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2023 U.S. Department of Veterans Affairs and U.S. Department of Defense Clinical Practice Guideline for the Management of Headache

Jason J. Sico, MD, MHS; Natasha M. Antonovich, PharmD; Jennifer Ballard-Hernandez, DNP, NP; Andrew C. Buelt, DO; Amy S. Grinberg, PhD, PharmD; Franz J. Macedo, DO; Ian W. Pace, PharmD; James Reston, PhD, MPH; James Sall, PhD; Friedhelm Sandbrink, MD; Karen M. Skop, PT, DPT, MS; Thomas R. Stark, DDS; Rebecca Vogsland, DPT; Lisa Wayman, PhD, RN; and Aven W. Ford, MD

Description: Headache medicine and therapeutics evidence have been rapidly expanding and evolving since the 2020 U.S. Department of Veterans Affairs (VA) and U.S. Department of Defense (DoD) clinical practice guideline (CPG) for the management of headache. Therefore, the CPG was revised in 2023, earlier than the standard 5-year cycle. This article reviews the 2023 CPG recommendations relevant to primary care clinicians for treatment and prevention of migraine and tension-type headache (TTH).

Methods: Subject experts from the VA and the DoD developed 12 key questions, which guided a systematic search using predefined inclusion and exclusion criteria. After reviewing evidence from 5 databases published between 6 March 2019 and 16 August 2022, the work group considered the strength and quality of the evidence, patient preferences, and benefits versus harms on critical outcomes before making consensus recommendations.

Recommendations: The revised CPG includes 52 recommendations on evaluation, pharmacotherapy, invasive interventions, and nonpharmacologic interventions for selected primary and secondary headache disorders. In addition to triptans and aspirin–acetaminophen–caffeine, newer calcitonin gene–related peptide (CGRP) inhibitors (gepants) are options for treatment of acute migraine. Medications to prevent episodic migraine (EM) include angiotensin-receptor blockers, lisinopril, magnesium, topiramate, valproate, memantine, the newer CGRP monoclonal antibodies, and atogepant. AbobotulinumtoxinA can be used for prevention of chronic migraine but not EM. Gabapentin is not recommended for prevention of EM. Ibuprofen (400 mg) and acetaminophen (1000 mg) can be used for treatment of TTH, and amitriptyline for prevention of chronic TTH. Physical therapy or aerobic exercise can be used in management of TTH and migraines.

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Headache disorders, including migraine and tension-type headache (TTH), continue to be some of the most common and disabling neurologic conditions worldwide (1–7). The lifetime prevalence of headache disorders is 66% (7, 8), and more than half of people with a history of headache have active headache disease.

Headache-related disability has a pronounced effect on individuals, their social support networks, and health care systems. Headache is the second leading cause of years lived with disability across all age groups, and more disability-adjusted life-years are attributed to headache than to all other neurologic disorders combined (9).

Health-related quality-of-life scores, or measures of an individual's perceived mental and physical health over time, are consistently lower among those living with migraine than among headache-free, age-matched control participants. Quality-of-life scores are also lower during times when headache is more active. Pain intensity, headache frequency, headache-associated symptoms (such as nausea and photophobia), comorbid conditions (such as depression), stigma, and catastrophizing are significant contributors to headache-related disability and impaired quality of life (10–13).

Headache has both direct and indirect societal costs, with indirect annual costs mainly attributed to missed days of work (absenteeism) and impaired work function during a headache (presenteeism) (14–16). In the United States, indirect and direct medical costs for migraine alone are approximately $36 billion annually. The negative outcomes to persons living with headache and to society can be mitigated by delivering guideline-concordant headache care (17).

Two new classes of medications and several devices have been approved for headache indications by the U.S. Food and Drug Administration since the last U.S. Department of Veterans Affairs (VA) and U.S. Department of Defense (DoD) clinical practice guideline (CPG) in

See also:

Web-Only
Supplement

2020. Calcitonin gene–related peptide (CGRP), a protein that contributes to trigeminal nerve pain and inflammation, and its receptor have critical roles in migraine pathophysiology. Monoclonal antibodies targeting CGRP either block the peptide from binding to the receptor (galcanezumab, fremanezumab, eptinezumab) or block the receptor-binding site (erenumab). Gepants also block the CGRP receptor-binding site. Ditans block release of CGRP by binding to 5-hydroxytryptamine (serotonin) receptor 1_F ($5\text{-}HT_{1F}$) receptors on trigeminal nerve cells that transmit pain signals of a migraine (rather than the $5\text{-}HT_{1B}$ and $5\text{-}HT_{1D}$ receptors that triptans bind to). Several neuromodulatory devices have been newly cleared or have received expanded indications for headache care. These treatments work by stimulating nerves in the head or neck through electrodes or magnets, either noninvasively or invasively. Because of these new developments, the VA/DoD headache guideline was updated in 2023 ahead of the scheduled 5-year update.

Guideline Development Process

To develop CPG recommendations, the VA/DoD used a process outlined by the VA/DoD Evidence-Based Practice Working Group (18, 19). The group selected 4 guideline work group (WG) champions, 2 from the VA and 2 from the DoD. Leadership from the VA and DoD then selected a multidisciplinary WG of practicing clinician stakeholders (**Supplement Table 1**, available at Annals.org). All WG members completed conflict-of-interest disclosure forms for relationships in the previous 2 years and affirmed the disclosures verbally throughout the duration of the project. No conflicts of interest were identified.

