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CLINICAL GUIDELINE

Prevention of Episodic Migraine Headache Using Pharmacologic Treatments in Outpatient Settings: A Clinical Guideline From the American College of Physicians

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Description: The American College of Physicians (ACP) developed this clinical guideline for clinicians caring for adults with episodic migraine headache (defined as 1 to 14 headache days per month) in outpatient settings.

Methods: ACP based these recommendations on systematic reviews of the comparative benefits and harms of pharmacologic treatments to prevent episodic migraine, patients' values and preferences, and economic evidence. ACP evaluated the comparative effectiveness of the following interventions: angiotensin-converting enzyme inhibitors (lisinopril), angiotensin II–receptor blockers (candesartan and telmisartan), antiseizure medications (valproate and topiramate), β-blockers (metoprolol and propranolol), calcitonin gene-related peptide (CGRP) antagonist-gepants (atogepant or rimegepant), CGRP monoclonal antibodies (eptinezumab, erenumab, fremanezumab, or galcanezumab), selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors (fluoxetine and venlafaxine), and a tricyclic antidepressant (amitriptyline). ACP used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to analyze the effects of pharmacologic treatment on the following outcomes: migraine frequency and duration, number of days medication was taken for acute treatment of migraine, frequency of migraine-related emergency department visits, migraine-related disability, quality of life and physical functioning, and discontinuations due to adverse events. In addition, adverse events were captured through U.S. Food and Drug Administration medication labels and eligible studies.

Recommendations: In this guideline, ACP makes recommendations for clinicians to initiate monotherapy for episodic migraine prevention in nonpregnant adults in the outpatient setting as well as alternative approaches if initial treatments are not tolerated or result in an inadequate response. All 3 ACP recommendations have conditional strength and low-certainty evidence. Clinical considerations provide additional context for physicians and other clinicians.

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Migraine is a prevalent and disabling condition that ranks as the second leading cause of global disability (expressed as years lived with disability) in all adults and the top cause in females aged 15 to 49 years (1, 2). Migraine affects approximately 16% of people in the United States, with females being more affected than males (21% vs. 11%) (3). There is a disproportionate prevalence of migraine in adults aged 18 to 44 years (18%), people who are unemployed (21%), and those with a household income less than $35 000 per year (20%) (4). Migraine-related disability has increased in the United States despite the prevalence of migraine having remained relatively consistent over the past 30 years (5). Migraine has been found to account for about 4 million emergency department visits and more than 4.3 million office visits in a year (3), representing an important health problem and a substantial economic burden of more than $78 billion annually in medical expenses and lost productivity in the United States (6).

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Migraine is characterized by recurrent episodes of usually moderate- to severe-intensity headache lasting 4 to 72 hours with or without aura (sensory disturbances), generally pulsating and often accompanied by nausea, vomiting, photophobia, or phonophobia. A disabling migraine can interfere with daily living and affect quality of life (QoL). The main goal of prevention is to reduce the frequency and severity of migraine headache. Considerations for preventive pharmacologic treatments for episodic migraine include frequency, severity, duration, and functional disability.

Migraine is underdiagnosed and undertreated, with only a small percentage of eligible people receiving preventive pharmacologic treatments (7). One study showed that 40% of U.S. participants with migraines were eligible for pharmacologic treatments to prevent migraines but only 17% were using them (7). Many pharmacologic treatments were originally developed for conditions other than migraine prevention and are used off-label for this indication (for example, angiotensin-converting enzyme [ACE] inhibitors and angiotensin II–receptor blockers [ARBs]). Other pharmacologic treatments have been granted U.S. Food and Drug Administration (FDA) approval for migraine prevention (for example, propranolol, topiramate, and valproate), including newer options of calcitonin gene-related peptide antagonists (CGRP antagonists-gepants) and monoclonal antibodies (CGRP-mAbs).

Purpose and Scope

The purpose of this clinical guideline from the American College of Physicians (ACP) is to present clinical recommendations to prioritize among effective pharmacologic treatments for the prevention of episodic migraine headache, based on the best available evidence on the comparative benefits and harms of these treatments (8), consideration of patients' values and preferences (9), and economic evidence (8, 10).

Pharmacologic treatments considered in this guideline for the prevention of episodic migraine headache were initially defined based on scoping of the scientific literature and clinical input from the topic expert panel and the ACP Clinical Guidelines Committee (CGC). The final list of pharmacologic treatments included in this guideline was selected using a stepwise approach based on the following criteria: availability in the United States, evidence supporting efficacy (compared with placebo) in published systematic reviews, and alignment with eligibility criteria defined in the comparative effectiveness systematic review used to inform this ACP clinical guideline (8). Additional details on the selection of treatments are available in **Figure 1**.

