A (for CM)[b]	Magnesium preparetions[b]			
	Vitamin B2[b]			
	Tizanidine[b]			

Note: Group 1 (effective), Group 2 (somowhat effective), Group 3 (empirically effective), Group 4 (effective, though caution for adverse effects is required.), Group 5 (not effective). Those that have never been approved for any formulation or indication in Japan are indicated in italics.
Abbreviations: Ab, antibody; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CM, chronic migraine.
[a]Covered by health insurance in Japan for off-label use for migraine.
[b]Not covered by health insurance in Japan for migraine.
[c]Not available in Japan.

- β blockers, such as propranolol
- Antiepileptic drugs, including valproate and topiramate*
- Antidepressants, such as amitriptyline**, selective serotonin reuptake inhibitors (SSRIs)**, and serotonin–noradrenaline reuptake inhibitors (SNRIs)*
- Calcium channel blockers, such as lomerizine
- Angiotensin-converting enzyme (ACE) inhibitors* and angiotensin II receptor blockers (ARBs)*
- CGRP-targeting drugs, including galcanezumab, fremanezumab, and erenumab

No gold-standard drug for preventing migraine exists. Therefore, clinicians should consider various factors, such as the patient's condition, headache characteristics, and comorbidities as well as the effectiveness and side effects of each drug. The effectiveness of migraine prophylaxis is commonly confirmed by a 50% or greater reduction in the frequency of attacks or number of migraine days.

As non-pharmacological prophylactic modalities, neuromodulation, cognitive behavioral therapy, and acupuncture may be considered.

* Not covered by health insurance in Japan.

** covered by health insurance in Japan for off-label use to treat migraine.

Weak recommendation.

Level of evidence: B.

4.18 | CQ II-3-4. How Should Clinicians Select a Specific Prophylactic Therapy for a Patient With Migraine?

4.18.1 | Recommendations

For preventive therapy, the recommendation is to start with a small dose of a drug that has scientifically proven effectiveness and a low risk of adverse events at a small dose. If no adverse events occur, the dose should be gradually increased, and therapeutic effectiveness should be evaluated over the first 2 to 3 months. If the drug is not effective at an adequate dose after this period, it should be switched to another. The choice of drug should be based on the patient's comorbid disorders and pregnancy status.

Weak recommendation.

Level of evidence: B.

4.19 | II-3-5. How Long Should Prophylactic Treatment for Migraine Be Continued?

4.19.1 | Recommendations

Determining the effectiveness of a prophylactic treatment of migraine takes at least 2 months. After confirming the effectiveness, the treatment is continued for at least 3 months, unless any adverse events occur. If well tolerated, the prophylactic treatment should be continued for 6 to 12 months. Once the migraine is well controlled, the dose of prophylactic treatment should be slowly tapered and, if feasible, discontinued.

Weak recommendation.

Level of evidence: B.

4.20 | CQ II-3-6. Are β Blockers, Including Propranolol, Effective in Preventing Migraine?

4.20.1 | Recommendations

β blockers (e.g., propranolol) are effective in preventing migraine attacks and their use is recommended as a first option for patients with migraine attacks that impact quality of life. Propranolol should be initiated at a dose of20 to 30 mg/day and, if ineffective, the dose should be increased to 60 mg/day. β blockers have the benefit of treating comorbid hypertension and coronary artery disease.

Strong recommendation.

Level of evidence: A.

4.21 | CQ II-3-7. Are Calcium Channel Blockers, Including Lomerizine, Effective in Preventing Migraines?

4.21.1 | Recommendations

The calcium channel blocker, lomerizine, is effective in preventing migraines; it is recommended as a prophylactic agent for patients whose migraine attacks interfere with their quality of life. The starting dose is 10 mg/day, which can be increased to 20 mg/day. Because of its excellent safety profile, the dosage can be increased until a sufficient effect is obtained.

Weak recommendation.

Level of evidence: B.

4.22 | CQ II-3-8. Are Angiotensin-Converting Enzyme Inhibitors, Including Lisinopril, and Angiotensin II Receptor Blockers, Including Candesartan, Effective in Preventing Migraines?

4.22.1 | Recommendations

ACE inhibitors, including lisinopril, and ARBs, including candesartan, are effective in preventing migraines with comorbid hypertension. Lisinopril should be started at 5 mg/day, with the dosage titrated up to 20 mg/day until migraine frequency can be sufficiently reduced. Candesartan should be administered at 8 mg/day.

Weak recommendation.

Level of evidence: B.

