VA/DoD CLINICAL PRACTICE GUIDELINE FOR MANAGEMENT OF HEADACHE

Department of Veterans Affairs
Department of Defense

QUALIFYING STATEMENTS

The Department of Veterans Affairs (VA) and the Department of Defense (DoD) guidelines are based on the best information available at the time of publication. The guidelines are designed to provide information and assist decision making. They are not intended to define a standard of care and should not be construed as one. Neither should they be interpreted as prescribing an exclusive course of management.

This clinical practice guideline (CPG) is based on a systematic review of both clinical and epidemiological evidence. Developed by a panel of multidisciplinary experts, it provides a clear explanation of the logical relationships between various care options and health outcomes while rating both the quality of the evidence and the strength of the recommendation.

Variations in practice will inevitably and appropriately occur when providers consider the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Therefore, every health care professional using these guidelines is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation with a patient-centered approach.

These guidelines are not intended to represent VA or DoD policies. Further, inclusion of recommendations for specific testing, therapeutic interventions, or both within these guidelines does not guarantee coverage of civilian sector care.

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Prepared by

Management of Headache Work Group

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and

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I. Introduction

The VA and DoD Evidence-Based Practice Work Group (EBPWG) was established and first chartered in 2004, with a mission to advise the VA/DoD Health Executive Committee "on the use of clinical and epidemiological evidence to improve the health of the population . . ." across the Veterans Health Administration (VHA) and Defense Health Agency (DHA), by facilitating the development of CPGs for the VA and DoD populations.(1) Development and update of VA/DoD CPGs is funded by VA Evidence Based Practice, Office of Quality and Patient Safety. The system-wide goal of evidence-based CPGs is to improve patient health and wellbeing.

In July 2020, the VA and DoD published a CPG for The Primary Care Management of Headache (2020 VA/DoD Headache CPG), which was based on evidence reviewed through March 2019. Since the release of that CPG, the evidence base on Headache has expanded. Consequently, the EBPWG initiated the update of the 2020 VA/DoD Headache CPG in 2023. This updated CPG's use of Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach reflects a more rigorous application of the methodology than previous iterations.(2) Therefore, the strength of some recommendations may have been modified due to the confidence in the quality of the supporting evidence (see Evidence Quality and Recommendation Strength).

This CPG provides an evidence-based framework for evaluating and managing care for individuals living with Headache toward improving clinical outcomes. Successful implementation of this CPG will:

- Assess the patient's condition and collaborate with the patient, family, and caregivers to determine optimal management of patient care;
- Emphasize the use of patient-centered care and shared decision making;
- Minimize preventable complications and morbidity; and
- Optimize individual health outcomes and quality of life (QoL).

II. Background

A. Classification of Headache

The current diagnostic criteria for headache disorders[a] are found in the International Classification of Headache Disorders, 3rd edition (ICHD-3), accessible for free online (see Appendix B).[b] In broad terms, headache disorders can be divided into two types: primary headache disorders and secondary headache disorders. Primary headache disorders refer to a set of headaches that are idiopathic, recurrent, and stereotyped, without underlying secondary causes. Secondary headache disorders include those headaches

[a] Unless otherwise specified, the term "headache" refers to general headache.
[b] ICHD-3 diagnostic criteria are available at https://ichd-3.org/.

that can be attributed to trauma to the head, the neck, or both; a cranial or cervical vascular disorder; a non-vascular intracranial disorder; a substance or its withdrawal; an infection; a disorder of homeostasis; a disorder of the cranium, neck, eyes, ears, nose, sinuses, mouth, or other facial or cervical structure; or a psychiatric disorder.

a. Language to Reduce Stigma

When communicating with Veterans and active duty Service members, considering that language can shape perceptions is important. For example, the term “attack” is frequently used within the headache community to distinguish among the acute symptoms an individual is experiencing from the chronic disease itself, yet it can hold negative connotations, often signifies an external locus of control, and might have strong connotations for Veterans and active duty Service members.(3) Although communicating the severity and fluctuating nature of headache diseases is essential, you might consider using phrases such as “symptom onset” or “symptom escalation” rather than the word attack. As part of providing patient-centered care and to most accurately understand their experiences, asking the Veteran or active duty Service member their language preference can be helpful to describe both discrete headaches and their overall headache disease.

b. Primary Headache Disorders

Any primary or secondary headache type can occur in DoD or VA populations. However, outside the most common primary headache types, little evidence exists regarding optimal treatment. Thus, the treatment of rare headache types is outside the scope of this CPG, and individuals should be referred to the appropriate specialist for evaluation and treatment. The most common primary headache disorders include tension-type headache (TTH), migraine, and cluster headache, which are reviewed in Table 1. This table is intended only to assist with the rapid classification of headaches and should not be used as a substitute for the full ICHD-3 criteria.

A diagnosis of “definite” TTH requires at least 10 headaches lasting 30 minutes to 7 days with at least two defining characteristics (i.e., bilateral location, non-pulsating quality, mild to moderate intensity, not aggravated by routine physical activity) and both of the associated features (i.e., no nausea or vomiting; either photophobia or phonophobia, but not both). If headaches fulfill all but one of the TTH criteria (e.g., having both photophobia and phonophobia), the diagnosis would be probable TTH.

A diagnosis of definite migraine requires at least five headaches lasting 4–72 hours with at least two defining headache characteristics (i.e., unilateral throbbing or pulsating, moderate or severe intensity, aggravated, or caused by routine physical activity) and at least one associated feature (i.e., nausea, vomiting, or both and both photophobia and phonophobia). If headaches fulfill all but one of the migraine criteria (e.g., photophobia or phonophobia but not photophobia and phonophobia), the diagnosis would be probable migraine.

A diagnosis of cluster headache requires at least five headaches of severe to very severe unilateral orbital, supraorbital, or temporal pain or any combination of such pain lasting 15–180 minutes and occurring once every other day to no more than eight times a day. Either or both autonomic features and a feeling of restlessness or agitation are required. Definite cluster headache must fulfill all these criteria. “Probable” cluster headache fulfills all criteria except one. Autonomic symptoms include conjunctival injection, lacrimation, or both; nasal congestions, rhinorrhea, or both; eyelid edema; forehead and facial sweating; miosis, ptosis, or both.

Across primary headache disorders, the term “chronic” is used differently based on the primary headache diagnosis. For migraine and TTH, chronic refers to having frequent headaches occurring on 15 or more days per month for more than 3 months; however, when applied to cluster headaches, chronic refers to headaches occurring for 1 year or longer without remission or with remission periods lasting fewer than 3 months. Primary headaches are recurrent by nature, so a single or first-time headache should prompt appropriate evaluation for secondary causes, as guided by the history and physical examination. As with all criteria-based diagnoses, these criteria apply only if the diagnosis is not better accounted for by another ICHD-3 diagnosis.

Table 1. Common Primary Headache Disorders[*]

		Tension-Type Headache [a]	Migraine Headache [b]	Cluster Headache [c]
Headache Symptom Duration and Frequency	**Duration**	30 minutes to 7 days	4–72 hours	15–180 minutes
	Frequency	Variable	Variable	Once every other day to eight per day; often occurring at the same time of day
Headache Characteristics	**Severity**	Mild to moderate	Moderate to severe	Severe or very severe
	Location	Bilateral	Unilateral	Unilateral orbital, supraorbital, or temporal pain or any combination of such pain
	Quality	Pressing or tightening, non-pulsating	Throbbing or pulsating	Stabbing, boring
	Aggravated by routine physical activity	Not aggravated by routine activity	Aggravated by routine activity	Causes a sense of agitation or restlessness; routine activity might improve symptoms

		Tension-Type Headache [a]	Migraine Headache [b]	Cluster Headache [c]
Associated Features	**Photophobia and phonophobia**	Can have one but not both	Both	Variably present
	Nausea, vomiting, or both	Neither	Either or both	Might be present
Other Features	**Autonomic features**[d]	None	Might occur but are often subtle and not noticed by the patient	Prominent autonomic features ipsilateral to the pain (see Appendix B)

* There are definitions for probable TTH, probable migraine, or probable cluster headache where patients might not fulfill all criteria listed above. The Work Group suggests that providers should not withhold therapy when patients do not meet all criteria listed for TTH, migraine, or cluster headache (i.e., are diagnosed with probable TTH, probable migraine, or probable cluster headache).(4) Providers should continually reassess patients during therapy.

[a] A diagnosis of TTH requires at least 10 headache episodes lasting 30 minutes to 7 days with at least two defining characteristics (i.e., bilateral location, non-pulsating quality, mild to moderate intensity, not aggravated by routine physical activity) and both associated features (i.e., no nausea or vomiting; either photophobia or phonophobia, but not both). If headaches fulfill all but one of the TTH criteria (e.g., having both photophobia and phonophobia), the diagnosis would be probable TTH.

[b] A diagnosis of migraine requires at least five headache episodes lasting 4–72 hours with at least two defining headache characteristics (i.e., unilateral throbbing or pulsating, moderate or severe intensity, aggravated, or caused by routine physical activity) and at least one associated feature (i.e., nausea, vomiting, or both and both photophobia and phonophobia). If headaches fulfill all but one of the migraine criteria (e.g., photophobia or phonophobia but not photophobia and phonophobia), the diagnosis would be probable migraine.

[c] A diagnosis of cluster headache requires at least five headache episodes of severe to very severe unilateral orbital, supraorbital, or temporal pain or any combination of such pain lasting 15–180 minutes and occurring once every other day to no more than eight times a day. Either or both autonomic features and a feeling of restlessness or agitation are required.

[d] Autonomic features include nasal congestion, rhinorrhea, or both; periorbital edema; miosis, ptosis, or both; conjunctival injection, lacrimation, or both.

c. Secondary Headache Disorders

The initial evaluation of patients with headache should focus on determining whether a secondary cause for the headache exists or whether a primary headache diagnosis is appropriate. Emergent evaluation should be considered based on the presence of red flag features (see Sidebar 1). In general, a secondary headache can be diagnosed if the headache is new and occurs in close temporal relation to another disorder known to cause headache or when a preexisting headache disorder significantly worsens in close temporal relation to a causative disorder. In instances where a preexisting headache disorder is worsened by a causative disorder, both the primary and secondary headache diagnoses should be given (e.g., migraine and medication overuse headache [MOH]).

This CPG addresses the management of three secondary headache types: cervicogenic headache, posttraumatic headache (PTH) (described in the ICHD-3 as a headache attributed to traumatic injury to the head, neck, or both), and MOH. These secondary headache types are the most encountered, based on the clinical experience

of the Work Group members; thus, the systematic evidence review was limited to these three secondary headache types.

Cervicogenic headache refers to a headache that results from disorders in the bony, intervertebral disc or in the muscular or other soft tissue elements of the neck and is usually associated with neck pain. The diagnosis requires clinical or imaging evidence of a disorder in the upper cervical region known to cause headaches. In addition, criteria must be met showing that the cervical disorder is the cause of the headache, as evidenced by at least two of the following: the headache developed in temporal relation to the cervical disorder, the headache significantly improves or resolves in parallel with the cervical disorder, cervical range of motion is reduced and the headache is worsened by provocative maneuvers, the headache is abolished following diagnostic blockade of the cervical structure or its nerve supply.

Posttraumatic headaches are headaches attributed to traumatic injury of the head, neck, body, or any combination of these areas. Posttraumatic headache is one of the most common complaints following traumatic brain injury (TBI), whiplash, or other physical traumas. It can occur after mild, moderate, or severe TBI and is divided into an acute form and a persistent form. To meet the diagnostic criteria, a PTH must have a close temporal relationship with the index injury, developing within 7 days of the injury or within 7 days of discontinuation of medications that could mask the headache. It should be noted that the ICHD-3 states that, “the stipulation that headache must be reported to have developed within 7 days is somewhat arbitrary.”(4) For clarification, the ICHD-3 also recognizes PTH can have “delayed onset” acute and persistent headache attributed to either mild or moderate-to-severe injury to the head that begins after 7 days and within 3 months of the index head injury. An acute PTH requires a headache of fewer than 3 months duration that can be attributed to a TBI. A persistent PTH extends beyond this period.

In addition, after a TBI, ruling out other possible secondary causes of headaches, such as cerebrospinal fluid leak or such potentially life-threatening conditions as intracranial hemorrhages (i.e., epidural hemorrhage, subdural hemorrhage, subarachnoid hemorrhage, intraparenchymal hemorrhage) is important.(5)

For more information regarding the management of non-headache symptoms following a mild traumatic brain injury (mTBI), see the VA/DoD CPG for the Management and Rehabilitation of Post-Acute Mild Traumatic Brain Injury (VA/DoD mTBI CPG).[c]

Medication overuse headache, which had previously been called medication-misuse headache, rebound headache, or drug-induced headache, is an exceedingly common type of headache seen in primary and specialty care settings resulting from the excessive

[c] See the VA/DoD Clinical Practice Guideline for the Management and Rehabilitation of Post-Acute Mild Traumatic Brain Injury, available at https://www.healthquality.va.gov/.

use of nonprescription or prescription abortive headache medications (see Appendix B).(6) Patients with MOH might take as-needed abortive headache medications most days of the month and even multiple times a day within a given month without realizing the potentially negative consequences of doing so.(7) Medication overuse typically happens because the underlying headache condition for which they are taking abortive medications is inadequately controlled.(8) To illustrate the point, in the United States (U.S.), nearly one-quarter of people with chronic headaches take abortive medications daily.(6) Headache attributed to MOH occurs 15 or more days per month among patients with a prior diagnosis of headache (e.g., migraine) who have overused one or more medications for acute headache treatment for more than 3 months.

The ICHD-3 separates the type of MOH based on which abortive medications are overused. Medication overuse headache can be diagnosed among patients with a preexisting headache condition when they use non-opioid analgesic (e.g., acetaminophen, ibuprofen, triptans, butalbital-containing agents), opioid, or combination analgesic medications for the acute treatment of headache more than 10–15 days each month (dependent on the type of medication or medications used) (see Appendix B and Sidebar 1). The association between butalbital containing compounds and developing MOH is especially important for health care providers to be aware of, given the rate at which MOH can develop and the importance of not abruptly stopping these medications (because abrupt cessation can precipitate withdrawal seizures).(9) Medication overuse headache is a frequently missed diagnosis when evaluating chronic headache disorders. When MOH is unrecognized, treatment of the underlying headache disorder becomes more difficult. Medication overuse headache is a condition that can be treated or even prevented with judicious and infrequent use of abortive pain medications, close communication and collaboration between patients and health care providers regarding the degree of headache control, appropriate use of headache preventive medications, and accurate assessment of the use of as-needed pain medication.(6)

B. Epidemiology of Headache and Its Importance in the General Population

Headache is exceedingly prevalent and imposes a high burden on individuals living with the disease.(4, 10-15) Worldwide, TTH, migraine, and MOH are the most common headache disorders. The lifetime prevalence of any headache disorder is 66%; one-half of the people with a history of headache actively experience headache.(15, 16) Headache is the second leading cause of years lived with disability across all age groups, trailing only low back pain.(15) Moreover, more disability-adjusted life years (DALY) are attributable to headache than all other neurological disorders combined.(17) In addition, DALYs attributable to headache disorders have increased over time. Among persons ages 25 to 49, headache was the seventh leading condition associated with DALYs in 1990 and the fifth leading condition in 2019.(18) Ten percent of people living with headache report having multiple different types of headaches each week, and 3% report having some type of headache daily.(19)

Headache-related disability has a pronounced impact on individuals, their family members, and healthcare systems. Headache disability is linked to headache characteristics (e.g., throbbing, stabbing), frequency (e.g., hundreds of times a day, annually), associated features (e.g., nausea, photophobia, unilateral weakness), and conditions highly comorbid with headache (e.g., depression, stroke).(20) Furthermore, health-related QoL scores, a measure of an individual's perceived mental and physical health over time, might decrease during a headache and in periods between headaches.(20, 21) Although TTH is the most common type of headache, migraine contributes more to the total amount of disability seen in people with headaches. Health-related QoL scores are consistently lower among patients with migraine compared with healthy, age-matched comparators.(21, 22) Headaches negatively affect family life, group activities, relationships, and financial stability.(23) Stigma, or "a set of negative and often unfair beliefs that a society or group of people have about something," is commonly experienced by those living with migraine and other types of headache and is increasingly being recognized as an important contributor to headache disability.(24) Furthermore, stigma can worsen headache symptoms and is associated with impaired QoL.(3)

The prevalence of headache is higher in women and people ages 25 to 55.(4, 10-15) Within the U.S., the prevalence of self-reported migraine, severe headache, or both ranges between 15–18% in women and 6–10% in men; nearly one-half of women and men experience TTH.(25-27) Fluctuation in hormone levels can influence migraine and TTH in women.(28) Several studies note that migraine prevalence in women increases after menarche and peaks before menopause, affecting up to 25% of individuals of childbearing age.(11, 29, 30) Studies have found significant relationships between migraine and placental abruption, preeclampsia, and stroke during pregnancy.(31) Migraine might change throughout the menstrual cycle, specifically in terms of the severity of pain and most bothersome symptoms (MBS) and frequency. As such, pure menstrual migraine (i.e., migraine "occurring exclusively on day 1 ± 2 [days, -2 to + 3] of menstruation in at least two out of three menstrual cycles and at no other times of the cycle") and menstrually related migraine (i.e., migraine "occurring exclusively on day 1 ± 2 [days, -2 to +3] of menstruation in at least two of three menstrual cycles and additionally at other times of the cycle") might require different treatment approaches.(32) Given the high prevalence and increased risk of adverse outcomes related to migraine in individuals of childbearing age, discussion regarding contraception and early treatment to reduce the burden of disease while minimizing teratogenic effects should be considered among this population.(29) With the continued emergence of new therapies for migraine and other types of headache, such as calcitonin gene-related peptide (CGRP) inhibitors (both monoclonal antibodies [mAb] and -gepants) and neuromodulation, recognizing that little is known regarding their safety in pregnancy and lactation is important. Such resources as the World Health Organization (WHO) pharmacovigilance database and ongoing trials examining safety

of neuromodulation among pregnant patients will aid in the understanding of the efficacy, safety, and tolerability of these therapeutics.

Even less is known about the prevalence and treatment of headache in trans-identifying individuals, particularly trans-identifying women. A study done in the Netherlands of more than 900 trans-identifying women showed a prevalence of migraine of 26%, which was similar to cisgender women in the same population.(33) Although, a much smaller study done in Italy showed an increase in headaches among trans-identifying females posttreatment with estrogens and a decrease in headaches in most trans-identifying males posttreatment with androgens.(34) Beyond these studies, there is a paucity of literature regarding the treatment of headache in trans-identifying populations. Although most expert recommendations suggest that treatments are the same, as with all patients, a new headache requires an evaluation before treatment, particularly with the concern of the risk of estrogen increasing the risk of possible cerebral venous thrombosis and possibly even meningioma.(35, 36)

Headache also imposes societal costs that are direct (i.e., attributable to diagnosis and treatment) and indirect (i.e., the impact on productivity).(37, 38) The estimated annual direct and indirect medical costs of caring for people with migraines in the U.S. is approximately $36 billion. Sixty percent of costs are accounted for by physician office visits. The indirect annual cost is largely attributed to missed days of work (i.e., absenteeism) and impaired work function when people come to work while impaired by their headache (i.e., presenteeism).(37, 39)

Understanding health disparities as they relate to headache care has largely been unexplored. Men are historically underrepresented in headache research, including clinical trials and epidemiological work. For example, historically more than 80% of subjects enrolled in migraine clinical trials have been women, whereas 43% of women and 18% of men have migraine sometime during their lifetime.(40) When comparing differences between men and women receiving their headache care across VA, men are more likely to be diagnosed with “headache not otherwise specified,” less likely to have appointments for headache care, and less likely to see a provider outside primary care for their headache management.(41) Beyond sex differences in headache care, limited evidence suggests poorer health care utilization, more inaccurate diagnoses, and poorer care quality among Black patients compared with White, non-Hispanic patients with migraine.(42) Other marginalized and underserved groups also seem to bear disproportionate burden of migraine, including Hispanics and Latinos, people with low socioeconomic status, and persons living in rural areas.(43-45) These groups are underrepresented in headache and migraine research.

C. Headache within the VA Population

The management of headache in the Veteran population is complex, with literature suggesting that diagnoses have increased over the past decade. Over a 12-year period

from 2008 to 2019, the 1-year prevalence of Veterans diagnosed with migraine has steadily increased, from 8.5% to 13.0% and from 1.1% to 2.5%, for women and men respectively.(46) Furthermore, more than one-half of these migraine-diagnosed Veterans have received multiple headache diagnoses.(46) During this time period, 1.6% of all headaches among Veterans receiving care within VHA were cluster headaches.(41) In fiscal year 2017, approximately 380,000 Veterans sought care in the VA system for a headache disorder and more than 75% of headache management occurred within primary care.(47) The diagnosis of migraine is increasing in Operation Enduring Freedom and Operation Iraqi Freedom Veterans as well as in Veterans younger than 60 years old (approximately 13%) compared with older Veterans (approximately 2%).(48, 49) TBI is a strong predictor of headache as a symptom in the first year of care for a Veteran within VA, with the severity of TBI and history of recurrent TBIs associated with greater headache severity.(50, 51) Psychiatric comorbidities increase the likelihood of headache among those with a TBI diagnosis.(51) Treatment decisions for primary care providers (PCP) have increased in complexity with the rapid expansion of new headache treatments, further necessitating a clear algorithm for the diagnosis and management of headache disorders.(52) Additionally, the impacts of mTBI extend beyond headache; the reader is encouraged to review the VA/DoD mTBI CPG for further information and guidance for evaluation and management.[d]

D. Headache within the DoD Population

Headache is common among active duty Service members, although prevalence data is limited. In a longitudinal study including a large cohort of 77,000 participants (active duty Service members, Reservists, and National Guard), the self-reported prevalence of provider-diagnosed migraine was 6.9% in males and 20.9% in females.(53) This prevalence is similar to the civilian population.(53, 54) In contrast, the diagnosis of headache in the DoD population is steadily increasing with the rising incidence of PTH, mirroring increased rates of mTBI in the DoD population. More than 450,000 individuals in the military have reported mTBI over an 18-year period.(55) Mild traumatic brain injury can result in a complex set of physical, behavioral, and cognitive symptoms. The incidence of mTBI and concurrent headache in this population is four to five times higher than that in the general U.S. population.(56) Headaches are reported in 30–90% of active duty Service members diagnosed with TBI, according to the VA/DoD mTBI CPG.[e] This risk is even higher in active duty Service members who have previously deployed, with deployment status showing a five-fold increased risk for headaches related to head injury.(57) Clinical management of PTHs, migraine headaches, and other primary and secondary headaches in DoD populations continues to be a high priority.(58)

[d] See the VA/DoD Clinical Practice Guideline for the Management and Rehabilitation of Post-Acute Mild Traumatic Brain Injury, available at https://www.healthquality.va.gov/.

[e] See the VA/DoD Clinical Practice Guideline for the Management and Rehabilitation of Post-Acute Mild Traumatic Brain Injury, available at https://www.healthquality.va.gov/.

Department of Defense patients, especially those with special duties, can hesitate to report headaches or other painful conditions to their health care providers. This hesitation might stem from not wanting to appear "weak," not wanting to be taken off special duties or assignments, or both. For example, a recent study showed that military pilots self-report healthcare avoidance because of fear of loss of flight status.(59) This avoidance causes significant delay in accurately diagnosing and treating headache conditions and might lead to additional care challenges for the patients and providers.

In addition, many military duties have guidelines regarding the types of medications that are appropriate for use. Providers must be diligent in reviewing their patient's occupational history and job-specific duties before developing a treatment plan. A medication clinically indicated and medically appropriate might lead to duty limitations or even a review for military retention. Providers should strongly consider placing duty and mobility restrictions on active duty Service members when starting new medications, even if only temporarily, to allow for evaluation of treatment effect and assessment of potential side effects. Occupational medicine and flight medicine specialists can be consulted by primary care as needed for guidance and recommendations.

E. Posttraumatic Headache among Service Members

Similarly to the 2020 VA/DoD Headache CPG, PTH remains of particular interest within the Veteran and active duty Service member population. The incidence of mTBI and concurrent headache in this population is four to five times higher than that in the general U.S. population.(56) The financial impact of the diagnosis and treatment of mTBI in active duty Service members is estimated to range from $95 million to nearly $150 million.(60) Acute mTBI often presents itself among active duty Service members as a multifaceted, heterogeneous injury with myriad cognitive, sleep, and physical dysfunctions (e.g., visual, vestibular, headache, pain).(61) The stigma associated with reporting a TBI might lead to more chronic symptom burden. In active duty Service members and Veterans, the diagnosis and treatment of PTH can be complicated by the high prevalence of comorbidities such as posttraumatic stress disorder (PTSD) and cognitive, sleep, and other behavioral health disorders.(61)

Although PTH is most often associated with mTBI or concussion, whether the mechanism of TBI impacts headache presentation, treatment, or outcome is unclear.(62, 63) Researchers have reviewed the prevalence of post-deployment, concussion-related headaches as well as blast-related headaches. Specifically, blast-related headaches have been shown to account for 60% of post-deployment headaches, and 81% of all deployed active duty Service members reporting a concussion also report a headache.(64, 65)

Treatment of this type of secondary headache is guided by its symptom qualities. Researchers have begun to explore various types of headache "phenotypes" to aid in diagnosis and treatment.(66) Migraine, TTH, and a mixture of migraine and TTH tend to

be the most common phenotypes. “Treat the phenotype” is commonly used guidance when treating those living with PTH. However, there is a lack of high-quality, evidence-based acute and preventive pharmacotherapy for PTH, making it difficult to discern whether PTH will respond to the same care as treatment of a similar, primary headache type.

III. Scope of This Guideline

This CPG is based on published clinical evidence and related information available through August 16, 2022. It is intended to provide general guidance on best evidence-based practices (see Appendix A for additional information on the evidence review methodology). Although the CPG is intended to improve quality of care and clinical outcomes (see Introduction), it is not intended to define a standard of care (i.e., mandated or strictly required care).

A. Guideline Audience

This CPG is intended for use by PCPs and others involved in managing or co-managing patients with headache. Additionally, this CPG is intended for community-based clinicians involved in the care of active duty Service members, beneficiaries, or Veterans with headache.

B. Guideline Population

The patient population of interest for this CPG is patients who are living with headache who are eligible for care in the VA or DoD healthcare delivery systems, and those who receive care from community-based clinicians. It includes Veterans and active duty Service members as well as their dependents.

IV. Highlighted Features of This Guideline

A. Highlights in This Guideline

The field of headache medicine is rapidly expanding. The current document is an update to the 2020 VA/DoD Headache CPG to reflect a growing number of abortive and preventive pharmacotherapies and neuromodulation (aka “devices”) available for the management of migraine and other types of headaches. The following significant updates make it important that providers review this version of the CPG.

- The Work Group added 17 new recommendations, carried forward 13 recommendations, amended 7 recommendations, replaced 15 recommendations, and eliminated 2 recommendations (see Table 4 for definitions of recommendation categories and Appendix F for the 2020 VA/DoD Headache CPG recommendations and categories).
- Using more rigorous application of GRADE methodology (see Appendix A), the Work Group revisited prior recommendations, restructuring the critical and

important outcomes to better reflect those based on the evolving headache literature. The Work Group prioritized relevant outcomes seen in headache medicine (e.g., pain freedom and MBS as co-primary endpoints in acute migraine trials) and studies conducted in patient populations historically underrepresented in headache clinical trials.(67)

- Recommendations were developed on three additional abortive therapies (Recommendation 20, Recommendation 22, and Recommendation 24), seven preventive therapies (Recommendation 6, Recommendation 12, Recommendation 13, Recommendation 16, Recommendation 18, Recommendation 29, and Recommendation 30), one device (Recommendation 39), and three others (Recommendation 35, Recommendation 36 and Recommendation 40). These recommendations include new families of U.S. Food and Drug Administration (FDA)-approved medications (e.g., -gepants, -ditans) and FDA-cleared neuromodulation devices (e.g., remote electrical neuromodulation [REN]) for migraine or cluster headache or both).
- When available for critical and important outcomes for key questions (KQ), the Work Group considered clinically meaningful changes (also known as minimally important differences (MID) or minimum clinically important differences) in addition to statistically significant findings noted within the reviewed literature.(68)
- Therapeutics were divided into the following categories: (1) pharmacotherapies; (2) injections, procedures, and invasive interventions; and (3) non-pharmacologic modalities.
- The Work Group completed a critical appraisal and review of the comparative effectiveness and combination therapies (e.g., behavioral intervention and pharmacotherapy, and acute versus preventive pharmacotherapies).

The pace of clinical research on headache continues to grow every year. This CPG includes recommendations on the following key topics.

- Evaluation and management of MOH
- Pharmacotherapies
- Injections, infusions, and procedures
- Neuromodulation
- Behavioral interventions
- Rehabilitation approaches, including exercise
- Complementary and integrative health (CIH), including nutraceuticals
- Comparative effectiveness of acute and preventive pharmacotherapies
- Role of combination therapies (e.g., behavioral intervention and a pharmacotherapy)

Given the Work Group's more rigorous application of GRADE methodology, changes in critical and important outcomes, and consideration of relevant clinical meaningful application of the research, the strength of several recommendations has changed, as noted below and throughout the CPG.

For the following topics, recommendation strength was changed from *Weak for* to *Strong for*

- Erenumab, fremanezumab, or galcanezumab for the prevention of episodic or chronic migraine (Recommendation 5)
- Frovatriptan or rizatriptan for the acute treatment of migraine (Recommendation 19)

For the following topics, recommendation strength was changed from *Neither for nor against* to *Weak for*

- Valproate for the prevention of episodic migraine (Recommendation 11)
- Oxygen therapy for the acute treatment of cluster headache (Recommendation 32)

For the following topics, recommendation strength was changed from *Neither for nor against* to *Weak against*

- Gabapentin for the prevention of episodic migraine (Recommendation 17)
- Immunoglobulin G (IgG) antibody testing for dietary trigger avoidance for the prevention of headache (Recommendation 47)

For the following topics, recommendation strength was changed from *Weak for* to *Neither for nor against*

- Intravenous (IV) magnesium for the acute treatment of headache (Recommendation 37)
- Mindfulness-based therapies for the treatment or prevention of migraine or both (Recommendation 44)
- Dietary trigger avoidance for the prevention of migraine (Recommendation 46)

We have also included a Glossary of terms used throughout the CPG related to headache definitions, assessments, and interventions (Appendix H).

B. Components of this Guideline

This CPG provides clinical practice recommendations for the care of patients with Headache (see Recommendations). In addition, the Algorithm incorporates the recommendations in the context of the flow of patient care. This CPG also includes Research Priorities, which list areas the Work Group identified as needing additional research.

To accompany this CPG, the Work Group also developed toolkit materials for providers and patients, including a provider summary, a patient summary, and a pocket card, which can be found at https://www.healthquality.va.gov/index.asp.