The comparative effectiveness review included the following pharmacologic treatments:

- ACE inhibitor: lisinopril
- Antiseizure medications: topiramate and valproate
- ARBs: candesartan and telmisartan
- Beta-adrenergic blockers (β-blockers): metoprolol and propranolol
- CGRP antagonists-gepants: atogepant and rimegepant
- CGRP-mAbs: eptinezumab, erenumab, fremanezumab, and galcanezumab
- Selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs): fluoxetine and venlafaxine
- Tricyclic antidepressant (TCA): amitriptyline
- Combination of any of these treatments

Population

The population is adults with episodic migraine headaches (defined as 1 to 14 headache days per month) managed in outpatient settings. This guideline does not address adults who experience chronic migraine (defined as ≥15 headache days per month) or chronic cluster headache (severe headaches that occur multiple times a day, with each cluster lasting for weeks or months).

Intended Audience

The intended audience is physicians and other clinicians caring for adults with episodic migraine headache in outpatient settings.

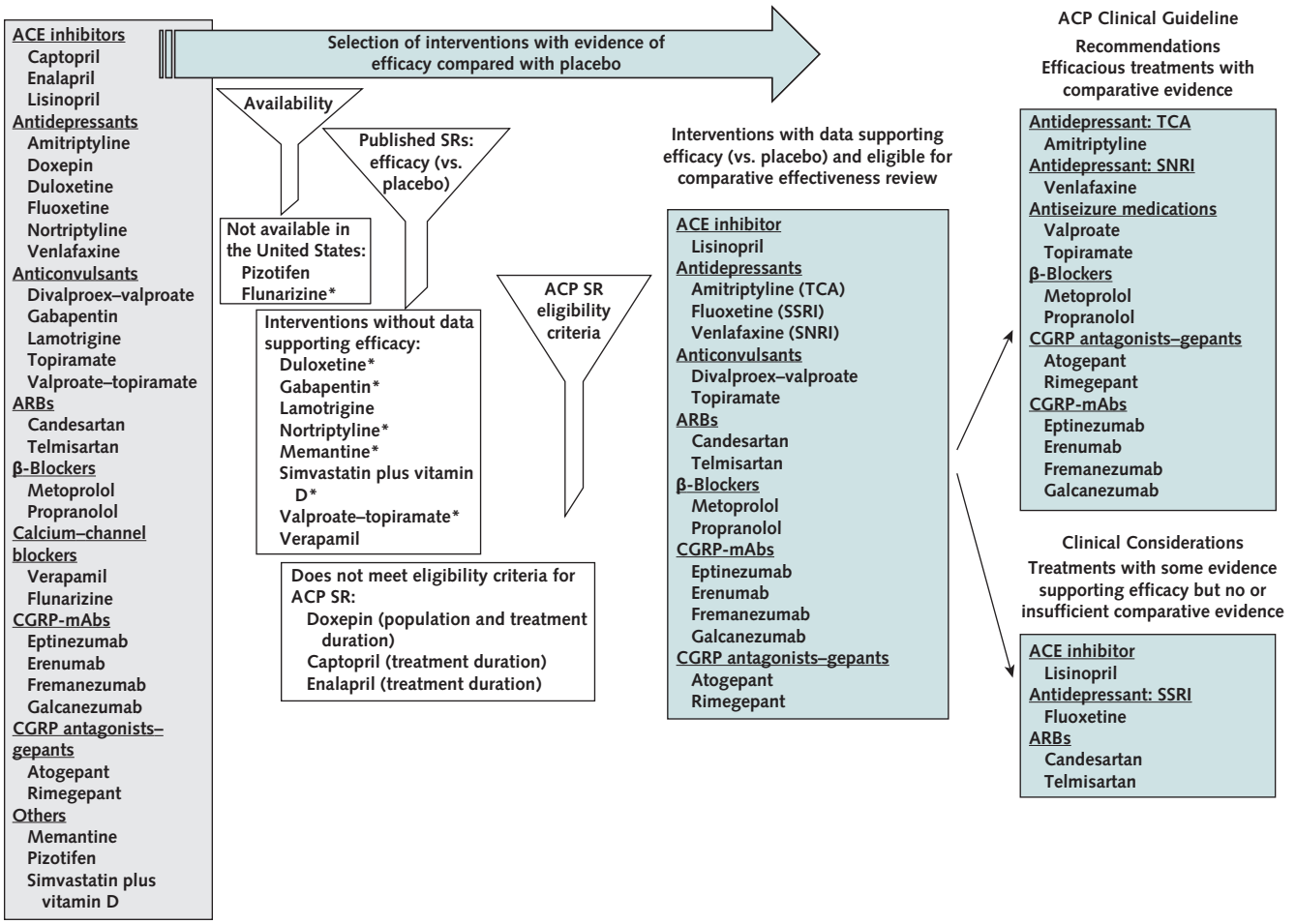
Clinical Guideline Development Process

The CGC developed this guideline according to ACP's guideline development process (11) and its policy on disclosure of interest and management of conflicts of interest (12). ACP is a GRADE (Grading of Recommendations Assessment, Development and Evaluation) Center, and the CGC used GRADE methods to develop this guideline, including Evidence-to-Decision tables when reporting the evidence (**Figure 2**; **Supplement**, available at Annals.org) (13). The Appendix (available at Annals.org) lists the key questions (**Appendix Table 1**, available at Annals.org) for the supporting systematic reviews (8, 9) and details the methods for the guideline and systematic review. ACP completes the Guidelines International Network (GIN) Standards for Reporting form (14) for each guideline it publishes; the form can be found in GIN's International Guidelines Library or on ACP's website (www.acponline.org/clinical-information/guidelines/guideline-process).

Systematic Review of Benefits and Harms and Summary of the Evidence

This guideline is based on an accompanying systematic review and network meta-analysis (NMA) of randomized controlled trials of at least 12 weeks' treatment duration and follow-up that examined the comparative benefits and harms of pharmacologic treatments for the prevention of episodic migraine headaches (8). The ACP Center for Evidence Reviews (CER) at Cochrane

Figure 1. Selection of interventions for the comparative effectiveness review and clinical guideline recommendations.



ACE = angiotensin-converting enzyme; ACP = American College of Physicians; ARB = angiotensin II–receptor blocker; CGRP = calcitonin gene-related peptide; mAb = monoclonal antibody; SNRI = serotonin–norepinephrine reuptake inhibitor; SR = systematic review; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.
* Excluded before publication of the protocol.

Netherlands completed the systematic review and NMA that informed this guideline, and ACP funded it. The systematic review (8) and Evidence-to-Decision tables (**Supplement Tables 1 to 6**, available at Annals.org) provide a detailed summary of the findings.

Outcomes of Interest

Benefits and Harms