4.23 | CQ II-3-9. Are Antiepileptic Drugs Effective in Preventing Migraines?

4.23.1 | Recommendations

Oral administration of valproate and topiramate to patients with migraine who have two or more headache attacks per month is expected to reduce the number of attacks per month. However, valproate should not be used as a first-line option for women of child-bearing age because it is contraindicated during pregnancy. The use of other prophylactic agents should be preferred.

Valproate (Strong recommendation; Level of evidence: A).

Topiramate (Strong recommendation; Level of evidence: A).

4.24 | CQ II-3-10. Are Antidepressants, Including Amitriptyline, Effective in Preventing Migraines?

4.24.1 | Recommendations

Amitriptyline is one of the best studied medications for migraine prevention. This medication should be started at a low dose (5–10 mg/day) and titrated upward while monitoring its effect.

Strong recommendation.

Level of evidence: B.

4.25 | CQ II-3-11. Can Antidepressants (Selective Serotonin Reuptake Inhibitors/Serotonin–Noradrenaline Reuptake Inhibitors) and Triptans Be Administered Concurrently?

4.25.1 | Recommendations

Triptans and antidepressants (SSRI/SNRI) can be administered concomitantly. Caution is required for serotonin syndrome, but no clear evidence that concomitant use significantly increases the risk of developing this syndrome exists.

Weak recommendation.

Level of evidence: B.

4.26 | CQ II-3-12. Are Magnesium Preparations, Vitamin B2 (Riboflavin), Coenzyme Q10, Feverfew, and Analgesics Effective in Preventing Migraines?

4.26.1 | Recommendations

Magnesium preparations, vitamin B2 (riboflavin), coenzyme Q10, feverfew, and their combinations are expected to have some preventive effect on migraines. As these substances have no serious side effects and are inexpensive, they may be considered as options for migraine prophylaxis. Naproxen has been shown to have a significant preventive effect for migraine compared to placebo, but it should be used only for short-term prevention due to concerns about side effects and the risk of MOH.

Weak recommendation.

Level of evidence: C.

4.27 | CQ II-3-13. What Other Drugs Are Available for Migraine Prophylaxis?

4.27.1 | Recommendations

- **Dihydroergotamine** is used to prevent migraine in various countries but is currently unavailable in Japan. (Weak recommendation; Level of evidence: B)
- Anecdotal evidence suggests that melatonin may be beneficial for migraine prevention. However, of the limited number of randomized controlled trials (RCTs) that have been conducted, none have demonstrated any significant clinical benefit. Nonetheless, due to its safety profile, melatonin may be an option when other prophylactic therapies are ineffective. (Weak recommendation; Level of evidence: C)
- Despite limited evidence, administering olanzapine has been reported to be effective. This drug may be considered when other prophylactic therapies are ineffective, with caution for side effects. (Weak recommendation; Level of evidence: C)
- Only one randomized controlled trial involving orexin receptor antagonists has been conducted. This trial did not show that these drugs had clear efficacy in preventing migraine. However, some reports suggest potential benefits; orexin receptor antagonists may be considered when other prophylactic therapies are ineffective. (Weak recommendation; Level of evidence: C)
- **Dimetotiazine**, a serotonin and histamine antagonist, has shown efficacy in double-blind clinical studies, though no RCTs involving this antagonist have been conducted. As of September 2021, dimetotiazine is under consideration for approval as an over-the-counter medication and may be considered for migraine prophylaxis. (Weak recommendation; Level of evidence: C)

4.28 | CQ II-3-14. Are CGRP-Targeted Drugs (CGRP Receptor Antagonists, Anti-CGRP Antibodies, and Anti-CGRP Receptor Antibody) Effective in Preventing Migraines?

4.28.1 | Recommendations

Monoclonal antibodies against CGRP or its receptor have been demonstrated to be safe and efficacious for migraine prophylaxis in several large-scale randomized placebo-controlled double-blind clinical studies. They are now also approved in Japan. These medications have also been shown to be efficacious in cases refractory to preexisting preventive drugs.

The efficacy and safety of CGRP receptor antagonists in aborting and preventing migraines have been demonstrated in large-scale randomized placebo-controlled double-blind clinical studies. These medications are already approved as acute and preventive therapy outside Japan, but are still under development in Japan.

Strong recommendation.

Level of evidence: A.

4.29 | CQ II-3-15. Is Botulinum Neurotoxin Effective in Preventing Migraines?