C. Racial and Ethnic Demographic Terminology in this Guideline

Demographic terms referring to an individual's race or ethnicity (e.g., Hispanic, Latino or Latina, Asian, Native American, Black, African American, White, Caucasian) can be ambiguously defined and understood, reflecting diverse geographies, histories, cultures, and experiences. Aligned with the recent Executive Order on Further Advancing Racial Equity and Support for Underserved Communities through the Federal Government,[f] the Work Group used terms such as Black rather than African American and White rather than Caucasian to avoid presumptions about ancestry and to promote inclusivity, clarity, and consistency. However, to represent accurately the evidence on which this CPG is based, the Work Group generally deferred to racial and ethnic terminology as reported in the published systematic reviews (SR), clinical trials, and other studies comprising that evidence when summarizing or otherwise referring to those studies. Consequently, usage of demographic terms in this CPG might appear inconsistent.

D. Sex Terminology in this Guideline

Sex terminology is an area of rapidly evolving language and understanding within the healthcare sphere. The Work Group strove to use sex inclusive language throughout the guideline and notes that trans-identifying and nonbinary individuals might desire, seek, and experience pregnancy. However, to represent accurately the evidence on which this CPG is based, the Work Group generally deferred to sex terminology as reported in the published SRs, clinical trials, and other studies comprising the evidence when summarizing or otherwise referring to those studies. Consequently, sex terminology might appear to vary in this CPG.

V. Guideline Development Team

The VA Evidence Based Practice, Office of Quality and Patient Safety, in collaboration with the Clinical Quality Improvement Program, Defense Health Agency, identified the following four providers to serve as Champions (i.e., leaders) of this CPG's Work Group: Jason Sico, MD, MHS, FAHA, FACP, FAAN and Franz Macedo, DO from VA; and Christopher Spevak, MD, MPH, JD and Lt. Col Aven Ford, MD from DoD.

The Work Group comprised individuals with the following areas of expertise: counseling, internal medicine, mental health, nursing, pharmacy, primary care, psychiatry, psychology, and social work. Table 2 lists the Work Group and Guideline Development Team members.

[f] Executive Order on Further Advancing Racial Equity and Support for Underserved Communities Through The Federal Government | The White House

This CPG Work Group, led by the Champions, was tasked with

- Determining the scope of the CPG;
- Crafting clinically relevant KQs to guide the systematic evidence review;
- Identifying discussion topics for the patient focus group and considering the patient perspective;
- Providing direction on inclusion and exclusion criteria for the systematic evidence review and the assessment of the level and quality of evidence; and
- Developing evidence-based clinical practice recommendations, including determining the strength and category of each recommendation.

The Lewin Team, including The Lewin Group, ECRI, Sigma Health Consulting, and Duty First Consulting, was contracted by VA to help develop this CPG.

Table 2. Guideline Work Group and Guideline Development Team

Organization	Names*
Department of Veterans Affairs	**Jason Sico, MD, MHS, FAHA, FACP, FAAN (Champion)**
	Franz J. Macedo, DO (Champion)
	Natasha M. Antonovich, PharmD, BCPS
	Andrew C. Buelt, DO
	Amy S. Grinberg, PhD
	Ian W. Pace, PharmD
	Ronald G. Riechers II, MD
	Friedhelm Sandbrink, MD
	Karen M. Skop, PT, DPT, MS
	Rebecca Vogsland, DPT, OCS
	Karen A. Williams, DNP, FNP-BC, AQH, FAANP
Department of Defense	**Christopher J. Spevak, MD, MPH, JD (Champion)**
	Lt. Col Aven W. Ford, MD (Champion)
	CDR Jane Abanes, PhD, DNP, MSN/Ed, PMHCNS, PMHNP-BC, RN
	Rachael Coller, PharmD, BCPS, BCPP
	CAPT Sarah D. Dang, MD
	CDR Christina L. La Croix, DO
	Gary McKinney, DHSc, CBIS, CPT
	Tara M. Sheridan, MD
	COL Thomas R. Stark, DDS
VA Evidence Based Practice, Office of Quality and Patient Safety Veterans Health Administration	James Sall, PhD, FNP-BC
	René Sutton, BS, HCA
	Jennifer Ballard-Hernandez, DNP, RN, FNP-BC

Organization	Names*
Clinical Quality Improvement Program Defense Health Agency	Elaine P. Stuffel, MHA, BSN, RN
	Cynthia F. Villarreal, BSN, RN
	Isabella Alvarez, MA, BSN, RN
The Lewin Group	Cliff Goodman, PhD
	Erika Beam, MS
	Jennifer Weil, PhD
	Ryan Wilson, BA
	Peter Baroff, BA
	Inveer Nijjar, BS
	Elizabeth Himes, MPH
	Katherine McCracken, BA
ECRI	Jim Reston, PhD, MPH
	Amy Tsou, MD, MSc
	Michele Datko, MS
Sigma Health Consulting	James G. Smirniotopoulos, MD
	Frances M. Murphy, MD, MPH
Duty First Consulting	Kate Johnson, BS
	Rachel Piccolino, BA
	Anita Ramanathan, BA

* Additional contributor contact information is available in Appendix I.

VI. Summary of Guideline Development Methodology

The methodology used in developing this CPG follows the *Guideline for Guidelines*, an internal document of the VA/DoD EBPWG updated in January 2019 that outlines procedures for developing and submitting VA/DoD CPGs.(69) The *Guideline for Guidelines* is available at http://www.healthquality.va.gov/policy/index.asp. This CPG also aligns with the National Academy of Medicine's (NAM) principles of trustworthy CPGs (e.g., explanation of evidence quality and strength, management of potential conflicts of interest [COI], interdisciplinary stakeholder involvement, use of SR and external review).(70) Appendix A provides a detailed description of the CPG development methodology.

A. Evidence Quality and Recommendation Strength

The Work Group used the GRADE approach to craft each recommendation and determine its strength. Per the GRADE approach, recommendations must be evidence based and cannot be made based on expert opinion alone. The GRADE approach uses the following four domains to inform the strength of each recommendation (see Determining Recommendation Strength and Direction).(71)

1. Confidence in the quality of the evidence

2. Balance of desirable and undesirable outcomes
3. Patient values and preferences
4. Other considerations, as appropriate (e.g., resource use, equity, acceptability, feasibility, subgroup considerations)

Using these four domains, the Work Group determined the relative strength of each recommendation (*Strong* or *Weak*). The strength of a recommendation is defined as the extent to which one can be confident that the desirable effects of an intervention outweigh its undesirable effects and is based on the framework above, which incorporates the four domains.(72) A *Strong* recommendation generally indicates *High* or *Moderate* confidence in the quality of the available evidence, a clear difference in magnitude between the benefits and harms of an intervention, similar patient values and preferences, and understood influence of other implications (e.g., resource use, feasibility).

In some instances, insufficient evidence exists on which to base a recommendation for or against a particular therapy, preventive measure, or other intervention. For example, the systematic evidence review might have found little or no relevant evidence, inconclusive evidence, or conflicting evidence for the intervention. The manner in which this finding is expressed in the CPG might vary. In such instances, the Work Group might include among its set of recommendations a statement of insufficient evidence for an intervention that might be in common practice although it is unsupported by clinical evidence and particularly if other risks of continuing its use might exist (e.g., high opportunity cost, misallocation of resources). In other cases, the Work Group might decide to exclude this type of statement about an intervention. For example, the Work Group might remain silent where an absence of evidence occurs for a rarely used intervention. In other cases, an intervention might have a favorable balance of benefits and harms but might be a standard of care for which no recent evidence has been generated.[g]

Using these elements, the Work Group determines the strength and direction of each recommendation and formulates the recommendation with the general corresponding text as shown in Table 3.

[g] FDA approval for medications and FDA clearance for devices in and of itself is not a consideration within the GRADE approach.

Table 3. Strength and Direction of Recommendations and General Corresponding Text

Recommendation Strength and Direction	General Corresponding Text
Strong for	We recommend . . .
Weak for	We suggest . . .
Neither for nor against	There is insufficient evidence to recommend for or against . . .
Weak against	We suggest against . . .
Strong against	We recommend against . . .

That a recommendation's strength (i.e., *Strong* versus *Weak*) is distinct from its clinical importance (e.g., a *Weak* recommendation is evidence based and still important to clinical care) is important to note. The strength of each recommendation is shown in Recommendations.

This CPG's use of GRADE reflects a more rigorous application of the methodology than previous iterations; the determination of the strength of the recommendation is more directly linked to the confidence in the quality of the evidence on outcomes that are critical to clinical decision making. The confidence in the quality of the evidence is assessed using an objective, systematic approach independent of the clinical topic of interest. Therefore, recommendations on topics for which designing and conducting rigorous studies might be inherently more difficult (e.g., randomized controlled trials [RCT]) are typically supported by lower quality evidence and, in turn, *Weak* recommendations. Recommendations on topics for which rigorous studies can be designed and conducted might more often be *Strong* recommendations. Per GRADE, if the quality of evidence differs across the relevant critical outcomes, the lowest quality of evidence for any of the critical outcomes determines the overall quality of the evidence for a recommendation.(2, 73) This stricter standard provides a consistent approach to determining recommendation strengths. For additional information on GRADE or CPG methodology, see Appendix A.

B. Categorization of Clinical Practice Guideline Recommendations

Evidence-based CPGs should be current. Except for an original version of a new CPG, staying current typically requires revision of a CPG's previous versions based on new evidence or as scheduled subject to time-based expirations.(74) For example, the U.S. Preventive Services Task Force (USPSTF) has a process for monitoring the emergence of new evidence that could prompt an update of its recommendations, and it aims to review each topic at least every five years for either an update or reaffirmation.(75)

Recommendation categories were used to track how the previous CPG's recommendations could be reconciled. These categories and their corresponding definitions are similar to those used by the National Institute for Health and Care Excellence (NICE, England).(76, 77) Table 4 lists these categories, which are based on whether the evidence supporting a recommendation was systematically reviewed, the

degree to which the previous CPG's recommendation was modified, and whether a previous CPG's recommendation is relevant in the updated CPG.

Additional information regarding these categories and their definitions can be found in Recommendation Categorization. The 2023 CPG recommendation categories can be found in Recommendations. Appendix F outlines the 2020 VA/DoD Headache CPG's recommendation categories.

Table 4. Recommendation Categories and Definitions[a]

Evidence Reviewed	Recommendation Category	Definition
Reviewed[b]	New-added	New recommendation
	New-replaced	Recommendation from previous CPG was carried forward and revised
	Not changed	Recommendation from previous CPG was carried forward but unchanged
	Amended	Recommendation from previous CPG was carried forward with a nominal change
	Deleted	Recommendation from previous CPG was deleted
Not Reviewed[c]	Not changed	Recommendation from previous CPG was carried forward but unchanged
	Amended	Recommendation from previous CPG was carried forward with a nominal change
	Deleted	Recommendation from previous CPG was deleted

[a] Adapted from the NICE guideline manual (2012)(76) and Garcia et al. (2014)(77)

[b] The topic of this recommendation was covered in the evidence review carried out as part of the development of the current CPG.

[c] The topic of this recommendation was not covered in the evidence review carried out as part of the development of the current CPG.

Abbreviation: CPG: clinical practice guideline

C. Management of Potential or Actual Conflicts of Interest

Management of COIs for the CPGs is conducted as described in the *Guideline for Guidelines*.(40) Further, the *Guideline for Guidelines* refers to details in the VHA Handbook 1004.07 Financial Relationships between VHA Health Care Professionals and Industry (November 2014, issued by the VHA National Center for Ethics in Health Care),(49) as well as to disclosure statements (i.e., the standard disclosure form that is completed at least twice by CPG Work Group members and the guideline development team).(40) The disclosure form inquires regarding any relevant financial and intellectual interests or other relationships with, e.g., manufacturers of commercial products, providers of commercial services, or other commercial interests. The disclosure form also inquires regarding any other relationships or activities that could be perceived to have influenced, or that give the appearance of potentially influencing, a respondent's contributions to the CPG. In addition, instances of potential or actual COIs among the

CPG Work Group and the guideline development team were also subject to random web-based identification via standard electronic means (e.g., Centers for Medicare & Medicaid Services Open Payments and/or ProPublica).

No COIs were identified among the CPG Work Group or the guideline development team.

D. Patient Perspective

When developing a CPG, consideration should be given to patient perspectives and experiences, which often vary from those of providers.(73, 78) Focus groups can be used to help collect qualitative data on patient perspectives and experiences. VA and DoD Leadership arranged a virtual patient focus group on May 11, 2022. The focus group aimed to gain insights into patients with Headache of potential relevance and incorporate these insights into the CPG, as appropriate. Topics discussed included the patients' priorities, challenges they have experienced, information they have received regarding their care, and impacts of their care on their lives.

The patient focus group comprised a convenience sample of nine people. There were five males and four females. One participant was a Veteran who received care from the VA health system, and six participants were active duty Service members who received care from the DoD health system. Two participants received care from both VA and DoD health systems. The Work Group acknowledges this convenience sample is not representative of all patients with Headache within the VA and DoD health care systems and, thus, findings are ungeneralizable and do not comprise evidence. For more information on the patient focus group methods and findings, see Appendix D. The patient focus group participants were provided the opportunity to review the final draft and provide additional feedback.

E. External Peer Review

The Work Group drafted, reviewed, and edited this CPG using an iterative process. For more information, see Drafting and Finalizing the Guideline. Once the Work Group members completed a near-final draft, they identified experts from VA and DoD health care systems and outside organizations generally viewed as experts in the respective field to review it. The draft was sent to those experts for a 14-business-day review and comment period. The Work Group considered all feedback from the peer reviewers and modified the CPG where justified, in accordance with the evidence. Detailed information on the external peer review can be provided by the VA Office of Quality and Patient Safety.

F. Implementation

This CPG and algorithm are designed for adaptation by individual health care providers with respect to unique patient considerations and preferences, local needs, and resources. The algorithm serves as a tool to prompt providers to consider key decision

points in the care for a patient with Headache. The Work Group submits suggested performance metrics for VA and DoD to use when assessing the implementation of this CPG. Robust implementation is identified in VA and DoD internal implementation plans and policies. Additionally, implementation would entail wide dissemination through publication in the medical literature, online access, educational programs, and, ideally, electronic medical record programming in the form of clinical decision support tools at the point of care.

VII. Approach to Care in the Department of Veterans Affairs and the Department of Defense

A. Patient-Centered Care

Intended to consider patient needs and preferences, guideline recommendations represent a whole/holistic health approach to care that is patient centered, culturally appropriate, and available to people with limited literacy skills and physical, sensory, or learning disabilities. VA/DoD CPGs encourage providers to use a patient-centered, whole/holistic health approach (i.e., individualized treatment based on patient needs, characteristics, and preferences). This approach aims to treat the particular condition while also optimizing the individual's overall health and wellbeing.

Regardless of the care setting, all patients should have access to individualized evidence-based care. Patient-centered care can decrease patient anxiety, increase trust in providers, and improve treatment adherence.(79, 80) A whole/holistic health approach (https://www.va.gov/wholehealth/) empowers and equips individuals to meet their personal health and wellbeing goals. Good communication is essential and should be supported by evidence-based information tailored to each patient's needs. An empathetic and non-judgmental approach facilitates discussions sensitive to sex, culture, ethnicity, and other differences.

B. Shared Decision Making

This CPG encourages providers to practice shared decision making, a process in which providers, patients, and patient care partners (e.g., family, friends, caregivers) consider clinical evidence of benefits and risks as well as patient values and preferences to make decisions regarding the patient's treatment.(81) Shared decision making is emphasized in *Crossing the Quality Chasm,* an Institute of Medicine (IOM), now NAM, report in 2001 (82) and is inherent within the whole/holistic health approach. Providers must be adept at presenting information to their patients regarding individual treatments, expected risks, expected outcomes, and levels or settings of care or both, especially where patient heterogeneity in weighing risks and benefits might exist. Veterans Health Administration and DHA have embraced shared decision making. Providers are encouraged to use shared decision making to individualize treatment goals and plans based on patient capabilities, needs, and preferences.

C. Patients with Co-occurring Conditions

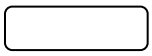
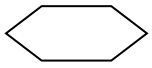
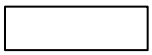
Co-occurring conditions can modify the degree of risk, impact diagnosis, influence patient and provider treatment priorities and clinical decisions, and affect the overall approach to managing Headache. Many Veterans, active duty Service members, and their families have one or more co-occurring conditions. Because Headache is sometimes accompanied by co-occurring conditions, managing Headache collaboratively with other care providers is often best. Some co-occurring conditions might require early specialist consultation to determine necessary changes in treatment or to establish a common understanding of how care will be coordinated. This approach might entail reference to other VA/DoD CPGs (e.g., for Diabetes Mellitus, mTBI, obesity and overweight, pregnancy, PTSD).[h]

VIII. Algorithm

This CPG's algorithm is designed to facilitate understanding of the clinical pathway and decision-making process used in managing patients with Headache. This algorithm format represents a simplified flow of the management of patients with headache and helps foster efficient decision making by providers. It includes

- Steps of care in an ordered sequence,
- Decisions to be considered,
- Decision criteria recommended, and
- Actions to be taken.

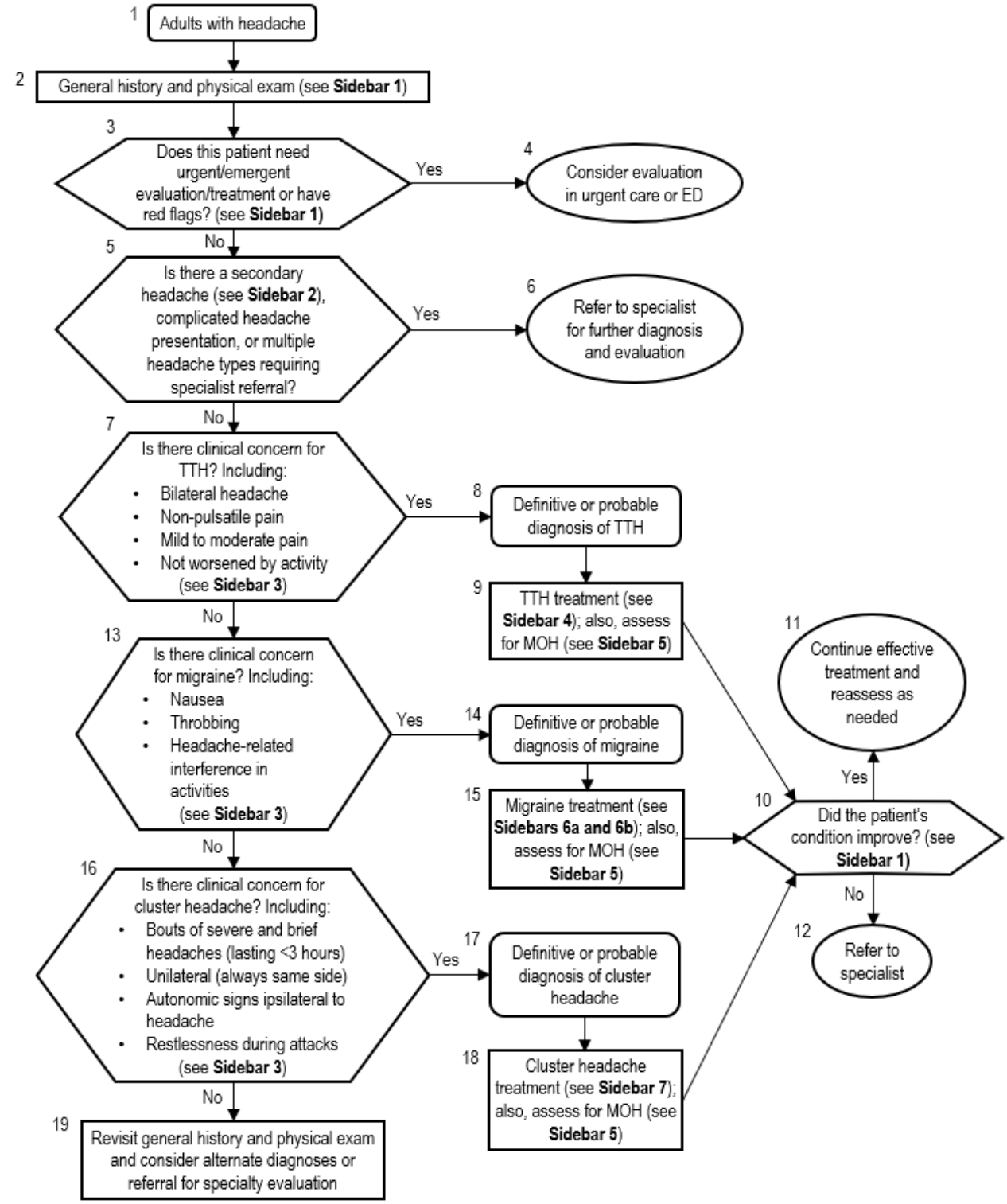
The algorithm is a step-by-step decision tree. Standardized symbols display each step, and arrows connect the numbered boxes indicating the order in which the steps should be followed.(83) Sidebars 1–7 provide more detailed information to assist in defining and interpreting elements in the boxes.

Shape	Description
	Rounded rectangles represent a clinical state or condition.
	Hexagons represent a decision point in the process of care, formulated as a question that can be answered "Yes" or "No."
	Rectangles represent an action in the process of care.
	Ovals represent a link to another section within the algorithm.

Appendix K contains alternative text descriptions of the algorithms.

[h] The VA/DoD Clinical Practice Guidelines are available at: https://www.healthquality.va.gov/

Module A: Evaluation and Treatment of Headache



Abbreviations: ED: emergency department; MOH: medication overuse headache; TTH: tension-type headache

Sidebar 1: General History and Physical Exam

History

- Frequency, character
- Onset, prodrome/aura
- Location, duration
- Relieving or exacerbating factors
- Associated symptoms
- Autonomic symptoms
- Jaw symptoms
- Neck symptoms
- Visual deficits/changes
- Dizziness and imbalance
- Current medications, abortive dose and frequency per month, prophylactic dose
- Prior medication trials
- Diet and nutrition, hydration
- Alcohol, caffeine intake
- Sleep
- Exercise
- Aggravated by routine physical activity
- Sense of restlessness
- Foreign body sensation in the eye
- Nicotine and other stimulant use
- Risk factors for MOH
- History of trauma to the head, neck, or both
- Other comorbid conditions that might contribute to or exacerbate headaches
- Mental health (e.g., depression, anxiety, PTSD)
- Menstrual cycle and proximity to menopause

Red flags SNOOP(4)E (84)

- **S**ystemic symptoms, illness, or condition (e.g., fever, chills, myalgias, night sweats, weight loss or gain, cancer, infection, giant cell arteritis, pregnancy or postpartum, or an immunocompromised state—including HIV)
- **N**eurologic symptoms or abnormal signs (e.g., confusion, impaired alertness or consciousness, changes in behavior or personality, diplopia, pulsatile tinnitus, focal neurologic symptoms or signs, meningismus, or seizures, ptosis, proptosis, pain with eye movements)
- **O**nset (e.g., abrupt or "thunderclap" where pain reaches maximal intensity immediately or within minutes after onset; first ever, severe, or "worst headache of life")
- **O**lder onset (age ≥50 years)
- **P**rogression or change in pattern (e.g., in headache frequency, severity, clinical features)
- **P**recipitated by Valsalva (e.g., coughing, bearing down)
- **P**ostural aggravation
- **P**apilledema
- **E**xertion

Examination

- Blood pressure
- General neurologic (upper extremities reflexes, sensation, strength, UMN, pathologic reflexes)
- Cranial nerves (including funduscopic exam)
- Cervical spine and surrounding musculature (palpation, ROM, Spurling's sign test)
- Temporomandibular joint (palpation, ROM, symmetry, jaw claudication)
- Pericranial muscle palpation
- Temporal artery palpation; pertinent findings might include tenderness, cord-like artery, or lack of pulse

Standardized headache assessments

- MIDAS (migraine-related disability) (85)
- HIT-6 (impact of headache on daily life and pain severity) (86)
- MSQL (quality of life) (87)
- ID Migraine (migraine) (88)
- Patient Headache Diary (7 day, 3 months)[a]

Additional screening tools

- PHQ-2 and PHQ-9 (depression) (89, 90)
- GAD-2 and GAD-7 (anxiety) (91, 92)
- CAGE (ethanol overuse headache) (93)
- AUDIT-C (ethanol overuse headache) (94)
- PC-PTSD (PTSD) (95)
- STOP-BANG (sleep) (96)

[a] See the headache diaries included in the Patient Provider Tools for the VA/DoD CPG for the Management of Headache, available at https://www.healthquality.va.gov/guidelines/Pain/headache/index.asp.

Abbreviations: AUDIT-C: Alcohol Use Disorders Identification Test-Concise; CAGE: Cut, Annoyed, Guilty, and Eye; GAD-2: Generalized Anxiety Disorder 2-item; GAD-7: Generalized Anxiety Disorder 7-item; HIT-6: Headache Impact Test, 6th edition; HIV: human immunodeficiency virus; MIDAS: Migraine Disability Assessment Test; MOH: medication overuse headache; MSQL: Migraine-Specific Quality of Life Questionnaire; PC-PTSD: Primary Care PTSD Screen for DSM-5; PHQ-2: Patient Health Questionnaire-2; PHQ-9: Patient Health Questionnaire-9; PTSD: posttraumatic stress disorder; ROM: range of motion; SNOOP(4)E: Systemic, Neurologic, Onset sudden, Onset after 50, Pattern change, Precipitated, Postural, Papilledema, Exertion; STOP-BANG: Snoring history, Tired during the day, Observed stop breathing while sleep, High blood pressure, BMI more than 35 kg/m2, Age more than 50 years, Neck circumference more than 40 cm, and male Sex; UMN: upper motor neuron

Sidebar 2: Criteria for Determining Primary versus Secondary Headache Disorders

Initial evaluation of headache should aim to determine whether a secondary cause for the headache exists or whether the diagnosis of a primary headache disorder is appropriate. Emergent evaluation should be considered based on red flag features. In general, a secondary headache can be diagnosed if the headache is new and occurs in close temporal relation to another disorder known to cause headache. It can also be diagnosed when a preexisting headache disorder significantly worsens in close temporal relation to a causative disorder, in which case both the primary and secondary headache diagnoses should be given. ICHD-3 diagnostic criteria are below.(4)

General Diagnostic Criteria for Secondary Headaches

A. Any headache fulfilling C

B. Another disorder scientifically documented to be able to cause headache has been diagnosed
   Evidence of causation demonstrated by at least two of the following
   a. Headache has developed in temporal relation to the onset of the presumed causative disorder.
   b. Either or both of the following: headache has significantly worsened in parallel with worsening of the presumed causative disorder or headache has significantly improved in parallel with improvement of the presumed causative disorder.
   c. Headache has characteristics typical for the causative disorder.
   d. Other evidence of causation exists.

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

The secondary headaches include headache attributed to trauma or injury to the head, neck, or both; cranial or cervical vascular disorder; non-vascular intracranial disorder; substance or its withdrawal; infection; disorder of homeostasis; disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, other facial or cervical structure; or psychiatric disorder.

Abbreviations: ICHD-3: International Classification of Headache Disorders, 3rd edition

Sidebar 3: Common Primary Headache Disorders Criteria*

		Tension-Type Headache[a]	Migraine Headache[b]	Cluster Headache[c]
Headache Duration and Frequency	**Duration**	30 minutes to 7 days	4–72 hours	15–180 minutes
	Frequency	Variable	Variable	Once every other day to eight per day; often occurring at the same time of day
Headache Characteristics	**Severity**	Mild to moderate	Moderate to severe	Severe or very severe
	Location	Bilateral	Unilateral	Unilateral orbital, supraorbital, or temporal pain or any combination of such pain
	Quality	Pressing or tightening, non-pulsating	Throbbing or pulsating	Stabbing, boring
	Aggravated by routine physical activity	Not aggravated by routine activity	Aggravated by routine activity	Causes a sense of agitation or restlessness; routine activity might improve symptoms

Sidebar 3: Common Primary Headache Disorders Criteria*				
		Tension-Type Headache[a]	**Migraine Headache[b]**	**Cluster Headache[c]**
Associated Features	**Photophobia and phonophobia**	Can have one but not both	Both	Variably present
	Nausea, vomiting, or both	Neither	Either or both	Might be present
Other Features	**Autonomic features**	None	Might occur but are often subtle and not noticed by the patient	Prominent autonomic features ipsilateral to the pain (see Appendix B)

* There are definitions for probable TTH, probable migraine, or probable cluster headache where patients might not fulfill all criteria listed above. The Work Group suggests that providers should not withhold therapy when patients do not meet all criteria listed for TTH, migraine, or cluster headache (i.e., are diagnosed with probable TTH, probable migraine, or probable cluster headache).(4) Providers should continually reassess patients during therapy (see Box 19 in Module A).

[a] A diagnosis of "definite" TTH requires at least 10 headaches lasting 30 minutes to 7 days with at least two defining characteristics (i.e., bilateral location, non-pulsating quality, mild to moderate intensity, not aggravated by routine physical activity) and both of the associated features (i.e., no nausea or vomiting; either photophobia or phonophobia, but not both). (See ICHD-3 "Definite" Definition, available at 2. Tension-type headache (TTH) – ICHD-3.) If headaches fulfill all but one of the TTH criteria (e.g., having both photophobia and phonophobia), the diagnosis would be probable TTH. (See ICHD-3 "Probable" Definition, available at 2.4 Probable tension-type headache – ICHD-3.)

[b] A diagnosis of "definite" migraine requires at least 5 headaches lasting 4–72 hours with at least two defining headache characteristics (i.e., unilateral throbbing or pulsating, moderate or severe intensity, aggravated, or caused by routine physical activity) and at least one associated feature (i.e., nausea, vomiting, or both and both photophobia and phonophobia). (See ICHD-3 "Definite" Definition, available at 1. Migraine - ICHD-3.) If headaches fulfill all but one of the migraine criteria (e.g., photophobia or phonophobia but not photophobia and phonophobia), the diagnosis would be probable migraine. (See ICHD-3 "Probable" Definition, available at 1.5 Probable migraine – ICHD-3.)

[c] A diagnosis of cluster headache requires at least 5 headaches of severe to very severe unilateral orbital, supraorbital, temporal pain or any combination of such pain lasting 15–180 minutes and occurring once every other day to no more than eight times a day. Either or both autonomic features and a feeling of restless or agitation are required. "Definite" cluster headache must fulfill all these criteria. (See ICHD-3 "Definite" Definition, available at 3.1 Cluster headache – ICHD-3.) "Probable" cluster headache fulfills all criteria except one. (See ICHD-3 "Probable" Definition, available at 3.5 Probable trigeminal autonomic cephalalgia - ICHD-3.) Autonomic symptoms include conjunctival injection, lacrimation, or both; nasal congestions, rhinorrhea, or both; eyelid edema; forehead and facial sweating miosis, ptosis, or both.