The WG developed 12 key questions (KQs) using the PICOTS (population, intervention, comparator, outcomes, timing of outcomes measurement, and setting) framework to evaluate the benefits and harms associated with various pharmacologic and nonpharmacologic interventions for prevention and treatment of all types of headaches, including migraines and TTH (**Table 1**). Full details on the methods and recommendations can be found on the VA website (20).

To make recommendations, the WG considered peer-reviewed, English-language literature published from 6 March 2019 to 16 August 2022 relevant to the PICOTS questions. At least 80% of patients in an included study were adults diagnosed with headache; the remaining patients were in subgroup analyses specifically for adults with headache (Part 4 of the **Supplement**, available at Annals.org). When appropriate, systematic reviews (SRs) and meta-analyses (MAs) were prioritized and supplemented with individual randomized controlled trials (RCTs) (Part 4 of the **Supplement**).

The GRADE (Grading of Recommendations Assessment, Development and Evaluation) method guided the evidence quality assessment and the rating of the strength of the recommendation (21–23). Critical and important outcomes for each KQ were identified (**Table 1**). When revisiting prior recommendations, the WG restructured the critical and important outcomes to better reflect those used in the current headache literature (for example, pain freedom and most bothersome symptom are now regarded as co–primary end points in acute migraine trials) (24). Across all KQs and when available for critical and important outcomes for KQs, the WG considered clinically meaningful changes (also called minimally important differences or minimum clinically important differences) (25). Specifically, values for clinically meaningful changes that were available in the literature at the time of this CPG included a mean monthly reduction in headache days from baseline of 1 day for both episodic migraine (EM) and chronic migraine (CM).

A patient focus group provided input on patient values and care concerns. In addition to patient values and preferences, the WG considered the confidence in the quality of the evidence, balance of desirable and undesirable outcomes, and other important implications, such as resource use and availability, health equity, acceptability, and feasibility (20). In the GRADE system, the ultimate strength of a recommendation is based on the lowest quality-of-evidence rating (20, 26) for any critical outcome in the body of literature being reviewed for a particular recommendation. Each recommendation was supported by evidence (**Table 2**). "Weak for" or "neither for nor against" recommendations are solely a reflection of the strength of the evidence. Some interventions may be efficacious but are not supported by evidence. The algorithms and sidebars (Part 2 of the **Supplement**) include suggestions from clinician expertise beyond the limitations of the available evidence.

Highlighted 2023 Guideline Updates

This paper summarizes some of the important updates from the 2020 guideline that are particularly relevant to primary care, especially recommendations that were updated from the prior CPG and are new to this iteration. The full guideline (20) includes 17 new recommendations, 7 amended recommendations, 13 carried-forward recommendations, and 2 eliminated recommendations (**Table 2**).

New recommendations address new pharmacotherapies that target the CGRP pathway (for example, gepants), another new family of migraine pharmacotherapies (that is, ditans), and either new neuromodulatory devices or the expansion of indications for devices previously cleared by the U.S. Food and Drug Administration. New recommendations have also addressed more invasive headache therapeutic approaches (such as nerve blockades), the comparative effectiveness of acute and preventive pharmacotherapies,

Table 1. Key Questions

Number	Key Question	Studies
1	What is the safety and effectiveness of prophylactic prescription pharmacologic agents in the prevention of A) cluster headache, B) migraine, and C) tension-type headache?	14 SRs and 10 RCTs
2	What is the comparative effectiveness of prophylactic prescription pharmacologic agents (including CGRP inhibitors and botulinum toxin) in the prevention of A) cluster headache, B) migraine, and C) tension-type headache?	4 SRs and 8 RCTs
3	What treatments are effective for the short-term, long-term, or preventive management of posttraumatic headache?	5 RCTs
4	What is the safety and effectiveness of short-term use of prescription and nonprescription pharmacologic agents in the treatment of A) cluster headache, B) migraine, and C) tension-type headache?	10 SRs and 5 RCTs
5	What is the comparative effectiveness of short-term use of prescription and nonprescription pharmacologic agents in the treatment of A) cluster headache, B) migraine, and C) tension-type headache?	1 SR, 1 NMA, and 4 RCTs
6	What is the safety and effectiveness of invasive (e.g., injection or IV-based treatments) and interventional procedures for short-term treatment and/or prevention of headache?	2 SRs and 3 RCTs
7	What is the effectiveness of complementary integrative health interventions in the treatment and/or prevention of headache?	7 SRs and 11 RCTs
8	What is the effectiveness of nonpharmacologic behavioral health approaches for the treatment and/or prevention of headache?	3 SRs and 13 RCTs
9	What is the safety, effectiveness, and comparative effectiveness of noninvasive neuromodulation (neurostimulation) on treatment and/or prevention of headache?	4 SRs and 14 RCTs
10	What is the effectiveness of combination therapies (e.g., combining pharmacotherapies, enhancing pharmacotherapy with behavioral interventions, neuromodulation, interventional procedures, and complementary integrative health) for headache prevention?	6 RCTs
11	What is the effect of co-occurring conditions on treatment outcomes in patients with headache?	1 SR, 4 secondary analyses of RCTs, and 1 secondary analysis of a prospective cohort study
12	Is medication withdrawal an effective strategy to manage suspected medication overuse headache?	2 RCTs (in 4 publications)
–	Total evidence base	129 studies (in 131 publications)

CGRP = calcitonin gene–related peptide; IV = intravenous; NMA = network meta-analysis; RCT = randomized controlled trial; SR = systematic review.

and combinations of therapies (for example, a behavioral intervention and a pharmacotherapy for migraine). A change in strength, or direction, of a "reviewed, amended" recommendation could be due to either a new evidence basis or review of the prior evidence basis within the context of revised critical outcomes.