The CGC, the CGC Public Panel, and members of the topic expert panel for the systematic review independently rated the importance of clinical outcomes as "critical," "important," or "less important" for decision making (**Appendix Table 2**, available at Annals.org). The prioritized outcomes used in the Summary of Findings tables and appraised for certainty of evidence are migraine frequency, migraine duration, number of acute medication intake days, frequency of migraine-related emergency department visits, migraine-related disability, QoL, physical functioning, and discontinuations due to adverse events (AEs). However, the accompanying systematic review did not identify eligible studies that assessed physical functioning or the frequency of emergency department visits. In addition, AEs were captured through FDA labels and eligible studies (**Supplement Table 7**, available at Annals.org) if the studies reported a significant difference in the incidence of an AE or the difference was 5% or more between groups. AEs were not rated using the GRADE approach. The CGC considered the directionality, magnitude of effects, confidence intervals, and GRADE ratings when interpreting the effects of individual prioritized outcomes and made judgments across all outcomes for each comparison to develop the recommendations.

Public and Patient Values and Preferences

The CGC incorporated public and patient values and preferences for the eligible interventions when

Figure 2. Grading the certainty of evidence and strength of recommendations in ACP clinical guidelines using GRADE.

Grading Certainty of Evidence			
High	Confident that the true effect lies close to that of the estimate of the effect (the intervention "results in" the effect)		
Moderate	Moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a sizable possibility that it is substantially different (the intervention "probably results in" the effect)		
Low	Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect (the intervention "may result in" the effect)		
Grading Strength of Recommendations			
Strength	**Balance of Benefits and Harms**	**Applicable Patient Population**	**Policy Implications**
Strong (ACP recommends)	Confidence that the benefits clearly outweigh the risks and burden or vice versa	Applies to most patients in most circumstances	Only strong recommendations could be considered as quality indicators to guide the development of accountability, reporting, and payment programs
Conditional (ACP suggests)	The benefits probably outweigh the risks and burden, or vice versa, but there is appreciable uncertainty	Applies to many patients but may differ depending on circumstances or patients' values and preferences	Policymaking will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Quality indicators would have to focus on the fact that adequate deliberation about the management options has taken place.

ACP = American College of Physicians; GRADE = Grading of Recommendations Assessment, Development and Evaluation.

developing this clinical guideline. The CGC considered evidence about the values and preferences of the public and patients from 2 sources: the accompanying systematic review of evidence regarding patients' values and preferences (9), and consultation with the CGC Public Panel. The CGC Public Panel participated in the outcome rating exercise, provided preferences for interventions based on the systematic review's findings on benefits and harms (8), and provided feedback on the draft guideline recommendations.