Sidebar 4: Treatment Options for Tension-Type Headache[a, b]					
Type	**Rec #**	**Treatment**	**Episodic**	**Chronic**	**Notes**
Non-pharmacologic Therapy – Preventive	42	Physical therapy	x	x	• *Weak for* • "Physical therapy" refers to a range of interventions carried out by licensed physical therapists, including manual therapy, therapeutic exercise, strength and endurance training, self-management training, and adjunctive modalities.
	43	Aerobic exercise or progressive strength training	x	x	• *Weak for*
Pharmacotherapy – Preventive	25	Amitriptyline*		x	• *Weak for* • Accessible for general practitioners to prescribe, inexpensive, and might help with patients who suffer from insomnia. Side effects include cognitive impairments, dry mouth, dry eyes, weight gain, sedation, dizziness, blurred vision, GI distress, and nausea. • Amitriptyline, as with all tricyclic antidepressants, can be fatal in overdose so caution should be used when prescribing in patients with history of suicidality. • Consider Beer's Criteria for age-related safety concerns.
Pharmacotherapy – Abortive	27	Ibuprofen 400 mg or acetaminophen 1,000 mg*	x	x	• *Weak for*

* Indicates that the treatment has not yet received FDA approval

[a] For the full recommendation language, see Recommendations.

[b] See Appendix C for additional treatment options for general headache.

Abbreviations: GI: gastrointestinal; mg: milligram

Sidebar 5: Medication Overuse Headache Criteria
ICHD-3 diagnostic criteria include: A. Headache occurring on 15 or more days per month in a patient with a preexisting headache disorder B. Regular overuse for more than 3 months of one or more drugs that can be taken for the acute or symptomatic treatment of headache (see table below) C. No better accounted for by another ICHD-3 diagnosis

Medication Overuse Headache Type	Medication Overuse Frequency
Butalbital overuse[a]	≥5 days/month for >3 months
Opioid overuse[a]	≥8 days/month for >3 months
Triptan overuse	≥10 days/month for >3 months
Ergotamine overuse	
Combination-analgesic overuse (any combination of classes, not to include combinations that include only non-opioid analgesics)[a, b]	
Non-opioid analgesic overuse (e.g., aspirin, NSAIDs, acetaminophen, steroids, and combinations of non-opioid analgesics)	≥15 days/month for >3 months

[a] The Work Group notes that for opioids and barbiturates, some population studies suggest lower thresholds for these drug classes. The frequency threshold is approximately 8 days of opioid use per month and 5 days of butalbital use per month.(97-101) The Work Group also suggests that providers ask patients about use of these drug classes for non-headache indications as days per month are a total for any use of these medications.

[b] Combination-analgesic refers to a headache abortive medication that contains more than one active ingredient and might refer to over-the-counter or prescription agents. Over-the-counter combination analgesics often contain a mix of NSAIDS and caffeine with the most common ones containing aspirin, acetaminophen, and caffeine. Common brand names include Excedrin Migraine™, Goody's Powder™, BC Powder™, and Vanquish™. Prescription combination medications often contain butalbital or opioids. Common brand names include Fiorinal™, Fioricet™, Percocet™, and Tylenol #3™.

Abbreviations: ICHD-3: International Classification of Headache Disorders, 3rd Edition; NSAID: nonsteroidal anti-inflammatory drug

Sidebar 6a: Pharmacologic Treatment Options for Migraine[a, b]					
Type	**Rec #**	**Treatment**	**Episodic[c]**	**Chronic[c]**	**Recommendation Strength**
Pharmacotherapy – Preventive	4	Candesartan or telmisartan*	x		*Strong for*
	7	Lisinopril*	x		*Weak for*
	11	Valproate	x		*Weak for*
	12	Memantine*	x		*Weak for*
	13	Atogepant	x		*Weak for*
	16	Rimegepant	x		*Neither for nor against*
	18	Levetiracetam*	x		*Neither for nor against*
	5	Erenumab, fremanezumab, or galcanezumab	x	x	*Strong for*
	10	Propranolol	x	x	*Weak for*
	8	Magnesium, oral	x	x	*Weak for*
	9	Topiramate	x	x	*Weak for*
	3	Fluoxetine* or venlafaxine*	x	x	*Neither for nor against*
	52	Combination pharmacotherapy	x	x	*Neither for nor against*
Pharmacotherapy – Abortive	20	Aspirin/Acetaminophen/Caffeine	NA		*Strong for*
	19	Eletriptan, frovatriptan, rizatriptan, sumatriptan (oral or subcutaneous), the combination of sumatriptan/ naproxen, or zolmitriptan			*Strong for*
	21	Acetaminophen*, aspirin, ibuprofen, naproxen*, or oral solution celecoxib			*Weak for*
	22	Rimegepant or ubrogepant			*Weak for*
	24	Lasmiditan			*Neither for nor against*

* Indicates that the treatment has yet to receive FDA approval for this indication.

[a] For the full recommendation language, see Recommendations. *Weak against* and *Strong against* recommendations have been excluded from this table.

[b] See Appendix C for additional treatment options for general headache.

[c] "x" indicates that evidence exists to support use of the treatment for the specified headache type; a blank cell indicates that no evidence exists to support use of the treatment or that there was evidence of ineffectiveness; "NA" indicates that the treatment is not specified to either episodic or chronic headache type.

Abbreviations: FDA: U.S. Food and Drug Administration

Sidebar 6b: Infusion, Procedural, Invasive, and Non-pharmacologic Treatment Options for Migraine[a, b]					
Type	**Rec #**	**Treatment**	**Episodic[c]**	**Chronic[c]**	**Recommendation Strength**
Preventive	14	OnabotulinumtoxinA		x	*Weak for*
	35	GON block		x	*Neither for nor against*
	38	Pulsed radiofrequency of upper cervical nerves or sphenopalatine ganglion block		x	*Neither for nor against*
	6	Eptinezumab IV	x	x	*Weak for*
	42	Physical therapy	x	x	*Weak for*
	43	Aerobic exercise or progressive strength training	x	x	*Weak for*
	48	Neuromodulation[c]			*Neither for nor against*
Abortive	34	GON block	NA		*Weak for*
	36	SON block			*Neither for nor against*
	37	IV antiemetics (e.g., chlorpromazine, metoclopramide, prochlorperazine)*, IV magnesium*, or intranasal lidocaine*			*Neither for nor against*
	48	Neuromodulation[d]			*Neither for nor against*

* Indicates that the treatment or treatments have yet to receive FDA approval.

[a] For the full recommendation language, see Recommendations. *Weak against* and *Strong against* recommendations have been excluded from this table.

[b] See Appendix C for additional treatment options for general headache.

[c] "x" indicates that evidence exists to support use of the treatment for the specified headache type; a blank cell indicates that no evidence exists to support use of the treatment or that there was evidence of ineffectiveness; "NA" indicates that the treatment is not specified to either episodic or chronic headache type.

[d] For the full list of neuromodulation devices reviewed, see Recommendation 48.

Abbreviations: FDA: U.S. Food and Drug Administration; GON: greater occipital nerve block; IV: intravenous; SON: supra orbital nerve

Sidebar 7: Treatment Options for Cluster Headache[a, b]					
Type	**Rec #**	**Treatment**	**Episodic[c]**	**Chronic[c]**	**Recommendation Strength**
Non-pharmacologic Therapy – Abortive	41	Non-invasive vagus nerve stimulation	x		*Weak for*
Pharmacotherapy – Preventive	28	Galcanezumab	x		*Weak for*
	30	Verapamil*	x	x	*Neither for nor against*
Pharmacotherapy – Abortive	31	Sumatriptan subcutaneaous	NA		*Weak for*
	31	Zolmitriptan nasal spray*			*Weak for*
	32	Oxygen therapy*			*Weak for*

* Indicates that the treatment has yet to receive FDA approval.

[a] For the full recommendation language, see Recommendations. *Weak against* and *Strong against* recommendations have been excluded from this table.

[b] See Appendix C for additional treatment options for general headache.

[c] "x" indicates that no evidence exists to support use of the treatment for the specified headache type; a blank cell indicates that no evidence exists to support use of the treatment or that there was evidence of ineffectiveness; "NA" indicates that the treatment is not specified to either episodic or chronic headache type.

Abbreviations: FDA: U.S. Food and Drug Administration

IX. Recommendations

The evidence-based clinical practice recommendations listed (see Table 5) were made using a systematic approach considering four domains as per the GRADE approach (see Summary of Guideline Development Methodology). These domains include confidence in the quality of the evidence, balance of desirable and undesirable outcomes (i.e., benefits and harms), patient values and preferences, and other implications (e.g., resource use, equity, acceptability).

Table 5. Evidence-Based Clinical Practice Recommendations with Strength and Category

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Medication Overuse Headache Screening and Other Considerations		1	We suggest 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 (greater than or equal to 7 days per month) • Migraine diagnosis • Medication use: frequent use of anxiolytics, analgesics (for any condition, including use of opioids or non-opioid analgesics for acute treatment of migraine), or sedative hypnotics • History of anxiety or depression, especially in combination with musculoskeletal complaints or gastrointestinal complaints • Physical inactivity • Sick leave of greater than 2 weeks in the last year • Self-reported whiplash • Smoking (tobacco use)	Weak for	Not reviewed, Amended
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
		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
	Migraine – Preventive	4	We recommend candesartan or telmisartan for the prevention of episodic migraine.	Strong for	Reviewed, New-replaced
		5	We recommend erenumab, fremanezumab, or galcanezumab for the prevention of episodic or chronic migraine.	Strong for	Reviewed, New-replaced
		6	We suggest intravenous eptinezumab for the prevention of episodic or chronic migraine.	Weak for	Reviewed, New-added
		7	We suggest lisinopril for the prevention of episodic migraine.	Weak for	Reviewed, Not changed
		8	We suggest oral magnesium for the prevention of migraine.	Weak for	Not reviewed, Not changed
		9	We suggest topiramate for the prevention of episodic and chronic migraine.	Weak for	Reviewed, New-replaced

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Pharmacotherapy (cont.)	*Migraine – Preventive (cont.)*	10	We suggest propranolol for the prevention of migraine.	Weak for	Reviewed, Not changed
		11	We suggest valproate for the prevention of episodic migraine.	Weak for	Reviewed, New-replaced
		12	We suggest memantine for the prevention of episodic migraine.	Weak for	Reviewed, New-added
		13	We suggest atogepant for the prevention of episodic migraine.	Weak for	Reviewed, New-added
		14	We suggest onabotulinumtoxinA injection for the prevention of chronic migraine.	Weak for	Reviewed, Not changed
		15	We suggest against abobotulinumtoxinA or onabotulinumtoxinA injection for the prevention of episodic migraine.	Weak against	Reviewed, Not changed
		16	There is insufficient evidence to recommend for or against rimegepant for the prevention of episodic migraine.	Neither for nor against	Reviewed, New-added
		17	We suggest against the use of gabapentin for the prevention of episodic migraine.	Weak against	Reviewed, New-replaced
		18	There is insufficient evidence to recommend for or against levetiracetam for the prevention of episodic migraine.	Neither for nor against	Reviewed, New-added
	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 acute treatment of migraine.	Strong for	Reviewed, New-replaced
		20	We recommend aspirin/acetaminophen/caffeine for the acute treatment of migraine.	Strong for	Reviewed, New-added
		21	We suggest acetaminophen, aspirin, ibuprofen, or naproxen for the acute treatment of migraine.	Weak for	Reviewed, Amended
		22	We suggest rimegepant or ubrogepant for the acute treatment of migraine.	Weak for	Reviewed, New-added
		23	We suggest against intravenous ketamine for the acute treatment of migraine.	Weak against	Reviewed, Amended
		24	There is insufficient evidence to recommend for or against lasmiditan for the acute treatment of migraine.	Neither for nor against	Reviewed, New-added

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Pharmacotherapy (cont.)	*Tension-Type Headache – Preventive*	25	We suggest amitriptyline for the prevention of chronic tension-type headache.	Weak for	Reviewed, Not changed
		26	We suggest against botulinum/neurotoxin injection for the prevention of chronic tension-type headache.	Weak against	Reviewed, Not changed
	Tension-Type Headache – Abortive	27	We suggest ibuprofen (400 mg) or acetaminophen (1,000 mg) for the acute treatment of tension-type headache.	Weak for	Reviewed, Not changed
	Cluster Headache – Preventive	28	We suggest galcanezumab for the prevention of episodic cluster headache.	Weak for	Reviewed, Not changed
		29	We suggest against galcanezumab for the prevention of chronic cluster headache.	Weak against	Reviewed, New-added
		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
	Cluster Headache – Abortive	31	We suggest subcutaneous sumatriptan (6 mg) or intranasal zolmitriptan (10 mg) for the acute treatment of cluster headache.	Weak for	Reviewed, New-replaced
		32	We suggest the use of normobaric oxygen therapy for the acute treatment of cluster headache.	Weak for	Not reviewed, Amended
	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

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Injections, Procedures, and Invasive Interventions		34	We suggest greater occipital nerve block for the acute treatment of migraine.	Weak for	Reviewed, Not changed
		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
		36	There is insufficient evidence to recommend for or against supra orbital nerve block for acute treatment of migraine.	Neither for nor against	Reviewed, New-added
		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 acute treatment of headache.	Neither for nor against	Reviewed, New-replaced
		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
		39	We suggest against an implantable sphenopalatine ganglion stimulator for the treatment of cluster headache.	Weak against	Reviewed, New-added
		40	We suggest against patent foramen ovale closure for the treatment or prevention of migraine.	Weak against	Reviewed, New-added
Non-pharmacologic Therapy		41	We suggest non-invasive vagus nerve stimulation for the acute treatment of episodic cluster headache.	Weak for	Reviewed, Not changed
		42	We suggest physical therapy for the management of tension-type, migraine, or cervicogenic headache.	Weak for	Reviewed, New-replaced
		43	We suggest aerobic exercise or progressive strength training for the prevention of tension-type and migraine headache.	Weak for	Not reviewed, Amended
		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 heartrate variability monitoring • Cognitive behavioral therapy • Mindfulness-based therapies • Progressive muscle relaxation	Neither for nor against	Reviewed, New-replaced
		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
		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

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Non-pharmacologic Therapy (cont.)		47	We suggest against immunoglobulin G antibody testing for dietary trigger avoidance for the prevention of headache.	Weak against	Not reviewed, Amended
		48	There is insufficient evidence to recommend for or against any form of neuromodulation for the treatment and/or prevention of migraine: • Non-invasive 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
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
		50	There is insufficient evidence to recommend for or against any specific medication over another for the acute treatment of migraine.	Neither for nor against	Reviewed, New-added
		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
		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

[a] For additional information, see Determining Recommendation Strength and Direction.

[b] For additional information, see Recommendation Categorization.

A. Medication Overuse Headache Screening and Other Considerations

Recommendation

1. We suggest 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 (greater than or equal to 7 days per month)
   - Migraine diagnosis
   - Medication use: frequent use of anxiolytics, analgesics (for any condition, including use of opioids or non-opioid analgesics for acute treatment of migraine), or sedative hypnotics
   - History of anxiety or depression, especially in combination with musculoskeletal complaints or gastrointestinal complaints
   - Physical inactivity
   - Sick leave of greater than 2 weeks in the last year
   - Self-reported whiplash
   - Smoking (tobacco use).

   (Weak for | Not reviewed, Amended)

Discussion

Medication overuse headache is a frequent consideration in the management of headache conditions, and criteria for diagnosis are listed in the algorithm (see Sidebar 5). Identifying and minimizing treatable risk factors might help providers and patients prevent the development of MOH. An 11-year prospective cohort study by Hagen et al. (2012) (n=25,596), including a population with a mean age of 47 years and 57% females, analyzed risk factors associated with an increased risk of MOH incidence among patients with headache.(102) They reported the risk factors as an adjusted odds ratio (OR), adjusted for age, sex, education level, factors other than headache characteristics, and headache frequency. Headache frequency at baseline was the strongest risk factor for the development of MOH; headache for 7–14 days per month versus no headache resulted in an OR of 19.4.(102) A history of migraine conferred greater risk for MOH (OR: 8.1) than non-migrainous headache (OR: 4.9). Other factors resulting in a higher likelihood of development of MOH were the use of anxiolytics (OR: 5.2), analgesics for any condition (OR: 3.0), and sleep-inducing medications (OR: 2.5).

Another study also documented high-frequency use of acute headache medications (13–23 days per month) as an MOH risk factor.(103) Regarding abortive medication use for migraine, evidence suggests triptan and ergot medications have a lower risk for future development of MOH than non-opioid analgesic medication or opioids. An SR of 29 observational studies (n=3,092) by Thorlund et al. (2016) found that triptans were associated with a significantly lower risk for MOH compared with non-opioid analgesics or

opioids, with a relative risk (RR) reduction of 35% compared with non-opioid analgesics.(104) Regarding ergotamine medications, the same SR included 14 observational studies that found no significant difference in MOH prevalence between patients receiving ergots and patients receiving triptans. Additionally, 12 observational studies found ergots were associated with a significantly lower risk than analgesics.(104) Based on this evidence, frequent use of opioids and non-opioid analgesics for the treatment of acute migraine are specifically included in this list of MOH risk factors. Thus, in patients at high risk for MOH, triptans might have an advantage over analgesics because of lower risk of MOH. Nevertheless, high use of triptans (i.e., above the upper limit of dosage recommendation) also carries risk for MOH.

Hagen et al. (2012) used the Hospital Anxiety and Depression Scale (HADS) scores to identify psychological risk factors associated with a higher incidence of MOH.(102) The risk of MOH was twice as high among respondents with high anxiety (Hospital Anxiety and Depression Scale-Anxiety [HADS-A]>11; OR: 2.0), high depression scores (HADS-D>11; OR: 2.6), or both and almost five-fold risk of MOH for respondents with HADS-A, Hospital Anxiety and Depression Scale-Depression (HADS-D)>11, or both in combination with musculoskeletal and gastrointestinal (GI) complaints (OR: 4.7).

Other factors associated with an increased risk of developing MOH included physical inactivity (OR: 2.7), sick leave of more than 2 weeks in the last year (OR: 2.5), self-reported whiplash (OR: 2.2), and smoking (daily versus never) (OR: 1.8).

Other studies reviewed had evidence consistent with the above findings.(103, 105, 106) MOH risk factors included combination medicines, lack of headache prevention, allodynia, headache frequency before drug withdrawal, and higher Headache Impact Test-6 (HIT-6) scores.

Patients generally appreciate a thorough evaluation, including their history, to determine the appropriate diagnosis and assessment of risks, as per suggestions from the patient focus group. Also, patients might report only the number of moderate to severe headache days per month rather than the total number of headache days. One approach to this reporting is to inquire about the number of days in the last month without any headache. Some patients might be reluctant to have a discussion with providers or implement behavior changes not directly related to headache care, such as smoking or exercise habits.

This recommendation is carried forward from the 2020 VA/DoD Headache CPG, with modifications for clarity. Modifications include (1) the addition of frequency of headache and history of migraine as risk factors for developing MOH based on further review of the previously obtained evidence and (2) a comment on the use of opioid and non-opioid analgesic medications for the acute treatment of headache, both of which were previously part of a separate recommendation.

The Work Group considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG.(102-106) Therefore, this recommendation is categorized as *Not reviewed, Amended*. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including a lack of reported exclusion criteria.(102) The benefits of preventing MOH by thoroughly assessing risk factors outweighed the potential harm of a prolonged office visit to assess history carefully. Patient values and preferences were similar because patients generally appreciate a thorough evaluation, and most providers ask about these risk factors routinely. Thus, the Work Group made the following recommendation: We suggest 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 (greater than or equal to 7 days per month)
- Migraine diagnosis
- Medication use: frequent use of anxiolytics, analgesics (for any condition, including use of opioids or non-opioid analgesics for acute treatment of migraine), or sedative hypnotics
- History of anxiety or depression, especially in combination with musculoskeletal complaints or gastrointestinal complaints
- Physical inactivity
- Sick leave of greater than 2 weeks in the last year
- Self-reported whiplash
- Smoking (tobacco use)

B. Pharmacotherapy

a. Headache – Preventive

Recommendation

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)

Discussion

The evidence for coenzyme Q10 (CoQ10) in reducing the frequency of migraine headache days is inconsistent.(107-109) An SR by Parohan et al. (2019), including four RCTs (n=221), found a weighted mean reduction of 1.87 headache days per month, which was statistically significant compared with placebo.(108) An SR by Okoli et al. (2019), including two RCTs (n=97), showed no difference between CoQ10 compared with placebo in reduction of headache days per month.(107) Zeng et al. (2019)

reviewed three RCTs and one observational study (n=266) and demonstrated no significant difference between CoQ10 and placebo.(109)

The evidence for feverfew was limited to an SR of four placebo controlled RCTs by Wider et al. (2015).(110) They reported a change in migraine frequency per month (n=433). The results were mixed, with two studies showing a statistically significant reduction and two studies showing no difference compared with placebo.

The evidence for melatonin was limited to an SR by Long et al. (2019).(111) Three of the four RCTs (n=285) were included in a meta-analysis that demonstrated a reduction in headache frequency favoring melatonin. As a result of differences in the outcome measures used, a mean change in headache frequency could not be calculated.

The evidence for omega-3 supplementation consisted of an SR by Maghsoumi-Norouzabad et al. (2018), which included five RCTs.(112) The weighted mean difference (WMD) in headache frequency was not statistically significantly different than placebo.

The evidence for vitamin B2 was limited to one placebo-controlled RCT (n=54) within an SR by Okoli et al. (2019), which considered other vitamins and minerals for migraine prophylaxis.(107) This study demonstrated a mean reduction of two headaches per month, which was statistically significantly lower than placebo.

The evidence for vitamin B6 was limited to one placebo-controlled RCT (n=54) that reported no difference in reducing migraine frequency but did demonstrate a reduction in migraine intensity versus placebo.(113)

Patient preferences vary regarding this treatment. Evidence supporting several nutraceuticals for headache prevention, including these options, is limited and sometimes conflicting. The patient focus group expressed an interest in non-pharmacologic treatment; however, whether these treatments are considered non-pharmacologic might vary by patient and provider. Some individuals might express concerns regarding the cost of supplements in addition to lack of FDA regulation. Considering medication interactions and the ability of pregnant and lactating patients to use nutraceuticals is also important.

The Work Group considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG.(107-113) Therefore, this recommendation is categorized as *Not reviewed, Amended*. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including small sample sizes, limited numbers of studies, and significant variability in results. The Work Group determined the benefits were balanced with the harms and burdens. Small but inconsistent benefits in reducing migraine frequency were found, potentially because of dose variability in supplements, and specific harms (e.g., post-feverfew syndrome, vitamin B6 neurotoxicity in high and sustained doses). Patient values and preferences varied because of lack of regulation of nutraceuticals. Access to these treatments might

be reduced because some are not listed on DoD or VA formularies, and patients would likely have to pay for them out of pocket. Finally, the number of active ingredients in nutraceuticals can vary. Thus, the Work Group made the following recommendation: 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.

Recommendation

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)

Discussion

Evidence is insufficient to suggest for or against fluoxetine or venlafaxine use in headache prevention. Wang et al. (2020) conducted an SR of six RCTs, evaluating the use of serotonin and norepinephrine reuptake inhibitors (SNRI) for the prevention of migraine and vestibular migraine.(114) The RCTs involved subjects treated with SNRIs (five of the RCTs were conducted with venlafaxine, one with duloxetine) (n=202) and patients treated with a placebo or another active drug (n=216). Four studies included in the SR (n=279) enrolled subjects with migraine, and two studies (n=139) enrolled subjects with vestibular migraine.(114) Of the subjects with migraine, the pooled studies found that patients treated with SNRIs had fewer migraine days than those receiving a placebo. Patients given duloxetine had a reduction of 2 headache days versus those given placebo. Patients given venlafaxine had a reduction of 2–4 headache days, dependent on dose, versus placebo. The effects of SNRIs with other active drugs were comparable. However, confidence in the quality of the evidence was very low. The pooled studies were very small, had unclear risk of bias (ROB), and did not reflect the critical outcome of interest for migraine prophylaxis (i.e., change in headache and migraine days).(114) The evidence in this iteration of the CPG is consistent with the 2020 VA/DoD Headache CPG that analyzed two SRs by Jackson et al. (2015), which examined the evidence for fluoxetine and venlafaxine, and Banzi et al. (2015), which also primarily examined the evidence for the fluoxetine and venlafaxine but also sertraline, fluvoxamine, and escitalopram.(115, 116) In both prior SRs, no evidence was found that the selective serotonin reuptake inhibitors (SSRI) or SNRI medications studied prevented migraine.

The potential benefits are balanced with harms and burdens. A risk of serotonin syndrome exists, particularly when taken in combination with other serotonergic medications, although the overall toxicity of these medications is low. All antidepressant medications carry a boxed warning for increased risk of suicidality in children, adolescents, and young adults.(117) Antidepressants have multiple adverse events (AE), such as nausea, weight gain, dry mouth, sexual dysfunction, constipation, and in the case of SNRIs, increased blood pressure. However, tolerability to the side effects is high and usually improves over time.

Patient preferences vary largely regarding this treatment. Some patients might prefer non-invasive treatments, and others might not want to consume daily medication. The patient focus group indicated that patients prefer combination treatments rather than just oral medications. Patients might also have concerns related to the stigma associated with taking medication with a psychiatric indication and might want to avoid medications with known sexual side effects. In terms of subgroup analysis, many active duty Service members would prefer to avoid medications with psychotropic effects because of potential concerns of duty limitations or career advancement. However, these medications might be preferred by patients who have comorbid conditions that can be treated by this class of medications because multiple conditions could be treated by one medication (e.g., depression, diabetic neuropathy). Further, access to these medications is extensive because they can be prescribed by PCPs familiar with their use and comfortable with their risks and AEs.

The Work Group systematically reviewed evidence related to this recommendation (114) and considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG.(115, 116) Therefore, it is categorized as *Reviewed, Not-changed*. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including a small sample size and ROB. The benefits of reduction in migraine days were balanced with the potential harm of AEs, including side effects, which were small. Patient values and preferences vary largely because some patients might have a preference for non-invasive treatments and the possible benefit of treating comorbid conditions, although other patients might be concerned about sexual side effects and the potential stigma associated with the use of a medication with psychotropic effects. Thus, the Work Group made the following recommendation: There is insufficient evidence to recommend for or against fluoxetine or venlafaxine for the prevention of headache.

b. Migraine – Preventive

Recommendation

4. We recommend candesartan or telmisartan for the prevention of episodic migraine.
   (Strong for | Reviewed, New-replaced)

Discussion

An SR by Jackson et al. (2015) reported results of three RCTs examining angiotensin II receptor blockers (ARB) in the prevention of episodic migraine, with two studies focusing on candesartan and the third on telmisartan.(116, 118-120)

The SR by Jackson et al. (2015) found a significant reduction in headache frequency per month in the prevention of episodic migraine, favoring the aforementioned ARBs over placebo (standardized mean difference [SMD]: -1.12; 95% confidence interval [CI]: -1.97 to -0.27; I^2: 29.1%).(116) However, rates of AEs were either on par with placebo

or higher in those receiving ARBs.(118, 120) A parallel design RCT randomized patients (n=60) with migraine with or without aura who experienced 2–6 migraine days per month to two separate treatment periods.(120) After a 12-week period, the mean number of headache days was statistically lower among patients receiving candesartan than those randomized to placebo (13.6 versus 18.5 days; p=0.001). Additionally, the mean reduction in monthly migraine days was lower among those receiving candesartan compared with placebo (12.6 versus 9.0 days; p<0.001). Outcomes, including hours with migraine, hours with headache, level of disability, and days of sick leave, statistically favored candesartan over placebo. Adverse events were similar in the two treatment periods, such that acceptability and tolerability of candesartan approximated what was seen in the placebo arm.

A crossover RCT randomized adults (n=72) with episodic (n=71) or chronic migraine (n=1) into three 12-week treatment periods: candesartan (16 mg), slow-release propranolol (160 mg), or placebo.(119) The primary outcome for this study was migraine days per 4 weeks with a secondary outcome of headache days per 4 weeks. A statistically significant reduction of migraine days was found in both the candesartan (0.58) and propranolol (0.62) groups, compared with placebo. Reduction in headache days for each active pharmacotherapy was not reported.

Diener et al. (2009) reported a significant improvement in migraine days in patients receiving telmisartan compared with placebo (1.65 versus 1.15; p=0.03) from the 4-week baseline period compared with the last 4 weeks of a 12-week treatment period. The rate of AEs was similar between groups.(118)

Because ARBs are associated with hyperkalemia, renal failure, and hypotension, providers should monitor electrolytes, renal function, and blood pressure. Providers considering prescribing these ARBs should be aware that this class is contraindicated in pregnancy and that appropriate counseling among individuals of childbearing age regarding ARB-associated fetal toxicity should be provided.(116) Patient and provider values and preferences would be similar because ARBs are accessible and well tolerated and could be prescribed by primary and specialty care providers alike.

The Work Group considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG.(116, 118-120) No new studies on the effect of candesartan or telmisartan met the inclusion criteria for the 2023 VA/DoD Headache CPG systematic evidence review. Therefore, this recommendation is categorized as *Reviewed, New-replaced*. Although the available evidence base has not changed since the 2020 VA/DoD Headache CPG, the Work Group noted that across the three studies reviewed in the SR by Jackson et al. (2015), only one study either had a diagnosis of or met criteria for chronic migraine. Hence, this recommendation is now restricted to episodic migraine, whereas the 2020 VA/DoD Headache CPG included both episodic and chronic migraine. The Work Group's confidence in the quality of the evidence was moderate. A statistically significant reduction in the number of headache or migraine

days or both was found. The benefits of improved headache control outweighed the burden of taking a daily medication with a favorable side-effect profile. Thus, the Work Group made the following recommendation: We recommend candesartan or telmisartan for the prevention of episodic migraine.

Recommendation

5. We recommend erenumab, fremanezumab, or galcanezumab for the prevention of episodic or chronic migraine.
   (Strong for | Reviewed, New-replaced)

Discussion

Erenumab, fremanezumab, and galcanezumab are mAbs that act by antagonism of the CGRP pathway. Since their initial approval for the prevention of episodic and chronic migraine, SRs and meta-analyses have been conducted on their efficacy, safety, and tolerability. Additional clinical trials in patient populations poorly represented in trials leading to FDA-approval (e.g., Middle East, Latin America, Asia) and the results of open-label and real-world evidence have become available to better understand their expanding role in the prevention of migraine. Alongside the evidence presented below, there was additional support for the use of erenumab, fremanezumab, or galcanezumab included in the 2020 VA/DoD Headache CPG.(121-130)

Erenumab

Wang et al. (2021) reported on the efficacy and safety of erenumab among patients in the Middle East, Latin America, and Asia.(131) The primary efficacy outcome was a change in monthly migraine days from baseline over 3 months. Erenumab at 70 mg and 140 mg led to a 4.8- and 4.2-day reduction in monthly migraine days, respectively, with each erenumab dose being statistically significant compared with the reduction seen among those receiving placebo (3.1-day reduction). There was also a statistically significant reduction from baseline in other endpoints at 3 months, including (1) the use of monthly acute migraine-specific medication; (2) the proportion of patients experiencing a ≥50% reduction in monthly migraine days; and (3) HIT-6 scores at 3 months compared with baseline. Overall, active pharmacotherapy was well tolerated with low AE rates, and AEs did not lead to discontinuation of therapy. Takeshima et al. (2021) conducted an RCT (n=261) among patients with either episodic or chronic migraine comparing erenumab 70 mg with placebo.(132) Patients with episodic (-1.57 days; 95% CI: -3.39–0.24; p=0.089) and chronic migraine (-1.67 days; 95% CI: -2.56 to -0.78; p<0.001) experienced a statistically significant reduction in mean monthly migraine days. Similarly to other studies, erenumab 70 mg also had a favorable safety profile when compared with placebo.