4.29.1 | Recommendations

Botulinum neurotoxin type A (onabotulinum toxin A) has been shown to relieve symptoms associated with chronic migraine in placebo-controlled randomized double-blind clinical trials. Botulinum neurotoxin type A has been demonstrated to have similar efficacy to topiramate in treating patients with chronic migraine in randomized double-blind clinical trials. However, its efficacy for preventing episodic migraine is unclear. Hence, botulinum neurotoxin type A might be considered for preventing chronic migraine if other treatments prove ineffective.

However, it is not covered for the prevention by health insurance in Japan of chronic migraine.

Strong recommendation.

Level of evidence: A.

4.30 | CQ II-3-16. How Should Clinicians Diagnose and Treat Typical Migraine Aura Without Headache?

4.30.1 | Recommendations

1. Diagnosis:

   Diagnosis should be made according to the diagnostic criteria of the ICHD-3.

   Recommendation grade: N/A.

2. Treatment:

Although patients with migraine with aura have been shown to have an increased risk of ischemic stroke, the absolute number of cases is very small. No reports that migraine with typical aura without headache increases the risk of ischemic stroke exist. Therefore, proactive treatment is currently considered unnecessary. However, if frequent or prolonged attacks are experienced, migraine prophylaxis, especially with valproate or lomerizine, may be considered.

Weak recommendation.

Level of evidence: C.

4.31 | CQ II-3-17. How Should Chronic Migraine Be Treated?

4.31.1 | Recommendations

The mainstay of treatment for chronic migraine is prophylactic therapy. Appropriate prophylactic treatment (starting or adjusting the dose of migraine prophylaxis, switching or adding prophylaxis) should be offered and the use of acute medications minimized. Trigger avoidance, search for causes of chronicity, and treatment of comorbidity should be encouraged. Concurrent non-pharmacological therapy should also be considered.

Weak recommendation.

Level of evidence: B.

4.32 | CQ II-3-18. Is Neuromodulation Effective in Migraine Treatment?

4.32.1 | Recommendations

Noninvasive neuromodulation techniques, such as noninvasive vagal nerve stimulation (nVNS), external trigeminal nerve stimulation (eTNS), single-pulse transcranial magnetic stimulation (sTMS), external combined occipital and trigeminal neurostimulation (eCOT-NS), remote electrical neuromodulation (REN), and transcutaneous auricular vagus nerve stimulation, have been clinically applied for treating migraine in other countries. These techniques have proven to be relatively safe and effective for treating migraine; therefore, they offer an important option for migraine treatment. Noninvasive neuromodulation can be used either as monotherapy or in combination with conventional medications. These techniques are not currently covered by insurance in Japan.

Weak recommendation.

Level of evidence: A.

5 | Tension-Type Headache

5.1 | CQ III-4. How Should Tension-Type Headache Be Treated?

5.1.1 | Recommendations

Therapeutic measures vary depending on the type of tension-type headache. Infrequent episodic tension-type headaches are not usually treated. Treatment is indicated if frequent episodic and chronic tension-type headaches interfere with daily life. Therapy is divided into acute and prophylactic treatments, each consisting of pharmacological and non-pharmacological approaches. For acute treatment, caution should be taken to prevent MOH; for prophylactic treatment, monitoring should be undertaken for the development of side effects.

Strong recommendation.

Level of evidence: Individualized for each treatment.

5.2 | CQ III-5. What Types of Acute Treatment Are Available for Tension-Type Headache and How Should They Be Used?

5.2.1 | Recommendations

Pharmacotherapy plays a central role in the acute treatment of tension-type headache. The main therapeutic agents are acetaminophen and NSAIDs, both of which have proven efficacy. Little evidence regarding the choice of specific therapeutic drugs is available. When using acute-phase agents, consideration of the risk of MOH is essential. Specifically, avoiding the use of these medications for more than 2 to 3 days a week is critical.

Strong recommendation.

Level of evidence: Table 5.

TABLE 5 | Acute medications for tension-type headache.

Drug class	Generic name	Product name	Level of evidence	Recommended dose
Simple analgesic	Acetaminphen	Calonal	A	500–1000 mg
NSAID	Aspirin and dialuminate	Bufferin	A	500–1000 mg
	Mefenamic acid	Pontal	A	500 mg
	Loxoprofen[a]	Loxonin	A	60 mg
	Indomethacin farnesil[a]	Infree	A	200 mg
	Diclofenac[a]	Voltaren	A	12.5–50 mg
	Ibuorofen[b]	Brufen	A	100–200 mg
	Naproxen[b]	Naixan	A	100–300 mg
Combination analgesic	+ Caffeine[a]		B	65–200 mg (as caffeine)
Muscle relaxant	Tizanidine[a]	Ternelin	B	3–6 mg/day
Selective COX-2 inhibitor	Celecoxib[b]	Celecox	C	100–200 mg/day

[a]Covered by health insurance in Japan for off-label use for tension-type headache.
[b]Not covered by health insurance in Japan for off-label use for tension-type headache.