Economic Evidence

The CGC considered costs and economic burden of care when assessing the value of the pharmacologic treatments. The CGC also considered annualized wholesale acquisition costs (WAC) (**Supplement Tables 8** and **9**, available at Annals.org) for eligible pharmacologic treatments (10). The accompanying systematic review (8) provided a summary of the evidence on the economic value of pharmacologic treatments for the prevention of episodic migraine headache based on willingness-to-pay thresholds reported in high-quality cost-effectiveness analyses (CEAs) that are applicable to the United States (**Appendix Table 3**, available at Annals.org). The appraised results from 2 eligible CEAs are presented in **Supplement Table 10** (available at Annals.org).

RECOMMENDATIONS

A visual clinical guideline for this topic displaying a visual summary of the recommendations, rationales, and clinical considerations, alongside an interactive data visualization, is available at Annals.org (15).

Recommendation 1: ACP suggests clinicians initiate monotherapy to prevent episodic migraine headache in nonpregnant adults in outpatient settings by choosing one of the following pharmacologic treatments (conditional recommendation; low-certainty evidence):

- *A beta-adrenergic blocker, either metoprolol or propranolol*
- *The antiseizure medication valproate*
- *The serotonin and norepinephrine reuptake inhibitor venlafaxine*
- *The tricyclic antidepressant amitriptyline*

Recommendation 2: ACP suggests clinicians use monotherapy with a calcitonin gene-related peptide (CGRP) antagonist-gepant (atogepant or rimegepant) or a CGRP monoclonal antibody (eptinezumab, erenumab, fremanezumab, or galcanezumab) to prevent episodic migraine headache in nonpregnant adults in outpatient settings who do not tolerate or inadequately respond to a trial or trials of a beta-adrenergic blocker (metoprolol or propranolol), the antiseizure medication valproate, the serotonin and norepinephrine reuptake inhibitor venlafaxine, or the tricyclic antidepressant amitriptyline (conditional recommendation; low-certainty evidence).

Recommendation 3: ACP suggests clinicians use monotherapy with the antiseizure medication topiramate to prevent episodic migraine headache in nonpregnant adults in outpatient settings who do not tolerate or inadequately respond to a first trial or trials of a beta-adrenergic blocker (metoprolol or propranolol), the antiseizure medication valproate, the serotonin and norepinephrine reuptake inhibitor venlafaxine, or the tricyclic antidepressant amitriptyline and a further trial with a calcitonin

gene-related peptide (CGRP) antagonist-gepant (atogepant or rimegepant) or a CGRP monoclonal antibody (eptinezumab, erenumab, fremanezumab, or galcanezumab) (conditional recommendation; low-certainty evidence).

Clinicians should use an informed decision-making approach and discuss benefits; harms; costs; patients' values and preferences, including financial burden and mode of administration; contraindications; pregnancy and reproductive status in females; clinical comorbidities; and availability when selecting a pharmacologic treatment to prevent episodic migraine.

Rationale

The CGC used economic evidence and data on patients' values and preferences as primary factors in its rationale for clinical recommendations because the relative net benefit of the recommended treatments for the prevention of episodic migraine headache did not clearly favor any treatment over another. The exceptions were low-certainty evidence of a small but favorable net benefit of β-blockers and CGRP-mAbs compared with just 1 other migraine preventive medication (topiramate), mainly because of fewer discontinuations due to AEs (**Supplement Tables 2a** and **3a**). CGRP-mAbs may also reduce migraine frequency and the need for acute medication compared with topiramate. Conversely, low-certainty evidence suggested that CGRP-mAbs may also reduce migraine frequency compared with valproate (**Supplement Table 3a**) and the SNRI venlafaxine may reduce migraine duration compared with amitriptyline (**Supplement Table 4a**). However, all other prioritized outcomes, particularly harms, for both comparisons either had insufficient certainty or were not reported. As a result, the CGC concluded that the net benefit of these comparisons was uncertain.

The vast majority of findings from analyses of prioritized outcomes for this topic showed no comparative differences in effect, insufficient comparative evidence, or no comparator data (8). However, the CGC wanted to highlight the few differences that were observed in select outcomes. β-Blockers may reduce discontinuations due to AEs compared with topiramate (157 fewer events per 1000 treated people) (low-certainty evidence [**Supplement Table 2a**]). Compared with topiramate, CGRP-mAbs may reduce migraine frequency (0.80 fewer days per month) and acute medication intake (1.02 fewer days per month) (low-certainty evidence) and probably reduce discontinuations due to AEs (162 fewer events per 1000 treated people) (moderate-certainty evidence [**Supplement Table 3a**]). CGRP-mAbs may also reduce migraine frequency (0.76 fewer days per month) compared with valproate (low-certainty evidence [**Supplement Table 3a**]), and the SNRI venlafaxine may reduce migraine duration (6.11 fewer hours per migraine headache) compared with amitriptyline (low-certainty evidence [**Supplement Table 4a**]). The CGC recognized the unfavorable tolerability of topiramate when compared with β-blockers and CGRP-mAbs but otherwise concluded that limited differences in desirable effects were small and inconsistent or had no data across prioritized outcomes and comparisons (**Supplement Tables 2b**, **3b**, **4b**, **5b**, and **6b**).