In an SR and network meta-analysis (NMA), Yang et al. (2022) examined the efficacy and safety of erenumab across five RCTs among patients (n=2,453) with episodic migraine and patients who had failed two or more migraine preventive treatments.(133) Change in

monthly migraine days compared with placebo showed reduction for erenumab 70 mg or 140 mg (-1.41 days; 95% CI: -1.80 to -1.03), erenumab 70 mg (-1.28 days; 95% CI: -1.62 to -0.95), and erenumab 140 mg (-1.67 days; 95% CI: -2.08 to -1.25).(133) When 70 mg and 140 mg doses of erenumab were compared, patients receiving the 140 mg dose of erenumab had significantly fewer monthly migraine days (-0.51 days; 95% CI: -0.79 to -0.23).(133) Although statistically significant, the reduction in monthly migraine days experienced by those with prior treatment failures was not clinically significant. When considering safety outcomes, no statistically significant differences were found between erenumab and placebo for AEs, including serious AEs. In analyses restricted to patients with two or more preventive medication treatment failures, patients receiving erenumab 140 mg experienced a statistically significant reduction in monthly migraine days compared with placebo (-1.98 days; 95% CI: -2.93 to -1.03); however, a statistically significant reduction of monthly migraine days was not observed among patients receiving erenumab 70 mg (-0.9 days; 95% CI: -2.41–0.61).(133) Neither dose of erenumab showed a statistically significant difference in AEs, including serious AEs, compared with placebo among patients with episodic migraine who had previously failed two or more preventive medication treatment options.

Fremanezumab

Gao et al. (2020) conducted an SR and NMA of fremanezumab related to its efficacy and safety among patients with migraine.(134) Data across five RCTs (n=3,379) was examined. Primary endpoints were mean monthly migraine and headache data, from baseline to week 12. Subgroup analyses were conducted on episodic and chronic migraine and different schedules of fremanezumab.

Mean monthly migraine and headache day reduction was not statistically significant between patients with episodic migraine and those with chronic migraine. Fremanezumab demonstrated statistically significant reductions in mean monthly migraine days (-2.21 days; 95% CI: -3.03 to -1.38) and headache days (-2.36 days; 95% CI: -3.17 to -1.56). (134) Patients with episodic migraine demonstrated a statistically significant reduction in both mean monthly migraine days (-2.36 days; 95% CI: -3.55 to -1.17) and headache days (-1.99 days; 95% CI: -2.55 to -1.43) at 12 weeks compared with placebo.(134) Similarly, patients with chronic migraine demonstrated a statistically significant reduction in both mean monthly migraine days (-2.43 days; 95% CI: -3.70 to -1.17) and headache days (-1.90 days; 95% CI: -2.88 to -0.92) at 12 weeks compared with placebo.(134) When comparing monthly and quarterly dosing of fremanezumab, no statistically significant difference was found between the two schedules for reducing either monthly migraine or monthly headache days.

Patients treated with fremanezumab were significantly more likely to have at least one AE and an AE related to the trial regimen, compared with placebo.(134) Although the incidence rate of injection-site reactions was higher in the fremanezumab group compared with the placebo group (RR: 1.24; 95% CI: 1.07–1.43), the proportion of AEs

did not differ whether patients received monthly or quarterly pharmacotherapy. Compared with placebo, patients with episodic migraine had similar rates of at least one AE or serious AE, whereas those with chronic migraine had a statistically significant higher RR of experiencing at least one AE but were not more likely to experience a severe AE.

In two separate clinical trials, Sakai et al. (2021a) and Sakai et al. (2021b) examined the efficacy and safety of fremanezumab for Japanese and Korean patients living with either episodic or chronic migraine.(135, 136) Within the episodic migraine trial, patients (n=357) were randomized to receive either fremanezumab 225 mg monthly (at baseline, week 4, and week 8), fremanezumab 675 mg quarterly, or placebo.(136) The primary efficacy standpoint was a change in mean monthly migraine days during the 12-week treatment period. The primary safety endpoint was the occurrence of treatment-emergent AEs. At 12 weeks, both scheduling regimens were associated with a statistically significant reduction in mean monthly migraine days (-4.0 ± 0.4 days for both fremanezumab groups) compared with placebo (-1.0 ± 0.4 days; $p<0.0001$ for both comparisons). Treatment-emergent AEs were most common in the placebo group (65.8%), followed by fremanezumab quarterly (62.7%) and monthly (57.0%), with the most common event being injection-site reactions.

The chronic migraine trial had a primary efficacy endpoint of mean monthly headache days.(135) At 12 weeks, both scheduling regimens were associated with a statistically significant reduction in mean monthly headache days (-4.1 ± 0.4 days for both fremanezumab groups) compared with placebo (-2.4 ± 0.4 days). A similar rate of treatment-emergent AEs was seen in the placebo group (61.8%) and any regimen of fremanezumab (61.4%).

Galcanezumab

Hu et al. (2022) examined the efficacy and safety of galcanezumab among patients with episodic migraine from Russia, India, and China.(137) Patients (n=520) were randomized to receive galcanezumab 120 mg with a 240 mg loading dose or placebo.(137) The primary efficacy endpoint was a change in mean monthly migraine days over 3 months compared with baseline. Safety endpoints included treatment-emergent AEs, serious AEs, death, and discontinuations because of AEs. Galcanezumab use resulted in a statistically significant improvement in monthly migraine days compared with placebo (-3.81 days versus -1.99 days; $p<0.0001$). Treatment-emergent AEs occurred commonly within the galcanezumab (49.8%) and placebo (43.2%) groups, with the most common event being injection-site pain. Serious AE rates were low across both groups, and none were considered related to the treatment or led to study withdrawal. No deaths occurred in the study.

Abu-Zaid et al. (2020) conducted an SR and NMA of six randomized, placebo-controlled trials (n=4,023) evaluating galcanezumab efficacy for migraine.(138) Both

galcanezumab 120 mg (-2.39 days; 95% CI: -2.04 to -2.74) and galcanezumab 240 mg (-2.14 days; 95% CI: -1.73 to -2.55) doses were associated with a statistically significant reduction in mean monthly headache days compared with placebo. In considering AEs, when compared with placebo, both galcanezumab 120 mg and 240 mg doses showed no statistically significant differences in injection-site pain or nasopharyngitis, although the risk ratios for upper respiratory tract infections were higher for both doses of galcanezumab compared with placebo.

Studies across CGRP Inhibitors

Alasad et al. (2020) conducted an NMA using data from 13 RCTs (n=6,979) examining the efficacy and safety of CGRP mAbs among patients with episodic or chronic migraine.(139) The primary outcomes included a reduction in monthly migraine days and treatment-related AEs among patients receiving erenumab 70 mg, fremanezumab 225 mg, and galcanezumab 120 mg. Secondary outcomes included acute migraine medication use from baseline and ≥50% reduction in monthly migraine days. In considering efficacy outcomes, these pharmacotherapies and doses resulted in statistically significant reductions in mean monthly migraine days after 4 weeks (migraine days [MD]: -2.07 days; 95% CI: -2.47 to -1.43), 8 weeks (MD: -1.78 days; 95% CI: -2.26 to -1.49), and 12 weeks (MD: -1.80 days; 95% CI: -2.16 to -1.43; p<0.001 for all). Compared with placebo, mAbs also resulted in a statistically significant reduction in acute migraine medication use from baseline (MD: -1.73 days; 95% CI: -2.15 to -1.32, p<0.001) and a significantly greater proportion of patients experiencing ≥50% reduction in monthly migraine days (MD: 2.46 days; 95% CI: 2.08–2.90; p<0.001). Similar results were noted for each individual pharmacotherapy and both episodic and chronic migraine. The primary safety outcome was treatment-related AEs. No statistically significant differences were found between active pharmacotherapy and placebo regarding treatment-related AEs (OR: 1.12; 95% CI: 0.72–1.72; p=0.84), secondary outcomes of serious AEs (OR: 0.96; 95% CI: 0.63–1.46), all AEs (OR: 1.10; 95% CI: 0.99–1.21; p=0.07), or specific AEs such as nasopharyngitis, sinusitis, injection-site pain, and injection-site erythema.

In considering acceptability of mAbs in chronic migraine, all mAbs showed no statistically significant difference to the placebo or control group regarding dropout rate with the exception of galcanezumab 240 mg, which was associated with a statistically lower dropout rate than placebo or control group.(140) When examining acceptability of mAbs, only fremanezumab and galcanezumab had statistically significant higher rates of AEs when compared with placebo or control groups. All other mAbs at the above dosing regimens did not statistically differ regarding acceptability when compared with placebo control groups.

Because Yang et al. (2021) also compared mAbs with topiramate and onabotulinumtoxinA for chronic migraine, see Recommendation 52 regarding the

comparative effectiveness of these pharmacotherapies.(140) See Recommendation 6 regarding additional information on eptinezumab.

Summary of the Evidence for CGRP Inhibitors

Since the 2020 VA/DoD Headache CPG, literature (not included in the evidence base nor impacting the strength of this recommendation) suggests that the use of erenumab, fremanezumab, and galcanezumab has grown and providers have become increasingly more familiar and comfortable with the use of mAbs for the prevention of episodic and chronic migraine.(141) Overall, these therapies are efficacious, well tolerated, and safe. They have been found to work in a broader array of patient populations, including patients living in the Middle East, Latin America, Japan, Korea, and other parts of Asia. Monoclonal antibodies have also been shown to be efficacious when patients have experienced treatment failures with other migraine preventive pharmacotherapies. Although erenumab, fremanezumab, and galcanezumab all resulted in statistically significant reductions in monthly migraine days, NMA data shows that erenumab is associated with the greatest reduction in monthly migraine days, followed by galcanezumab and then fremanezumab. These therapies are largely well tolerated, with some dosing regimens of fremanezumab and galcanezumab having statistically higher rates of AEs when compared with placebo or control groups. There have been no comparative effectiveness clinical trials of mAbs. When selecting an mAb, providers should be aware that some studies have shown, compared with placebo, an increased risk of developing hypertension while on erenumab, whereas other studies (not included in the evidence base nor impacting the strength of this recommendation) have not demonstrated this finding to be the case.(142, 143) Although not included in the evidence base nor impacting the strength of this recommendation, severe constipation has also been reported with erenumab in some studies, whereas other studies have reported a constipation risk to be similar between erenumab and other mAbs.(144, 145)

Continued collection and analyses of real-world data for mAb use, alone or in combination with other therapies, among patients living with migraine should continue. In one real-world data study of patients with episodic or chronic migraine (not included in the evidence base nor impacting the strength of this recommendation), they received erenumab for an average of 6.9 ± 2.7 months. Compared with baseline, a change occurred in both mean monthly headache days (-7.5 days; CI: 14.9 ± 6.6–7.4 ± 6.2; $p<0.0001$) and mean monthly migraine days (-6.2 days; CI: 12.1 ± 5.9–5.9 ± 5.5; $p<0.0001$) after 3 months of erenumab therapy.(146) In a combination therapy study (not included in the evidence base nor impacting the strength of this recommendation), Scuteri et al. (2022) conducted an SR and NMA examining the efficacy and safety of combination mAbs and onabotulinumtoxinA for chronic migraine.(147) The combination of each therapy resulted in a change of monthly headache days of -2.67 (95% CI: -4.42–0.93; n=393) after 3 months of combined treatment, higher than both mAb (1.94 days; $p<0.0001$) and onabotulinumtoxinA (1.86 days; $p<0.0001$) alone when compared

with baseline. The authors for this SR and NMA reported that the quality of evidence was moderate.

The Work Group systematically reviewed evidence related to this recommendation (131-140) and considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG.(121-130) Therefore, it is categorized as *Reviewed, New-replaced*. The Work Group's confidence in the quality of the evidence was moderate. The Work Group determined that the benefits of erenumab, fremanezumab, and galcanezumab outweighed the harms and burdens because the AEs were generally not statistically significant or significantly harmful. Patients would likely have some variation related to values and preferences for injectable mAbs. For example, patients might prefer a once monthly option compared with treatments that might be once, twice, or thrice daily and have higher AE rates than placebo. Even though some might not want to experience a needle, patients are generally tolerant of injections given via an auto-injector. Moreover, providers are generally comfortable with prescribing auto-injectable therapies. Providers likely have become more comfortable with CGRP mAbs because this class of medications now has longer-term efficacy, effectiveness, safety, and tolerability data. In considering the safety profile of CGRP inhibitors in pregnancy and lactation, no human data is currently available. In an analysis from the WHO pharmacovigilance database, "no specific maternal toxicities, patterns of major birth defects, or increased reporting of spontaneous abortion were found" for galcanezumab, fremanezumab, and erenumab.(148) As such, the role of mAbs in pregnancy and lactation has not been established. Thus, the Work Group made the following recommendation: We recommend erenumab, fremanezumab, or galcanezumab for the prevention of episodic or chronic migraine.

Recommendation

6. We suggest intravenous eptinezumab for the prevention of episodic or chronic migraine.
   (Weak for | Reviewed, New-added)

Discussion

Ashina et al. (2020) examined the efficacy and safety of eptinezumab as a preventive treatment in a phase 3, randomized, double-blind, placebo-controlled study within an episodic migraine population.(149) Patients were randomized to either 30 mg of eptinezumab (n=224), 100 mg of eptinezumab (n=225), 300 mg of eptinezumab (n=224), or a placebo (n=225) via IV infusion. The primary efficacy endpoint was observed through a change in mean monthly migraine days for weeks 1–12 from the baseline. At 30 mg, 100 mg, and 300 mg doses of eptinezumab, there was a -4.0, -3.9, and -4.3 day reduction in monthly migraine days, respectively, compared with placebo (-3.2; p=0.0001). Treatment-emergent AEs, including upper respiratory tract infections and fatigue, occurred at low rates, though at higher rates than seen in the placebo arm.

Lipton et al. (2020) examined the efficacy and safety of eptinezumab as a preventive treatment within a phase 3, randomized, double-blind, placebo-controlled study within the chronic migraine population.(150) Patients were randomized to be administered 100 mg of eptinezumab (n=356), 300 mg of eptinezumab (n=350), or a placebo (n=366) via IV infusion. On average, patients reported 16.1±4.6 monthly migraine days and 20.5±3.1 monthly headache days at baseline across groups. The primary efficacy endpoint was observed through a change in mean monthly migraine days for weeks 1-12 from the baseline. Eptinezumab significantly improved monthly migraine days during weeks 1–12 (i.e., first dosing interval) at both the 100 mg dose (-7.7) and the 300 mg dose (-8.2) compared with placebo (-5.6; p<0.0001). Treatment-emergent AEs were fairly distributed across the three groups and included nasopharyngitis, upper respiratory tract infections, and fatigue. Silberstein et al. (2020) reported an incremental reduction in mean monthly migraine days and lower rates of treatment-emergent AEs from weeks 13–23 (i.e., second dosing interval) through 24 weeks.(151)

Ashina et al. (2022) examined the efficacy and safety of eptinezumab as a preventive treatment for episodic or chronic migraine among patients who had experienced two to four previous preventive treatment failures within a phase 3b, multi-arm, randomized, double-blind, placebo-controlled trial.(152) Patients who had at least 4 monthly migraine days (n=891) were randomized to receive at least one dose of 100 mg eptinezumab (n=299), 300 mg eptinezumab (n=294), or a placebo (n=298). The primary efficacy outcome was observed through a change in mean monthly migraine days from baseline to weeks 1–12. Both the eptinezumab 100 mg dose (-4.8) and eptinezumab 300 mg dose (-5.3) resulted in a statistically significant reduction in mean monthly migraine days from baseline throughout the study period compared with both doses of the placebo (p<0.0001). As both the 100mg and 300 mg doses of eptinezumab saw a reduction in HIT-6 score by more than six points, both doses also resulted in a clinically significant reduction in HIT-6 scores. Further, a statistically significant improvement was observed in key secondary endpoints, such as HIT-6 scores at week 12, both ≥50% and ≥75% responder rates and mean monthly migraine days in weeks 13–24 for eptinezumab 100 mg and 300 mg doses compared with placebo. COVID-19 was the most reported treatment-emergent AE, followed by nasopharyngitis and fatigue.

In an SR and meta-analysis examining the efficacy and safety of eptinezumab for the prevention of episodic or chronic migraine, Siahaan et al. (2022) analyzed data from patients with migraine (n=2,730) who participated in any of four RCTs of eptinezumab.(153). This analysis demonstrated that eptinezumab use was associated with a greater reduction in both monthly migraine days from baseline through week 12 and migraine reduction the day after infusion. Eptinezumab use was also associated with lower HIT-6 scores at weeks 4 and 12 and ≥50 and ≥75% responder rates compared with placebo. Additionally, rates of AEs between eptinezumab and placebo were comparable (RR: 1.01; 95% CI: 0.96–1.07; p=0.63; I^2 = 0%). Interestingly, outcomes were unaffected by the duration of migraine, age, sex, or body mass index

(BMI). A separate meta-analysis of eptinezumab by Yan et al. (2021), which examined different dosing regimens and their efficacy and safety, reported that all doses used in the RCTs significantly reduced mean monthly migraine days; this finding was especially true of the 300 mg dose.(154) Similarly to the analysis by Siahaan et al. (2022), no statistically significant difference occurred between eptinezumab and placebo in regard to treatment-emergent AEs.(153, 154)

In a subgroup analysis (not included in the evidence base nor impacting the strength of this recommendation) focusing on patients diagnosed with both chronic migraine and MOH, patients meeting the criteria for both headache types experienced 16.7±4.6 monthly migraine days across treatment groups.(155) Both the eptinezumab 100 mg dose (-8.4) and eptinezumab 300 mg dose (-8.6) resulted in a statistically significant reduction in mean monthly migraine days from baseline throughout the study period compared with the placebo dose ($p<0.0001$).

Patient preferences vary regarding this treatment. As per administration protocol, an infusion of eptinezumab is administered over a 30-minute period (±15 minutes) with additional time attributed to being monitored for at least 2 hours after the infusion is completed. Patients would also have to travel to and from the infusion center and arrange for time off from personal and professional responsibilities. However, these visits could potentially be coupled with another needed visit to health care providers co-located within the same medical center. Additionally, patient response to eptinezumab is observed quickly after the first dose. According to Diener et al. (2021), a statistically significant reduction in migraine occurred 1 day after infusion; 28.6% of patients receiving the 100 mg dose had a migraine and 27.8% of patients receiving the 300 mg dose had a migraine, whereas 42.3% of patients receiving the placebo had a migraine ($p<0.0001$).(155) Across studies, eptinezumab is proven to be an efficacious, safe, and tolerable treatment option for the prevention of episodic and chronic migraine, regardless of the duration of migraine, age, sex, or BMI. Eptinezumab also has value among patients who have been treating refractory migraine and those who experience MOH. In considering the safety profile of eptinezumab in pregnancy and lactation, the risk of adverse outcomes in pregnancy has not been characterized.

The Work Group systematically reviewed evidence related to this recommendation. (149, 150, 152-154) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was high. The Work Group determined that the benefits of eptinezumab slightly outweighed the harms and burdens because the treatment was found to be efficacious for the prevention of both episodic and chronic migraine as well as safe and tolerable for patients. Patient values and preferences varied, with an important differentiating factor for patients being the commitment to receiving infusions. Despite the high confidence in the quality of the evidence, efficacy of eptinezumab, and favorable safety and tolerability profile, the Work Group acknowledged that there is a lack of long-term safety data for eptinezumab.

Additionally, given that eptinezumab received its FDA approval for migraine prevention in 2020, the Work Group recognized that drug withdrawals in the U.S. occur in a bimodal distribution (within 1–5 years of release to the market, later at 15–20 years, or near the time of patent expiration). Furthermore, in the U.S., it is estimated that fewer than 1% of AEs are reported; hence, by the time safety signal becomes apparent, more than just those for whom AEs were reported might have been affected.(156-160) Thus, the Work Group made the following recommendation: We suggest intravenous eptinezumab for the prevention of episodic or chronic migraine.

Recommendation

7. We suggest lisinopril for the prevention of episodic migraine.
   (Weak for | Reviewed, Not changed)

Discussion

As an angiotensin-converting enzyme inhibitor, lisinopril is commonly used within primary and specialty care settings.

An SR by Jackson et al. (2015) reported the results of one RCT examining the efficacy of lisinopril as a preventive therapy for migraine.(116) Patients (n=60) ages 18–60 years with an episodic migraine received either lisinopril (10 mg once daily for 1 week followed by 20 mg once daily for 11 weeks) or placebo. After a 12-week intervention period, among the patients who completed the study (n=47), several endpoints were significantly improved among those taking lisinopril, including the number of headache days (-1.4 [-2.6 to -0.2]; mean reduction of 17%; standard deviation [SD]: 5–30%), migraine days (reduction of 21%; SD: 9–34%), and hours with headache (reduction of 20%; SD: 5–36%) compared with placebo. The headache severity index was significantly reduced by 20% (SD: 3–37%) among patients taking lisinopril compared with placebo. In considering this trial, the SR by Jackson et al. (2015) favored the treatment of episodic migraine with lisinopril over placebo (SMD: -0.47; 95% CI: -0.88–0.06).(116)

Lisinopril is contraindicated in pregnant patients and individuals of childbearing age who are not actively using contraception.(161) Human studies have not been conducted regarding the risks or benefits of use while breastfeeding.

The Work Group considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG because no new studies on the effect of lisinopril met inclusion criteria for the 2023 VA/DoD Headache CPG systematic evidence review.(116) Therefore, this recommendation is categorized as *Reviewed, Not changed*. The Work Group's confidence in the quality of the evidence was low. The benefits slightly outweighed the harms, especially because most patients who develop migraine headaches are between ages 18 and 55 years and, therefore, are generally in a separate demographic from those who develop vascular disease. Because the medication is well tolerated and does not have a similar stigma reported in patients taking antidepressants

for headache control, patients likely have similar preferences regarding this treatment. Provider preferences would also be similar because lisinopril is widely prescribed within primary and specialty care settings. Thus, the Work Group made the following recommendation: We suggest lisinopril for the prevention of episodic migraine.

Recommendation

8. We suggest oral magnesium for the prevention of migraine.
   (Weak for | Not reviewed, Not changed)

Discussion

Formulations of oral magnesium salt varied in the evidence, including magnesium oxide, magnesium sulfate, and magnesium 2-propyl valerate. Magnesium 2-propyl valerate (a magnesium salt of valproic acid) might have had migraine preventive effects from the valproic acid rather than the magnesium.

The Work Group considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG.(107, 162, 163) An SR by Okuli et al. (2019) included four placebo-controlled RCTs of magnesium (n=266) demonstrating a mean reduction of 2.6 migraine headaches per month after 12-weeks of treatment.(107) Doses in the four RCTs ranged from 500–600 mg of oral magnesium daily (citrate and oxide formulations). In another SR of eight RCTs (n=568), patients reported an OR of 0.2 for change in migraine days, which was statistically significant.(162) This SR also found a statistically significant reduction in migraine intensity. Oral magnesium formulations varied in this SR, including 1–2 g magnesium sulfate, 200–800 mg magnesium 2-propyl valerate, and 400–600 mg magnesium oxide.(162) An additional randomized crossover study compared 500 mg magnesium oxide to 400 mg valproate sodium twice daily (n=70; however, only 63 completed the study).(163) Both treatment groups demonstrated a similar reduction from five to approximately three headaches per month, with no statistically significant difference between groups. The Work Group determined that the benefits slightly outweighed the harms of oral therapy in patients with normal renal function, where side effects are largely limited to GI intolerance. Magnesium toxicity has been associated with doses greater than 5,000 mg per day, with side effects of hypotension, ileus, muscle weakness, and lethargy that can progress to cardiac arrest (not included in the evidence base nor impacting the strength of the recommendation).(164) The risk of these AEs is increased with reduced renal function.(164)

The Work Group considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG.(107, 162, 163) Therefore, this recommendation is categorized as *Not reviewed, Not changed*. The Work Group's confidence in the quality of the evidence was moderate.(107, 162, 163) The body of evidence had limitations including variability in the oral formulations used and lack of information on AEs. However, the benefits of migraine reduction slightly outweighed the limited harms of this intervention.

Patient preferences vary because some might prefer not to experience its potential for GI side effects (e.g., it might be poorly tolerated in patients with irritable bowel syndrome or renal dysfunction), and some patients prefer not to take daily medication long-term. Thus, the Work Group made the following recommendation: We suggest oral magnesium for the prevention of migraine.

Recommendation

9. We suggest topiramate for the prevention of episodic and chronic migraine. **(Weak for | Reviewed, New-replaced)**

Discussion

Evidence suggests topiramate improves monthly migraine days for episodic and chronic migraines as demonstrated in two SRs.(140, 165) An SR by Overeem et al. (2021) demonstrated a statistically significant improvement in monthly migraine days by -1.11 in patients with episodic migraine (n=1,903), with a number needed to treat (NNT) of seven (50% responder rate) and number needed to harm (NNH) of 12, which includes cognitive, sensory, pain, and GI side effects.(165) An SR by Yang et al. (2021) demonstrated a statistically significant improvement in monthly migraine days by -2.30 compared with placebo in patients with chronic migraine.(140) These findings were consistent with the 2020 VA/DoD Headache CPG findings based largely on an SR by Mulleners et al. (2015), which examined the efficacy of topiramate as a treatment option for adults with episodic migraine.(166) This SR included 17 unique studies comparing various doses of topiramate (50–200 mg per day across studies) and examined the effect of topiramate on the Migraine-Specific Quality of Life Questionnaire (MSQL) and ≥50% responder rate. The mean duration of therapy was 19 weeks. When compared with placebo, topiramate significantly reduced the frequency of headaches and improved the ≥50% responder rate.

Adverse events increased with escalating topiramate doses, including cognitive, sensory, and GI side effects. Compared with placebo, topiramate has greater odds of AEs, including nausea, dizziness, and somnolence (OR: 1.35; 95% CI: 1.06–1.73) and withdrawal because of AEs (OR: 2.08; 95% CI: 1.56, 2.78).(167) The most common AEs included dizziness or vertigo, paresthesia, cognitive complaints, somnolence, and taste perversion.(140, 165, 166) Providers are encouraged to titrate slowly when starting a patient on topiramate to reduce the risk of side effects, including cognitive side effects.

Consideration of comorbidity profiles is important when discussing potential benefits and harms. For instance, topiramate might be effective for patients with concurrent obesity, epilepsy, or alcohol use disorder. On the other hand, it might be less appropriate for patients with renal calculi, low weight, eating disorders, and baseline cognitive difficulties. Topiramate also has a risk of causing metabolic acidosis. Providers should engage in discussions with patients regarding effective contraception because of

the reduced efficacy of contraception at topiramate doses >200 mg. Additionally, topiramate use during pregnancy (particularly during the first trimester) has an increased risk of teratogenicity.(168)

Patient preferences vary regarding this treatment. The patient focus group noted that topiramate can be burdensome because of side effects and that it can be difficult to remember to take medication daily. On the other hand, this medication is easily obtained and prescribed in primary care settings, although topiramate must be titrated slowly to minimize side effects, which can be burdensome for prescribers and patients. The cognitive side effects can also be extremely bothersome for patients, especially in patients with TBI or PTH, and should be used cautiously or avoided; however, patients with concomitant alcohol use disorders, seizures, or obesity might prefer this treatment.

The Work Group systematically reviewed evidence related to this recommendation (140, 165) and considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG.(166, 167) Therefore, it is categorized as *Reviewed, New-replaced*. The Work Group's confidence in the quality of the evidence was moderate. The body of evidence had some limitations including ROB.(140, 165) The benefits of topiramate in improving monthly migraine days in patients with chronic and episodic migraines slightly outweighed the potential harm of AEs, such as cognitive effects and paresthesia. Patient values and preferences vary because some patients might prefer not to take medication, and they might have concerns about potential cognitive effects or other side effects of topiramate. Other patients might prefer to take a medication that might help with weight loss, such as topiramate. Thus, the Work Group made the following recommendation: We suggest topiramate for the prevention of episodic and chronic migraine.

Recommendation

10. We suggest propranolol for the prevention of migraine.
    (Weak for | Reviewed, Not changed)

Discussion

No new evidence on propranolol for the prevention of migraine headache was retrieved during the systemic evidence review carried out as part of this CPG update. An SR of three RCTs (n=238) by He et al. (2017) from the 2020 VA/DoD Headache CPG suggested propranolol decreases migraine headache days: −0.29 (CI: -0.49 to -0.09) when compared with placebo.(167) The SR found the ≥50% responder rate was not statistically significant when compared with placebo. He et al. (2017) also demonstrated no statistically significant differences in all-cause study withdrawal or withdrawal because of AEs when compared with placebo.(167) AEs of propranolol can include fatigue, dizziness, lightheadedness, exercise intolerance, and sexual dysfunction. The systematic evidence review did not provide specific dosing recommendations or dosing strategies (e.g., long-acting versus short-acting preparations). In patients requiring high

doses or with a history of cardiac disease, electrocardiograms (ECG) might be needed for monitoring. Propranolol is used to treat hypertension and certain types of tremors and might be effective for patients with these comorbid conditions.

Patient preferences vary regarding this treatment. Some patients might find propranolol less favorable than other evidence-based treatments, such as topiramate or the CGRP receptor antagonists, because of propranolol's effect on heart rate, particularly in patients who exercise frequently and are unable to maximize their heart rate during cardiovascular (CV) activity. Further, dosing multiple times a day and the risk of orthostasis and bradycardia might be burdensome and could potentially cause discontinuation. Patients with concomitant anxiety might find propranolol helpful for their headaches and anxiety.

The Work Group considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG.(167) Therefore, this recommendation is categorized as *Reviewed, Not changed*. The Work Group's confidence in the quality of the evidence was moderate. The body of evidence had some limitations including small sample size, limited duration of follow-up (12–16 weeks), and imprecision.(167) The benefits of propranolol slightly outweighed the potential harms and AEs. Patient values and preferences were similar because of the low side-effect profile. The Work Group also considered this recommendation's impact on patients with anxiety, tremors, or hypertension. Thus, the Work Group made the following recommendation: We suggest propranolol for the prevention of migraine.

