Original Article

Headache Pain Res 2025;26(1):5-20
pISSN: 3022-9057 · eISSN: 3022-4764
https://doi.org/10.62087/hpr.2024.0019

Headache and Pain Research

Evidence-Based Recommendations on Pharmacologic Treatment for Migraine Prevention: A Clinical Practice Guideline from the Korean Headache Society

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Abstract

Purpose: The aim of this clinical practice guideline (CPG) from the Korean Headache Society is to provide evidence-based recommendations on the pharmacologic treatment for migraine prevention in adult migraine patients.

Methods: The present CPG was developed based on the guideline adaptation methodology through a comprehensive systematic search for literature published between January 2012 and July 2020. The overall quality of the CPGs was assessed using the Korean version of the Appraisal of Guidelines for Research and Evaluation II tool. High-quality CPGs were adapted to make key recommendations in terms of strength (strong or weak) and direction (for or against).

Results: The authors selected nine available high-quality guidelines throughout the process of assessment of quality. Regarding oral migraine preventive medications, propranolol, metoprolol, flunarizine, sodium divalproex, and valproic acid are recommended to adult patients with episodic migraines based on high-quality evidence ("strong for"). Topiramate can be recommended for either episodic or chronic migraine ("strong for"). For migraine prevention using calcitonin gene-related peptide monoclonal antibodies, galcanezumab, fremanezumab, erenumab, and eptinezumab are recommended for adult patients with either episodic or chronic migraine on the basis of high-quality evidence ("strong for"). OnabotulinumtoxinA is recommended for adult patients with chronic migraine based on high-quality evidence ("strong for"). Last, frovatriptan, naratriptan, and zolmitriptan are recommended for short-term prevention in women with menstrual migraine ("strong for").

Conclusion: In the present CPG, the authors provide specific, straightforward, and easy-to-implement evidence-based recommendations for pharmacologic migraine prevention. Nevertheless, these recommendations should be applied in real-world clinical practice based on optimal individualization.

Keywords: Appraisal of Guidelines for Research and Evaluation II, Calcitonin gene-related peptide, Guideline, Migraine, Prevention

Received: June 23, 2024; **Revised:** September 4, 2024; **Accepted:** September 11, 2024

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INTRODUCTION

Migraine is a common cycling brain disorder that can be characterized of recurrent episodic disabling headache attacks.[1] Migraine affects an estimated more than 12% of the population worldwide, and the prevalence of migraine in Korea was estimated to be 6% (3% in men and 9% in women).[2,3] Since the prevalence of migraine is highest amongst individuals aged 20 to 50, migraine attacks can result in headache-related disability and negative impact on social and occupational function in daily lives, particularly in young and middle-aged population.[4]

For a subset of migraineurs, episodic migraine (EM) attacks may be more frequent over time, which can substantially increase the burden of migraine. In terms of the frequency of monthly migraine days (MMDs) and monthly headache days (MHDs), migraine diagnosis can be conceptualized and subdivided into EM and chronic migraine (CM) as a disease spectrum.[5] CM is defined as having ≥8 MMDs and ≥15 MHDs for at least 3 months, while EM having <15 MHDs. CM and EM patients with frequent headaches generally require preventive therapy to reduce the frequency, duration, or severity of migraine attacks and to reinforce the efficacy of acute (abortive) therapy. Successful preventive therapy reportedly has potential to improve quality of life and reduce migraine-related medical cost.

The purpose of this clinical practice guideline (CPG) is globally to provide evidence-based recommendations on pharmacologic treatment for migraine prevention to guide clinicians treating patients with EM, CM, and menstrual migraine and pregnant women. The CPG committee of the Korean Headache Society (KHS) recommends that migraine prevention based on the recommendations of this CPG should be cooperatively determined by healthcare providers and patients.

MATERIALS AND METHODS

1. Design and participants

The present CPG was based on guideline adaptation methodology and developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[6] The development working group (DWG) in the CPG Committee of the KHS included 16 neurologists who had specialty and interest in headache disorders and one KHS guideline methodologist. The members of DWG developed key question (KQ) that were clinically essential for migraine prevention in patients with EM, CM, and menstrual migraine, using the framework of Patient; Intervention; Comparison and Outcome (PICO) question.[7] The CPG oversight committee approved the composition of the working group and development of evidence-based recommendations with respect to the PICO KQs. All CPG committee members were required to disclose any conflict of interest that may potentially affect their participation and work. The DWG members have regularly communicated using e-mail and online conference during the CPG development period.

2. Patient; Intervention; Comparison and Outcome key questions

First, the DWG set the patient as adult patients with migraine (EM, CM, pregnancy, and menstrual migraine). Next, regarding the intervention and comparison, a systematic review of literature aimed to focus on pharmacologic treatments for migraine prophylaxis. Non-pharmacologic treatments and neuromodulation were not considered for intervention. The migraine prophylactics selected were as follows: beta-blockers (KQ 3), calcium channel blockers (KQ 4), angiotensin receptor blockers (KQ 5), angiotensin-converting enzyme inhibitors (KQ 5), antidepressants (KQ 6), antiseizure medications (KQ 7 and 9), calcitonin gene-related peptide (CGRP) monoclonal antibodies (mAbs) (KQ 8 and 12), botulinum toxin (KQ 11), and triptans (KQ 14). Last, outcome was determined by clinical improvement, in terms of reduction of number of MMDs, MHDs, and menstrual migraine days and proportions of 50% reduction of MMDs and/or MHDs. In this regard, the DWG discussed and settle search terms for each KQ. Consequently, the DWG proposed 16 PICO KQs related to pharmacologic treatment of EM, CM, and menstrual migraine. The CPG oversight committee reviewed the proposed PICO KQs. Then, these were revised according to advice from the CPG oversight committee. Finally, the PICO KQs were approved by the CPG oversight committee.