5.3 | CQ III-6. How Should Clinicians Offer Prophylactic Treatment for Tension-Type Headache?

5.3.1 | Recommendations

The prophylactic therapy of tension-type headache is divided into pharmacological and non-pharmacological treatments. Pharmacological treatment mainly involves antidepressants, whereas non-pharmacological treatment includes electromyography biofeedback therapy, cognitive behavioral therapy, relaxation techniques (such as exercises to relax the neck and occipital muscles), and acupuncture. Whether to continue or discontinue pharmacological treatment should be determined after 3 to 6 months. In contrast, no clear evidence regarding the appropriate therapeutic duration of non-pharmacological treatment is available.

Strong recommendation.

Level of evidence: Table 6.

5.4 | CQ III-7. Other Than Pharmacological Treatment, What Are the Types of Treatment for Tension-Type Headache?

5.4.1 | Recommendations

Non-pharmacological treatments for tension-type headache include psychotherapy, behavioral therapy, physical therapy, and acupuncture. These options should be considered when pharmacological treatment is contraindicated or used in combination with pharmacological treatments.

Weak recommendation.

Level of evidence: Individualized for each treatment, as follows.

① Psycho-behavioral therapy

- Electromyographic biofeedback (A)
- Cognitive behavioral therapy (mindfulness) (C)
- Relaxation training (C)
- Hypnotherapy (C)

② Physical therapy

- Exercise program (C)

*Exercise for relief of headache (B)

- Massage, neck acupressure
- Ultrasound and electrical stimulation
- Improvement of posture
- Oromandibular treatment
- Hot and cold packs

③ Acupuncture (C).

5.5 | CQ III-8. Is the Botulinus Toxin Effective in Preventing Tension-Type Headache?

5.5.1 | Recommendations

The efficacy of botulinum neurotoxin type A (BoNT-A) for tension-type headache has not been established. Most side effects associated with BoNT-A are due to its excessive pharmacological effects and are not severe. Currently, therefore, this agent should not be used, except in cases of chronic tension-type headache when other treatments have proven ineffective. Moreover, its use is not covered by insurance in Japan.

TABLE 6 | Prophylactic drugs for tension-type headache.

Drug class	Generic name	Product name	Level of evidence	Recommended dose (mg/day)
Antidepressant				
Tricyclic antidepressant	Amitriptyline[a]	Tryptanol	A	5–75
	Clomipramine[b]	Anafranil	B	75–150
Tetracyclic antidepressant	Maprotiline[b]	Ludiomil	B	75
	Mianserin[b]	Tetramide	B	30–60
NaSSA	Mirtazapine[b]	Remeron	B	30
SNRI	Venlafaxine[b]	Effexor SR	B	150
Antiepileptic drug	Topiramate[b]	Topina	C	50–200

Abbreviations: NaSSA, noradrenergic and specific serotonergic antidepressant; SNRI, serotonin noradrenaline reuptake inhibtor.
[a]Covered by health insurance in Japan for off-label use for tension-type headache.
[b]Not covered by health insurance in Japan for tension-type headache.

Weak recommendation.

Level of evidence: C.

6 | Cluster Headache

6.1 | CQ IV-6. What Drugs Are Available for Treating Cluster Headache Attacks During the Cluster Period, and How Effective Are They?

6.1.1 | Recommendations

- As regards triptans, subcutaneous injection of sumatriptan (3 mg; up to 6 mg/day) is covered by health insurance and recommended in Japan. (Strong recommendation; Level of evidence: A)
- The effectiveness of sumatriptan nasal spray (20 mg) and oral zolmitriptan (5 and 10 mg) has been demonstrated outside Japan, but these treatments are currently not covered by health insurance in Japan. Additionally, the effectiveness of intranasal administration of zolmitriptan has been demonstrated outside Japan. (Weak recommendation; Level of evidence: B)
- The effectiveness of oxygen inhalation is established. High-concentration oxygen is used, with oxygen administration via a side tube of a face mask at a flow rate of 7 L/min for 15 min recommended. (Strong recommendation; Level of evidence: A)
- Neuromodulation techniques, such as sphenopalatine ganglion stimulation and noninvasive vagus nerve stimulation, are clinically applied outside Japan but not yet available in Japan. (Weak recommendation; Level of evidence: C)
- The efficacy of the somatostatin analog, octreotide, has been reported in a clinical trial conducted outside Japan, but this treatment is not currently covered by health insurance in Japan. The effectiveness of lidocaine, cocaine, dihydroergotamine (discontinued in Japan), and NSAIDs has not been established. (Weak recommendation; Level of evidence: C)

6.2 | CQ IV-7. How Should Home Oxygen Therapy for Cluster Headache Be Implemented?