Recommendation

11. We suggest valproate for the prevention of episodic migraine.
    (Weak for | Reviewed, New-replaced)

Discussion

Mulleners et al. (2015) performed a meta-analysis of antiepileptics in migraine prophylaxis that included 10 eligible valproate studies.(166) Active interventions included topiramate, propranolol, and flunarizine in a range of doses (400–1,500 mg per day) and study duration (8–12 weeks, average 11 weeks).(166)

In six placebo-controlled trials, valproate was found to be more effective in treating episodic migraine at all assessed time points, including 4, 8, and 12 weeks.(169-174) Four placebo-controlled divalproex sodium trials showed patients receiving active treatment were twice as likely to experience a 50% reduction in headache frequency.(172, 175-177) One trial found that sodium valproate was significantly superior to placebo for the same metric but different between treatments.(171)

Mulleners et al. (2015), which included two crossover trials of sodium valproate, showed significant headache frequency reduction in the active group compared with the placebo group of approximately four headaches per 28 days.(170, 171) Comparisons with

flunarizine (176) and propranolol (172) were not significantly different between treatments. No placebo-controlled studies reported QoL measures. No evidence of a difference in response to increased dose was found.

Side effects of valproate include boxed warnings for hepatotoxicity and pancreatitis, including fatal hemorrhagic cases. Hepatotoxicity can be fatal and might occur within the first 6 months of treatment. Monitoring liver function for the occurrence of thrombocytopenia, leukopenia, eosinophilia, and anemia might be warranted, especially in patients with a risk of mitochondrial disease. Valproate can cause serious congenital malformations, especially affecting the brain and spinal cord, and can also cause disabilities in coordination, learning, communication, and behavior in babies exposed to the medication before birth.(178) Potential weight gain might be of particular concern in active duty Service members.(166, 179-181). Additional noteworthy AEs associated with valproate include alopecia, somnolence, GI upset, tremors, and hyperammonemia.(182)

Evidence from an SR by Jackson et al. (2015) included four RCTs on valproate for episodic or mixed chronic daily headache or both with a primary outcome of headache days per month.(116) In all four RCTs, valproate showed a clear benefit in terms of reduction of headache days per month compared with placebo for episodic migraine (-1.5 headache per month; 95% CI: -2.1 to -0.8). The quality of evidence for this review was moderate.

The Work Group considered the evidence put forth in the 2020 VA/DoD Headache CPG because no additional studies met inclusion criteria for the 2023 VA/DoD Headache CPG systematic evidence review.(116, 166) Therefore, this recommendation is categorized as *Reviewed, New-replaced*. The Work Group's confidence in the quality of the evidence was moderate. The body of evidence had some limitations, including a lack of relevant newly published studies on the topic. The benefits slightly outweighed the harms and burdens of this medication because valproate has demonstrated a beneficial reduction of headache days per month for individuals with episodic migraine. Patient values and preferences varied because certain patients might be willing to take valproate formulations for prophylaxis given its long-standing evidence for benefit. However, other patients might find hair loss and weight gain especially burdensome, and women migraineurs of child-bearing age would have to consider the implication of contraceptive compliance. Despite its long history in medical use, serious but rare side effects limit the use of this medication by providers when prescribing. Thus, the Work Group made the following recommendation: We suggest valproate for the prevention of episodic migraine.

Recommendation

12. We suggest memantine for the prevention of episodic migraine.
    (Weak for | Reviewed, New-added)

Discussion

Evidence suggests memantine improves monthly migraine headaches and monthly migraine days as well as migraine-related disability in patients with episodic migraine. This recommendation is based on two RCTs by Noruzzadeh et al. (2016) (n=52) and Shanmugam et al. (2019) (n=59) within an SR by Mistry et al. (2021).(183-185) In both RCTs, the authors found improvement in the primary endpoint of monthly frequency of migraine headaches; two fewer migraines per month at 12 weeks and three fewer per month at 24 weeks versus placebo in the Noruzzadeh et al. (2016) (184) and Shanmugan et al. (2019) trials,(185) respectively. The two RCTs also evaluated different secondary endpoints. Norrazudeh et al. (2016) examined reduction in monthly migraine days (baseline of 10 days to 2 days for memantine versus 10 days to 8 days for placebo) and improvement in Migraine Disability Assessment (MIDAS) rank (baseline of moderate disability improved to mild with memantine versus no change with placebo), although Shanmugam et al. (2019) included an assessment of ≥50% improvement from baseline (85% for memantine versus 51% for placebo) and number of rescue treatments needed (approximate baseline of 9 treatments reduced to 0.75 treatments for memantine and 3.72 treatments for placebo).(184, 185) Effect sizes were large (Cohen d>0.8), though both RCTs were small.(184, 185) Based on the trial by Shanmugam et al. (2019), the NNT with memantine for a 50% reduction in migraine frequency is three.(185)

Patient preferences vary regarding this treatment. Memantine is easily accessible to patients and can be offered by any prescriber (i.e., no specialist appointment required). Memantine has some adverse effect burden for the patient (e.g., dizziness, somnolence, nausea reported both in the reviewed RCTs and product labelling). Memantine has minimal resource implications for the health system.

The Work Group systematically reviewed evidence related to this recommendation.(183) Therefore, it is categorized as *Reviewed, New Added*. Using USPSTF criteria, both RCTs were rated as good quality, but concerns arose about small sample sizes and external validity (e.g., generalizability) with a VA or DoD population. Therefore, the Work Group's confidence in the quality of the evidence was moderate.(183) The benefits of memantine for reduction in migraine frequency and monthly migraine days outweighed the potential harms of AEs, which were determined to be mild and not clearly different from placebo. Patient values and preferences were deemed similar because most patients would prefer an effective treatment with minimal side effects and low cost as well as no referral to advanced specialty care required. Thus, the Work Group made the following recommendation: We suggest memantine for the prevention of episodic migraine.

Recommendation

13. We suggest atogepant for the prevention of episodic migraine.
    (Weak for | Reviewed, New-added)

Discussion

The Work Group reviewed the evidence for the use of atogepant for the prevention of episodic migraine. Tao et al. (2022) performed a meta-analysis of three RCTs (n=2,466), including Goadsby et al. (2020), Ailani et al. (2021), and Allergan et al. (2021).(186) The primary outcome was mean monthly migraine days compared with placebo. Secondary indicators included the mean number of headache days per month, the number of "acute migraine medication use" days per month, and the number of half remissions. In all three trials, at a variety of dosing strategies, atogepant demonstrated a significant reduction in monthly migraine days, monthly headache days, and monthly medication use days.(186) Goadsby et al. (2020) reported that, in all atogepant dose groups, the proportions of participants with at least a 50% reduction in monthly migraine days across 12 weeks of treatment ranged between 52% and 62%. Similarly, Ailani et al. (2021) reported an average reduction of ≥50% migraine days per month in 55.6% to 60.8% of atogepant dose groups compared with 29.0% of the placebo group ($p<0.001$ for all comparisons with placebo).(186) The most commonly reported AEs were nausea, constipation, nasopharyngitis, and upper respiratory infections. Serious AEs included one case each of asthma and optic neuritis in the 10 mg atogepant group.(186) No strong dose-response relationship was demonstrated for primary or secondary outcomes.

The benefits of atogepant slightly outweighed the harms. Atogepant is an oral, daily prevention strategy medication belonging to a new class of targeted treatment with a low side-effect profile. Patient preferences vary regarding atogepant. The patient focus group requested that providers stay informed on contemporary treatments. First- and second-generation oral CGRP antagonists, namely gepants, might be attractive as a novel approach to migraine care and an especially attractive option for the active duty Service member population, for whom injectable medications elicit retention and deployment questions.

The Work Group systematically reviewed evidence related to this recommendation. (186) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was moderate. The body of evidence had some limitations, including the small number of RCTs and ROB, lack of blinding of those recording and adjudicating outcomes, and a lag time in the publication in one of the cited studies. All three studies were supported by industry.(186) Patient values and preferences varied. Some patients might prefer a daily oral prophylactic medication, such as atogepant, although others might prefer the convenience of a monthly or quarterly prevention strategy, such as IV or subcutaneous CGRP mAb treatment or a combination treatment to address co-occurring medical conditions (e.g., propranolol for patients with episodic migraine and CV disease). The benefits, including a reduction in monthly migraine and headache days at up to 12 weeks follow-up, slightly outweighed the potential AEs.(186) Thus, the Work Group made the following recommendation: We suggest atogepant for the prevention of episodic migraine.

Recommendation

14. We suggest onabotulinumtoxinA injection for the prevention of chronic migraine. **(Weak for | Reviewed, Not changed)**

Discussion

The Work Group reviewed two SRs by Barad et al. (2022) and Yang et al. (2021).(140, 187) Barad et al. (2022) completed an SR of the literature on local interventional procedures, including nerve blocks, trigger point injections, implantable stimulation, and chemodenervation.(187) An additional SR was included in the 2020 VA/DoD Headache CPG evidence base supporting this recommendation.(188) The review that focused on chemodenervation with onabotulinumtoxinA included two RCTs of moderate size (n=1384); these trials demonstrated a decrease in 1.8 headache days per month for chemodenervation compared with placebo. The SMD for this intervention was -0.28, which is considered small, a statistically significant effect size favored onabotulinumtoxinA.(187) The Work Group's confidence in the quality of this evidence was moderate. Yang et al. (2021) completed an SR that focused on the comparative effectiveness of interventions for chronic migraine, including erenumab, onabotulinumtoxinA, and topiramate.(140) The Work Group focused on the five RCTs in this SR evaluating onabotulinumtoxinA (n=1,574), a few of which were also included in the SR by Barad et al. (2022).(140, 187) For the critical outcome of change in headache days, the SR by Yang et al. (2021) found a reduction of 1.9 headache days in patients treated with onabotulinumtoxinA compared with placebo.(140) The Work Group's confidence in the quality of this evidence was also moderate.

Adverse events were greater for the onabotulinumA treatment arms in both SRs. Barad et al. (2022) reported an AE rate of 29% in the treatment arm compared with 12% in the placebo arm, and Yang et al. (2021) noted an OR of 0.64 for AEs in the placebo group compared with the treatment arm.(140, 187) Despite the higher rate of AEs, these AEs were mild (e.g., neck pain, injection-site pain, drooping eyelid) and the treatment was well tolerated with decreasing AE rates with repeated treatments. Burdens for the individual include quarterly travel to receive the injections. Overall, the systematic evidence review shows a small, but statistically significant treatment effect with limited burdens to the patient, which supports this intervention as a treatment option for the management of chronic migraine.

Large variation occurs in patient preferences regarding this treatment. The patient focus group noted a desire for treatments beyond oral medications but also expressed a need for more virtual care options, through which onabotulinumtoxinA cannot be administered. The relative infrequency of the treatment for many would be viewed as a benefit; however, some patients have "needle phobia" and would not tolerate the necessary multiple injections. System considerations include the resource use related to the cost of training personnel and equity concerns because the treatment requires

specialized providers and the medication must be stored in controlled temperatures and reconstituted by the treatment team at, or near, the time of the injection.

The Work Group systematically reviewed evidence related to this recommendation (140, 187) and considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG.(188) Therefore, it is categorized as *Reviewed, Not changed*. The Work Group's confidence in the quality of the evidence was moderate. The body of evidence had some limitations, including industry sponsoring of the large RCTs and small statistical effect sizes.(140, 187) The benefits of onabotulinumtoxinA injections slightly outweighed the potential harm given the mild AE profile and limited patient burden. Patient values and preferences varied largely because some patients might prefer the relatively infrequent need for treatment and lack of oral medications and potential side effects, although others would opt against injections. Thus, the Work Group made the following recommendation: We suggest onabotulinumtoxinA injection for the prevention of chronic migraine.

Recommendation

15. We suggest against abobotulinumtoxinA or onabotulinumtoxinA injection for the prevention of episodic migraine.
    (Weak against | Reviewed, Not changed)

Discussion

With no new evidence to review since the 2020 VA/DoD Headache CPG, the Work Group maintains the position that no evidence exists that treatment with onabotulinumtoxinA and abobotulinumtoxinA is effective for the prevention of headaches or migraines in patients with episodic migraine when compared with placebo. The evidence reviewed in 2020 included an SR by Herd et al. (2018) of 28 trials.(188) One RCT captured in the SR showed that treatment with onabotulinumtoxinA failed to reduce monthly migraine days and monthly headache days in patients with episodic migraine.(188) In addition, four RCTs in the SR by Herd et al. (2018) showed that the outcome of AEs frequency favored placebo over treatment. One RCT in the SR regarding abobotulinumtoxinA failed to show evidence for any relevant outcomes.(188)

Patient preferences vary largely regarding this treatment. The patient focus group noted a desire for treatments beyond oral medications but also expressed a need for more virtual care options, through which onabotulinumtoxinA cannot be administered. The relative infrequency of the treatment for many would be viewed as a benefit; however, some patients have needle phobia and would not tolerate the necessary multiple injections. System considerations include the resource use related to the cost of training personnel and equity concerns because the treatment requires specialized providers and the medication must be stored at controlled temperatures and reconstituted by the treatment team at, or near, the time of the injection.

The Work Group considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG.(188) No new studies met the inclusion criteria for the 2023 VA/DoD Headache CPG systematic evidence review related to the effect of abobotulinumtoxinA or onabotulinumtoxinA injection for the prevention of episodic migraine. Therefore, this recommendation is categorized as *Reviewed, Not changed*. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations, including a small sample size and some imprecision. The potential harm of onabotulinumtoxinA or abobotulinumtoxinA injections outweighed the benefits from injection for episodic migraine because no significant benefits were shown. Patient values and preferences varied largely because although some patients prefer an infrequent treatment that requires no oral medication, many dislike receiving multiple injections. Thus, the Work Group made the following recommendation: We suggest against abobotulinumtoxinA or onabotulinumtoxinA injection for the prevention of episodic migraine.

Recommendation

16. There is insufficient evidence to recommend for or against rimegepant for the prevention of episodic migraine.
    (Neither for nor against | Reviewed, New-added)

Discussion

The Work Group reviewed the evidence for rimegepant for the prevention of episodic migraine.(189)

Croop et al. (2021) compared the safety, tolerability, and efficacy of rimegepant 75 mg taken every other day with placebo for preventive treatment of episodic migraine in a multicenter, double-blind, randomized, placebo-controlled trial.(189) The study comprised a 4-week observational screening phase, a 12-week double-blind treatment phase, and a 52-week open-label extension phase. The primary study endpoint was change in mean number of migraine days per month from the 4-week observation period compared with the last 4 weeks of the double-blind treatment phase.(189) After the screening of 1,591 patients, 741 individuals received study medication and were included in the safety analysis (370 received rimegepant and 371 received placebo). Results demonstrated that rimegepant decreased monthly migraine days by 4.3 days per month during weeks 9–12, compared with 3.5 days for placebo (p=0.0099).(189) Secondarily, 49% of participants reported at least a 50% reduction in the mean number of moderate or severe migraine days per month in the last 4 weeks of the 12-week double-blind treatment phase compared with 41% in the placebo group. AEs were reported equally (36% of both treatment groups), were mild to moderate, and included nasopharyngitis, nausea, urinary tract infection, and upper respiratory tract infection.(189)

The quality of the evidence for this recommendation was moderate. The primary endpoint results demonstrated rimegepant was superior to placebo. However, the least

squares mean difference (MD) between the rimegepant and placebo treatment groups was -0.8 days, which the Work Group did not consider clinically significant.

The benefits and the harms and burdens were determined by the Work Group to be balanced. Rimegepant offers an oral CGRP targeted treatment option, with a significantly shorter half-life relative to IV or subcutaneous mAbs (11 hours versus 1 month). Rimegepant's recommended dose is 75 mg, taken as needed, up to once daily or every other day, to treat or prevent migraines. This relatively complex schedule might potentially impede compliance. The fewer than 1 per month reduction in headache days this therapy provides might make other prevention options more appealing. However, patients might value abortive and preventive care provided with one medication, and flexible dosing accommodates migraine influenced by dynamic changes (i.e., hormonal fluctuations, weather variation). Facilitating patients' sense of personal control in headache care was emphasized as important by the focus group. Active duty Service members might favor rimegepant compared with the sedative effects of tricyclics, cognitive effects of topiramate, or the CV limitations associated with beta blockers. Use in pregnancy has unknown fetal effects. Transfer of rimegepant into breast milk is low (<1%).[i]

The Work Group systematically reviewed new evidence related to this recommendation.(189) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was moderate. The limitations of the study include the relatively small sample of chronic migraine participants, patient exclusions (greater than 18 headache days during the observation period, non-response history to more than two drug categories for migraine prevention, or both), and lack of active comparator. The benefits of rimegepant, including improved outcome in headache days, were balanced with the potential harm of AEs, which were small (avoid use in end stage renal disease and with certain cytochrome P450 3A4 [CYP3A4] inhibitors).(189) Patient values and preferences varied. Thus, the Work Group made the following recommendation: There is insufficient evidence to recommend for or against rimegepant for the prevention of episodic migraine.

Recommendation

17. We suggest against the use of gabapentin for the prevention of episodic migraine.
    (Weak against | Reviewed, New-replaced)

Discussion

Evidence suggests gabapentin is ineffective for the prevention of episodic migraine. An SR by Mulleners et al. (2015) examined the efficacy of gabapentin as a treatment option for adults with episodic migraine.(166) This SR included six RCTs comparing

[i] Nurtec ODT. Package insert. Biohaven Pharmaceuticals Inc.

gabapentin at doses ranging between 900–2,400 mg with placebo and examined its effect on headache frequency and responder rate. There was a median 12-week treatment phase (range 12–20 weeks) across the studies. Regardless of the dose, gabapentin was found to be inefficacious for the treatment of episodic migraine when compared with placebo.

Adverse events were higher in patients taking gabapentin (68%) versus placebo (57%) and included abnormal thinking, somnolence, flu-like syndrome, and dizziness, vertigo or both.(166) Additional symptoms commonly seen in practice include edema, weight gain, cognitive dysfunction, sedation, dependence, and withdrawal.

It should be noted that several states consider gabapentin a Drug Enforcement Agency (DEA) Schedule V drug, with stricter regulations for prescribing and dispensing from pharmacies, and some have included gabapentin in their prescription drug monitoring programs. Cases of gabapentin abuse, dependence, and withdrawal (not included in the evidence base nor impacting the strength of the recommendation) have also been documented; most notably, abuse and dependence are considered to be at higher risk in patients with preexisting alcohol or drug abuse history.(190) However, no current retroactive data on reason for misuse or addiction exists.

Patient preferences vary regarding treatment with gabapentin. The patient focus group noted that combination treatments were often more effective than oral medication alone, and gabapentin notably has a high pill burden because it is usually dosed three times per day. Ease of access to gabapentin is reasonable because most PCPs are familiar with gabapentin and its possible side effects. In terms of subgroup considerations, gabapentin might be a reasonable treatment option for patients with comorbidities for which there are FDA approved indications (e.g., seizures, post-herpetic neuralgia) and off-label uses (e.g., painful peripheral neuropathy, musculoskeletal pain, alcohol abuse disorder, anxiety). Some concern about weight gain exists in both military and non-military populations, and some military duties (most notably flight) could also be limited by the more common AEs (e.g., altered thinking, dizziness) and should be carefully considered when prescribing this medication.

The Work Group considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG because no studies on the effect of gabapentin met inclusion criteria for the 2023 VA/DoD Headache CPG systematic evidence review.(166) Therefore, this recommendation is categorized as *Reviewed, New-replaced*. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations, including a small treatment effect in one study within the SR, and although clinically significant, it failed to address the critical outcome of interest (change in headache and migraine days) for the 2023 VA/DoD Headache CPG systematic evidence review. The potential harms associated with the extensive side-effect profile of gabapentin slightly outweighed the benefits of this medication. Patient values and preferences varied because although some patients prefer having ease of access to

treatment from their PCP, the relative pill burden of gabapentin is high, with extensive side effects, while the treatment effect appears to be small. Thus, the Work Group made the following recommendation: We suggest against the use of gabapentin for the prevention of episodic migraine.

Recommendation

18. There is insufficient evidence to recommend for or against levetiracetam for the prevention of episodic migraine.
    (Neither for nor against | Reviewed, New-added)

Discussion

Yen et al. (2021) performed an SR and meta-analysis regarding the efficacy of levetiracetam in migraine prophylaxis.(191) The group analyzed eligible data from four RCTs (n=192) and four prospective studies (n=85) published between 2005 and 2019. Two trials focused on the efficacy of levetiracetam on pediatric migraine,(192, 193) while the others discussed use of levetiracetam in adult migraines.(194-197) The studies employed a variety of levetiracetam dosing strategies within the therapeutic range of 500–3,000 mg per day, and follow-up periods ranged from 1–12 months.

The main outcome was the number of patients with >50% headache frequency reduction. Meta-analysis of the four RCTs demonstrated a significantly larger number of participants with >50% headache frequency reduction in the levetiracetam group than the placebo group (overall RR: 0.46; 95% CI: 0.35–0.61).(194-197)

Other outcomes included degree of disability, drug intake value, and number of patients achieving migraine free status. The mean degree of disability was assessed in only one RCT, which reported a significant reduction in migraine disability in the levetiracetam group (from baseline 3.33 ± 0.81 to 1.66 ± 0.76) compared with the placebo group (baseline 3.19 ± 0.94 to 2.38 ± 0.94).(194) Rapoport et al. (2005) assessed the degree of disability using MIDAS score, which was significantly reduced after using levetiracetam for 3 months (62.8 days per month at baseline to 40.8 days per month).(198) Pizza et al. (2011) reported a significant reduction in abortive drug intake for acute headache symptoms compared with baseline values.(199) Some studies reported the number of patients being migraine free after intervention. In Brighina et al. (2006), 7 of 16 patients, and 4 of 20 patients in Pakalnis et al. (2007) were completely migraine-free after the entire medication process.(200, 201)

Mild to moderate adverse effects of levetiracetam were observed in the studies, including irritability;(194, 201) somnolence;(194, 197, 199-201) dizziness or lethargy;(196, 197, 199, 200) asthenias;(194, 201) daytime sedation;(196) weight gain; memory problems;(201) lack of concentration;(198, 199) epigastric pain;(199, 200) and moodiness and hyperactive behavior.(197) The studies reported no significant difference between levetiracetam and placebo groups, and no severe adverse effects were attributed to levetiracetam.

The Work Group systematically reviewed evidence related to this recommendation.(191) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was very low. All studies reported acceptable randomization processes and blinding of patients and providers. There was heterogeneity in the included patients, although some studies did not distinguish between migraine types (episodic or chronic; with or without aura), which might have influenced the results of pooled data, and the participant age groups varied among the studies (4–72 years). The benefits of levetiracetam, including reduced headache frequency and severity in adult and pediatric migraineurs, were balanced with the potential harms of adverse effects. Levetiracetam might present an attractive prophylactic option for migraine because of lack of hepatic metabolism and minimal drug interactions.(202) Levetiracetam was generally well tolerated in this SR and meta-analysis, with mild-to-moderate AEs. Patient values and preferences varied. Patients with epilepsy might prefer to treat both conditions with one medication, noting that teratogenic potential appears to be less relative to other antiepileptic medications.(203) However, patients with comorbid PTSD or depression might prefer to avoid adverse effects that could worsen mood. Thus, the Work Group made the following recommendation: There is insufficient evidence to recommend for or against levetiracetam for the prevention of episodic migraine.

c. Migraine – Abortive

Recommendation

19. We recommend eletriptan, frovatriptan, rizatriptan, sumatriptan (oral or subcutaneous), the combination of sumatriptan and naproxen, or zolmitriptan (oral or intranasal) for the acute treatment of migraine.
    (Strong for | Reviewed New-replaced)

Discussion

Updated Evidence Review of Triptans

The 2023 systematic evidence review revealed no new evidence regarding the safety and effectiveness of triptans for the acute treatment of migraine. However, there was a change in the strength of the evidence based on our predetermined critical outcomes for this iteration of the CPG. When the evidence from the 2020 Headache CPG for frovatriptan and rizatriptan was reviewed with this change in critical and important outcomes, the overall quality of evidence changed from low to moderate for the critical outcomes.

Frovatriptan

In an RCT by Moon et al. (2010), patients (n=122) received frovatriptan to treat an acute migraine episode.(204) This study demonstrated that frovatriptan significantly increased the 2-hour headache response rate compared with placebo for an NNT of 5.3. Headache response rates at 4, 6, and 12 hours were also significantly higher in the

frovatriptan group than in the placebo group, as was the pain-free rate at 2 hours, 4 hours (40.7% versus 23.0%; p=0.006), and 6 hours (56.1% versus 34.0%; p=0.002). The median time to a headache response was significantly shorter in the frovatriptan group than in the placebo group (2 hours versus 3.5 hours; p<0.001).(204) Abortive medication use was more common in the placebo group (p=0.005).

Rizatriptan

An RCT by Cady et al. (2009) evaluated the effects of rizatriptan.(205) Of the patients (n=207) enrolled in the trial, 91% experienced an acute episode of migraine that was treated. Outcomes favored rizatriptan compared with placebo for reported pain freedom at 2 hours (66.3% versus 28.1%; p<0.001), for an NNT of 2.6, and 24-hour sustained pain freedom (52.2% versus 17.7%; p<0.001) for an NNT of 2.9. A greater proportion of patients in the rizatriptan plus education group reported pain freedom at 2 hours compared with those in the rizatriptan plus no education group (71.7% versus 60.9%; p=0.430).

Sumatriptan (Oral) and Eletriptan

A Cochrane review by Derry et al. (2012a) included 61 studies (n=37,250) that compared oral sumatriptan with placebo or an active comparator.(206) Most of the trials were for sumatriptan 50 mg and 100 mg doses. Sumatriptan surpassed placebo for all efficacy outcomes. For sumatriptan 50 mg versus placebo, the NNTs were 6.1, 7.5, and 4.0 for pain freedom at 2 hours and headache relief at 1 and 2 hours, respectively.(206) The NNTs for sustained pain freedom and sustained headache relief during the 24 hours post-dose were 9.5 and 6.0, respectively. For sumatriptan 100 mg versus placebo, the NNTs were 4.7, 6.8, 3.5, 6.5, and 5.2, respectively, for the same outcomes. Results for the 25 mg dose were similar to the results for the 50 mg dose, although sumatriptan 100 mg was significantly better than 50 mg for pain-free and headache relief at 2 hours and for sustained pain-free relief for 24 hours. Treating early (i.e., during the mild pain phase) gave significantly better NNTs for pain-free relief at 2 hours and sustained pain-free relief for 24 hours compared with treating established episodes or those with moderate or severe pain intensity. Relief of associated symptoms, including nausea, photophobia, and phonophobia, was greater with sumatriptan than with placebo. The use of abortive medication was lower with sumatriptan than with placebo. Several studies included an active comparator arm to sumatriptan. Comparing sumatriptan 50 mg to eletriptan (40 mg and 80 mg) demonstrated an NNT of 9.7 in favor of eletriptan. Increasing, the dose of sumatriptan to 100 mg resulted in NNTs of 11 (eletriptan 40 mg) and 6.4 (eletriptan 80 mg) in favor of eletriptan.

Adverse events were transient and mild; however, higher doses of sumatriptan were associated with more AEs.(206) Individual AEs were reported inconsistently among studies. Most studies reported only the most commonly occurring AEs; for example, those occurring in greater than 3% of participants in any of the treatment arms, although others used different terms to describe the same or similar events. Reported AEs

included malaise, fatigue, asthenia, dizziness, and vertigo at lower doses (25–100 mg), but with increased risk at a dose of 100 mg compared with 25 mg. Higher doses of sumatriptan (100–300 mg) were associated with an increased rate of disturbance in taste perversion (i.e., metallic taste in the mouth), nausea, vomiting, or both, and chest pain symptoms.

Sumatriptan (Subcutaneous)

A Cochrane review by Derry et al. (2012b) incorporated 35 studies (n=9,365) comparing subcutaneous sumatriptan with placebo or an active comparator.(207) Most of the data represented the sumatriptan 6 mg dose. Sumatriptan surpassed placebo for all efficacy outcomes including pain freedom at 1 and 2 hours, headache relief at 1 and 2 hours, and sustained pain freedom at 24 hours. The 4 mg and 8 mg dose results were similar to the 6 mg dose results. Sumatriptan was compared directly with several other active treatments, but insufficient data existed to draw a firm conclusion related to comparative efficacy.

Subcutaneous sumatriptan (6 mg) resulted in pain reduction from moderate or severe to no pain by 2 hours in 59% participants compared with 15% taking placebo and pain reduction from moderate or severe to no worse than mild pain by 2 hours in 79% taking sumatriptan compared with 31% taking placebo.(207) Subcutaneous sumatriptan can be used in patients who need rapid administration, have vomiting, or both.

Sixteen studies (n=11,599) provided data on sumatriptan of any dose versus active comparators.(207) Comparing sumatriptan to other triptan agents, zolmitriptan (all doses) demonstrated an AE incidence of 0.23% in comparison with sumatriptan (25 mg, 50 mg) at 0.51%; the overall incidence was 0% for sumatriptan (100 mg) and 0.12% for all doses of rizatriptan (5–40 mg).

Common side effects of subcutaneous sumatriptan include an injection-site reaction, chest pressure or heaviness, flushing, weakness, drowsiness, dizziness, malaise, feeling of warmth, and paresthesia. Most of these reactions occur soon after the injection and resolve spontaneously within 30 minutes. The proportion of participants experiencing AEs within 24 hours with sumatriptan 6 mg was 44% versus 24% for placebo.(207)

Sumatriptan and Naproxen Combination

A Cochrane review by Law et al. (2016) included 13 studies using sumatriptan 85 mg or 50 mg plus naproxen 500 mg to treat migraine episodes of mild, moderate, or severe pain intensity.(208) Twelve studies contributed data for analyses, which included participants who received combination treatment (n=3,663), placebo (n=3,682), sumatriptan (n=964), and naproxen (n=982). The combination of sumatriptan plus naproxen was better than placebo for relieving acute migraine episode in adults. The best efficacy of the combination was demonstrated in patients with a mild intensity migraine at the onset (statistically significant, $p<0.0001$). Using an outcome of pain

freedom at 2 hours, the combination formulation was better than placebo for mild, moderate, and severe pain at baseline. The NNTs were 3.1 and 4.9, with 50% and 28% of people being pain free with mild or moderate-to-severe pain, respectively. The combination was better than the same dose of either drug given alone; 52% responded favorably to sumatriptan alone, while 44% responded favorably with naproxen alone. More AEs were reported with the combination product; however, the incidence of any single AE was low (<4%). The development of AEs did not appear to increase withdrawal rates in treated patients.