There is no comparative evidence from CEAs on the value of available pharmacologic classes or treatments for the prevention of episodic migraine headache. However, when compared with each other, the costs of the CGRP antagonists-gepants atogepant and rimegepant and the CGRP-mAbs eptinezumab, erenumab, fremanezumab, and galcanezumab are much higher than the costs of the β-blockers metoprolol and propranolol, amitriptyline, topiramate, and valproate (**Supplement Tables 8** and **9**). The CGC also integrated evidence of patients' preferences for oral treatments over injectables (CGRP-mAbs) (moderate-certainty evidence) and considered that people with migraines may place a higher value on the benefits of treatment (such as migraine frequency) over AEs (low-certainty evidence; see the Values and Preferences section in the **Supplement**). The CGC believes recommendations considering economic evidence and patients' values and preferences will help improve health care access, reduce disparities, alleviate inequities, and promote higher-value care for the prevention of episodic migraine.

Adverse event profiles differed across drug classes (**Supplement Table 7**), but most medications were associated with generally mild AEs, such as paresthesia, pain, reduced physical activity, rash, or dizziness. Some treatments, particularly topiramate, were associated with a higher number of AEs, which influenced the CGC's prioritization of less costly treatments with similar efficacy and more favorable AE profiles. Clinicians should inform patients about AE profiles when discussing migraine prevention treatment options and should consider black box warnings reported in the FDA labels for recommended treatments (see Supplement Table 23 in the accompanying systematic review) (8).

There were no comparative data for any evaluated treatment on frequency of emergency department visits and measures of physical functioning. The CGC's recommendations do not include the ACE inhibitor lisinopril, the ARBs candesartan and telmisartan, or the SSRI fluoxetine because of the lack of comparative studies or insufficient-certainty evidence for prioritized outcomes. Further comments on these treatments are provided in the Clinical Considerations section.

Economic Evidence

Annualized WAC differed substantially between pharmacologic classes (**Supplement Tables 8** and **9**). For example, the median costs for annual treatment with injectable CGRP-mAbs (eptinezumab, erenumab, fremanezumab, and galcanezumab) and oral CGRP antagonists-gepants (atogepant and rimegepant)

ranged from $7071 to $22 790. These treatments are currently unavailable as generic formulations. Conversely, median annual costs of recommended initial treatments (metoprolol [$123], propranolol [$393], valproate [$274], venlafaxine [$378], and amitriptyline [$67]) were substantially lower. The CGC only assessed WAC of eligible interventions and did not calculate associated costs of care, such as an outpatient intravenous infusion every 3 months with the CGRP-mAb eptinezumab. There was no evidence from CEAs that directly compared pharmacologic drug classes for episodic migraine headache prevention. The CER concluded with low certainty that the CGRP-mAbs erenumab and fremanezumab may have intermediate value compared with no preventive treatment in people with at least 1 previous treatment failure (**Supplement Table 10**) (8). The CGC determined that the CGRP antagonist-gepants atogepant and rimegepant may have low value compared with no preventive medications in people with at least 1 previous treatment failure (**Supplement Table 10**) (8).

Values and Preferences

The evidence on patients' values and preferences (9) showed that they may have prioritized the effect of migraine prevention treatments on migraine-related outcomes over AEs (low-certainty evidence) (see the Values and Preferences section in the **Supplement**). Duration of migraine headache and its effect on daily activities was more important than migraine recurrence (high-certainty evidence; see the Values and Preferences section in the **Supplement**), and migraine severity may have been more important than migraine frequency (low-certainty evidence); both migraine duration and migraine severity may have been more important than AEs (low-certainty evidence). However, the route of administration of pharmacologic treatments for the prevention of episodic migraine headache is probably as important as their effect on migraine frequency (moderate-certainty evidence) (9). People probably prefer oral treatments over injectables, such as CGRP-mAbs (moderate-certainty evidence). The CGC Public Panel acknowledged the difficulties in choosing preferred treatments because of a lack of appreciable differences in prioritized outcomes between pharmacologic treatments. Findings from the panel showed a preference for the use of amitriptyline, CGRP-mAbs, and the SSRI/SNRI. Factors that drove those preferences were benefits, harms, and cost. The CGC Public Panel preferred CGRP-mAbs when cost was not a factor in decision making; however, when cost was a factor, other less costly alternatives were preferred.