3. Search and selection of literature

The KHS guideline methodologist conducted comprehensive search for the systematic review of literature to answer the KQs (Figure 1). Based on the fact that the American Headache Society (AHS) and American Academy of Neurology (AAN) jointly published CPGs on migraine prevention in 2012, we searched literature published between January 1, 2012, and July 1, 2020, throughout databases (Guideline international network, Ovid MEDLINE/EMBASE, Cochrane library, and KoreaMed), using the key search terms migraine, prevention, prophylaxis, and treatment. The literature search process was conducted separately for each KQ using a search equation that included the relevant prophylactic agent. We considered only studies involving adult patients (>18 years) with the full article available in English. Two or more DWG members assigned to each KQ independently screened titles and abstracts from the primary literature identification. All disagreements were discussed between the two members or by a third DWG member to reach a consensus. If we could not find an answer to the KQs in the guidelines, we tried to answer the KQs through discover new evidence with recency search of systematic reviews, meta-analyses, and randomized controlled trials (RCTs). Likewise, if we could not find an answer again, we searched and reviewed non-RCT, cohort study, case-control study, case series (single arm before-after study), cross-sectional study, case report, and expert opinion.

Of the guidelines and studies retrieved, the following selection criteria were applied for inclusion in quality assessment of evidence: 1. included PICOs that aligned with the KQs; 2. were peer-reviewed; 3. were published in English; 4. used evidence-based methodology; and 5. were published after 2012. Subsequently, a total of 19 guidelines that met the inclusion criteria were retrieved during the comprehensive literature search.[8-26]

4. Analysis of evidence and recommendations

Regarding assessment of quality of those guidelines, two DWG members were assigned to each guideline, and they independently rated the score of each retrieved guideline using the Appraisal of Guidelines for Research and Evaluation (AGREE) II framework.[27,28] AGREE II consists of 23 items in six domains and two overall assessments. Consequently, of the 19 guidelines, we excluded 10 guidelines that scored less than 60% in the domain 3. Rigour of development (Table 1).

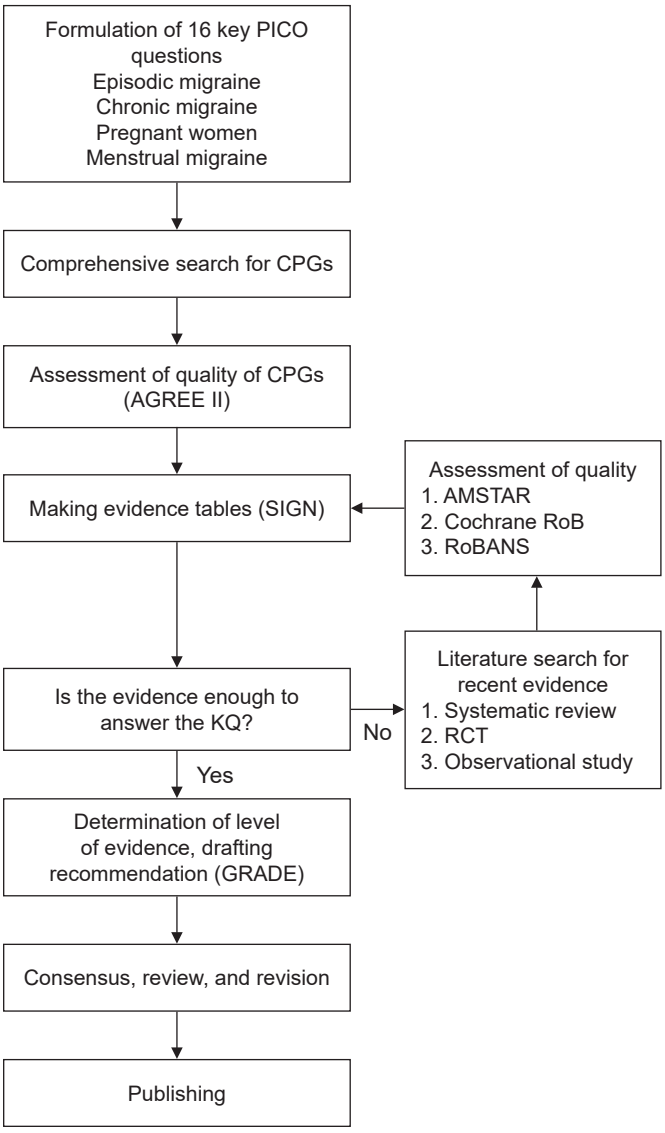

Figure 1. Flowchart of the development of this clinical practice guideline on pharmacologic treatment for migraine prevention.
PICO, Patient; Intervention; Comparison and Outcome; CPG, clinical practice guideline; AGREE II, Appraisal of Guidelines for Research and Evaluation II; SIGN, Scottish Intercollegiate Guidelines Network; KQ, key question; GRADE, Grading of Recommendations Assessment, Development and Evaluation; AMSTAR, A MeaSurement Tool to Assess systematic Reviews; RoB, risk of bias in randomized trials; RoBANS, Risk of Bias Assessment Tool for Nonrandomized Studies; RCT, randomized controlled trial.