In the following sections, we summarize the recommendations we found most relevant for primary care clinicians, including recommendations for pharmacotherapy or invasive therapies (injections, procedures, and invasive interventions) for treatment and prevention of migraines and TTHs, as well as for the use of nonpharmacologic interventions (NPIs).

Abortive Therapies for Migraine

Migraine was an area with a large evidence basis resulting in over 2 dozen recommendations in the updated 2023 guideline. The goals of treating acute migraine include rapid and sustained alleviation of pain and most bothersome symptom and restoration of function. The abortive treatment of migraine (that is, short-term treatment of symptomatic migraine) is focused on early treatment with therapies commensurate to pain severity (mild vs. moderate to severe), the presence or absence of nausea and vomiting (which may limit use of orally administered therapies), patient preference, comorbid conditions, vascular risk, and the health care setting where therapies would be administered. Most of the recommendations in this CPG are related to outpatient therapies and strategies. Critical outcomes considered for acute migraine therapies included time to pain freedom, time to freedom from most bothersome symptom, and headache or migraine intensity.

Pharmacotherapies

Newly added recommendations included a "strong for" recommendation for aspirin–acetaminophen–caffeine (Recommendation 20), a "weak for" recommendation for ubrogepant and rimegepant (Recommendation 22), and a "neither for nor against" recommendation for lasmiditan (Recommendation 24). Aspirin–acetaminophen–caffeine was found to have a statistically significant improvement in critical outcomes, with a number needed to treat of 9 for pain freedom at 2 hours and 4 for pain relief at 2 hours (27). Benefits of aspirin–acetaminophen–caffeine outweighed risks because no serious adverse events (AEs) occurred, and the AEs reported were mild, consistent with what would be expected from the individual components (for example, aspirin dyspepsia, caffeine nervousness). Systematic reviews (28–30, 299) of gepants for acute migraine treatment demonstrated moderately robust and clinically significant effects on critical outcomes of interest (for example, a number needed to treat of 13 for pain freedom at 2 hours for both gepant drugs reviewed). Lasmiditan, first in a new class of pharmacotherapies (ditans), is a centrally and peripherally acting

Table 2. Recommendations With Supporting Evidence

Number	Recommendation*	Strength	Category	Supporting Evidence
Medication overuse headache screening and other considerations				
1	We suggest that providers assess for and consider the following high-risk factors for medication overuse headache in patients with headache (in order of relative impact): Headache frequency (≥7 d/mo) Migraine diagnosis Medication use: frequent use of anxiolytics, analgesics (for any condition, including use of opioids or nonopioid analgesics for the short-term treatment of migraine), or sedative hypnotics History of anxiety or depression, especially in combination with musculoskeletal or gastrointestinal symptoms Physical inactivity Sick leave of >2 wk in the past year Self-reported whiplash Smoking (tobacco use)	Weak for	Not reviewed, amended	92–96
Pharmacotherapy: headache: preventive				
2	There is insufficient evidence to recommend for or against coenzyme Q10, feverfew, melatonin, omega-3, vitamin B2, or vitamin B6 for the prevention of headache.	Neither for nor against	Not reviewed, amended	97–103
3	There is insufficient evidence to recommend for or against fluoxetine or venlafaxine for the prevention of headache.	Neither for nor against	Reviewed, not changed	51, 77, 104 Additional evidence: 105
Pharmacotherapy: migraine: preventive				
4	We recommend candesartan or telmisartan for the prevention of episodic migraine.	Strong for	Reviewed, new-replaced	51, 106–108
5	We recommend erenumab, fremanezumab, or galcanezumab for the prevention of episodic or chronic migraine.	Strong for	Reviewed, new-replaced	43, 48, 109–126 Additional evidence: 42, 44, 45, 127–131
6	We suggest intravenous eptinezumab for the prevention of episodic or chronic migraine.	Weak for	Reviewed, new-added	132–136 Additional evidence: 137–143
7	We suggest lisinopril for the prevention of episodic migraine.	Weak for	Reviewed, not changed	144 Additional evidence: 143
8	We suggest oral magnesium for the prevention of migraine.	Weak for	Not reviewed, not changed	97, 145, 146 Additional evidence: 147
9	We suggest topiramate for the prevention of episodic and chronic migraine.	Weak for	Reviewed, new-replaced	48–50, 148 Additional evidence: 149
10	We suggest propranolol for the prevention of migraine.	Weak for	Reviewed, not changed	148
11	We suggest valproate for the prevention of episodic migraine.	Weak for	Reviewed, new-replaced	50, 51 Additional evidence: 135, 150–162
12	We suggest memantine for the prevention of episodic migraine.	Weak for	Reviewed, new-added	163
13	We suggest atogepant for the prevention of episodic migraine.	Weak for	Reviewed, new-added	46
14	We suggest onabotulinumtoxinA injection for the prevention of chronic migraine.	Weak for	Reviewed, not changed	48, 53, 54
15	We suggest against abobotulinumtoxinA or onabotulinumtoxinA injection for the prevention of episodic migraine.	Weak against	Reviewed, not changed	54
16	There is insufficient evidence to recommend for or against rimegepant for the prevention of episodic migraine.	Neither for nor against	Reviewed, new-added	47
17	We suggest against the use of gabapentin for the prevention of episodic migraine.	Weak against	Reviewed, new-replaced	50 Additional evidence: 52
18	There is insufficient evidence to recommend for or against levetiracetam for the prevention of episodic migraine.	Neither for nor against	Reviewed, new-added	164 Additional evidence: 165–175