Ultimately, because of the lack of a relative net benefit among amitriptyline, the β-blockers metoprolol and propranolol, CGRP antagonist-gepants, CGRP-mAbs, valproate, and venlafaxine, the CGC primarily used economic evidence and evidence on patients' values and preferences to prioritize migraine prevention treatments in its recommendations. There were large differences in costs between these medications, with CGRP-mAbs and CGRP antagonist-gepants being substantially more costly (**Supplement Tables 9** and **10**). Furthermore, data on patients' values and preferences favored oral over injectable medications. As a result, the CGC suggests that clinicians and patients use a β-blocker (metoprolol or propranolol), the antiseizure medication valproate, the SNRI venlafaxine, or the TCA amitriptyline to prevent episodic migraine headache in nonpregnant adults before using a CGRP-mAb or a CGRP antagonist-gepant. Finally, because β-blockers and CGRP-mAbs had low-certainty evidence of a small net benefit compared with topiramate and topiramate had a higher frequency of AEs (**Supplement Table 7**), the CGC suggests that clinicians use topiramate if a patient does not tolerate or inadequately responds to a trial or trials of a β-blocker (metoprolol or propranolol), the antiseizure medication valproate, the SNRI venlafaxine, or the TCA amitriptyline and a further trial with a CGRP antagonist-gepant (atogepant or rimegepant) or a CGRP-mAb (eptinezumab, erenumab, fremanezumab, or galcanezumab).

Applicability

These recommendations apply to nonpregnant or nonlactating adults with episodic migraine. The majority of participants in the included studies were females of reproductive age who had episodic migraine headache with or without aura, had an average headache frequency of 7 to 8 days per month (range, 2 to 14 days per month), and were initiating treatment for the prevention of episodic migraine headache and had a previous preventive treatment failure.

CLINICAL CONSIDERATIONS

- This guideline assessed the comparative effectiveness of medications that are beneficial to prevent episodic migraine to help clinicians select which medications to use for prevention (**Figure 1**).
- Before initiation of any pharmacologic treatment to prevent episodic migraine, explore whether there are modifiable triggers and factors that contribute to an acute migraine headache. Discuss the importance of lifestyle interventions, such as staying hydrated and maintaining regular and adequate sleep and physical activity. Also evaluate whether the patient is using appropriate and adequate-strength medications to treat an acute migraine headache.
- There are no evidence-based definitions or thresholds that can be used as a reference to guide initiation of pharmacologic treatments for episodic migraine headache prevention. Consider pharmacologic treatment for the prevention of episodic migraine headache in people experiencing severe debilitating headache despite adequate acute treatment, and also consider pharmacologic treatment for the prevention of episodic migraine headache in people who are unable to tolerate or have contraindications to acute

treatment or are using their acute treatment more often than recommended.
- Emphasize that adherence to pharmacologic treatment is crucial because improvement may occur gradually after initiation of a long-term treatment option for prevention of episodic migraine, with an effect that may become apparent after the first few weeks of treatment.
- Because of similar net benefits of recommended treatments, ACP's recommendations consider cost as a key factor in prioritizing different classes of migraine prevention treatments. However, the actual cost of treatment for people may vary. Therefore, it is important to carefully assess each person's economic circumstances and personal preferences during the decision-making process when choosing the most appropriate treatment.
- If recommended treatments are not tolerated or result in an inadequate response, consider an ACE inhibitor (lisinopril), an ARB (candesartan or telmisartan), or an SSRI (fluoxetine).
- In people of childbearing potential and in those who are pregnant or breastfeeding, discuss AEs of pharmacologic treatments during pregnancy and lactation.
- Initiate pharmacologic treatment for the prevention of migraine at a low dose and gradually increase the dose until desired outcomes are achieved.
- Switch pharmacologic treatment for the prevention of episodic migraine headache if an adequate response is not achieved during a reasonable trial period (generally 2 to 3 months), or earlier if an AE occurs.
- The use of a headache diary may help to determine treatment efficacy, identify analgesic overuse, and follow up on migraine progression. There is uncertainty about whether and when to discontinue a medication for migraine prevention. However, consider reevaluating the balance of benefits, harms, and costs of preventive treatment with the patient.
- Certain behavioral interventions, such as cognitive behavioral therapy, relaxation training, or mindfulness-based treatment alone or combined with other components, may decrease the frequency of migraine headaches, and education alone that focuses on behavioral changes may also improve migraine-related disability (16).
- Prescribe less costly recommended medications (17).