Table 1. Quality assessment of clinical practice guidelines on migraine prevention using the AGREE II framework

Clinical practice guideline	Domain 1: Scope and purpose	Domain 2: Stakeholder involvement	Domain 3: Rigour of development	Domain 4: Clarity of presentation	Domain 5: Applicability	Domain 6: Editorial independence	Overall assessment
2012 AHS/AAN[8]	94.4	77.8	88.5	91.7	79.2	100.0	87.5
2012 Canadian Headache Society[9]	100.0	94.4	96.9	100.0	91.7	100.0	95.8
2012 Croatian Medical Association[10]	52.8	47.2	32.3*	69.4	14.6	0.0	66.7
2012 Danish Headache Society[11]	91.7	66.7	24.0*	75.0	20.8	100.0	58.3
2012 SFEMC[12]	77.8	77.8	76.0	91.7	43.8	87.5	83.3
2012 SISC[13]	63.9	55.6	60.4	88.9	31.3	66.7	75.0
2013 ICSI[14]	94.4	86.1	90.6	86.1	64.6	95.8	95.8
2015 NICE[15]	50.0	50.0	31.3*	72.2	16.7	0.0	41.7
2016 AAN[16]	80.6	44.4	41.7*	50.0	0.0	100.0	70.8
2019 AHS[17]	63.9	63.9	46.9*	69.4	45.8	45.8	54.2
2017 RSSHA[18]	61.1	52.8	34.4*	47.2	50.0	58.3	33.3
2020 EAN[19]	97.2	58.3	74.0	97.2	45.8	83.3	66.7
2019 EHF[20]	97.2	61.1	81.3	94.4	50.0	66.7	75.0
2019 Spanish Society of Neurology[21]	16.7	22.2	7.3*	13.9	16.7	66.7	41.7
2015 Alberta, Canada[22]	66.7	44.4	51.0*	75.0	25.0	87.5	37.5
2018 EHF[23]	77.8	52.8	62.5	72.2	37.5	54.2	79.2
2018 EMA/EHF[24]	61.1	61.1	40.6*	52.8	54.2	79.2	62.5
2013 Latin American and Brazilian Headache Societies[25]	66.7	44.4	35.4*	61.1	16.7	50.0	58.3
2018 SIGN[26]	100.0	77.8	93.8	100.0	58.3	75.0	83.3

Values are average scores independently rated rated by two development working members using the AGREE II framework.
AGREE, Appraisal of Guidelines for Research and Evaluation; AHS, American Headache Society; AAN, American Academy of Neurology; SFEMC, French Society for the Study of Migraine Headache; SISC, Italian Society for the Study of Headaches; ICSI, Institute for Clinical Systems Improvement; NICE, National Institute for Health and Care Excellence; RSSHA, Russian Society for the Study of Headache; EAN, European Academy of Neurology; EHF, European Headache Federation; EMA, European Medicines Agency; SIGN, Scottish Intercollegiate Guidelines Network.
*Guidelines that scored less than 60% in the domain 3. Rigour of development were excluded.

For each KQ, relevant studies were evaluated in terms of level of evidence (LOE). In this regard, we used the grading of the Agency for Healthcare Research and Quality, with modifications, to define levels of evidence as follows: LOE I, evidence obtained from meta-analysis or at least one RCT; LOE II, evidence obtained from at least one well-designed controlled study without randomization, or at least one other type of well-designed quasi-experimental study; LOE III: evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies; and LOE IV, evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.[29]

Two or more DWG members drafted guidelines for each PICO KQ. In this guideline, evidence-based recommendation was proposed in terms of strength (strong or weak) and direction (for or against) according to the GRADE methodology.[30] This strength of recommendation (SOR) was determined on basis of quality of evidence, balance scale between desirable and undesirable effects, values and preferences, and resources (costs).

All DWG members reviewed the guideline document. They made consensus according to the Delphi method. The guideline was verified by external panels (2 family physicians, 1 urologist, 1 anesthesiologist, 1 nurse, and 1 pharmacist).

RESULTS

1. Key question 1. What factors should be considered for migraine prevention in adult patients with episodic migraine?

1) Analysis of evidence

The recommendations related to this KQ in existing guidelines are all based on expert consensus, which means that the LOE is low and clinical studies are difficult to conduct.[9,12-14,17,26]

Existing guidelines summarize the important associated factors to consider when initiating migraine prevention for adult patients with EM: (1) headache frequency, (2) headache intensity, (3) effectiveness of acute migraine treatment. In addition, (4) the patient's personal preferences and (5) the physician's individual judgment may also play a role in the decision to initiate migraine prevention. In particular, migraine prevention should be initiated when there is a high risk of migraine chronification, (6) when they experience frequent or incremental frequency of migraine attacks, and (7) when they have comorbid medication overuse headache (MOH). Migraine prevention may also be considered even if the frequency of migraine attacks is low, (8) the effectiveness of migraine acute treatment is insufficient, or (9) migraine patients have contraindications to acute migraine treatment that preclude the use of acute migraine treatment. Lastly, migraine prevention may also be considered in (10) some patients whose migraines are accompanied by neurologic disorders, such as migraine with brainstem aura or hemiplegic migraine.

2) Recommendation

- Migraine prevention is recommended for patients with migraine who experience meaningful disability from migraine despite adequate attempts at lifestyle modification and acute migraine treatment (LOE: IV, SOR: Strong for).
- Migraine prevention is recommended for migraine patient (1) if acute migraine treatment does not effectively treat migraine or if they experience migraine-related disability, even if the headache frequency is low, or (2) if acute migraine treatment is effective but the headache frequency is frequent (LOE: IV, SOR: Strong for).
- If migraine patient uses acute migraine medications more than 10 to 15 days per month, migraine prevention is recommended due to the risk of development of MOH (LOE: IV, SOR: Strong for).
- Migraine prevention may be considered if the migraine patient prefers it, regardless of headache frequency, or if the physician determines that migraine prevention is clinically indicated (LOE: IV, SOR: Weak for).
- Migraine prevention may be considered if migraine patient has a medical contraindication to acute migraine treatment (LOE: IV, SOR: Weak for).