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Table 2–Continued

Number	Recommendation*	Strength	Category	Supporting Evidence
Pharmacotherapy: migraine: abortive				
19	We recommend eletriptan, frovatriptan, rizatriptan, sumatriptan (oral or subcutaneous), the combination of sumatriptan and naproxen, or zolmitriptan (oral or intranasal) for the short-term treatment of migraine.	Strong for	Reviewed, new-replaced	176–181 Additional evidence: 182–185
20	We recommend aspirin–acetaminophen–caffeine for the short-term treatment of migraine.	Strong for	Reviewed, new-added	27
21	We suggest acetaminophen, aspirin, ibuprofen, or naproxen for the short-term treatment of migraine.	Weak for	Reviewed, amended	186–193
22	We suggest rimegepant or ubrogepant for the short-term treatment of migraine.	Weak for	Reviewed, new-added	28–30
23	We suggest against intravenous ketamine for the short-term treatment of migraine.	Weak against	Reviewed, amended	194 Additional evidence: 195, 196
24	There is insufficient evidence to recommend for or against lasmiditan for the short-term treatment of migraine.	Neither for nor against	Reviewed, new-added	31–65 Additional evidence: 36, 37
Pharmacotherapy: tension-type headache: preventive				
25	We suggest amitriptyline for the prevention of chronic tension-type headache.	Weak for	Reviewed, not changed	197 Additional evidence: 198, 199
26	We suggest against botulinum/neurotoxin injection for the prevention of chronic tension-type headache.	Weak against	Reviewed, not changed	58, 59
Pharmacotherapy: tension-type headache: abortive				
27	We suggest ibuprofen (400 mg) or acetaminophen (1000 mg) for the short-term treatment of tension-type headache.	Weak for	Reviewed, not changed	55–57
Pharmacotherapy: cluster headache: preventive				
28	We suggest galcanezumab for the prevention of episodic cluster headache.	Weak for	Reviewed, not changed	200 Additional evidence: 131, 201
29	We suggest against galcanezumab for the prevention of chronic cluster headache.	Weak against	Reviewed, new-added	200 Additional evidence: 131, 202, 203
30	There is insufficient evidence to recommend for or against verapamil for the prevention of episodic or chronic cluster headache.	Neither for nor against	Reviewed, new-added	78 Additional evidence: 112, 204, 205
Pharmacotherapy: cluster headache: abortive				
31	We suggest subcutaneous sumatriptan (6 mg) or intranasal zolmitriptan (10 mg) for the short-term treatment of cluster headache.	Weak for	Reviewed, new-replaced	206 Additional evidence: 207, 208
32	We suggest the use of normobaric oxygen therapy for the short-term treatment of cluster headache.	Weak for	Not reviewed, amended	206, 209–211
Pharmacotherapy: medication overuse headache				
33	There is insufficient evidence to recommend for or against the addition of any specific preventive agent or withdrawal strategy to guide the treatment of medication overuse headache.	Neither for nor against	Reviewed, new-replaced	212–218
Injections, procedures, and invasive interventions				
34	We suggest greater occipital nerve block for the short-term treatment of migraine.	Weak for	Reviewed, not changed	38–41 Additional evidence: 219, 220
35	There is insufficient evidence to recommend for or against greater occipital nerve block for the prevention of chronic migraine.	Neither for nor against	Reviewed, new-added	53, 87, 221 Additional evidence: 219, 220