Treatments With No Recommendations

The CGC determined that comparative evidence was inconclusive to inform recommendations for the ACE inhibitor lisinopril, the ARBs candesartan and telmisartan, and the SSRI fluoxetine but addressed these pharmacologic treatments in the Clinical Considerations section. Ultimately, all had some limited evidence from studies with small sample sizes and "some" to "high" risk of bias, supporting efficacy, but had no or insufficient comparative effectiveness data. The CGC did not develop recommendations for use of combination therapy with topiramate and amitriptyline due to the absence of added benefit compared with monotherapies and the potential for an increase in AEs with use of both.

Evidence Gaps and Research Needs

Funding agencies, such as the Patient-Centered Outcomes Research Institute or the National Institute of Neurological Disorders and Stroke, need to support well-designed comparative clinical effectiveness trials and evaluate cost-effectiveness of all relevant pharmacologic treatments for the prevention of episodic migraine headache. These studies should evaluate patient-centered outcomes, including utility-based measures of QoL, such as the EQ-5D. New studies should consider evaluating the effect of treatments on subgroups of interest determined by age and by race and ethnicity.

Areas of Insufficient Evidence

Most of the studies analyzed in the accompanying systematic review compared an intervention of interest with a placebo (the common comparator in the NMA), and there were few direct head-to-head comparison studies. As a result, most comparative effectiveness findings had insufficient-certainty evidence or had no data for any of the prioritized outcomes. These head-to-head comparisons are listed in bullet points in Supplement Tables 1a to 6a.

Only 1 study evaluating lisinopril (compared with placebo) was eligible, but data from this crossover trial could not be used in the NMA. The certainty of evidence for the comparative desirable and undesirable effects of ARBs (candesartan and telmisartan) was mainly insufficient (8) or unavailable for prioritized outcomes, with only 1 data point with low-certainty evidence showing no differences in discontinuations due to AEs compared with β-blockers. For most comparisons between pharmacologic classes, the certainty of evidence across outcomes was low or uncertain, which is partly attributable to the dearth of comparative studies eligible for this topic. The CER described results from only 2 studies evaluating the effect of CGRP-mAbs on subgroups of interest determined by age and by race and ethnicity (8). The systematic review did not identify CEAs directly comparing different drug classes with each other (8).

Areas of No Evidence

Comparative studies did not report data on physical functioning or frequency of emergency department visits for any of the pharmacologic treatments for prevention of episodic migraine. The accompanying systematic review (8) searched for but did not find placebo-controlled trials eligible for this clinical guideline to support the efficacy of captopril, doxepin, duloxetine, enalapril, gabapentin, lamotrigine, memantine, nortriptyline, simvastatin plus vitamin D, valproate plus topiramate, or verapamil. Furthermore, there were no comparative effectiveness studies of lisinopril (Figure 1).

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Note: Clinical guidelines are meant to guide care based on the best available evidence and may not apply to all patients or individual clinical situations. They should not be used as a replacement for a clinician's judgment. Any reference to a product or process contained in a guideline is not intended as an endorsement of any specific commercial product. All ACP clinical guidelines are considered automatically withdrawn or invalid 5 years after publication or once an update has been issued.

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Appendix: Detailed Methods

Detailed Methods of the Systematic Review and Guideline

Details of the ACP guideline development process can be found in ACP's methods articles (11, 12).

Committee Composition and Stakeholder Involvement

The CGC is a multidisciplinary group of 14 to 15 members; 12 to 13 of the members are internal medicine physicians representing various clinical areas of expertise across hospital and ambulatory medicine, including internal medicine subspecialties, and 2 of the members are nonphysician public members. The CGC Public Panel, involving 6 members from the public, provided input at various points in the guideline development process (see the "Public and Patient Values and Preferences" section). The CGC convened a topic expert panel made up of clinical topic experts, clinicians, and epidemiologists to inform the systematic review and assist in refining the scope and key questions.

Disclosures of Interests and Management of Conflicts of Interest

All financial and intellectual disclosures of interest were declared, and potential conflicts were discussed and managed in accordance with CGC policy (12). Disclosure of interests and management of any conflicts can be found on ACP's website (www.acponline.org/about-acp/who-we-are/leadership/boards-committees-councils/clinical-guidelines-committee/disclosure-of-interests-and-conflict-of-interest-management-summary-for-clinical-guidelines).

Key Questions and Clinical Outcomes of Interest

The CGC identified the key questions (Appendix Table 1). The CER assessed the efficacy of potentially eligible interventions when compared with placebo and included only efficacious interventions. Members of the CGC (clinicians and nonclinician public members) and the CGC Public Panel independently rate the importance of evaluated outcomes a priori (Appendix Table 2). The CGC prioritized outcomes for decision making based on the ratings.