2. Key question 2. How should discontinuation of migraine prevention be decided in adult migraine patients?

1) Analysis of evidence

In line with the KQ 1, existing guidelines provide recommendations for discontinuation of migraine prevention based on expert opinion and are similarly worded.[9,12,14,17,26] To determine the efficacy of migraine prevention of specific medication, guidelines recommend trying the optimal or maximum tolerated dose for at least 2–3 months or 8 weeks.

The effectiveness of migraine prevention is considered significant if it reduces the frequency of migraine episodes by 50% or more. Even if migraine prevention does not significantly reduce the frequency of migraine episodes, it may be continued for a period of time and then slowly tapered and discontinued if there are clinical findings of reduced migraine-related disability, reduced pain intensity or duration, or improved response to acute migraine treatment. Guidelines recommend that migraine preventive medications be maintained for 6 months to 1 year. In addition, it is consistently recommended that the effectiveness of migraine preventive medications should be determined solely by patient. In this regard, guidelines also emphasize the significance of keeping a headache diary during migraine prevention.

2) Recommendation

- The efficacy of migraine prevention in adult patients with migraine can only be determined after at least 2 months of use at the optimal or maximal tolerable dose (LOE: IV, SOR: Weak for).
- If migraine prevention is effective, it may be continued for at least 3 months before a dose reduction or discon-

tinuation is attempted. The duration of migraine prevention is individualized for each patient, depending on the frequency and intensity of headaches and the impact of migraine on daily life (LOE: IV, SOR: Weak for).
- If migraine frequency increases after tapering or discontinuation of migraine preventive medication, consider increasing or restarting medication dose (LOE: IV, SOR: Weak for).
- Keeping a headache diary is recommended to assess efficacy, side effects, and adherence to migraine prevention and to determine the duration of maintenance (LOE: IV, SOR: Strong for).

3. Key question 3. Are beta-blockers effective in relieving headache compared to other drugs, placebo, or no treatment in adults with episodic migraine?

1) Analysis of evidence

Propranolol has been recommended as effective for migraine prevention in all guidelines to date.[8,9,12-14,26] In particular, propranolol and metoprolol are strongly recommended in most guidelines for migraine prophylaxis based on the highest LOE. Atenolol and nadolol, on the other hand, are rated as weakly recommended in most guidelines with moderate quality evidence. In a recent meta-analysis, propranolol was reported to reduce the number of headache days per month by 1.5 days at 8 weeks (95% confidence interval [95% CI], –2.3 to –0.65), and to reduce headache frequency by 50% at 12 weeks (relative risk, 1.4; 95% CI, 1.1– 1.7).[31]

2) Recommendation

- Propranolol is recommended for use as migraine prevention in adult patients with EM (LOE: I, SOR: Strong for).
- Metoprolol is recommended for use as migraine prevention in adult patients with EM (LOE: I, SOR: Strong for).
- Atenolol may be considered for use as migraine prevention in adult patients with EM (LOE: II, SOR: Weak for).
- Nadolol may be considered for use as migraine prevention in adult patients with EM (LOE: II, SOR: Weak for).
- Nebivolol may be considered for use as migraine prevention in adult patients with EM (LOE: II, SOR: Weak for).

4. Key question 4. Are calcium channel-blockers effective in relieving headache compared to other drugs, placebo, or no treatment in adults with episodic migraine?

1) Analysis of evidence

Flunarizine is not marketed in the United States and was not evaluated in the 2012 AHS/AAN guideline, but is recommended for use in migraine prevention guidelines in many other countries.[9,11-13,26] The recommendation for flunarizine for migraine prevention is strongly recommended in Italy and Scotland, and weakly recommended in Canada. Calcium channel blockers other than flunarizine were not included in many guidelines, with cinnarizine, nicardipine, and verapamil each receiving a recommendation rating in one or two guidelines. Nimodipine and nifedipine were only reviewed by the AHS and rated as insufficient evidence. In a 2015 meta-analysis, flunarizine's effectiveness versus placebo in episodic migraine prevention was demonstrated at 8 and 12 weeks (standardized mean difference: –0.60 [95% CI, –1.20 to 0.00]; –0.84 [–1.34 to –0.34]), but not at 4 weeks (standardized mean difference: –0.27 [–0.76 to 0.23]).[32] However, a recently published meta-analysis demonstrated the effectiveness of migraine prevention of flunarizine even at 4 weeks.[33] In an analysis of 5 placebo-controlled studies out of a total of 25 clinical studies, flunarizine reduced migraine attacks by 0.4 migraine attacks per week more than placebo when taken for 4 weeks (mean difference: 95% CI, –0.61 to –0.26), with a response rate 8.86 times higher than placebo (95% CI, 3.57–22.0).

2) Recommendation

- Flunarizine is recommended for use as migraine prevention in adult patients with EM (LOE: I, SOR: Strong for).
- Cinnarizine may be considered for use as migraine prevention in adult patients with EM (LOE: IV, SOR: Weak for).
- Verapamil, nicardipine, nifedipine, and nimodipine are not recommended for use as migraine prevention in adult patients with EM (LOE: I, SOR: Strong against).