Zolmitriptan

A Cochrane review by Bird et al. (2014) included 25 studies that involved more than 20,000 participants reporting the effects of zolmitriptan on migraine episodes.(209) For zolmitriptan 1 mg (oral or intranasal) versus placebo, the NNT for pain freedom at 2 hours was 7.0. Increasing the dose to 2.5 mg, the NNT became 5.0. A dose of zolmitriptan 5 mg versus placebo had an NNT of 4.8 for the oral formulation and 3.0 for the intranasal product. Oral zolmitriptan 10 mg had an NNT of 3.0. Additionally, zolmitriptan 10 mg (oral) was superior to 5 mg (p=0.0001). Oral zolmitriptan 2.5 mg and 5 mg provided headache relief at 2 hours, comparable to oral sumatriptan 50 mg, with no difference in AEs.

The proportion of AEs with zolmitriptan 2.5 mg (oral and nasal), 5 mg (oral and nasal), and 10 mg (oral) demonstrated in 12 studies compared with placebo resulted in a dose-dependent increase in AEs.(209) Comparing the AE rates in studies of zolmitriptan to an active comparator (sumatriptan 50 mg) demonstrated similar rates of AE development in the treatment groups. Adverse events were described as mild to moderate and were self-limited. No serious AEs were reported with zolmitriptan.

High-quality evidence supports that oral zolmitriptan 2.5 mg and 5 mg provided headache relief at 2 hours to the same proportion of people as oral sumatriptan 50 mg (66%, 67%, and 68%, respectively), although these patient populations were unequal in all baseline measures.(209)

Summary of the Evidence for Eletriptan, Frovatriptan, Rizatriptan, Sumatriptan, Sumatriptan and Naproxen Combination, and Zolmitriptan

Evidence reveals that triptans, as a class, are most effective when taken early during a migraine and may be repeated in 2 hours as needed, with a maximum of two doses daily. Although different formulations of a specific triptan may be used in the same 24-hour period, only one triptan may be used during this timeframe. The effectiveness and tolerability of triptans vary among patients. Lack of response or side effects experienced with one triptan does not predict the response to another (based on a study not included in the evidence base nor impacting the strength of the recommendation).(210)

The safety of triptans is well established, and the risk of de novo coronary vasospasm from triptan use is exceedingly rare. However, triptans are contraindicated in patients with known or suspected coronary artery or cerebrovascular disease because they might increase the risk of myocardial ischemia, infarction, or other cardiac or cerebrovascular events. Triptans should not be prescribed for patients taking ergot because of risk of synergistic effect causing vasospasm or in patients with hemiplegic or basilar migraine because of risk of vasospastic stroke (based on studies not included in the evidence base nor impacting the strength of the recommendation).(211, 212)

Information regarding the safety of triptans during pregnancy and breast feeding is limited, and non-pharmacologic treatment methods are emphasized in these situations. Emerging evidence (not included in the evidence base nor impacting the strength of the recommendation) suggests that if prescription abortive medication is considered necessary, triptans are as safe as, and more effective than, older agents, such as butalbital containing compounds, and can be considered in select cases under close observation.(213)

The Work Group considered the assessment of the evidence put forth in the 2020 Headache CPG because no new studies on this topic met inclusion criteria for the 2023 Headache CPG systematic evidence review.(204-209) Therefore, the recommendation is categorized as *Reviewed, New-replaced.* The Work Group's confidence in the quality of the evidence was moderate. The benefits outweighed the potential harm of AEs because reducing the pain was deemed worth experiencing mild and infrequent side effects. Patient preferences vary because not all patients tolerate needles. Small subgroups of patients are intolerant of triptans, experience hemiplegic migraine and cannot use these medications, or both. Subcutaneous medications are also more expensive than oral medications, though they are less expensive than newer migraine abortive medications or evaluation and treatment in the emergency department (ED) or inpatient settings. Thus, the Work Group made the following recommendation: We recommend eletriptan, frovatriptan, rizatriptan, sumatriptan (oral or subcutaneous), the combination of sumatriptan and naproxen, or zolmitriptan (oral or intranasal) for the acute treatment of migraine.

Recommendation

20. We recommend aspirin/acetaminophen/caffeine for the acute treatment of migraine.
    (Strong for | Reviewed, New-added)

Discussion

Simple nonsteroidal anti-inflammatory drugs (NSAID), aspirin and acetaminophen as single agents are evidence-based options for the acute treatment of migraine and are further addressed in Recommendation 21. The combination product of aspirin, acetaminophen, and caffeine (AAC) was assessed in an SR by Diener et al. (2022),

which included seven RCTs (n=3,306) comparing active treatment to placebo.(214) The analysis strongly favored a benefit of AAC versus placebo for the critical outcomes of pain freedom at 2 hours, pain relief at 2 hours, reduction in photophobia and phonophobia, and nausea. Effect size was deemed robust with the NNT of 9 for pain freedom at 2 hours and the NNT of 4 for pain relief at 2 hours. Adverse events were higher in the AAC arm than the placebo arm across all studies with pooled results reporting 10.9% (AAC) and 7.8% (placebo) of patients having at least one AE. This finding is consistent with the known side effects of the active ingredients (e.g., aspirin - dyspepsia/nausea, caffeine - nervousness).

Some variation in patient preferences occurs regarding this treatment because most patients would prefer an effective, inexpensive treatment that requires neither a physician's visit nor prescription (i.e., can be purchased over the counter [OTC]). It was noted that some patients genuinely prefer a non-pill, non-medical intervention. There are also populations for whom this medication might be inappropriate (e.g., those with peptic ulcer disorder, pregnant patients in the third trimester, individuals with greater than seven migraines per month), and although easier access can be beneficial, it might increase the risk for MOH if used excessively. Therefore, despite OTC level access, selecting the appropriate treatment for patients experiencing migraines is still necessary.

The Work Group systematically reviewed evidence related to this recommendation.(214) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was high, and the ROB in each study was low. The body of evidence had some limitations, including that three of the RCTs in the SR, representing approximately one-third of the pooled population, excluded patients who typically experienced vomiting or had incapacitating migraines (e.g., bedrest), and none of the studies included patients who had more than seven migraines per month. Therefore, the evidence might or might not be generalizable to a VA or DoD primary care population.(214) Nonetheless, the benefits of AAC (e.g., pain freedom and pain relief at 2 hours) outweighed the potential harm (e.g., known, mild, and expected side effects of aspirin and caffeine). Patient values and preferences were similar because most patients prefer safe, effective, easily accessible medications. Thus, the Work Group made the following recommendation: We recommend aspirin/acetaminophen/caffeine for the acute treatment of migraine.

Recommendation

21. We suggest acetaminophen, aspirin, ibuprofen, or naproxen for the acute treatment of migraine.
    (Weak for | Reviewed, Amended)

Discussion

Acetaminophen

An SR by Derry et al. (2013) included 11 RCTs comparing paracetamol (acetaminophen), with or without an antiemetic, with placebo or an active comparator in patients with acute migraine with or without aura or both.(215) For percentage of pain-free response at 2 hours, results suggest a statistically significant difference between the group for paracetamol 1,000 mg versus placebo, favoring paracetamol (RR: 1.80; 95% CI: 1.24–2.62; p=0.0022). All efficacy outcomes demonstrated paracetamol was superior to placebo when the medication was taken for moderate to severe pain, including pain freedom at 2 hours (NNT=12), headache relief at 2 hours (NNT=5), and headache relief at 1 hour (NNT=5.2). Paracetamol 1,000 mg alone is statistically superior to placebo in the treatment of acute migraine, but the NNT of 12 for pain-free response at 2 hours is higher than other commonly used analgesics, suggesting, but not showing, inferiority.(215) The maximum dose of acetaminophen for acute use is 4,000 mg per day, and this dose of acetaminophen should include any other acetaminophen-containing products, such as cold, flu, sinus, or allergy combination products.

Aspirin

An SR by Kirthi et al. (2013) included 13 RCTs comparing aspirin, with or without an antiemetic, with placebo or active comparator in patients with acute migraine with or without aura or both.(216) Thirteen studies (n=4,222) compared aspirin 900 mg or 1,000 mg, alone or in combination with oral metoclopramide 10 mg, with placebo or other active comparators. For all efficacy outcomes, all active treatments were superior to placebo. For aspirin alone versus placebo, efficacy outcomes included pain freedom at 2 hours (NNT=8.1), headache relief at 2 hours (NNT=4.9), and 24-hour headache relief (NNT=6.6). For aspirin plus metoclopramide versus placebo, efficacy outcomes included pain freedom at 2 hours (NNT=8.8), headache relief at 2 hours (NNT=3.3), and 24-hour headache relief (NNT=6.2). It should be noted that the doses used in this SR are higher than the recommended daily dose for OTC aspirin. In the active comparator trials included in the SR, aspirin 1,000 mg demonstrated similar outcomes as sumatriptan 50 mg or 100 mg.(216) However, AEs were higher in the sumatriptan treated patients.

Ibuprofen

An SR by Rabbie et al. (2013) examined the use of ibuprofen as an acute management therapy for migraine.(217) The analysis included nine studies and a large study population (n=4,373 with 5,223 acute migraines). For ibuprofen 400 mg versus placebo, outcomes assessed included pain freedom at 2 hours (NNT=7.2), headache relief at 2 hours (NNT=3.2), and 24 hour sustained headache relief (NNT=4.0). For ibuprofen 200 mg versus placebo, outcomes assessed included pain freedom at 2 hours (NNT=9.7) and headache relief at 2 hours (NNT= 6.3). Adverse events from this

analysis included dizziness, paresthesia, somnolence, nausea, dyspepsia, dry mouth, and abdominal discomfort.

An RCT conducted by Yadav et al. (2016) (n=150) in patients with episodic migraine reported a 28.2% pain-free response at 2 hours for the ibuprofen 400 mg and placebo groups.(218) However, these findings were inconclusive because of the study design; the effect sizes and p-values were not reported.

Naproxen

An SR by Law et al. (2013) addressed the efficacy of naproxen relative to placebo.(219) The SR included six RCTs comparing naproxen 275 mg, 500 mg, or 825 mg, with or without an antiemetic, to placebo or an active comparator in patients with acute migraine with or without aura, or both. Follow-up was 24 hours post-treatment. For percentage of pain-free response at 2 hours, results suggest a statistically significant between-group difference for naproxen (all doses combined) versus placebo, favoring naproxen (RR: 2.03; 95% CI: 1.61–2.58; p<0.00001). The reported AE incidence within 24 hours of dosing supported a significantly lower rate for placebo versus the patients receiving either dose of naproxen. Given the increased incidence of AEs with doses of naproxen greater than 500 mg and relatively equal efficacy, naproxen 500 mg or fewer is advised over higher doses. For naproxen versus placebo, NNT for pain freedom at 2 hours, headache relief at 2 hours, and 24-hour sustained headache relief was 11, 6, and 24, respectively.

Several of these studies are limited by varying outcome measures and definitions of migraine, but all NSAIDs might be beneficial in patients who have migraine with or without aura. It should be noted that no studies compare the relative efficacy of different NSAIDs. Patients should be advised that many combination products for flu, cold, sinus, and allergy available without a prescription can contain ibuprofen or naproxen and these amounts must be included in the daily total.

Oral Solution Celecoxib

An SR by Deng et al. (2020) included three RCTs (n=682) comparing oral solution celecoxib to placebo in patients with migraine.(220) For pain freedom at 2 hours, results suggested a statistically significant improvement in pain, favoring celecoxib (RR: 1.65; 95% CI: 1.28–2.12; p=0.0001). Additionally, freedom from MBS demonstrated a significant improvement when compared with placebo (RR 1.40; 95% CI: 1.12–1.76; p=0.003). In patients with episodic migraines with or without aura, one RCT (n=567) demonstrated an improvement in pain freedom at 2 hours,(221) and one RCT (n=984) did not demonstrate a benefit in pain freedom at 2 hours.(222) These two RCTs demonstrated a statistically significant improvement in freedom from MBS, improvement in headache pain relief at 2 hours, and freedom from photophobia and nausea at 2 hours.(221, 222) Low-quality evidence demonstrated no significant difference in treatment AEs, including nausea and dysgeusia.

All NSAIDs have a boxed warning for increased risk of CV events and GI events, and these safety issues continue to be high priority when choosing an NSAID. Providers should consider CV risk and GI toxicity when choosing an NSAID. NSAIDs must be used cautiously or avoided in patients with renal impairment.

The Work Group systematically reviewed evidence related to this recommendation (220-222) and considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG.(215-219) Therefore, it is categorized as *Reviewed, Amended*. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations, including small sample size, evidence of bias, and poor methods. The benefits of ibuprofen, naproxen, aspirin, acetaminophen, and oral solution celecoxib outweighed the potential harm of AEs, which was small. Patient values and preferences varied because some patients might have contraindications to NSAIDs or aspirin and might prefer not taking any medications. Many of these medications are accessible OTC, which might be preferable for some patients. Thus, the Work Group made the following recommendation: We suggest acetaminophen, aspirin, ibuprofen, or naproxen for the acute treatment of migraine.

Recommendation

22. We suggest rimegepant or ubrogepant for the acute treatment of migraine. **(Weak for | Reviewed, New-added)**

Discussion

Rimegepant

The systematic evidence review for the 2023 VA/DoD Headache CPG retrieved three SRs (n=10,046) that evaluated the effectiveness and tolerability of rimegepant compared with placebo for the acute treatment of migraine.(223-225) The critical outcomes, reportedly favoring rimegepant over placebo, included pain freedom at 2 hours, pain relief at 2 hours, freedom from MBS, freedom from nausea, freedom from photophobia, and freedom from phonophobia. In combination, these studies provided moderate-quality evidence that rimegepant is more effective than placebo for all critical outcomes reported.(223-225)

Huang et al. (2022), an SR of three RCTs, favored the treatment with rimegepant for pain freedom at 2 hours (NNT=13).(224) Pak et al. (2022), an SR of three RCTs, reported the following outcomes that favored rimegepant over placebo: pain freedom, absence of MBS, pain relief, and freedom from nausea, all at 2 hours.(225) Gao et al. (2019), an SR of four RCTs, favored rimegepant over placebo for the outcomes of pain freedom at 2 hours, freedom from MBS at 2 hours, pain relief at 2 hours, absence of photophobia at 2 hours, absence of phonophobia at 2 hours, and absence of nausea at 2 hours.(223)

Although the individual studies included in Gao et al. (2019) found that rimegepant had more AEs than placebo, the meta-analysis found no difference in common AEs when compared with placebo.(223) Gao et al. (2019) found no statistically significant difference in the rate of significant liver damage, though one of the individual studies did find a difference. Overall, rimegepant was found to be generally well tolerated. Pak et al. (2022) reported nausea and urinary tract infection to be the most common side effects.(225) The authors also noted that although no CV side effects have been reported with CGRP receptor blockers used for the acute or preventive treatment of migraine, there is still insufficient evidence regarding the risk of vascular events in patients with migraine. It should also be noted that rimegepant is a new medication, and rare and serious side effects might occur.

Ubrogepant

The Work Group reviewed evidence from three SRs (n>9,000) that evaluated the effectiveness and tolerability of ubrogepant compared with placebo for the acute treatment of migraine.(224-226) The critical outcomes, reportedly favoring ubrogepant over placebo, included pain freedom, pain relief, freedom from MBS, freedom from nausea, and freedom from photophobia and phonophobia, all at 2 hours. In combination, these studies provided moderate-quality evidence that ubrogepant is more effective than placebo for all critical outcomes reported.

Huang et al. (2022), an SR of three RCTs, favored the treatment with ubrogepant for pain freedom at 2 hours (NNT=13).(224) Pak et al. (2022), an SR of two RCTs, favored ubrogepant over placebo for pain freedom, pain relief, absence of MBS, absence of photophobia and phonophobia, and absence of nausea at 2 hours.(225) Yang et al. (2020), an SR of three RCTs, favored ubrogepant over placebo for the outcomes of pain freedom at 2 hours, freedom from MBS at 2 hours, pain relief for 2 hours, freedom from photophobia at 2 hours, freedom from phonophobia at 2 hours, and freedom from nausea at 2 hours.(226)

Yang et al. (2020) reported eight serious AEs in the treatment group and none in the placebo group; however, the serious AEs were considered irrelevant to the treatment by the primary investigators.(226) No significant difference was found between treatment-related AEs when ubrogepant was compared with placebo. Pak et al. (2022) reported that nausea, somnolence, and dry mouth were the most common AEs related to ubrogepant.(225) Overall, ubrogepant was found to be generally well tolerated. The authors also noted that although no CV side effects have been reported with CGRP receptor blockers used for the acute or preventive treatment of migraine, still insufficient evidence exists regarding the risk of vascular events in patients with migraine. It should also be noted that ubrogepant is a new medication, and rare and serious side effects might occur.

Summary of the Evidence for Rimegepant and Ubrogepant

Some variation occurs in patient preferences regarding acute treatment with rimegepant and ubrogepant. The patient focus group noted a preference for inexpensive and easy to obtain agents, which these medications are not. Both rimegepant and ubrogepant can be a burden on the patient because they might require a visit with a specialist. Furthermore, issues with acceptability and feasibility of use might occur because providers and patients might be uncomfortable with new medications. There are resource use issues, as well, because these new medications are significantly more expensive than other available acute headache treatments. However, these resource use issues might be offset by decreased downstream health care system costs (e.g., ED visits, inpatient evaluations).

Overall, both medications were well tolerated, and the most common side effects included nausea, somnolence, dry mouth, and urinary tract infection. It should also be noted that although no CV side effects have been reported with CGRP receptor blockers used for the acute or preventive treatment of migraine, still insufficient evidence exists regarding the risk of vascular events in patients with migraine. These medications are new, so rare and serious side effects might yet occur.

The Work Group systematically reviewed evidence related to this recommendation.(223-226) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was moderate. The body of evidence had serious limitations regarding study design and ROB. However, no serious inconsistency, indirectness, or imprecision was identified in the critical outcomes. Gao et al. (2019), Huang et. al (2022), and Pak et al. (2022) provided moderate-quality evidence for all critical outcomes that each study reported, including pain freedom at 2 hours, pain relief at 2 hours, freedom from MBS, freedom from nausea, freedom from photophobia, and freedom from phonophobia.(223-225) Rimegepant and ubrogepant for the acute treatment of migraine performed better than placebo, and the benefits of these medications outweighed the potential harm. Although some of the included RCTs showed increased risk of AEs, the meta-analyses failed to show increased risk with either agent. Although there is much potential benefit of small-molecule oral CGRP inhibitors, as a newer class of medications, the Work Group recognizes that long-term follow-up data and additional reports of real-world experience with these medications will be necessary to determine their role in the acute treatment of migraine. Thus, the Work Group made the following recommendation: We suggest rimegepant or ubrogepant for the acute treatment of migraine.

Recommendation

23. We suggest against intravenous ketamine for the acute treatment of migraine. **(Weak against | Reviewed, Amended)**

Discussion

The Work Group did not identify any new studies regarding the use of ketamine for the acute treatment of migraine. The 2020 VA/DoD Headache CPG identified only a single, small RCT comparing IV ketamine to placebo in the ED setting.(227)

Etchison et al. (2018) enrolled patients (n=34) presenting to a single academic ED with migraine headache and randomized them to acute treatment with ketamine or a placebo.(227) The study found no significant difference in pain scores at 30 minutes after administration and, in fact, this primary outcome favored placebo, though the change was not statistically or clinically significant. Patient rating of functional disability, which was not one of the Work Group's outcomes of interest but was evaluated in the study, also favored placebo.(227) Intravenous ketamine has the potential to cause significant neuropsychiatric side effects (e.g., hallucinations, confusion, behavioral changes, mood changes), which might be worse after head injury and might be related to structural brain damage. These side effects can be minimized if low doses are used, as was the case in this study; however, low doses might not have an analgesic effect. The common side effects reported in this study were fatigue, nausea, and generalized discomfort. In addition, ketamine requires close observation in patients with elevated blood pressure and those with cardiac decompensation.(228) Ketamine crosses the placenta and might affect fetal brain development. Therefore, obstetric use is not recommended by the manufacturer.(228) The safety of ketamine in breast feeding has not been established. Intravenous ketamine carries additional risk of abuse and diversion relative to other medications used for headache treatment. For this reason, it is a DEA Schedule III medication.(229)

Patient focus group participants requested that attempts be made to help reduce the stigma of headache. Promoting the use of medications with abuse potential, such as IV ketamine, in the absence of evidence of benefits, conflicts with these preferences. Furthermore, access to this treatment is limited, and high resource use is a consideration because of increased monitoring needs and lack of provider comfort.

The Work Group considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG because no new studies on this topic met the inclusion criteria for the 2023 VA/DoD Headache CPG systematic evidence review.(227) Therefore, this recommendation is categorized as *Reviewed, Amended*. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations because it included only a single study with a small sample size that used a low dose of the study medication, which was unlikely to provide analgesic effects.(227) Although the overall strength of the evidence was deemed moderate for the critical outcomes, the Work Group determined that the overall strength of the evidence should be downgraded to low because of the noted study limitations. The potential harms of neuropsychiatric side effects, although low, were determined to slightly outweigh the benefits of IV ketamine for the acute treatment of headache because no clear benefit was

demonstrated. Patient values and preferences varied because of stigma related to ketamine as a potential drug of abuse and patient preference for non-invasive, non-ED delivered treatments. Thus, the Work Group made the following recommendation: We suggest against intravenous ketamine for the acute treatment of migraine.

Recommendation

24. There is insufficient evidence to recommend for or against lasmiditan for the acute treatment of migraine.
    (Neither for nor against | Reviewed, New-added)

Discussion

Evidence suggests that lasmiditan improves critical outcomes of pain freedom at 2 hours, pain relief at 2 hours, and freedom from MBS in patients with acute migraine. Two SRs (230, 231) and one RCT (232) found that treatment with lasmiditan was associated with statistically significant improvements in the aforementioned critical outcomes (OR: approximately 2; NNT=8). Findings from multiple other studies, conducted in a variety of patient populations, have been consistent with this finding.(233, 234)

However, evidence also indicates a significant level of harm associated with lasmiditan. Serious AEs (e.g., somnolence, fatigue, paresthesia) and AEs leading to treatment withdrawal (e.g., dizziness) were two-fold and almost six-fold greater than placebo (OR: 2.18 and 5.89), respectively,(231) with an NNH of 4 for treatment-emergent AEs based on the largest RCT referenced in the reviewed SR.(235) The Work Group recognizes that lasmiditan is a controlled substance (DEA Schedule V), and in a trial among patients with recreational poly-drug use, all doses of lasmiditan were preferred to placebo.(236) Furthermore, doses twice the recommended maximum were preferred similarly to 2 mg of alprazolam.

Large variation occurs in patient preferences regarding this treatment. The patient focus group noted that lasmiditan can be burdensome because it prevents participants from driving, operating machinery, or engaging in potentially hazardous activities requiring mental alertness. Furthermore, DoD and VA populations might have higher levels of concern with treatments that might pose a chemical dependency risk or impose an impairment that interferes with their job, mission duties, or both.

The Work Group systematically reviewed evidence related to this recommendation. (230-234) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations, including increasing ROB and internal validity concerns.(230, 231) The benefits of lasmiditan (e.g., pain freedom, freedom from MBS) were balanced with the potential harms (e.g., central nervous system AEs), which were significant. Patient values and preferences varied largely because most patients would prefer a treatment that has neither driving precautions nor excess central nervous system side effects.

Thus, the Work Group made the following recommendation: There is insufficient evidence to recommend for or against lasmiditan for the acute treatment of migraine.

d. Tension-Type Headache – Preventive

Recommendation

25. We suggest amitriptyline for the prevention of chronic tension-type headache. **(Weak for | Reviewed, Not changed)**

Discussion

Evidence suggests that treatment with amitriptyline might lower the number of headache days in patients with chronic TTH. An SR of three RCTs by Jackson et al. (2017) examined amitriptyline (50 mg and 100 mg dosing) versus placebo in patients with chronic TTH.(237) Evidence was found for a reduction of monthly headache days after 4 weeks (6.2 fewer days per month than placebo; 95% CI: -8.1 to -4.2). Similar findings were found at 8 weeks, 12 weeks, and 24 weeks for preventive treatment with amitriptyline. Although the reduction in monthly headache days was a critical outcome, the overall confidence in the quality of the evidence was low because of the imprecision in effect estimates and small sample size.(237)

The Work Group determined that the benefits slightly outweighed the harms and burdens. Tricyclic antidepressants (TCA) have well recognized AEs, including anticholinergic effects, such as dry mouth, dry eyes, blurred vision, GI distress, nausea, and sedation along with weight gain and risk for cardiac arrhythmia. Caution should be used in patients 65 years of age and older because of these anticholinergic effects. Regardless of cardiac history, although no guidelines exist, it is recommended that any patients at higher risk for cardiac arrhythmias, particularly with multiple risk factors (e.g., age over 65, female sex, myocardial hypertrophy, electrolyte disturbances, use of other drugs known to increase cardiac arrhythmias) consult with a cardiologist.(238)

Although the risk of overdose can occur with SSRIs and TCAs, the rate of hospitalization is greater with TCAs because of a narrower therapeutic index. When more than 10 mg/kg of a TCA is ingested, mild to moderate poisoning occurs with severe anticholinergic effects, including dry mouth, drowsiness, urinary retention, increased deep tendon reflexes, and extensor plantar responses. When more than 15-20 mg/kg is ingested (>1000mg, versus clinical dose of 10–20mg), the patient will present with the symptoms of severe poisoning, including coma, seizure, cardiac arrhythmias, and death.(239)

Risk of serotonin syndrome is present when amitriptyline is combined with other serotoninergic medications, and all antidepressants carry the boxed warning of increased risk of suicidality in children, adolescents, and young adults. Patient preferences vary regarding this treatment. Some patients might prefer non-invasive treatments, although others might not want to consume a daily medication. The patient

focus group indicated patients prefer combination treatments rather than just oral medications. Patients might also have personal views or concerns for stigma that preclude taking a medication with a psychiatric indication.

In terms of subgroup analysis, many active duty Service members would prefer to avoid medications with psychotropic effects because of potential concerns of duty or career advancement limitations. Additionally, amitriptyline comes with the side effect of weight gain, which is also of great concern for all active duty and reserve Service members. However, these medications might be preferred by patients who have comorbid conditions that can be treated by this class of medications (e.g., depression, anxiety, diabetic neuropathy, fibromyalgia, chronic pain, insomnia, diarrhea) because multiple conditions could be treated by one medication.

Access to these medications is extensive because they are inexpensive and prescribed by PCPs familiar with their use and comfortable with their risks and AEs.

The Work Group considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG because no studies on the effect of amitriptyline met inclusion criteria for the 2023 VA/DoD Headache CPG systematic evidence review.(237) Therefore, this recommendation is categorized as *Reviewed, Not changed*. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations, including small sample size and imprecision in effect estimates. The Work Group also recognized that the systematic evidence review covered searches for only the prior 10 years, limiting the evidence for older, generic medications such as amitriptyline. The benefits of amitriptyline slightly outweighed the potential harm of AEs, particularly if caution was used in patient selection. Patient values and preferences varied because of the possible stigma against a psychotropic medication, use of a daily medication versus the preference of some patients for non-invasive treatments, and potential benefit for patients with other comorbid conditions. Thus, the Work Group made the following recommendation: We suggest amitriptyline for the prevention of chronic tension-type headache.

Recommendation

26. We suggest against botulinum/neurotoxin injection for the prevention of chronic tension-type headache.
    (Weak against | Reviewed, Not changed)

Discussion

Evidence suggests that botulinum/neurotoxin injection is ineffective for the prevention of chronic TTH. Although the search criteria included a broad array of neurotoxins, the systematic evidence review found only studies related to onabotulinumtoxinA. The systematic evidence review included one SR by Roland et al. (2021) of 12 RCTs evaluating onabotulinumtoxinA.(240) The previous systematic evidence review from the 2020 VA/DoD Headache CPG included a single SR by Jackson et al. (2012) of 7 RCTs.

(241) Both SRs showed no statistically significant difference in the critical outcomes of incidence of monthly headaches or change in headache and migraine days when the intervention was compared with placebo in patients experiencing chronic TTH.(240, 241) The SR by Roland et al. (2021) demonstrated a statistically significant but small effect size (SMD: -0.35) difference over placebo for headache episode intensity and no difference in AEs.(240)

The Work Group noted the potential for large variation in patient preferences regarding this treatment. Additionally, there was a lack of evidence for benefits and potential harm related to the invasive procedure, which can be burdensome to acquire. This intervention is typically available only in a specialty setting, requires training of staff to administer, and needs proper storage infrastructure. It is also more costly than other pharmaceutical and non-pharmaceutical options. These issues are not only factors in resource use, but they might also present equity issues related to access for those out of range of specialty services.

The Work Group systematically reviewed evidence related to this recommendation (240) and considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG.(241) Therefore, it is categorized as *Reviewed, Not changed*. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including missing outcome data, small number of patients per arm, ROB, and concerns for both randomization issues and fidelity of treatment assignment.(240) The potential harm of botulinum toxin (e.g., Botox), which included opportunity cost and a small AE profile, outweighed the benefits of the small potential for reducing the intensity of headache episodes. Patient values and preferences varied largely because some patients do not prefer needle-based interventions or having to regularly attend specialist care. Thus, the Work Group made the following recommendation: We suggest against botulinum/neurotoxin injection for the prevention of chronic tension-type headache.

e. Tension-Type Headache – Abortive

Recommendation

27. We suggest ibuprofen (400 mg) or acetaminophen (1,000 mg) for the acute treatment of tension-type headache.
    (Weak for | Reviewed, Not changed)

Discussion

No new studies on the use of ibuprofen or acetaminophen for the acute treatment of TTH were identified in the current systematic evidence review. Two SRs and one RCT from the 2020 VA/DoD Headache CPG evaluated pharmacologic interventions for acute treatment of TTH.(242-244) Derry et al. (2015) reported a statistically significant between-group difference for ibuprofen 400 mg versus placebo, favoring ibuprofen, for TTH percent pain-free response for moderate to severe pain at 2 hours. However, the

study reported no statistically significant between-group difference for fast-acting ibuprofen sodium 400 mg versus placebo.(243) Neither Derry et al. (2015) nor Packman et al. (2015) reported statistically significant between-group differences for AEs of ibuprofen 400 mg versus placebo.(243, 244)

An SR by Stephens et al. (2016) included 23 RCTs comparing paracetamol to placebo, an active comparator, or both and addressed TTH percentage of pain-free response at 2 hours.(242) It suggested a statistically significant between-group difference for acetaminophen 1,000 mg versus placebo, favoring acetaminophen. Lower doses of acetaminophen 500–650 mg did not show statistical significance. Reported AEs did not show a statistically significant between-group difference for acetaminophen 500–650 mg (combined data) versus placebo or acetaminophen 1,000 mg versus placebo.

The 2020 VA/DoD Headache CPG found relevant studies for only NSAIDs and acetaminophen in the treatment of TTH. The patient focus group participants noted that a combination of treatments was effective for managing their headaches. One participant expressed that headaches are complex and that there might be different types of headaches from different sources. Patients prefer medications that are easy to obtain and well tolerated; thus, participants might support the use of NSAIDs and acetaminophen as an early option for TTH.