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Table 2–Continued

Number	Recommendation*	Strength	Category	Supporting Evidence
36	There is insufficient evidence to recommend for or against supraorbital nerve block for the short-term treatment of migraine.	Neither for nor against	Reviewed, new-added	38
37	There is insufficient evidence to recommend for or against intravenous antiemetics (i.e., intravenous chlorpromazine, intravenous metoclopramide, intravenous prochlorperazine), intravenous magnesium, or intranasal lidocaine for the short-term treatment of headache.	Neither for nor against	Reviewed, new-replaced	32, 79, 145, 222, 223
38	There is insufficient evidence to recommend for or against pulsed radiofrequency procedure of the upper cervical nerves or sphenopalatine ganglion block for the treatment of chronic migraine.	Neither for nor against	Reviewed, new-replaced	224, 225
39	We suggest against an implantable sphenopalatine ganglion stimulator for the treatment of cluster headache.	Weak against	Reviewed, new-added	226
40	We suggest against patent foramen ovale closure for the treatment or prevention of migraine.	Weak against	Reviewed, new-added	227, 228
Nonpharmacologic therapy				
41	We suggest noninvasive vagus nerve stimulation for the short-term treatment of episodic cluster headache.	Weak for	Reviewed, not changed	229, 230
42	We suggest physical therapy for the management of tension-type, migraine, or cervicogenic headache.	Weak for	Reviewed, new-replaced	70, 71, 231–238 Additional evidence: 239
43	We suggest aerobic exercise or progressive strength training for the prevention of tension-type and migraine headache.	Weak for	Not reviewed, amended	72, 73, 74–76 Additional evidence: 239
44	There is insufficient evidence to recommend for or against the following behavioral interventions for the treatment and/or prevention of headache: Biofeedback and smartphone application–based heart rate variability monitoring Cognitive behavioral therapy Mindfulness-based therapies Progressive muscle relaxation	Neither for nor against	Reviewed, new-replaced	60–69, 240–243
45	There is insufficient evidence to recommend for or against acupuncture, dry needling, or yoga for the treatment and/or prevention of headache.	Neither for nor against	Reviewed, new-replaced	69, 71, 224, 225, 244–260
46	There is insufficient evidence to recommend for or against dietary trigger avoidance for the prevention of headache.	Neither for nor against	Not reviewed, amended	261, 262
47	We suggest against IgG antibody testing for dietary trigger avoidance for the prevention of headache.	Weak against	Not reviewed, amended	263, 264
48	There is insufficient evidence to recommend for or against any form of neuromodulation for the treatment and/or prevention of migraine: Noninvasive vagus nerve stimulation Supraorbital, or external trigeminal, nerve stimulation Remote electrical neurostimulation External combined occipital and trigeminal neurostimulation system Repetitive transcranial magnetic stimulation Transcranial direct current stimulation	Neither for nor against	Reviewed, new-replaced	265–285
Comparative effectiveness and combination therapies				
49	There is insufficient evidence to recommend for or against choosing a specific treatment strategy for posttraumatic headache.	Neither for nor against	Reviewed, new-added	278, 286–289
50	There is insufficient evidence to recommend for or against any specific medication over another for the short-term treatment of migraine.	Neither for nor against	Reviewed, new-added	79–84
51	There is insufficient evidence to recommend for or against any specific medication over another for the prevention of migraine headache, tension headache, or cluster headache.	Neither for nor against	Reviewed, new-added	48, 49, 77, 78, 85–91
52	There is insufficient evidence to recommend for or against any specific combination of therapies for the prevention of headache.	Neither for nor against	Reviewed, new-replaced	290–298

* Two recommendations from 2020 were eliminated:
We suggest education regarding dietary trigger avoidance for the prevention of migraine.
There is insufficient evidence to recommend for or against an elimination diet based on IgG antibody test results for the prevention of headache.

5-HT_{1F} agonist that consistently demonstrated a robust benefit in the critical outcomes of pain freedom and pain relief at 2 hours. However, given its adverse effect profile (for example, driving restrictions) and low number needed to harm of 4 for treatment-emergent adverse effects (31–37), the WG did not assign a directional recommendation.

Injections, Infusions, and Procedures

Greater occipital nerve blockade for the abortive treatment of migraine received an unchanged "weak for" recommendation after review of new evidence and the evidence from the 2020 CPG (Recommendation 34). The new evidence base consisted of a single RCT (38) that showed improvement (that is, reduced pain) versus placebo. As in the 2020 guideline (39–41), the overall quality of the evidence was deemed low. When applying the GRADE criteria, we noted that greater occipital nerve blockade has balanced risks and benefits. It did not cause more AEs than placebo. Greater occipital nerve blockade meets some patient values and has a favorable resource impact (for example, the technical skill can be easily taught, it is less resource intensive than intravenous treatment, and it can be used in an outpatient clinic setting); therefore, the recommendation remained "weak for." This intervention can easily be learned and performed by primary care physicians and other clinicians.

PREVENTIVE THERAPIES FOR EM OR CM

Preventive migraine therapies should be initiated when patients have 4 or more migraine days per month or when they have 2 or more migraine days with significant disability despite the appropriate use of acute migraine therapies (42). The International Classification of Headache Disorders, 3rd Edition, differentiates between EM and CM: EM occurs when a patient has fewer than 15 headaches a month over a 3-month period, whereas CM causes symptoms on 15 or more days per month (Sidebar 3 in Part 3 of the **Supplement**) (300, 301). The same treatment method may have different evidence recommendations dependent on whether EM or CM is being considered. Goals of migraine prevention include reducing the severity, duration, and frequency of migraines; improving migraine-related disability; enhancing the responsiveness of abortive migraine treatments; and decreasing the overall number of abortive medication treatments used for migraines. Critical outcomes considered for preventive therapies are related to change in headache and migraine days and include change in mean monthly headache and mean monthly migraine days from baseline and change in number of moderate or severe headache days.

Pharmacotherapies

The WG reviewed new evidence for CGRP-acting agents, including CGRP monoclonal antibodies and gepants. This resulted in several new-added and new-replaced recommendations for these medications. Compared with those in the 2020 CPG, the recommendations for erenumab, fremanezumab, and galcanezumab for prevention of EM or CM increased in strength to "strong for" (Recommendation 5) on the basis of additional evidence supporting the efficacy of these agents. Updated evidence included a network MA of 6979 patients with EM or CM from 13 RCTs (43). In both EM and CM, these 3 CGRP monoclonal antibodies resulted in reductions in mean monthly migraine days and abortive medication use. Clinicians should be aware that some postmarketing studies have shown an increased risk for development or worsening of hypertension with erenumab (44, 45), and the prescribing information has since been revised to include this in the warning and precautions.