5. Key question 5. Are angiotensin receptor blockers or angiotensin-converting enzyme inhibitors effective in relieving headache compared to other drugs, placebo, or no treatment in adults with episodic migraine?

1) Analysis of evidence

Candesartan and lisinopril are recommended in existing migraine prevention guidelines based on weak evidence.[8,9,12,13,17,26] Telmisartan is not recommended for use (the 2012 AHS/AAN guideline) or is not included as a recommended agent in most guidelines.

2) Recommendation

- Candesartan may be considered for use as migraine prevention in adult patients with EM (LOE: I, SOR: Weak for).
- Lisinopril may be considered for use as migraine prevention in adult patients with EM (LOE: IV, SOR: Weak for).
- Telmisartan is not recommended for use as migraine prevention in adult patients with EM (LOE: I, SOR: Strong against).

6. Key question 6. Are antidepressants effective in relieving headache compared to other drugs, placebo, or no treatment in adults with episodic migraine?

1) Analysis of evidence

Previous guidelines suggested various antidepressants with varying levels of recommendation.[8,9,12-14,17,26] In particular, amitriptyline is highly recommended in most guidelines for migraine prevention. Venlafaxine is recommended as a low-grade recommendation due to its relatively low quality of evidence. Nortriptyline was only recommended with a low recommendation in the 2013 Institute for Clinical Systems Improvement guideline. Fluoxetine is not recommended or included as a recommended agent due to conflicting studies.

2) Recommendation

- Amitriptyline is recommended for use as migraine prevention in adult patients with EM (LOE: II, SOR: Strong for).
- Nortriptyline may be considered for use as migraine prevention in adult patients with EM (LOE: III, SOR: Weak for).
- Venlafaxine may be considered for use as migraine prevention in adult patients with EM (LOE: II, SOR: Weak for).
- Fluoxetine may not be recommended for use as migraine prevention in adult patients with EM (LOE: II, SOR: Weak against).

7. Key question 7. Are antiseizure medications effective in relieving headache compared to other drugs, placebo, or no treatment in adults with episodic migraine?

1) Analysis of evidence

Topiramate was highly recommended in all migraine prevention guidelines based on a strong LOE.[8,9,12-14,17,26] Valproic acid was also recommended in most guidelines based on higher levels of evidence. Gabapentin has a low LOE and conflicting recommendations in the guidelines. Levetiracetam and zonisamide have somewhat lower levels of evidence or were not mentioned in most guidelines. However, recent systematic reviews and meta-analyses have shown that levetiracetam effectively reduced the frequency of episodic migraine.[34,35] Levetiracetam should be used with caution due to side effects such as drowsiness and psychotic symptoms. Zonisamide was not cited in published guideline recommendations, but RCTs have shown it to be effective in preventing migraine.[36] No studies have compared zonisamide to placebo, but studies have compared it to topiramate and valproic acid.[37]

2) Recommendation

- Topiramate is recommended for use as migraine prevention in adult patients with EM (LOE: I, SOR: Strong for).
- Sodium divalproex and valproic acid are recommended for use as migraine prevention in adult patients with EM (LOE: I, SOR: Strong for).
- Levetiracetam may be considered for use as migraine prevention in adult patients with EM (LOE: I, SOR: Weak for).
- Zonisamide may be considered for use as migraine prevention in adult patients with EM (LOE: II, SOR: Weak for).
- Gabapentin may not be recommended for use as migraine prevention in adult patients with EM (LOE: II, SOR: Weak against).

3) Additional consideration

Divalproex sodium and valproic acid should be used with caution in women of childbearing potential due to the risk of teratogenicity, including neural tube defects, and are contraindicated in pregnant patients. In addition, divalproex sodium and valproic acid may be restricted in women due to side effects such as weight gain and polycystic ovary syndrome.

8. Key question 8. Are calcitonin gene-related peptide monoclonal antibodies effective in relieving headache compared to other drugs, placebo, or no treatment in adults with episodic migraine?

1) Analysis of evidence

Despite the fact that activation of the trigeminal neurovascular system is an important mechanism in the pathophysiology of migraine pain and that CGRP is the most important neurotransmitter involved in this activation, no specific drugs had been developed to prevent migraine.[17] Since late 2018, four mAbs targeting CGRP itself or its receptor have been approved by the U.S. Food and Drug Administration. These are erenumab, a mAb against the CGRP receptor, and fremanezumab, galcanezumab, and eptinezumab, mAbs against the CGRP ligand, and are the first preventive medications to be developed based on the specific mechanism of migraine. These agents have been shown to be effective, safe, and well-tolerated in well-designed clinical studies and are highly anticipated as preventive medications for CM as well as EM.[1] CGRP mAbs are a recently established class of agents that are not included in the majority of previously published guidelines and are only included in guidelines published after 2019. The European Headache Federation (EHF) guideline suggested that galcanezumab, fremanezumab, and erenumab were strongly recommended based on moderate to high quality evidence, while eptinezumab was moderately recommended based on low quality evidence.[20] After the publication of the EHF guideline, the results of an RCT of eptinezumab were published, confirming the efficacy and safety of this prophylactic treatment for EM.[38] Subsequently published meta-analyses confirmed the effectiveness and safety of CGRP mAbs compared to placebo, particularly for the only intravenously administered agent, eptinezumab.[39-43]

2) Recommendation

- Galcanezumab is recommended for use as migraine prevention in adult patients with EM (LOE: I, SOR: Strong for).
- Fremanezumab is recommended for use as migraine prevention in adult patients with EM (LOE: I, SOR: Strong for).
- Erenumab is recommended for use as migraine prevention in adult patients with EM (LOE: I, SOR: Strong for).
- Eptinezumab is recommended for use as migraine prevention in adult patients with EM (LOE: I, SOR: Strong for).