The Work Group considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG because no new studies on this topic met inclusion criteria for the 2023 VA/DoD Headache CPG systematic evidence review.(242-244) Therefore, this recommendation is categorized as *Reviewed, Not changed*. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including a small sample size and inconsistent reporting of outcomes.(242, 243) The benefits of improved outcomes of TTH pain-free response at 2 hours outweighed the potential harm of AEs from either intervention, which was not statistically significant when compared with placebo. However, provider education is recommended on limiting the use of OTC medications to no more than 2 days per week to reduce the possibility of MOH. Additionally, education is recommended on the concern for kidney, cardiac, and GI issues with the use of ibuprofen. Patient values and preferences were similar because these easily obtained OTC medications are familiar to most adults. Resource use was thought to be low because these medications are widely available. Thus, the Work Group made the following recommendation: We suggest ibuprofen (400 mg) or acetaminophen (1,000 mg) for the acute treatment of tension-type headache

f. Cluster Headache – Preventive

Recommendation

28. We suggest galcanezumab for the prevention of episodic cluster headache. **(Weak for | Reviewed, Not changed)**

Discussion

Goadsby et al. (2019) sought to determine the efficacy and safety of galcanezumab for the prevention of episodic cluster headache.(124) The study reported a significant reduction in the frequency of weekly cluster headaches among patients randomized to receive 300 mg once monthly of galcanezumab compared with those receiving placebo (-3.5 cluster headaches per week; p=0.04).(124) A greater percentage of patients randomized to galcanezumab had at least a 50% reduction in weekly cluster headache frequency at week 3 compared with patients receiving placebo (71% versus 53%; p=0.046). No serious AEs, deaths, or suicidal ideation or behavior were reported in either group. Rates of AEs were more common in the treatment group, where 8% of patients who received galcanezumab experienced pain at the injection site. Of note, the study was terminated before reaching the planned sample size (n=162) because too few patients met the eligibility criteria. After Goadsby et al. (2019), the FDA approved galcanezumab as the first medication for the preventive treatment of episodic cluster headache in adults at a dose of 300 mg subcutaneous, administered once monthly.(124)

In an SR and NMA of medications for episodic cluster headache, Pompilio et al. (2021) reported that galcanezumab had the highest probability of being the most effective treatment (66.33%) compared with both verapamil (31.58%) and placebo (2.09%).(245) Additionally, since the publication of the 2020 VA/DoD Headache CPG, a study of galcanezumab conducted across three university hospitals among patients (n=47) with episodic cluster headache found that one 240 mg dose of galcanezumab, administered monthly (given via two 120 mg syringes), was found to be effective in the prevention of cluster headache, either with or without other preventive therapies for cluster headache.(246) However, this study was not included in the systematic evidence review because it was published outside the study window of the current CPG. As such, it was not included in the evidence base, nor did it impact the strength of this recommendation.

In considering the safety profile of galcanezumab during pregnancy and lactation, there is currently no human data available. In an analysis from the WHO pharmacovigilance database (not included in the evidence base nor impacting the strength of the recommendation), “no specific maternal toxicities, patterns of major birth defects, or increased reporting of spontaneous abortion were found” for galcanezumab.(148)

Apart from continued research regarding the long-term effectiveness, safety, and tolerability of galcanezumab, including data from real-world use of this therapy, future research should focus on understanding the role of galcanezumab in other headache conditions (e.g., paroxysmal hemicrania, other trigeminal autonomic cephalalgias [TAC]) and those phenotypically similar to cluster headache (e.g., chronic PTH with cluster features). Of note, within community settings, there is greater availability of 120 mg syringes compared with 100 mg syringes.(246) Future research should also explore other dosing alternatives, given the difference in availability of 100 mg and 120 mg syringes.

The Work Group systematically reviewed evidence related to this recommendation (245) and considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG.(124) Therefore, it is categorized as *Reviewed, Not changed*. The Work Group's confidence in the quality of the evidence was low. The benefits of galcanezumab outweighed the harms and burdens. Patients likely have similar values regarding this medication because it has been shown to be efficacious, safe, and tolerable. Given the difficulty in treating cluster headaches and the fact that galcanezumab is the only FDA-approved pharmacotherapy for episodic cluster headache, patients might be willing to try this medication. Dosing for galcanezumab is different for episodic cluster headaches compared with migraine, with the former being administered at a dose of 300 mg monthly (via three separate 100 mg syringes) and the latter being administered with a single 240 mg syringe monthly. Although patient acceptability of needles varies, patients generally tolerate subcutaneous injections and might be more apt to do so given the paucity of efficacious treatments for episodic cluster headaches. Although the therapy requires three separate injections, given the excruciating pain those living with cluster headache experience during cluster cycles, an overwhelming majority of patients would likely forgo this inconvenience to mitigate cluster headache pain. Providers are generally comfortable with prescribing pharmacotherapies delivered via subcutaneous injections. Providers managing headache disorders likely will become more comfortable using immunologic therapies as health care systems gain more experience with galcanezumab and related agents and future work continues to examine the longer-term efficacy, safety, and tolerability. Thus, the Work Group made the following recommendation: We suggest galcanezumab for the prevention of episodic cluster headache.

Recommendation

29. We suggest against galcanezumab for the prevention of chronic cluster headache.
    (Weak against | Reviewed, New-added)

Discussion

Although cluster headache is a rare disease, chronic cluster headache constitutes 21% of all cluster headache diagnoses.(247) Similar to episodic cluster headache, there is a paucity of treatments for chronic cluster headache.

In a phase 3 RCT (n=237) of patients with chronic cluster headache, Dodick et al. (2020) compared the efficacy and safety of galcanezumab 300 mg monthly subcutaneous injection with placebo.(248) The primary endpoint of this 12-week double-blind, placebo-controlled trial was overall mean change from baseline in weekly cluster headache frequency. There was no statistically significant change in the primary endpoint of weekly headache frequency (-5.4 headaches for galcanezumab versus -4.6 headaches for placebo; p=0.334).(248) Injection-site reactions and erythema occurred more commonly among patients receiving galcanezumab than those receiving placebo. The overall safety

profile of galcanezumab was consistent with that seen in migraine and episodic cluster headache trials of galcanezumab. In an open-label, phase 3b study of galcanezumab conducted by Risenberg et al. (2022),(249) the safety profile of this CGRP inhibitor was comparable at 12-months to what was observed by Dodick et al. (2020).(248) The FDA has not approved the use of galcanezumab for the treatment of chronic cluster headache. In considering the safety profile of galcanezumab in pregnant and lactating patients, there is currently no human data available. In an analysis from the WHO pharmacovigilance database (not included in the evidence base nor impacting the strength of the recommendation), "no specific maternal toxicities, patterns of major birth defects, or increased reporting of spontaneous abortion were found" for galcanezumab, fremanezumab, and erenumab.(148)

The Work Group systematically reviewed evidence related to this recommendation.(248) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was low. The Work Group felt that the harms and burdens slightly outweighed the benefits of this therapy for chronic cluster headache because side effects associated with this therapy are without proven benefit in reducing weekly cluster headache frequency. In considering patient values and preferences, the Work Group determined that some variation would occur among patients; some would prefer not to take a therapy that is neither FDA-approved nor found to be efficacious in their treatment, whereas other patients might desire to try this pharmacotherapy. Thus, the Work Group made the following recommendation: We suggest against galcanezumab for the prevention of chronic cluster headache.

Recommendation

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)

Discussion

An SR by Pompilio et al. (2021) examined three RCTs related to pharmacologic preventive therapies for cluster headache.(245) One RCT evaluated galcanezumab versus placebo,(124) another focused on verapamil versus placebo,(250) and the third was on lithium versus placebo.(251) The RCT by Steiner et al. (1997) examined lithium but did not report its primary outcome as the identified critical outcome for efficacy (change in headaches per week).(251) No other studies were found on lithium or verapamil in the systematic evidence review.

The RCT on verapamil by Leone et al. (2000) found the effect size to be 1.9 and -0.49 for verapamil and placebo, respectively, at the end of the second week of treatment.(250) The quality of this evidence was limited by the small study population (n=30). The SR by Pompilio et al. (2021) assessed two other single-arm studies for verapamil that indicated about 87% of patients on verapamil experienced a 50% or

more reduction in headache frequency.(245) However, both studies were limited by a small sample size, and a limited number of critical outcome events were reported.

The AEs reported by Leone et al. (2000) were mild, and none of the patients prescribed verapamil stopped treatment because of AEs.(250) The most common AE was constipation (53%). As an antihypertensive medication, reductions in blood pressure and heart rate were observed. The verapamil group experienced an average decrease of 11 millimeters of mercury (mmHg) in systolic blood pressure, 6 mmHg in diastolic blood pressure, and 10 beats per minute in heart rate from baseline.

Patient preferences vary regarding the use of verapamil for cluster headache prevention. Although it is an oral medication, which some patients might prefer versus an injected pharmacotherapy, it is dosed multiple times a day, resulting in a high pill burden. Because verapamil is an antihypertensive medication, it could pose a benefit to patients who have concurrent hypertension or a potential risk for hypotension in those who are normotensive. Verapamil is also not recommended for heart failure with reduced ejection fraction. Other possible cardiac adverse reactions, including atrioventricular block, warrant ECG monitoring as clinically indicated and might limit its use in older adults as well as those with hepatic impairment. Other common side effects of verapamil, such as constipation and edema, might be intolerable to some patients. Safety monitoring, including ECGs, might pose a burden for patients who have difficulty coming to the clinic for monitoring. Verapamil is a commonly prescribed medication in the primary care setting, has been used for decades in the cluster headache population, and, overall, is easily accessible.

The Work Group systematically reviewed evidence related to this recommendation. (245) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was very low. The body of evidence consisted of a single SR that included some data from single-arm studies, but the critical efficacy outcome could be assessed by only one RCT, which had some limitations, including a small sample size. The Work Group noted that this limitation in the quality of evidence might be a consequence of cluster headache's being a rare but serious subtype of headache. Cluster headaches are characterized by a rapid onset of severe pain. The severe pain associated with this headache type is also associated with a higher suicide risk. Although none of the acute treatments discussed here assessed their potential to decrease suicide rate in this population, this higher suicide risk underlines the need for acute treatment options in this headache type. Thus, the Work Group determined that the benefits of verapamil for cluster headache prevention were balanced with the potential harms of AEs and burdens associated with monitoring requirements and medication administration. Patient values and preferences varied because of differences in tolerance and feasibility for the safety monitoring required for this drug. Thus, the Work Group made the following recommendation: There is insufficient

evidence to recommend for or against verapamil for the prevention of episodic or chronic cluster headache.

g. Cluster Headache – Abortive

Recommendation

31. We suggest subcutaneous sumatriptan (6 mg) or intranasal zolmitriptan (10 mg) for the acute treatment of cluster headache.
(Weak for | Reviewed, New-replaced)

Discussion

Law et al. (2013) conducted an SR to assess the efficacy and tolerability of triptan medications compared with placebo in the acute treatment of episodic and chronic cluster headache in adults.(252) This SR included three studies comparing sumatriptan to placebo and three studies comparing zolmitriptan to placebo. Pain freedom at 15 minutes was assessed by two zolmitriptan (intranasal 5 mg and 10 mg) versus placebo studies (n=340) and two sumatriptan (subcutaneous 6 mg) versus placebo studies (n=258). Intranasal zolmitriptan 5 mg showed no difference from placebo for pain freedom at 15 minutes. Intranasal zolmitriptan 10 mg and subcutaneous sumatriptan 6 mg did show a statistically significant difference versus placebo, with NNTs of 11 and 3.3, respectively. For pain freedom at 30 minutes, two zolmitriptan (intranasal 5 mg and 10 mg) studies (n=340) were assessed in the SR.(252) Both doses showed a statistically significant difference from placebo with NNTs of 6.9 and 3.3 for 5 mg and 10 mg doses, respectively. Albeit from limited data in this single SR, subcutaneous sumatriptan 6 mg was found to be superior to intranasal zolmitriptan 10 mg.(252) Subcutaneous sumatriptan 12 mg as well as all intranasal sumatriptan doses were not assessed for effect size in the SR because of limited evidence; however, these formulations offer a similar expected pharmacokinetic profile as the studied subcutaneous sumatriptan and intranasal zolmitriptan formulations.(253, 254)

Reported AEs included local reaction paresthesia (the most common), sweating, feeling of heaviness, somnolence, nausea and vomiting, injection-site reaction (e.g., pain, swelling, burning, erythema, tingling), neurologic symptoms (e.g., dizziness, tiredness, numbness of hands, tingling, feeling of paralysis in the face, cold and hot sensations), bad taste, discomfort of nasal cavity, and pain or tightness in the throat, chest, or neck.(252) Adverse events were more common with a triptan versus placebo but were generally mild or moderate in severity.

Patient preferences vary little regarding the acute treatment of cluster headache. Despite intranasal and subcutaneous administration methods typically being less preferred than oral medications, patients with cluster headaches have less variability in acceptance of these alternative administration methods because the preference for rapid pain freedom is much stronger. Triptans are readily available, have more than 20 years of safety and efficacy literature, and can be prescribed and monitored in the

primary care setting. In addition to the more common AEs reported above with these treatments, triptans are associated with vasoconstriction and present CV risk that might limit their use, particularly in patients at risk for ischemic events.

The Work Group considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG because no new studies on subcutaneous sumatriptan or intranasal zolmitriptan met inclusion criteria for the 2023 VA/DoD Headache CPG systematic evidence review.(252) Therefore, this recommendation is categorized as *Reviewed, New-replaced*. The Work Group's confidence in the quality of the evidence was low. The body of evidence consisted of a single SR by Law et al. (2013) and had some limitations, including allocation concealment and a high ROB because of the small number of treated headaches.(252) The Work Group noted that the latter limitation might be a consequence of this rare but serious subtype of headache. The benefits of rapid pain freedom outweighed the potential harm of typical class AEs of triptans and the more burdensome methods of administration. Cluster headaches are characterized by a rapid onset of severe pain. The severe pain associated with this headache type is also associated with a higher suicide risk. Though none of the acute treatments discussed here assessed their potential to decrease suicide rate in this population, this higher suicide risk underlines the need for effective acute treatment options in this headache type. Patient values and preferences were similar because of the high value placed on rapid pain freedom. Thus, the Work Group made the following recommendation: We suggest subcutaneous sumatriptan (6 mg) or intranasal zolmitriptan (10 mg) for the acute treatment of cluster headache.

Recommendation

32. We suggest the use of normobaric oxygen therapy for the acute treatment of cluster headache.
    (Weak for | Not reviewed, Amended)

Discussion

Although the exact mechanism by which oxygen potentially works to abort cluster headache attacks is unknown, it is proposed that oxygen neuromodulates and deactivates the trigeminal-autonomic reflex arch. Oxygen can be delivered as normobaric oxygen therapy (NBOT) or hyperbaric oxygen therapy (HBOT). NBOT is oxygen administered at one atmosphere of pressure and can be supplied via nasal cannula and face masks (e.g., non-rebreather masks). Flow rates for NBOT (e.g., "high-flow" oxygen being at least 12–15 liters per minute) and fraction of inspired oxygen (e.g., 100%) can both vary. In HBOT, oxygen is administered at a pressure greater than atmospheric pressure and occurs while a patient is inside a treatment chamber, breathing nearly 100% oxygen. NBOT is much more readily available than HBOT.

Evidence supporting oxygen therapy for the acute treatment of cluster headache is limited.(252, 255-257)

Bennett et al. (2015) examined the efficacy and safety of NBOT and HBOT for the treatment and prevention of migraine and cluster headache.(255) This SR assessed 11 RCTs that compared HBOT and NBOT with each other, active therapies, sham interventions, or no treatment. Findings revealed a considerable variance of ROB and poor-to-moderate quality across the trials. According to Bennett et al. (2015), 2 studies were abstracts and 1 trial was not a true randomization. The methodology of 7 studies lacked indications of blinding or randomization. Of the 11 trials, 10 used sham comparator therapy and allocation bias of masked assessments. The 11 trials examined by Bennett et al. (2015) included 5 acute migraine trials, 5 cluster headache trials, and 1 trial of mixed headache type.(255) Of the 5 cluster headache trials, 2 trials evaluated HBOT and 3 trials compared NBOT with either sham therapy or ergotamine tartrate. In 1 trial with low power of HBOT for cluster headache, HBOT did not effectively abort cluster headache attacks (RR: 11.38; 95% CI: 0.7–167.85; p=0.008). In the NBOT trials, NBOT was found to be more efficacious than sham (RR=7.88; 95% CI: 1.13–54.66) but inferior to ergotamine (RR: 1.17; 95% CI: 0.94–1.46) in aborting cluster headache attacks. The third trial was a double-blind, randomized, placebo-controlled crossover trial of cluster patients conducted by Cohen et al. (2009) to determine whether high-flow oxygen (100% oxygen, at 12 liters per minute delivered by face mask for 15 minutes) improved outcomes in patients with cluster headache compared with placebo delivery of high-flow air (for four episodes). The primary endpoint was pain freedom or adequate pain relief at 15 minutes.(256) Of the 109 participants, 57 with episodic cluster headache and 19 with chronic cluster headache completed the study. A statistically significant greater percentage of patients who used NBOT (78%; 95% CI: 71–85% for 150 attacks) obtained the primary endpoint compared with those who were randomized to air (20%; 95% CI: 14%–26% for 148 attacks; Wald test: $X^{2/5}$=66.7, p<0.001). Across these three studies, Cohen et al. (2009) reported that “more than 75% of headaches were likely to respond to NBOT.”(256) Of note, no serious AEs were reported across either the NBOT or the HBOT study.

The studies were heterogeneous concerning dosage and routes of administration. Bennett et al. (2015) reported weak evidence for efficacy of NBOT compared with high-flow air.(255) Investigators concluded that triptans might be a useful treatment option for acute cluster headaches and more convenient than oxygen therapy.

Oxygen therapy types vary for the treatment of cluster headache in addition to the modalities used in the SR and RCTs. The Work Group noted that oxygen therapy, specifically HBOT, can be challenging because of its limited availability, safety, and patient tolerability for the acute treatment of cluster headache.

The Work Group considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG related to this recommendation.(252, 255-257) Although no

updated systematic evidence review had been carried out related to oxygen therapy, the Work Group interpreted the existing evidence base in a way that resulted in clinically meaningful changes to the recommendation (e.g., modified strength, specified NBOT). Therefore, the Work Group categorized the 2023 recommendation as *Not reviewed, Amended*. For this specific instance, the word "amended" has a broadened meaning to include clinically meaningful changes. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including a small sample size and inconsistent findings. Further, the evidence base consisted of one SR and one RCT with heterogeneity of oxygen type (e.g., high-flow, hyperbaric), and some results favored oxygen for pain freedom at 15 minutes, although other results were inconclusive.(255, 256) Yet, the practice of oxygen therapy is widely accepted because of the pain severity associated with cluster headaches. The benefits of oxygen therapy, including its safety profile and effectiveness in aborting cluster headaches in the clinical setting, slightly outweighed the potential harms of epistaxis, delay of other treatments, running out of oxygen, and fire hazards and other dangers associated with oxygen use around smokers.(252, 255-257) Patient values and preferences varied because although oxygen therapy might be inconvenient for some and requires a prescription, others with cluster headache will accept most treatments for pain relief. Other implications include the resource use of requiring a prescription for oxygen therapy and other drug side effects that could be exacerbated by oxygen therapy and subgroup considerations. Thus, the Work Group made the following recommendation: We suggest the use of normobaric oxygen therapy for the acute treatment of cluster headache.

h. Medication Overuse Headache

Recommendation

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)

Discussion

The systematic evidence review identified two RCTs in four publications that analyzed the impact of medication withdrawal, the initiation of preventive treatment in patients with MOH, or both and found no clear indication to favor a particular approach.(258-261)

A large (n=720) open-label multicenter trial in the U.S. by Schwedt et al. (2022) (also known as the Medication Overuse Treatment Strategy trial), showed in MOH that the efficacy of starting or optimizing preventive medication does not depend on whether individuals first reduce their use of the overused acute medication.(261) This study showed that not switching and restricting the overused medication was equivocal (i.e., not inferior) to the previous convention of withdrawing the overused medication. In this trial, patients were randomized to receive migraine preventive medication and were either (group one) switched from the overused medication to an alternative to use

≤2 days per week (“switching”) or (group two) allowed to use the overused medication with no maximum limit (“without switching”).(261) The patients enrolled in this study were 87.5% female with an average age of 44. At baseline, participants averaged 22.5 (SD: 5.1) headache days over 4 weeks. The authors found that over 12 weeks migraine preventive medication without switching the overused medication (group two) was not inferior to preventive medication with switching (group one) for the primary outcome of moderate to severe headache day frequency.(261) During weeks 9–12, the group that switched the overused medication (group one) had a moderate to severe headache day frequency of 9.3 (SD: 7.2), and the group that did not switch (group two) had a moderate to severe headache day frequency of 9.1 (SD: 6.8; p=0.75; 95% CI: -1.0–1.3). The study showed reduced symptomatic medication days in the group that switched to an alternative medication to use ≤2 days per week versus the group that continued using the overused medication with no maximum limit.(261)

A smaller RCT (n=120) from Denmark (included in three publications) compared three groups: withdrawal plus pharmacologic preventive treatment; preventive treatment without withdrawal; and withdrawal with optional preventive treatment 2 months after withdrawal.(258-260) The RCT reported outcomes for 6 months (n=120) (258) and 1 year (n=96).(259) No difference was found between groups for the critical outcomes (i.e., change in monthly headache days, migraine days, or acute medication days) at 6-month or 1-year follow-ups.(258, 259) This study did find an advantage of withdrawal plus prevention over withdrawal alone at 6 months (but not 1 year) for reversion to episodic headache as well as an advantage of withdrawal plus prevention over prevention alone in overall response (freedom from MOH) at 6 months (but not 1 year).(258, 259) The strength of the evidence was very low. The main study limitations were the inability to blind providers and patients, who are the outcome assessors, with withdrawal and moderate or differential attrition or both between groups. An additional study by this group showed that dependence-like behavior was reduced most in the two withdrawal arms when assessed at 6 months (n=100).(260)

The results are well aligned with the evidence as reported in the 2020 VA/DoD Headache CPG. An SR by de Goffau et al. (2017) evaluated the treatment of MOH using multiple methods and health care settings and found no differences in any of the treatments.(262) This SR evaluated the use of prednisone or celecoxib in the treatment of MOH. The SR investigated methods of medication withdrawal, medical setting of withdrawal and abrupt withdrawal, inpatient or outpatient treatment, and follow-up with a general practitioner or neurologist. No statistically significant differences were found among any of these methods measuring the outcomes of reduction in headache days, headache frequency, or pain-related QoL. Additionally, no statistically significant differences were found between abrupt withdrawal and preventive treatment with medication. In inpatient versus outpatient treatment settings, no statistically significant differences were found in the reduction of headache days or symptomatic medication use. The use of preventive medication produced no statistically significant results for

reduction in headache days, number of headache days per month, headache frequency, or pain-related QoL.

An RCT by Karadas et al. (2017) evaluated the use of medication withdrawal alone and medication withdrawal in combination with greater occipital nerve (GON) block.(263) There was very low–quality evidence that favored a three-stage GON block for the reduction in the number of headache days and the number of triptans used for MOH. The benefit in effect size was insufficient to recommend the use of GON block for MOH.

The Work Group recognized that medication and patient factors should be considered when reducing dosage or discontinuing medication. Some medications are dangerous when stopped abruptly (e.g., barbiturates, benzodiazepines) and each patient's comorbidities should be considered when determining the withdrawal timing and method. Patient preference varies because some patients might be reluctant to stop using their medication because of fear of a "rebound" headache, although other patients might be reluctant to take daily preventive medication. Resource use is a consideration because of the need for multiple follow-up visits for medication adjustments, initiation of preventive treatment, withdrawal or switching of symptomatic medication for MOH, or any combination of these needs. Some patients might also require access to specialty care that might be unavailable. The Work Group noted that medication adjustments might be particularly challenging for patients with cognitive impairment.

The Work Group systematically reviewed evidence related to this recommendation (258-261) and considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG.(262, 263) Therefore, it is categorized as *Reviewed, New-replaced*. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including open-label assessments and limited follow-up (2 months) in the study by Schwedt et al. (2022),(261) and small sample size and attrition for the studies with 1-year follow-up.(258, 259) The benefits of the initiation of preventive treatment, withdrawal of overused medication in patients with MOH, or both slightly outweighed the potential harm. Patient values and preferences varied because some patients might not want to stop or restrict the use of symptomatic or daily preventive medications. Thus, the Work Group made the following recommendation: 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.

C. Injections, Procedures, and Invasive Interventions

Recommendation

34. We suggest greater occipital nerve block for the acute treatment of migraine. **(Weak for | Reviewed, Not changed)**

Discussion

Evidence from the 2020 VA/DoD Headache CPG suggests that GON blocks reduce pain intensity and decrease analgesic medication consumption when used for the acute treatment of migraine.(264-266) An SR and meta-analysis by Zhang et al. (2018) found that GON blocks, using either bupivacaine, lidocaine, or both, significantly reduced migraine pain intensity compared with placebo.(266) Two additional RCTs conducted in an ED setting demonstrated the comparative effectiveness of GON blocks to the standard ED pharmacologic treatments of metoclopramide or IV dexketoprofen (unavailable in the U.S.) plus metoclopramide.(264, 265) A third RCT, identified in the current systematic evidence review, found that GON blocks alone or combined with supraorbital nerve (SON) blocks demonstrated a statistically significant reduction in acute migraine pain versus placebo.(267) However, this RCT reported the effect at only 2 hours, did not include longer-term follow-up, and failed to show a significant reduction of nausea, vomiting, or dizziness. Evidence indicates that GON blocks do not cause more AEs than placebo, although needle site discomfort might be viewed negatively by some patients.(266) A small study (not included in the evidence base nor impacting the strength of this recommendation) reported that injecting certain corticosteroids might cause focal cutaneous alopecia and atrophy, which should be considered before use.(268) Additionally, based on another study (not included in the evidence base nor impacting the strength of this recommendation), adding a corticosteroid apparently does not provide an additional benefit to the duration or strength of benefit over a local anesthetic only, which should be considered before use.(269)

An RCT at two EDs enrolled patients (n=28) with moderate to severe persistent migraine after receiving IV metoclopramide.(264) The groups were allocated with 15 patients to sham and 13 to GON block. The primary outcome of headache freedom in 30 minutes was achieved by 31% in the GON block group and none in the sham group. The secondary outcome of headache freedom at 48 hours was achieved by 23% in the GON block group and none in the sham group. The study was stopped before *a priori* sample size because of slow enrollment. Side effects reported between the two groups were the same.

A prospective RCT enrolled patients (n=60) with acute migraine in the ED.(265) The groups were allocated with 20 in each group, including a GON blockade group (nerve blockade with bupivacaine), a placebo group (injection of normal saline into the GON area), and an IV treatment group (IV dexketoprofen and metoclopramide). Pain severity was assessed at 5, 15, 30, and 45 minutes with a 10-point pain scale score (PSS). The mean decreases in the PSS scores at all time points were greater in the GON blockade group than in the IV dexketoprofen and placebo groups. When comparing the 30- and 45-minute PSS changes, a statistically significant difference was found among the three groups (p=0.03 for both). Despite being an invasive procedure, a GON blockade might be an effective option for acute migraine treatment in the ED because of its rapid, easy,

and safe application. Limitations include that the study was conducted at a single ED and that the providers and patients were not blinded to the IV medication.

An SR including seven RCTs evaluated the primary outcome of pain intensity and the secondary outcome of headache duration, analgesic consumption, and AEs.(266) Compared with control intervention in patients with migraine, GON block intervention significantly reduced pain intensity MD: -1.24; 95% CI: -1.98 to -0.49; p=0.001) and analgesic medication consumption (MD: -1.10; 95% CI: -2.07 to -0.14; p=0.02) but had no significant impact on headache duration (MD: -6.96; 95% CI: -14.09–0.18; p=0.06) or AEs (RR: 0.93; 95% CI: 0.52–1.65; p=0.80). GON block intervention was able to significantly reduce pain intensity and analgesic medication consumption in patients with migraine. Limitations of this study included a small sample size, variable types and dosages of local anesthetics (several including a steroid), different timing and methods, and short follow-up time.

An RCT (n=128) on acute treatment of migraine in the ED compared pain levels (in both the Visual Analog Scale [VAS] and the Likert-type [LT] scale) at baseline and 120 minutes among four groups, including GON block (n=30), SON block (n=36), combined (n=37), and placebo (n =27).(267) Secondary outcomes included whether the patients had conditions such as nausea, vomiting, or dizziness at the time of admission and at the 120th minute as well as whether an additional analgesic was required at the 120th minute. The change in VAS scores from baseline to the 120th minute was less in the placebo group compared with the GON group, SON group, and combined group ($p<0.001$ for all three). The change observed in the SON group was less than that of the GON group and the combined group (p=0.001 for both). However, no significant difference was found between the GON group and the combined group ($p>0.05$). The median change in LT scores at discharge compared with admission for the GON group, SON group, and combined group was two units, although for the placebo group it was only one unit. At 120 minutes, additional treatment was required for 10% (n=3) of the GON group, 21.42% (n=6) of the SON group, 2.32% (n=1) of the combined group, and 74.07% (n=20) of the placebo group

Some variation occurs in patient preferences regarding this treatment. Some patients prefer non-invasive treatments or might dislike needles and would prefer oral medication. Others might not want to come into an ED or clinic, especially if they live far away, lack access to transportation to an in-person clinic, lack spare time, or have financial concerns. Other patients might find this favorable if they have infrequent severe migraines and need quick relief.

The Work Group systematically reviewed evidence related to this recommendation (267) and considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG.(264-266) Therefore, it is categorized as *Reviewed, Not changed*. The Work Group's confidence in the quality of the evidence was very low. The body of

evidence had some limitations, including small sample size and variability in injection technique and medicament.(264-267) The benefits of GON block for the acute treatment of migraine, which include reduction or resolution of an acute migraine and decreased analgesic medication consumption, were balanced with the potential harm of AEs, such as pain or bleeding at the injection site, or both, which were minimal. Patient values and preferences varied because some patients prefer non-invasive treatments. The Work Group also considered staffing and provider training required by this intervention. The procedures are easy to learn and use equipment readily available in an ED, urgent care, or clinic setting; the infrastructure cost is lower than infusing medications; and the GON block is safer than discharging the patient on opioids. However, providers who prefer to perform ultrasound-guided injections might be limited by equipment availability. Thus, the Work Group made the following recommendation: We suggest greater occipital nerve block for the acute treatment of migraine.