Recommendations related to gepants are new to the 2023 guideline. Atogepant has a "weak for" recommendation, and rimegepant has a "neither for not against" recommendation for EM prevention (Recommendations 13 and 16, respectively). An MA of 2466 patients with EM treated with atogepant from 3 RCTs demonstrated statistically significant reductions in monthly migraine days, monthly headache days, and monthly days with use of abortive medication (46). Rimegepant, when used for the prevention of EM, resulted in a statistically significant reduction in monthly migraine days (0.8), which the WG did not consider clinically significant (47).

Topiramate was given a new "weak for" recommendation for the prevention of both EM and CM (Recommendation 9). An SR by Yang and colleagues (48) demonstrated a statistically significant reduction of 2.30 monthly migraine days in patients with CM receiving topiramate versus placebo. Consistent with the 2020 evidence, an SR by Overeem and colleagues (49) demonstrated a significant reduction of 1.1 monthly migraine days in patients with EM receiving topiramate versus placebo. Reevaluation of evidence for valproate included 2 randomized, placebo-controlled trials (50, 51), resulting in a change from "neither for nor against" to a "weak for" recommendation for valproate for the prevention of EM (Recommendation 11). All statistically significant reductions in mean monthly migraine days for these therapies also reached the threshold for clinical significance.

The 2023 guideline now suggests against the use of gabapentin for the prevention of EM (Recommendation 17). In an SR by Mulleners and colleagues (50) that included 6 RCTs, no study met the predefined critical outcome for migraine prevention (change in monthly headache and migraine days). Although gabapentin misuse, dependence, and withdrawal were documented largely in non–headache-specific populations, the WG also noted evidence of these issues (52), which contributed to the risk-versus-benefit assessment of gabapentin.

Injections, Infusions, and Procedures

The role of neurotoxin injections differs on the basis of whether they are given for prevention of EM or CM. Systematic reviews examining onabotulinumtoxinA injection for CM have consistently found a statistically significant reduction in headache days per month compared with placebo, and we suggest its use for CM of 1.8 headache days per month ("weak for") (Recommendation 14) (48, 53, 54). In comparison, the injection of onabotulinumtoxinA or abobotulinumtoxinA for the prevention of EM has not demonstrated a reduction in monthly migraine days or monthly headache days, but AE frequency favors placebo over treatment; thus, we suggest against their use for prevention of EM ("weak against") (Recommendation 15) (54). Unlike for its role in the abortive treatment of migraine, evidence is insufficient to recommend for or against greater occipital nerve block for the prevention of CM (Recommendation 36).

Eptinezumab is the first intravenous CGRP antagonist available for the prevention of EM and CM. One SR and another SR and MA examining the efficacy and safety data reported a similar reduction in mean monthly migraine days, especially with the 300-mg dose (136). Across studies, treatment-emergent AEs did not differ significantly between eptinezumab and placebo. The WG found that the benefits of eptinezumab slightly outweighed the harms and burdens and noted that, although eptinezumab is efficacious and safe for the prevention of migraine, this treatment requires health care center infrastructure to provide the intravenous infusions and time commitment from the patient. Given all this, eptinezumab received a "weak for" recommendation (Recommendation 6).

Abortive and Preventive Therapies for TTH

Tension-type headache is the most common primary headache disorder, with a 26% global prevalence (8). The goals of abortive and preventive treatment of TTH are similar to those of migraine. Critical TTH outcomes included time to pain freedom and headache intensity 2 hours after treatment for studies related to abortive management and reduction in headache days from baseline and change in the number of moderate or severe headache days for studies focusing on prevention.

For treatment of acute TTH, we suggest ibuprofen (400 mg) or acetaminophen (1000 mg) ("weak for") because both demonstrate statistically significant improvement in pain-free response at 2 hours (Recommendation 27). Of note, acetaminophen doses lower than 1000 mg (for example, 500 to 650 mg) did not show statistically significant improvement (55–57). Amitriptyline at 50 mg and 100 mg is recommended for preventive treatment ("weak for") because both doses were found to significantly reduce monthly headache days (Recommendation 25). Clinicians should be aware of anticholinergic adverse effects, especially among older patients and those with multiple cardiac comorbid conditions, as well as the potential for overdose. In comparison, onabotulinumtoxinA for chronic TTH did not show statistically significant improvement in critical outcomes in an SR of 12 RCTs and is not recommended ("weak against") (Recommendation 26) (58, 59).

Nonpharmacologic Therapies for Headache Management: Behavioral Medicine, Rehabilitation Interventions, and Neuromodulation

Interest in NPIs has increased in the past 5 years. Health care organizations are starting to group NPIs into subsets, including behavioral health, acupuncture, neuromodulation, and physical therapies (302). For the CPG, a patient focus group was held before research questions were developed for this iteration: 9 veterans and active-duty service members were queried as to perceived barriers and facilitators to receiving care and its effect on their quality of life. Patients expressed beliefs that the cause of headaches is multifaceted and that the use of multiple types of therapies (for example, medication and NPIs) helped headache management; they also expressed the desire to better understand the cause of their headaches. The WG evaluated behavioral medicine interventions, rehabilitation interventions, and neuromodulation along with complementary integrative health (that is, acupuncture and yoga) approaches.