9. Key question 9. Are antiseizure medications effective in relieving headache compared to other drugs, placebo, or no treatment in adults with chronic migraine?

1) Analysis of evidence

Topiramate has the highest LOE for oral migraine preventive medication of CM, with proven effectiveness in the CM patients with or without comorbid MOH.[13,19,26] Other antiseizure medications of choice for the prevention of CM include sodium valproate and gabapentin, but the quality of evidence is low. Antiseizure medications used to prevent migraines are generally effective at lower doses than those used for anticonvulsants. Topiramate has been shown to be an effective prophylactic agent in the prophylaxis of CM in two RCTs in patients with CM and has been accepted as an effective prophylactic agent in CM with MOH. Valproic acid has relatively limited research in CM. In an RCT of patients with chronic daily headache, including CM, sodium valproate 500 mg twice daily improved headache frequency and intensity, with more improvement in the CM group than in the chronic tension-type headache group.

2) Recommendation

- Topiramate is recommended for use as migraine prevention in adult patients with CM (LOE: I, SOR: Strong for).
- Sodium divalproex and valproic acid may be considered for use as migraine prevention in adult patients with CM (LOE: II, SOR: Weak for).

3) Additional consideration

Divalproex sodium and valproic acid should be used with

caution in women of childbearing potential due to the risk of teratogenicity, including neural tube defects, and are contraindicated in pregnant patients. In addition, divalproex sodium and valproic acid may be restricted in women due to side effects such as weight gain and polycystic ovary syndrome.

10. Key question 10. Are beta-blockers, calcium channel-blockers, angiotensin receptor blockers, or antidepressants effective in relieving headache compared to other drugs, placebo, or no treatment in adults with chronic migraine?

1) Analysis of evidence

There is very limited research on preventive medications in CM patients. Furthermore, even when studies include patients with CM, chronic daily migraine, and mixed (chronic+episodic) migraine, the only medications studied are beta-blockers and antidepressants. However, even for these agents, the evidence is lacking, as there are no well-designed RCTs.

2) Recommendation

- Because EM and CM are on the same spectrum, clinicians may consider selecting agents based on the level of recommendation for EM, assuming that preventive agents that are effective in EM will also be effective in CM. (LOE: IV, SOR: Weak for).

11. Key question 11. Is onabotulinumtoxinA effective in relieving headache compared to other drugs, placebo, or no treatment in adults with chronic migraine?

1) Analysis of evidence

OnabotulinumtoxinA has been shown to be effective in the preventive treatment of CM.[17,23,26] In an RCT (PREEMPT I), there was no significant difference in headache frequency between the onabotulinumtoxinA and placebo groups, but there was a significant reduction in headache days and migraine days. In another RCT (PREEMPT II), onabotulinumtoxinA reduced the total number of headache days compared to placebo, and also significantly reduced the number of migraine days, severe headache days, and the total number of hours of headache per month, the proportion of patients with severe Headache impact test-6 scores, and the frequency of headache attacks. OnabotulinumtoxinA also significantly reduced disability and significantly improved quality of life compared to placebo. OnabotulinumtoxinA has the disadvantage of having to be injected in multiple areas, and the side effects of having some injections in the facial area. However, it is an effective preventive treatment that can be used when oral migraine preventive medications are not tolerated due to side effects or when oral migraine preventive medications are insufficiently effective.

2) Recommendation

- OnabotulinumtoxinA is recommended for use as migraine prevention in adult patients with CM (LOE: I, SOR: Strong for).

12. Key question 12. Are calcitonin gene-related peptide monoclonal antibodies effective in relieving headache compared to other drugs, placebo, or no treatment in adults with chronic migraine?

1) Analysis of evidence

The use of CGRP mAbs in patients with CM was recommended by the AHS statement and recommended in the 2019 EHF guideline.[17,20] The EHF guideline states that CGRP mAbs for the prophylaxis of CM is effective and safe based on the results of four RCTs of galcanezumab, fremanezumab, and erenumab. Subsequently published meta-analyses have also shown supportive results for preventive effectiveness in CM.[44] Following the publication of the EHF guideline, the results of an RCT of the remaining CGRP monoclonal antibody, eptinezumab, were published, confirming the efficacy and safety of prophylactic treatment for CM.[45]

2) Recommendation

- Galcanezumab is recommended for use as migraine prevention in adult patients with CM (LOE: I, SOR: Strong for).
- Fremanezumab is recommended for use as migraine prevention in adult patients with CM (LOE: I, SOR: Strong for).
- Erenumab is recommended for use as migraine prevention in adult patients with CM (LOE: I, SOR: Strong for).

- Eptinezumab is recommended for use as migraine prevention in adult patients with CM (LOE: I, SOR: Strong for).

13. Key question 13. Is pharmacological treatment effective in relieving headache compared to other drugs, placebo, or no treatment in pregnant women with migraine?