Systematic Review on Benefits and Harms

The ACP CER at Cochrane Netherlands conducted the supporting systematic review and NMA on benefits and harms (8), which was funded by ACP. The systematic reviewers searched databases (Ovid Medline ALL, Embase [Elsevier], and CENTRAL [Cochrane Library/Wiley]) for randomized controlled trials published in English from inception through 12 April 2024. The evidence review team and the CGC used the GRADE tables to summarize the review findings and to rate the certainty of evidence for clinical outcomes.

Public and Patient Values and Preferences

The authors of the accompanying systematic review (9) searched databases (Ovid Medline ALL and EBSCO CINAHL) from inception through 16 April 2024 for any quantitative studies published in English that reported values and preferences regarding pharmacologic treatment for prevention in adults with migraine. The evidence review team and the CGC used the GRADE approach to summarize review findings and rate the certainty of evidence about values and preferences (18, 19). The CGC Public Panel participated in the outcome rating exercise, provided its views on the findings from the systematic review about the benefits and harms of the interventions, and provided feedback on the draft guideline recommendations.

Economic Evidence

The accompanying systematic review (8) also included studies addressing CEAs of eligible interventions. The CER searched databases (Ovid Medline ALL; EMBASE [Elsevier]; the International HTA Database; and the repositories of the Center for Health Decision Science [Harvard], the Institute for Clinical and Economic Review, the National Health Service Economic Evaluation Database, and the Cost-Effectiveness Analysis [CEA] Registry) for any peer-reviewed, non–industry-conducted CEAs that reported

Appendix Table 1. Key Questions for the Systematic Review

KQ 1. What are the benefits and harms of pharmacologic preventive treatment in adults with episodic migraine headache?
KQ 1a: Do treatment benefits and harms vary by demographic characteristics (age, sex, race/ethnicity)?
KQ 2: What are patients' values and preferences on pharmacologic preventive treatment for episodic migraine headache?
KQ 3: What is the cost-effectiveness of various pharmacologic preventive treatments in adults with episodic migraine headache?

KQ = key question.

Appendix Table 2. Outcome Ratings

Outcomes rated as critical
Acute medication intake days*
Adverse events
Discontinuations due to adverse events*
Emergency department visits*
Hospitalization
Migraine duration*
Migraine frequency*
Migraine-related disability*
Physical functioning*
Quality of life*
Serious adverse events
Outcomes rated as important
Emotional functioning
Social functioning
Work productivity

CGC = Clinical Guidelines Committee.
* These outcomes were prioritized for decision making by the CGC after consideration of ratings from the CGC, the topic expert panel, and the CGC Public Panel.

outcomes with units of health (such as quality-adjusted life-years) in U.S. settings, included up-to-date reference cases, and were published in English from 2012 through 15 April 2024. The CER graded the certainty of the evidence from eligible CEAs in accordance with GRADE guidance (20, 21) and used the Drummond Checklist (22) for the critical appraisal of eligible CEAs. The CGC applied a predefined set of value thresholds, derived through informal consensus, to categorize interventions as having high, intermediate, low, or no value (Appendix Table 3).

The CGC estimated annualized WAC for each eligible pharmacologic treatment (10) and judged whether there were meaningful differences based on the distribution of costs associated with resource utilization (cost of interventions) (Supplement Tables 8 and 9).

Peer Review

The supporting systematic reviews and the clinical guideline each underwent a peer-review process through the journal. The guideline was posted online for comments from ACP Regents and Governors, who represent internal medicine and its subspecialty physician members at the national and international level. The CGC considered any feedback before finalizing the guideline.

Appendix Table 3. CGC Value Thresholds for Economic Evidence*

Level of Value	ICER per QALY Gained
High value	Cost-saving or <$100 000
Intermediate value	$100 000–$200 000
Low value	>$200 000
No value	Dominated†

CGC = Clinical Guidelines Committee; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.
* The table highlights the CGC's value thresholds for economic evidence. The Center for Evidence Reviews applied these thresholds in the accompanying systematic review of cost-effectiveness analyses to categorize interventions as having high, intermediate, low, or no value. The CGC may adjust thresholds on a topic-by-topic basis, based on the clinical aspects of disease severity, the uniqueness of life-saving interventions, and ethical considerations.
† The intervention is dominated by strict dominance (the intervention is less effective and more costly than an alternative) or extended dominance (there is an alternative that is more effective and more cost effective).

Guideline Expiration or Living Guideline Process

All ACP clinical guidelines are considered automatically withdrawn or invalid 5 years after publication or once an update has been issued.

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