6.2.1 | Recommendations

Oxygen inhalation via the side tube of a face mask at a flow rate of 7 L/min (> 90% oxygen) for 15 min is effective in aborting acute attacks of cluster headache. In Japan, both oxygen concentrators and liquid oxygen devices are approved for home oxygen therapy (HOT). Considering their advantages and disadvantages, an oxygen supply device that is best suited to the patient's daily needs should be selected. Physicians prescribing HOT must provide sufficient information to patients and their families on procedures for oxygen administration, emergency protocols, and fire safety measures.

Strong recommendation.

Level of evidence: A.

6.3 | CQ IV-8. What Prophylactic Treatments Are Available for Cluster Headache Attacks During the Cluster Period, and How Effective Are They?

6.3.1 | Recommendations

- **Prophylactic treatments common to episodic and chronic cluster headaches**
- Among the calcium channel blockers, verapamil 360 mg/day has shown a prophylactic effect for cluster headache in studies conducted outside Japan. However, adverse events, such as bradycardia and heart failure due to atrioventricular conduction disturbance, have been reported. In Japan, off-label use of verapamil is permitted for cluster headache, but the maximum dose is 240 mg/day. Based on results obtained in clinical trials, lomerizine is expected to exert mild

prophylactic effects, but—as of September 2021—it is not covered by insurance in Japan. (Weak recommendation; Level of evidence: B)

- Short-term use of steroids is considered to exert relatively rapid action in alleviating cluster headache attacks, but the evidence is unclear. However, prednisone in combination with verapamil has been demonstrated to have a short-term prophylactic effect. (Weak recommendation; Level of evidence: C)
- Short-term oral administration of ergotamine tartrate (1–2 mg) before bedtime may be effective in preventing cluster headache attacks. (Weak recommendation; Level of evidence: C)
- Suboccipital steroid injection has been reported to show a prophylactic effect of cluster headache. (Weak recommendation; Level of evidence: C)
- Melatonin and lithium carbonate have been reported to be effective in RCTs for cluster headache prophylaxis. (Weak recommendation; Level of evidence: C)
- **Prophylactic treatments for episodic cluster headache**
- Intranasal application of civamide (similar to capsaicin) has been reported to be efficacious in a study conducted outside Japan, but no clinical trials have been conducted in Japan. (Weak recommendation; Level of evidence: C)
- Subcutaneous injection of galcanezumab is used in the United States, but no clinical trials have been conducted in Japan. The European Medicines Agency has not approved its use. (Weak recommendation; Level of evidence: A)
- **Other prophylactic treatments**
- Gabapentin, topiramate, divalproex, baclofen, etc. have been reported to be effective for prophylaxis of cluster headache, but no evidence has been established. In cases in which pharmacotherapy is ineffective, nerve block therapy or nerve resection may be performed. These treatments include trigeminal nerve block, stellate ganglion block, sphenopalatine ganglion block, greater occipital nerve block, trigeminal nerve root resection, sphenopalatine ganglion resection, and gamma knife treatment. However, evidence supporting the efficacy of gamma knife treatment remains unestablished. (Weak recommendation; Level of evidence: C)

7 | Medication-Overuse Headache

7.1 | CQ VI-3. How Should Medication-Overuse Headache Be Managed, and What Is Its Prognosis?

7.1.1 | Recommendations

MOH is considered preventable: Educating patients about the causal relationship between the overuse of acute medications and the progression of headache associated with MOH is important. The principles of MOH management include (1) discontinuation of inciting medications, (2) management of headache after medication withdrawal, and (3) prophylactic therapy. CGRP-targeting antibodies have been reported to be effective for chronic migraine patients with medication overuse. Discontinuation of inciting medications in an outpatient setting is recommended. Although adequate counseling alone can ameliorate the condition, hospitalization may be required in severe cases.

MOH recurs within 1 year in approximately 30% of cases. Ongoing counseling should be provided after drug withdrawal. Patients are encouraged to maintain a headache diary to help treating physicians monitor the frequency of triptan, ergotamine, and analgesic use.

Weak recommendation.

Level of evidence: B.

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Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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