1) Analysis of evidence

Preventive migraine medications should be avoided in pregnant women due to the potential teratogenic effects on the fetus.[9,12,13,46,47] Particular care should be taken during the first trimester of pregnancy, as the risk of malformations is higher. Migraines often resolve spontaneously in the second and third trimesters, so starting migraine preventive medications in the first trimester should be avoided except in exceptional circumstances. It is important to educate and reassure patients that pregnancy has a positive effect on migraine relief. Avoiding migraine triggers and making lifestyle modifications that help prevent migraines, such as drinking plenty of fluids, eating regularly, and getting regular sleep, should be prioritized. In addition, migraine abortive medications that are relatively safe and only used during migraine attacks or non-pharmacologic migraine prevention should be prioritized over long-term use of migraine preventive medications.[46,47]

There are no RCTs to guide the choice of migraine prevention in pregnant women, and the authors of the various articles are often inconsistent in their recommendations. If it is necessary to start migraine prevention in a pregnant woman, the risks of the medication should be discussed with her. The medication should be used in minimal doses and for as short a period of time as possible. If the use of migraine preventive medications is essential in pregnant women, oral magnesium, propranolol, metoprolol, and tricyclic antidepressants may be considered.[9,12,13]

All antiseizure medications used for migraine prevention are not recommended due to the risk of fetal malformations.[9,13,46] Divalproex sodium and valproic acid are classified as pregnancy drug safety class X and should be avoided in pregnant women due to their teratogenicity for neural tube defects. Valproic acid should also be avoided in all women of childbearing potential who may become pregnant, even if the pregnancy is not planned. If an unplanned pregnancy occurs while taking valproic acid/divalproex sodium, it should be discontinued as soon as possible. Topiramate increases the risk of cleft palate to the fetus when taken in the first trimester of pregnancy. When used in combination with valproic acid, there is a risk of encephalopathic malformations. Therefore, topiramate should be avoided or used with caution in pregnant women or women who may become pregnant.

2) Recommendation

- Pharmacologic treatment is not recommended for use as migraine prevention in pregnant women with migraine (LOE: IV, SOR: Strong for).
- Pharmacologic treatment for migraine prevention may be considered if the risk to the mother and fetus from migraine symptoms is determined to be significantly higher than the risk from the pharmacologic treatment (LOE: IV, SOR: Weak for).
- Sodium divalproex and valproic acid are not recommended for use as migraine prevention in pregnant women with migraine (LOE: III, SOR: Strong against).
- Topiramate is not recommended for use as migraine prevention in pregnant women with migraine (LOE: III, SOR: Strong against).

14. Key question 14. Are triptans effective as short-term prevention in relieving headache compared to other drugs, placebo, or no treatment in women with menstrual migraine?

1) Analysis of evidence

Patients with menstrual migraine can be categorized into pure menstrual migraine, in which migraine attacks occur only during menstruation but not on other days, and menstrual-related migraine, in which migraine attacks occur both during menstruation and on other days. These patients may be considered for short-term prevention focused on the menstrual cycle rather than the usual ongoing migraine prevention.

To date, frovatriptan, naratriptan, and zolmitriptan are the drugs that have been reported in RCTs for the short-term prevention of menstrual migraine. In several guidelines, frovatriptan is strongly recommended as a high LOE for the short-term prevention of menstrual migraine, and naratriptan and zolmitriptan are also recommended for

		Episodic migraine	Chronic migraine	Menstrual migraine
Beta-blockers	Propranolol	KQ 3	KQ 10	
	Metoprolol	KQ 3	KQ 10	
	Atenolol	KQ 3	KQ 10	
	Nadolol	KQ 3	KQ 10	
	Nebivolol	KQ 3	KQ 10	
CCBs	Flunarizine	KQ 4	KQ 10	
	Cinnarizine	KQ 4	KQ 10	
	Verapamil	KQ 4		
	Nicardipine	KQ 4		
	Nifedipine	KQ 4		
	Nimodipine	KQ 4		
ARBs/ACEi	Candesartan	KQ 5	KQ 10	
	Telmisartan	KQ 5		
	Lisinopril	KQ 5	KQ 10	
Antidepressants	Amitriptyline	KQ 6	KQ 10	
	Nortriptyline	KQ 6	KQ 10	
	Venlafaxine	KQ 6	KQ 10	
	Fluoxetine	KQ 6		
ASMs	Topiramate	KQ 7	KQ 9	
	Sodium divalproex	KQ 7	KQ 9	
	Valproic acid	KQ 7	KQ 9	
	Levetiracetam	KQ 7	KQ 9	
	Zonisamide	KQ 7	KQ 9	
	Gabapentin	KQ 7		
CGRP mAbs	Galcanezumab	KQ 8	KQ 12	
	Fremanezumab	KQ 8	KQ 12	
	Erenumab	KQ 8	KQ 12	
	Eptinezumab	KQ 8	KQ 12	
Botulinum toxin	OnabotulinumtoxinA		KQ 11	
Triptans	Frovatriptan			KQ 14
	Naratriptan			KQ 14
	Zolmitriptan			KQ 14

Strength of recommendations

Strong for	Weak for	Weak for	Weak against	Strong against
LOE: I	LOE: I, II, III	LOE: IV	LOE: II, III	LOE: I

Figure 2. Heat map summarizing the evidence-based recommendations on pharmacologic treatment for migraine prevention.
CCB, calcium channel-blocker; ARB, angiotensin receptor blocker; ACEi, angiotensin-converting enzyme inhibitor; ASMs, antiseizure medications; CGRP mAb, calcitonin gene-related peptide monoclonal antibody; KQ, key question; LOE, level of evidence.