Behavioral Medicine Interventions

The WG reviewed biofeedback and smartphone application–based heart rate variability monitoring (60), cognitive behavioral therapy (61–63), mindfulness-based therapies (64–67), and progressive muscle relaxation (73, 74) approaches to the management of headache disease. Across studies reviewed by the WG, data either did not support the use of a specific approach (that is, biofeedback and smartphone application–based heart rate variability monitoring) (61–63) or were mixed (specifically for cognitive behavioral therapy, mindfulness-based therapies, and progressive muscle relaxation when not combined with another behavioral medicine intervention). Evidence was insufficient to recommend for or against biofeedback and smartphone application–based heart rate variability monitoring, cognitive behavioral therapy, mindfulness-based therapies, and progressive muscle relaxation (Recommendation 44).

Rehabilitation Interventions

Rehabilitation delivered through physical therapy (PT) received a "weak for" recommendation and is beneficial in the management of migraine and TTH

(Recommendation 42). A combination of techniques described in an SR of 7 RCTs (70, 71) included thermal methods, trigger point massage, and mobilization and manipulation techniques delivered by a physical therapist and were better than sham interventions or medications at reducing headache frequency and intensity.

Aerobic exercise or progressive strength training received a "weak for" recommendation for the prevention of both migraine and TTH (Recommendation 43) (72–76, 303). The frequency of aerobic exercise varied but was generally 2 to 3 times per week for 30 to 60 minutes. Upper-body progressive strength training was supervised, typically 3 times per week for 30 minutes. The benefits of PT outweighed the likelihood of AEs, which were not explicitly reported in the studies reviewed, although supervised PT is generally considered safe. Supervised aerobic exercise and PT are treatment options for those living with migraine and TTH and can be done with an eye toward improving headache control, weight reduction, and mitigation of future vascular risk.

Neuromodulation

Neuromodulation refers to a treatment approach where the central or peripheral nervous system is stimulated via energy (typically electric or magnetic) with the intention of regulating neural pathways and alleviating pain and other symptoms associated with headache. Studies assessing acute migraine treatment have recorded inconsistent outcomes, and those examining migraine prevention have had small sample sizes. Therefore, the WG believed that the strength of the evidence for neuromodulation was limited for critical and important outcomes for acute and preventive treatment of migraines; this resulted in insufficient evidence to recommend for or against any form of neuromodulation for the abortive or preventive treatment of migraine (Recommendation 48). When considering neuromodulation as a treatment option, clinicians should be aware of contraindications for each type of therapy and differences in the frequency of treatment duration between devices and within the same device dependent on whether the acute or preventive setting is being used.

Comparison With Other Guidelines

The 2023 VA/DoD headache guidelines provide a broad scope of recommendations for the 3 most common primary headache types and selected secondary headache types (such as medication overuse headache). Although these guidelines differ in scope and development from those of the American Academy of Neurology (AAN) and American Headache Society (AHS), which typically encompass a singular headache type (304–308), there are many consistent messages. For acute migraine, these include recommendations for triptans and avoidance of opioids (304, 305). For migraine prevention, these include recommendations for lisinopril, candesartan, topiramate, propranolol, and valproate (306). Similar to the 2016 AAN guideline for botulinum toxin use in headache, the VA/DoD guideline recommends botulinum toxin for the prevention of CM but not EM or TTH (307).

The most recent AAN and AHS guidelines for migraine did not discuss CGRP monoclonal antibodies, gepants, or lasmiditan because these pharmacotherapies were only recently approved. In 2021, the AHS released a consensus statement on integrating new migraine treatments into clinical practice (42). In 2024 (after the review period for the VA/DoD headache CPG), AHS released a position statement on CGRP-targeting therapies as a first-line option for the prevention of migraine (309). Both the VA/DoD guideline and this consensus statement recommend CGRP antibody therapy as an option for migraine prevention and gepants as an option for acute migraine treatment.

Recommendations related to rehabilitation approaches in the management of migraine, including PT and exercise, are unique to this guideline.

Comparative efficacy is a topic of increasing interest given the number of new headache pharmacotherapies. Yet, robust head-to-head evidence is largely unavailable because phase 3 trials still compare new pharmacotherapies versus placebo. Unique to the VA/DoD guidelines, evidence for comparative efficacy was evaluated for both abortive and preventive pharmacologic treatment of headache and separately for combinations of therapies for the prevention of headache. After reviewing multiple MAs, we found insufficient evidence to recommend for or against any specific medication over another for abortive or preventive headache treatment (Recommendations 50 to 53) (48, 49, 77–91).

Research Recommendations

The WG identified topics needing additional research, including the types of therapies and headache conditions studied, the patient populations enrolled, greater standardization of protocols for nonpharmacotherapies, comparative effectiveness studies beyond network MAs, and trial designs beyond those using patient-level randomization.

Meaningful comparative effectiveness studies that compare mechanistically similar active treatments (for example, medications in the same class or "older" vs. "newer" pharmacotherapies) or compare a pharmacotherapy with a nonpharmacotherapy would be helpful (310). Trials studying pharmacotherapies and nonpharmacotherapies for less well-studied headache types, including posttraumatic headache, are warranted.