Table 2. Range of the daily administration dose or single injection dose and common adverse events of migraine preventive medications

Medication	Range of daily dose or single injection dose (mg)	Adverse events
Beta-blockers		
Propranolol	20–160	Fatigue, dizziness, depression, and vivid dreams
Metoprolol	50–200	Fatigue, dizziness, depression, and vivid dreams
Atenolol	50–200	Fatigue, dizziness, depression, vivid dreams, dyspnea, bradycardia, palpitation, and vomiting
Nadolol	40–160	Fatigue, dizziness, depression, vivid dreams, dyspnea, bradycardia, palpitation, and vomiting
Nebivolol	2.5–5.0	Headache, dizziness, dysesthesia, nightmare, gastrointestinal disorder, dyspnea, itching, and edema
Calcium channel-blocker		
Flunarizine	5–10	Weight gain, somnolence, dry mouth, dizziness, hypotension, and depression
Cinnarizine	25–50	Weight gain, somnolence, dry mouth, dizziness, hypotension, and depression
Verapamil	120–480	Palpitation, edema, arrythmia, and rash
Nicardipine	40–80	Constipation, facial flushing, helplessness, headache, myalgia, tremor, and dizziness
Nifedipine	15–60	Constipation, facial flushing, helplessness, headache, myalgia, tremor, and dizziness
Nimodipine	90	Gastrointestinal disorder, headache, dizziness, somnolence, and tremor
Angiotensin receptor blockers and angiotensin-converting enzyme inhibitor		
Candesartan	4–16	Hypotension and aggravation of congestive heart failure
Telmisartan	40–80	Hyperkalemia, dizziness, hypotension, rash, and myalgia
Lisinopril	10–20	Dizziness, headache, cough, fatigue, muscle cramps, diarrhea, and hypotension
Antidepressants		
Amitriptyline	2.5–50.0	Weight gain, dry mouth, somnolence, fatigue, helplessness, dizziness, blurred vision, and constipation
Nortriptyline	25–150	Weight gain, dry mouth, somnolence, fatigue, helplessness, dizziness, blurred vision, and constipation
Venlafaxine	37.5–150.0	Somnolence, insomnia, dizziness, headache, vomiting, dry mouth, anxiety, and sexual dysfunction
Fluoxetine	10–80	Fatigue, vomiting, diarrhea, insomnia, loss of appetite, impotence, tremor, anxiety, and restlessness
Antiseizure medications		
Topiramate	12.5–150.0	Paresthesia, fatigue, anorexia, diarrhea, weight loss, and difficulty with memory
Sodium divalproex	250–1,500	Nausea, vomiting, weight gain, tremor, hair loss, somnolence, and dizziness
Valproic acid	600–2,000	Nausea, vomiting, weight gain, tremor, hair loss, somnolence, and dizziness
Levetiracetam	500–2,000	Fatigue, helplessness, somnolence, myalgia, dizziness, diplopia, rash, and cough
Zonisamide	100–600	Weight loss, diplopia, visual disturbance, somnolence, ataxia, and abnormal thinking
Gabapentin	300–1,800	Peripheral edema, dizziness, somnolence, ataxia, and weight gain
Calcitonin gene-related peptide monoclonal antibody		
Galcanezumab	120 or 240 mg SC (monthly)	Injection site pain, injection site reaction, injection site erythema/pruritis, upper respiratory tract infection, and constipation
Fremanezumab	225 mg SC (monthly) 675 mg SC (quarterly)	Injection site pain, injection site reaction, injection site erythema/pruritis, upper respiratory tract infection, and constipation
Erenumab	70 or 140 mg SC (monthly)	Injection site pain, injection site reaction, injection site erythema/pruritis, upper respiratory tract infection, and constipation

(Continued to the next page)

Table 2. Continued

Medication	Range of daily dose or single injection dose (mg)	Adverse events
Eptinezumab	100 or 300 mg IV (quarterly)	Hypersensitivity, infusion site extravasation, upper respiratory tract infection, and constipation
Botulinum toxin		
OnabotulinumtoxinA	155–195 units IM (12-wk interval)	Neck pain, muscular weakness, myalgia, injection site pain, and ptosis
Triptans		
Frovatriptan	2.5–5.0	Triptan sensation, dizziness, somnolence, fatigue, lethargy, headache, and vomiting
Naratriptan	1–2.0	Triptan sensation, dizziness, somnolence, fatigue, lethargy, headache, and vomiting
Zolmitriptan	2.5–7.5	Triptan sensation, dizziness, somnolence, fatigue, lethargy, headache, and vomiting

SC, subcutaneous; IV, intravenous; IM, intramuscular.

the short-term prevention of menstrual migraine based on high LOE.[8,12,17,26] The meta-analysis confirmed the efficacy of frovatriptan, naratriptan, and zolmitriptan compared to placebo, supporting the recommendations of these agents in previously published guidelines.[48,49]

2) Recommendation

- Frovatriptan is recommended for use as short-term prevention in women with menstrual migraine (LOE: I, SOR: Strong for).
- Naratriptan is recommended for use as short-term prevention in women with menstrual migraine (LOE: I, SOR: Strong for).
- Zolmitriptan is recommended for use as short-term prevention in women with menstrual migraine (LOE: I, SOR: Strong for).

Conclusions

The CPG committee of the KHS compiled and analyzed the evidence to provide specific, straightforward, and easy-to-implement recommendations for pharmacologic treatment of migraine prevention (Figure 2). Range of daily dose of oral migraine preventives and single injection dose of injectable therapies were summarized in Table 2. The authors hope that this guideline will be widely used in a variety of settings, including real-world clinical practice and research, and that it will provide real benefit to migraine patients. The specific recommendation for menstrual migraine would be useful to satisfy unmet clinical need of women with menstrual migraine.[50]

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AVAILABILITY OF DATA AND MATERIAL

Not applicable.

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

FUNDING STATEMENT

Not applicable.

ACKNOWLEDGMENTS

We thank external panels for reviewing the current CPG and giving helpful advice.

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