Future trials should extend to include underrepresented patient groups, including men and marginalized underserved groups. Current literature indicated that persons living in rural areas, those with lower socioeconomic

status, and people of Hispanic and Latino descent bear a disproportionate burden of migraine (311, 312).

Studying combinations of therapies and adaptive trial designs that may more closely align with real-world health care settings is needed as well. In clinical care, headache management is done in an individualized way and adapts to the response (or nonresponse) of a given treatment, which can be emulated using sequential multiple assignment randomized trials (313). Pragmatic trials that use health care units, rather than patients, as the unit of randomization (such as cluster RCTs) have been underused in headache research.

CONCLUSION

In recent years, there has been an unprecedented expansion in the number of headache therapies. The quality of evidence for these medications has expanded the ability to effectively treat and prevent key primary headache disorders.

This CPG provides clinicians with the most up-to-date, evidence-based recommendations available for the evaluation and treatment of headache, combined with tables and algorithms to make the clinically pertinent information easily available. Primary care clinicians should consider triptans, aspirin–acetaminophen–caffeine, and newer CGRP inhibitors (gepants) as options for treatment of acute migraine. Medications to prevent EMs include angiotensin-receptor blockers, lisinopril, topiramate, valproate, eptinezumab, and atogepant. AbobotulinumtoxinA can be used for prevention of CM but not EM. Gabapentin is not recommended for prevention of EM. Ibuprofen (400 mg) and acetaminophen (1000 mg) can be used for treatment of TTH, and amitriptyline for prevention of chronic TTH. Aerobic exercise or PT can be used in management of TTH and migraines.

Clinicians should work with their patients in crafting treatment plans that account for headache type or types, comorbid conditions, and values and preferences.

From Headache Centers of Excellence Program, VA Connecticut Healthcare System, West Haven, and Yale School of Medicine, New Haven, Connecticut (J.J.S., A.S.G.); VA National Pharmacy Benefits Management Service, Hines, Illinois (N.M.A.); Evidence-Based Practice, Office of Quality and Patient Safety, VA Central Office, Department of Veterans Affairs, Washington, DC (J.B., J.S.); Bay Pines VA Healthcare System, Tampa, Florida (A.C.B.); Headache Center of Excellence, Minneapolis VA Medical Center, Minneapolis, Minnesota (F.J.M.); South Texas Veterans Health Care System, San Antonio, Texas (I.W.P.); ECRI, Plymouth Meeting, Pennsylvania (J.R.); Department of Neurology, Pain Management Program, Washington VA Medical Center, Washington, DC (F.S.); Post-Deployment Rehabilitation and Evaluation Program TBI Clinic, James A. Haley Veterans' Hospital, Tampa, Florida (K.M.S.); Casualty Care Research Team, U.S. Army Institute of Surgical Research, Joint Base, San Antonio, and Brooke Army Medical Center, Fort Sam Houston, Texas (T.R.S.); Rehabilitation and Extended Care and Headache Center of Excellence, Minneapolis VA Health Care System, Minneapolis, Minnesota (R.V.); Office of Quality and Patient Safety, VA Central Office, Department of Veterans Affairs, Washington, DC (L.W.); and Aeromedical Consultation Service, U.S. Air Force School of Aerospace Medicine, Wright-Patterson Air Force Base, Ohio; Wright State University Boonshoft School of Medicine, Dayton, Ohio; and Uniformed Services University F. Edward Hebert School of Medicine, Bethesda, Maryland (A.W.F.).

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Corresponding Author: Jason J. Sico, MD, MHS, VA Connecticut Healthcare System, 200 Edison Road, Orange, CT 06477; e-mail, Jason.sico@va.gov.

Author contributions are available at Annals.org.

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Author Contributions: Conception and design: J.J. Sico, K.M. Skop, T.R. Stark, R. Vogsland, A.W. Ford, J. Ballard-Hernandez, A.S. Grinberg, F.J. Macedo, I.W. Pace.
Analysis and interpretation of the data: F. Sandbrink, K.M. Skop, T.R. Stark, R. Vogsland, A.W. Ford, A.S. Grinberg, F.J. Macedo, I.W. Pace, J. Reston.
Drafting of the article: J.J. Sico, K.M. Skop, T.R. Stark, R. Vogsland, L. Wayman, A.W. Ford, N.M. Antonovich, J. Ballard-Hernandez, A.C. Buelt, A.S. Grinberg, F.J. Macedo, I.W. Pace, J. Reston, J. Sall.
Critical revision for important intellectual content: J.J. Sico, F. Sandbrink, K.M. Skop, T.R. Stark, R. Vogsland, A.W. Ford, A.S. Grinberg, F.J. Macedo, I.W. Pace.
Final approval of the article: J.J. Sico, F. Sandbrink, K.M. Skop, T.R. Stark, R. Vogsland, L. Wayman, A.W. Ford, N.M. Antonovich, J. Ballard-Hernandez, A.C. Buelt, A.S. Grinberg, F. J. Macedo, I.W. Pace, J. Reston, J. Sall.
Provision of study materials or patients: K.M. Skop.
Statistical expertise: J.J. Sico.
Administrative, technical, or logistic support: L. Wayman, J. Ballard-Hernandez, J. Sall.
Collection and assembly of data: K.M. Skop, T.R. Stark, R. Vogsland, A.W. Ford, F.J. Macedo, J. Reston.