Recommendation

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)

Discussion

The SR by Barad et al. (2022) reported weak findings for the use of GON blocks for chronic migraine prevention.(187) However, an SR by Velásquez-Rimachi et al. (2022), using the same studies, reported low confidence in these studies' findings because of substantial bias and low-quality evidence.(270) Both Barad et al. (2022) and Velásquez-Rimachi et al. (2022) stated that the use of local anesthetic could be helpful when compared with placebo.(187, 270) Both SRs suggested that the procedure was relatively safe with few side effects.(187, 270) Both SRs also recognized the limitations and recommended larger studies with standardized protocols and at least 6 months of follow-up. However, the studies did not support the addition of corticosteroids because they did not improve outcomes. Small studies (not included in the evidence base nor impacting the strength of this recommendation) have reported that injecting certain corticosteroids might cause focal cutaneous alopecia and atrophy, which should be considered before use.(268, 269) An additional RCT, Chowdhury et al. (2022), had a three-way comparison: topiramate alone (n=41); topiramate combined with monthly GON block with lidocaine (n=39); and topiramate combined with monthly GON block with lidocaine and steroid (n=37).(271) At 3 months, patients in both the GON block groups showed a greater reduction in monthly migraine days, and a higher portion of patients achieved a 50% or more reduction in mean monthly headache days. Although this demonstrated effectiveness, the study was not set up to show the effectiveness of GON block but rather the effectiveness of combination therapy for the treatment of

chronic migraine. Additionally, the study has limitations, including small sample size, lack of a placebo arm, and investigators unblinded to the interventions.

Although evidence supporting the use of GON blocks in the treatment of chronic migraine is growing, the current studies are of small sample size, with varying techniques and times of administration (weekly to monthly), different medications (e.g., lidocaine, bupivacaine, steroid), and short follow-up intervals.

Patient preferences vary largely regarding this treatment. Some patients prefer non-invasive treatments or might dislike needles and would prefer oral medication. Others might not want to come into an ED or clinic, especially if they live in far locations, lack access to transportation to an in-person clinic, lack spare time, or have financial concerns. Other patients might find this favorable if they have infrequent severe migraines and need quick relief. The Work Group also considered burdens associated with staffing and provider training. Although the procedure is easy to learn and uses equipment readily available in the ED or clinic setting, is less expensive than infusing medications, and is safer than opioids, there might be some limits for providers who prefer to perform ultrasound-guided injections.

The Work Group systematically reviewed evidence related to this recommendation. (187, 270, 271) Therefore, is it categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations including a small sample size, high bias, and low-quality evidence.(270) The benefits of GON block for the prevention of chronic migraine (e.g., might reduce the number of monthly migraine days) slightly outweighed the potential harms, which were minimal (e.g., discomfort at the injection site, possible bleeding, dizziness). Thus, the Work Group made the following recommendation: There is insufficient evidence to recommend for or against greater occipital nerve block for the prevention of chronic migraine.

Recommendation

36. There is insufficient evidence to recommend for or against supra orbital nerve block for acute treatment of migraine.
    (Neither for nor against | Reviewed, New-added)

Discussion

One study included in the systematic evidence review examined the evidence of SON block.(267) In this double-blinded RCT conducted over 9 months, patients with acute migraine (n=128) were divided into four groups, one that received only GON block (n=30), another that received only SON block (n=28), a third that received both GON and SON blocks (n=43), and one that received placebo (n=27). Pain change at 0-120 minutes was reported by the change in both the VAS and the LT Verbal scale, which were used in determining the primary outcome.(267) Secondary outcomes

included whether the patients had conditions such as nausea, vomiting, and dizziness at the time of admission and the 120th minute as well as whether an additional analgesic was required at the 120th minute.

Treatment outcomes indicated that the decrease in VAS and LT scores with the SON block alone was greater than it was with placebo but less than in the GON block or the combined group (VAS: p=0.001, p<0.001, respectively; LT: p=0.001, p<0.001, respectively).(267) The overall confidence in the quality of evidence for these outcomes was determined to be low. Moreover, for secondary outcomes, the rating was found to be very low. Although this treatment was effective for pain outcomes, no difference occurred for the MBS.(267) There were no findings from multiple other studies, and this patient population was limited to one treatment center.

Evidence also indicates some minor level of harm associated with SON block because some minor injection-site bleeding was seen in most patients, and a need for a repeat injection arose because of lack of pain relief at 120 minutes in six of the patients who had previously received SON block. However, no major side effects were seen in this one study, and the benefits were thought to slightly outweigh the harms.

Large variation occurs in patient preferences regarding this treatment. The patient focus group preferred that their providers not prescribe solely oral medications, but the preference was for effective treatments and no strong evidence exists that this treatment is effective. Many patients prefer to avoid injections because of local pain or needle phobia. Patient values and preferences vary for several reasons. Some patients prefer non-invasive treatments and might not want to come into an ED or clinic, especially if they live far from the treatment center. Other patients might find this favorable if they have infrequent migraines and need quick relief. The Work Group also considered the increased staffing and provider training required by this intervention.

In addition, with SON block (unlike GON block) the injections are directly above the patient's eyes, which might increase a patient's psychological discomfort. For certain patient subgroups, SON block might be an attractive option, particularly for pregnant patients, who might be unable to receive other treatments because of teratogenic concerns. For active duty Service members, this treatment might be of benefit because it does not require long-term medication management and is not duty limiting, although the need for repeat treatments and subspecialty care might cause suitability issues.

The Work Group systematically reviewed evidence related to this recommendation.(267) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including a small sample size. The benefits of reduction in pain slightly outweighed the potential harm of AEs, which was small. Patient values and preferences varied largely because some patients prefer non-invasive treatments, particularly near the eye. Thus, the Work Group made the following recommendation: There is

insufficient evidence to recommend for or against supra orbital nerve block for acute treatment of migraine.

Recommendation

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 acute treatment of headache.
    (Neither for nor against | Reviewed, New-replaced)

Discussion

Evidence suggests that IV antiemetics (e.g., chlorpromazine, metoclopramide, prochlorperazine), IV magnesium, and intranasal lidocaine might improve outcomes of pain freedom and pain relief in individuals with acute migraine. Vanderpluym et al. (2021) found that treatment with parenteral chlorpromazine and prochlorperazine was associated with improvements in pain freedom and metoclopramide was associated with pain improvement when both were compared with placebo.(231) Placebo-controlled trials for magnesium in an SR by Choi et al. (2014) showed mixed results, and a more recent RCT by Kandil et al. (2021) found no difference between IV magnesium and IV antiemetics.(272, 273) Most studies analyzed in Vanderpluym et al. (2021) had active comparators of an in-class agent (e.g., chlorpromazine versus metoclopramide), and no clear difference in efficacy was found between the included IV antiemetics.(231) Results of most of the studies assessing IV magnesium were compared with an active comparator from the antiemetic class.(231, 273) Additional studies from the 2020 VA/DoD Headache CPG contributed to the evidence base for this recommendation.(162, 274)

Although both IV antiemetics and intranasal lidocaine were reviewed in the 2020 VA/DoD Headache CPG, the 2023 systematic evidence review included two additional placebo-controlled studies on parenteral chlorpromazine within the SR by VanderPluym et al. (2021).(231, 275, 276) The Work Group's confidence in the quality of the evidence was low. Sample sizes were small, study designs consistently poor, and older studies frequently did not address the outcomes of interest identified for the 2023 systematic evidence review (e.g., pain freedom, freedom from MBS at 2 hours, or both). The Work Group deemed the benefits to slightly outweigh the harms. Using IV antiemetics for headaches (e.g., sedation, hypotension, dystonia) involves some risk, albeit AEs are generally mild and manageable, especially in a monitored environment such as an ED. Research on headache treatment in the ED or inpatient-based settings has been limited by poor study designs. The Work Group found numerous trials lacking placebo comparators and the use of medications in combination versus in isolation, which greatly confounded the interpretation of results. Future trials are needed with larger sample sizes of single agents in direct comparison with placebo controls.

Some variation occurs in patient preferences regarding this treatment. The patient focus group noted that IV antiemetics or intranasal lidocaine can be burdensome because they require an ED encounter, and some patients might prefer to avoid needles necessary for IV treatments. However, most patients reported wanting rapid relief and, if already in extremis, IV access is an insignificant barrier. Additionally, the IV antiemetic class might have some access benefits in certain scenarios (e.g., in extremis, treatment refractory) and, although less studied for the acute treatment of migraine, are available in multiple, non-oral routes of administration (e.g., IV, intramuscular [IM], per rectum, intranasal).

The Work Group systematically reviewed evidence related to this recommendation (231, 273) and considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG.(162, 272, 274) Therefore, it is categorized as *Reviewed, New-replaced*. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations, including a small sample size, ROB, and failure to specifically address the currently used critical outcomes.(231, 274) The benefits of IV antiemetics (e.g., chlorpromazine, metoclopramide, prochlorperazine), IV magnesium, or intranasal lidocaine (e.g., pain freedom, pain relief) slightly outweighed the potential harms of mild and transient side effects (e.g., sedation, dizziness or hypotension, rare dyskinetic reactions) easily managed, especially in a monitored environment. Patient values and preferences varied because most patients would prefer not to go to the ED or might have limited access, but others might prefer an IV medication if oral therapies have been ineffective or not tolerated (e.g., because of vomiting). Thus, the Work Group made the following recommendation: 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 acute treatment of headache.

Recommendation

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)

Discussion

In a small RCT by Yang et al. (2015), the authors found that pulsed radiofrequency (pRF) of the posterior medial branches of the second and third cervical nerves decreased migraine disability (MIDAS), number of headache days, and mean aspirin dosage in patients with chronic migraine who had a prior positive response to a GON block with local anesthetic.(277) No serious AEs were reported. In a small RCT (n=38) by Cady et al. (2015), repetitive sphenopalatine ganglion (SPG) blockade using nasal catheter-delivered bupivacaine for chronic migraine resulted in no statistically significant benefit compared with saline for the number of headache days, disability (HIT-6), average pain, or acute medication usage.(278) No AEs were reported.

Patient preferences vary regarding these two treatments. Some patients prefer non-pharmacologic interventions, though others would prefer to avoid needle-based interventions. Although evidence demonstrates that pRF might be beneficial, the feasibility and acceptability of this intervention limits use. This intervention is not widely available and requires special training and equipment that confines its use to interventional pain specialists. For the SPG block procedure, multiple blockade technique options are available that make training more feasible across various provider types. For example, SPG blockade can be accomplished via an image-guided local anesthetic injection, nasally delivered topical anesthetic via a cotton tip applicator, or nasally delivered topical anesthetic via one of many patented nasal catheter devices that spray local anesthetic over the SPG area. The only study that met the search requirements of this systematic evidence review used the patented Tx-360® device.(278)

The Work Group considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG, because no studies on this topic met the inclusion criteria for the 2023 VA/DoD Headache CPG systematic evidence review.(277, 278) Therefore, this recommendation is categorized as *Reviewed, New-replaced*. The Work Group's confidence in the quality of the evidence was low. The body of evidence had limitations, including small sample sizes.(277, 278) The benefits and harms were balanced for both interventions because no side effects were reported for either intervention. Patient preferences might vary because this intervention is needle based, and some patients do not tolerate needles. Accessibility to repetitive SPG blockade treatment is limited because few providers are adequately trained. Thus, the Work Group made the following recommendation: 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.

Recommendation

39. We suggest against an implantable sphenopalatine ganglion stimulator for the treatment of cluster headache.
    (Weak against | Reviewed, New-added)

Discussion

In one very low–quality RCT by Goadsby et al. (2019), the authors reported freedom from pain at 15 minutes and a reduction in pain at both 15 and 60 minutes in the implantable SPG group relative to sham stimulation during headache attacks in patients with chronic cluster headache.(279) However, weekly attack frequency did not differ significantly between the groups. No serious inconsistencies were noted, but results from this trial were tracked for only 4 weeks.(279) In addition to this short experimental phase, the trial was determined to have serious limitations regarding study quality. The Work Group considered an elevated ROB in this RCT because of significant involvement of and potential COI with the device manufacturer. One author received

personal funds outside grants from the device company, although others involved with the publication were employed directly by the company.(279)

Evidence from the RCT also indicates some level of harm associated with implantable SPG neurostimulation. Of individuals in the treatment group, 20% reported serious AEs; however, some reported events might be related to the general anesthesia required for the procedure. Both groups required surgical implantation of the device, and numbness (transient or permanent) was reported in 67% of the treatment group and 75% of the control group. Further, the authors noted that the surgical implantation procedure itself might alter the disease condition and confound the results.(279)

Patient preferences and acceptance of the procedure vary widely. Some patients might not want a permanent implantable device when less invasive procedures to treat acute cluster headache attacks exist. Some patients might reject the risks of general anesthesia. the high probability of facial numbness, and other bothersome effects related to the device. On the other hand, some patients might seek non-pharmacologic alternatives. The Work Group discussed the lack of awareness about this procedure and about the medical specialist who would surgically implant the device and subsequently be responsible for monitoring and removing it, as needed. Barriers likely exist regarding resource use and equity because the procedure is expensive, with costs relating to providers, facilities, anesthesia, and the device itself. The Work Group noted that the procedure might not be covered by insurance, and the authors noted that implanted neurostimulation is more expensive compared with pharmacologic approaches.(279) Moreover, this procedure is an infeasible option for active duty Service members because it is incompatible with deployment to an austere environment. Furthermore, compatibility with magnetic resonance imaging (MRI) was also noted as a potential issue.

The Work Group systematically reviewed evidence related to this recommendation. (279) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including the short trial time and significant ROB; moreover, the average baseline headache severity was higher in the control group.(279) The potential harm of a surgically implanted SPG neurostimulation device and the AEs related to general anesthesia and the procedure itself slightly outweighed the benefits of potential pain reduction or freedom from pain over a short period of time. Patient values and preferences varied largely because some patients prefer non-invasive treatments, although others desire a non-pharmacologic treatment approach. Thus, the Work Group made the following recommendation: We suggest against an implantable sphenopalatine ganglion stimulator for the treatment of cluster headache.

Recommendation

40. We suggest against patent foramen ovale closure for the treatment or prevention of migraine.
    (Weak against | Reviewed, New-added)

Discussion

The systematic evidence review identified two studies on patent foramen ovale (PFO) closure for the treatment of migraine headache, including one SR by Zhang et al. (2022), with three embedded RCTs, and 1 RCT by Mas et al. (2021).(280, 281)

In the SR by Zhang et al. (2022) (n=1,165), PFO closure resulted in a reduction in monthly migraine attacks and days with a statistically significant OR of 0.2594.(281) However, the authors combined headache attacks and headache days, which made interpreting the clinical impact on the critical outcome of change in headache days difficult. Additionally, the effect size was small (SMD: 0.26). For the other critical outcome, freedom from migraine, no difference was found between PFO closure and sham or medication.(281)

The RCT by Mas et al. (2021) was a subgroup analysis of patients who underwent PFO closure for stroke.(280) This study assessed the change in headache attacks and freedom from migraine, comparing patients with migraine with aura to those with migraine without aura. No significant difference was found in the critical outcome of change in headache attacks between PFO closure and antiplatelet therapy versus antiplatelet therapy alone. However, the study did demonstrate a statistically significant change for the critical outcome of freedom from migraine in patients with migraine with aura (OR: 1.5856).(280) Despite this promising effect, the Work Group's confidence in the quality of the evidence was low.

The potential for harm and burdens is generally higher for invasive procedures. As such, percutaneous PFO closure was shown to have a significant AE profile in the SR by Zhang et al. (2022), which reported 25 serious AEs, of which 24 were procedure or device related.(281) These AEs included cardiac events, such as atrial fibrillation and pericardial effusions as well as procedure-related complications, including groin and retroperitoneal hematomas. Mas et al. (2021) did not report AE rates.(280) Beyond the potential for significant AEs, individuals receiving an invasive procedure might need some type of anesthesia and might have to travel to a specialized center to receive this treatment, which can be burdensome.

Patient preferences vary largely regarding this treatment. Although the patient focus group did express interest in nonpharmacologic and alternative therapies to medication, this procedure is invasive with potential morbidity. However, for some patients, the potential for complete resolution might be attractive. Significant system concerns are related to resource use because this procedure requires interventional cardiology

providers, a specialized treatment location, and a fixed facility. These resources are difficult to access in rural and deployed environments, resulting in equity concerns, as well.

The Work Group systematically reviewed evidence related to this recommendation. (280, 281) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations, including the lack of sham and blinding in one trial as well as imprecision in the application of outcome definitions.(280, 281) The potential harm of PFO closure, including procedure and device complications, slightly outweighed the benefits of small effect size on the critical outcome of change in headache attacks and the limited population of patients with migraine with aura who could potentially experience freedom from migraine. Patient values and preferences varied largely because of the invasive nature of the procedure. Thus, the Work Group made the following recommendation: We suggest against patent foramen ovale closure for the treatment or prevention of migraine.

D. Non-pharmacologic Therapy

Recommendation

41. We suggest non-invasive vagus nerve stimulation for the acute treatment of episodic cluster headache.
    (Weak for | Reviewed, Not changed)

Discussion

No new studies were found during the 2023 systematic evidence review on the use of non-invasive vagus nerve stimulation (n-VNS) devices for the acute treatment of cluster headache. In the 2020 VA/DoD Headache CPG, the Work Group evaluated the use of n-VNS in episodic and chronic cluster headaches, but the evidence supported its use only in individuals experiencing episodic cluster headache.(282, 283) The two RCTs by Goadsby et al. (2018) and Silberstein et al. (2016) did not support n-VNS treatment of chronic cluster headache because both studies demonstrated no statistically significant difference when compared with sham, and the Work Group's confidence in the quality of these studies was low.(282, 283)

Low- and moderate-quality evidence supports n-VNS for individuals experiencing episodic cluster headache.(282, 283) Goadsby et al. (2018) (n=102) found a statistically significant difference (OR: 9.19) in the proportion of all treated episodes that achieved pain-free status at 15 minutes for patients receiving n-VNS versus sham treatment.(282) In a similar group (n=150), Silberstein et al. (2016) found a statistically significant difference in individual responder rates (defined as a pain rating of 0-1 on a 5-point scale without the use of rescue medication) at 15 minutes and in the sustained treatment response rate (response at 15 minutes was sustained through 60 minutes).

(283) Additionally, Silberstein et al. (2016) found a statistically significant difference in subjects who were responders or pain free for at least 50% of their treated headache episodes 15 minutes after initiating treatment, favoring n-VNS over sham.(283) The same RCT also evaluated the use of rescue medication within 1 hour of the first attack and the mean change in the number of headache days from baseline and found no statistically significant difference in these critical outcomes when compared with sham treatment.(283) The primary AEs were site irritation, pain, erythema, and some musculoskeletal symptoms, such as twitching or lip or facial drooping.(282, 283) The evidence consistently demonstrated that the use of n-VNS was less effective for individuals with chronic cluster headache.(282, 283) Thus, the Work Group concluded that n-VNS should not be suggested as a primary treatment for patients experiencing chronic cluster headache. However, the Work Group identified episodic cluster headaches as some of the most debilitating and painful headaches described in this CPG. As such, the Work Group determined that any treatment that might provide some relief should be offered to patients with episodic cluster headache.

Likely some variation in patient preferences occurs regarding this treatment. Although the patient focus group expressed a desire for a mix of pharmacologic and non-pharmacologic treatment options, some patients do not prefer the physical sensation of electrical stimulation and might not wish to follow a protocol that involves multiple treatments per day, every day. However, given the debilitating and painful nature of cluster headaches, some individuals might prefer to try anything that has the potential for benefit. The commercially available n-VNS device has specific protocols and placement that require training of both the provider and the patient and might require the assistance of a caregiver for those with physical or cognitive impairments that prevent independent use. Additionally, the provider must be aware of significant contraindications that will narrow the pool of eligible patients. Moreover, the original commercial device contains potentially hazardous materials (e.g., lithium batteries) and must be disposed of after 1 month, raising concerns related to environmental waste. Finally, concerns with the current business model relate to the device's becoming inoperable after a certain number of days, which then requires multiple steps for the patient to receive a "renewal" for the device to operate again, causing delays in care. This potential burden is particularly impactful for patients with cluster headaches because episodes are often cyclical.

The Work Group considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG because no studies on this topic met inclusion criteria for the 2023 VA/DoD Headache CPG systematic evidence review.(282, 283) Therefore, this recommendation is categorized as *Reviewed, Not changed*. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations, including ROB and some imprecision.(282, 283) The device manufacturer or parent company funded both of the studies reviewed for this recommendation, and a number of the authors from both have financial relationships with the parent company.

The benefits of n-VNS for pain relief in this debilitating headache diagnosis outweighed the potential harm of AEs, which was small. Patient values and preferences varied because some patients might be unwilling to engage in the protocol, although others are willing to do so for potential relief. Thus, the Work Group made the following recommendation: We suggest non-invasive vagus nerve stimulation for the acute treatment of episodic cluster headache.

Recommendation

42. We suggest physical therapy for the management of tension-type, migraine, or cervicogenic headache.
    (Weak for | Reviewed, New-replaced)

Discussion

The Work Group considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG regarding physical therapy for the management of TTH.(284-291) Similarly to the 2020 VA/DoD Headache CPG Work Group findings, evidence continues to support physical therapy for the management of headache, with specific references to TTH and migraine. Additional evidence reviewed as part of the systematic evidence review carried out for this CPG update led the Work Group to support a *Reviewed, New-replaced* recommendation.(292, 293) Evidence from a low-quality SR with seven RCTs (n=173) found that physical therapy interventions, such as cryotherapy, soft-tissue mobilization, transcutaneous electrical nerve stimulation (TENS), trigger point therapy, and various mobilization and manipulation techniques, when performed by a physical therapist, improved the critical outcomes of headache frequency and intensity (MD: -3.88; CI: -7.39–0.037) compared with sham control.(292) Similar findings existed when delivering these physical therapy interventions compared with medication; however, relaxation therapy showed no significant improvement when compared with medication (MD: 6.61; CI: -0.92–1.67).(292) Rezaeian et al. (2019) randomized individuals (n=40) to receive placebo trigger point massage compared with the intervention group, which received passive stretching of the muscles of the upper body in supine.(293) Findings from this small RCT showed improvement in the critical outcomes of headache disability (measured using the Headache Disability Index [HDI]) (CI: 18.75–29.64; p<0.001), reduced headache intensity (CI: 1.71–2.68; p<0.001), duration (CI: 10.87–17.42; p<0.001), and frequency (CI: 2.1–3.19; p<0.001).(293) Follow-up was not included in the newly reviewed literature.

Physical therapists are licensed health care providers who specialize in movement and provide multimodal care that includes patient education, hands-on treatment, and exercise prescription with a focus on QoL and function across the lifespan. The term “physical therapy” encompasses a domain of various interventions, such as therapeutic exercise, active mobilization of tissue, stretching, manual therapy, manipulations, various forms of neuromodulation (e.g., TENS), and thermal and non-thermal modalities provided by a physical therapist. These interventions are often

used in combination in most physical therapy practices. The previous CPG Work Group found low-quality evidence to support the use of combined physical therapy interventions.(284-291) Although many of these techniques could be delivered by other disciplines, a physical therapist provided the interventions in the reviewed evidence. Physical therapists delivered care that included various manual therapy techniques and manual therapy combined with therapeutic exercise and postural training as active components of treatment.(289, 290, 292) The ability to employ various active (e.g., exercise, stretching) alongside passive (e.g., manual therapy, manipulation, cryotherapy, dry needling, neuromodulation) approaches contributes to the generalizability of these findings to typical physical therapy management and mitigates the potential pitfalls of monotherapy with a constrained approach. The 2020 systematic evidence review included follow-up at 4 and 8 weeks, although the newly reviewed evidence included no follow-up. No studies reported AEs. Given the low quality of the evidence and lack of generalizability in these studies, there was insufficient evidence to recommend any of these specific approaches.

Physical therapy is a non-pharmacologic beneficial treatment option that aligns with patient focus group participant preferences. Exercise, in general, improves physical and mental health alongside other co-morbidities.(294) Physical therapy, as part of a team approach, meets the patient focus group participant preferences related to care coordination. Initial training and services must be provided by a licensed professional, which might present barriers related to time for appointments and access to physical therapists. However, embedding physical therapists within primary care teams might help mitigate some barriers.

The Work Group systematically reviewed evidence related to this recommendation, (292, 293) and considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG.(284-291) Therefore, it is categorized as *Reviewed, New-replaced*. The Work Group's confidence in the quality of the evidence was low.(284-293) There were limitations in methodological quality and imprecision in the evidence. The benefits of physical therapy outweighed the likelihood of AEs, which were not explicitly reported in the studies reviewed because physical therapy is considered safe. The improved outcomes of reduced disability, decreased headache frequency and intensity, and patient preference for non-pharmacologic interventions creates generally high perceived value for this treatment option. Some variation in patient values and preferences might occur because individuals might prefer not to participate in physical therapy or might be unwilling to engage in active interventions (e.g., exercising at home) compared with passive interventions (e.g., manual therapy, thermal modalities, neuromodulation, dry needling). Some patients might view the variable decrease in headache frequency and intensity as not worth the opportunity cost of attending appointments. This could be mitigated by fewer visits to the physical therapist, by more time spent on independent home practice, or by including telemedicine visits for care.

Thus, the Work Group made the following recommendation: We suggest physical therapy for the management of tension-type, migraine, or cervicogenic headache.

Recommendation

43. We suggest aerobic exercise or progressive strength training for the prevention of tension-type and migraine headache.
    (Weak for | Not reviewed, Amended)

Discussion

Aerobic exercise or progressive strength training improves outcomes of headache frequency (headache days per month) and disability in patients with TTH and migraine headache.(295-300) This recommendation was updated from the 2020 VA/DoD Headache CPG to include language for the specific headache type studied. Lemmens et al. (2019) and Sertel et al. (2017) found that aerobic exercise was associated with improvements in headache frequency and intensity in most patients with TTH and migraine.(295, 297) Madsen et al. (2018) and Gram et al. (2014) studied the impact of strength training (free weight and resistance bands) on headache (not classified) and TTH.(296, 298) The four studies reviewed included an SR (295) and three RCTs.(296-298) Dosage of the interventions was thought to be important to highlight for providers. The Work Group found that the intervention dosage varied, ranging across the studies from two times per week for 30–50 minutes;(295) three times per week for 60 minutes;(297) three times per week, performing four upper body strength exercises;(296) and three times per week for 30 minutes.(298) Supervision was administered during either the entire intervention,(297) or at regular intervals.(296, 298) Supervision during time points was necessary to optimally increase the progressive load and intensity of the strength training exercises according to principles of periodization and progressive overload. Findings from these studies continue to align with the consensus that exercise is beneficial for overall health.(294) Other studies including headaches of interest, such as PTH (299) and cervicogenic headache,(300) showed similar results. Studies from the systematic evidence review reported no AEs with these trials, limiting overall harm associated with aerobic exercise and progressive strength training.

Regarding exercise training, there is general a consensus supporting either aerobic conditioning, progressive strength training, or both in adults with migraine or TTH. In all studies reviewed, no AEs were reported. Some variability occurs in patient preferences regarding these interventions, and equipment availability might be unequal across DoD and VA facilities. Aerobic or progressive strength training or both address the desire for non-pharmacologic therapies expressed by the patient focus group. Additionally, the mental and physical benefits of exercise, in general, can improve overall health and wellbeing. Patient values and preferences also vary given different patients' willingness to exercise. Equity was considered because patients might be able to exercise at inexpensive gyms or at home. Prior injuries or disabilities should be considered when

prescribing exercise. Further, this recommendation might be inappropriate for patients who have experience with exercise worsening headaches.

The Work Group considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG.(295-300) Therefore, this recommendation is categorized as *Not reviewed, Amended*. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations, including variability of comparators, small sample sizes, minimal effect size, and heterogeneity of headaches studied.(295-300) The benefits of aerobic exercise and progressive strength training (e.g., reduced headache frequency, reduced severity) outweighed the potential harm of AEs, which was small. Patient values and preferences varied because of patients' willingness and mental, physical, and cognitive capacity to exercise as well as access to exercise space, equipment, or both. Thus, the Work Group made the following recommendation: We suggest aerobic exercise or progressive strength training for the prevention of tension-type and migraine headache.

Recommendation

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 heartrate variability monitoring
    - Cognitive behavioral therapy
    - Mindfulness-based therapies
    - Progressive muscle relaxation
    - Smartphone application-based heartrate variability monitoring

    (Neither for nor against | Reviewed, New-replaced)

Discussion

Biofeedback and Smartphone Application–Based Heartrate Variability Monitoring

Evidence from one RCT (n=52) demonstrated no difference in disability or QoL outcomes in individuals with migraine who received biofeedback, through a smartphone application, compared with a waitlist control group.(301) The Work Group's confidence in the quality of evidence for biofeedback and the smartphone application-based program was very low given the current evidence and discussion of the intervention's burden. The Work Group concluded that the burden of use outweighed the benefits. Patient preference in the use of biofeedback through a smartphone device might differ depending on access to a device and proficiency in smartphone application usage. Additionally, the time and effort required for the provider to train the patient might increase the burden of use for biofeedback. Monitoring an individual's consistent use of biofeedback might also be challenging when the intervention is completed outside the clinic.

Cognitive Behavioral Therapy

Evidence supporting the use of cognitive behavioral therapy (CBT) for headache was mixed. An RCT by Soleimanian-Boroujeni et al. (2022) (n=35) demonstrated that CBT significantly reduced headache frequency, impact, and medication usage compared with relaxation or stress management.(302) In contrast, an RCT by Klan et al. (2022) (n=121) showed no difference in these outcomes as well as no differences in reported disability between patients receiving CBT and waitlist controls.(303) Because of serious concerns with the quality of the data and methodological inconsistencies from Mukhtar et al. (2022), the Work Group decided to recommend neither for nor against this intervention based on the findings from these studies.(304) Furthermore, although patients prefer non-pharmacologic interventions such as CBT because of the potential low side-effect profile, the burden of CBT treatment for both patients and providers might deem the intervention less feasible. A typical CBT intervention might require that the patient commits up to 2 hours per week for the therapy sessions. Finally, providers must be trained in the provision of CBT to ensure effectiveness of the intervention and patient adherence to recommended CBT strategies and homework.

Mindfulness-Based Therapies

Evidence supporting the use of mindfulness-based therapies for headache was mixed. Two RCTs showed that Acceptance and Commitment Therapy (ACT) significantly reduced headache-related disability, role restrictive and role preventive QoL, but not emotional function QoL or medical use, compared with control conditions (e.g., waitlist, treatment as usual [TAU]).(305, 306) Grazzi et al. (2021) showed that ACT did not significantly reduce headache-related disability or frequency but significantly reduced headache impact and medical utilization.(307) Evidence from six RCTs in one SR showed no differences in headache frequency between individuals treated with Mindfulness-Based Stress Reduction® or Mindfulness-Based Cognitive Therapy and those in control conditions such as TAU or active control (e.g., health education, stress management).(308) Given the inconsistent results and the studies' weak rigor (e.g., small sample sizes of RCTs, insufficient power for outcomes), the Work Group's confidence in the quality of evidence was very low.

Progressive Muscle Relaxation

Evidence from one RCT found no difference in monthly migraine days between patients with migraine using progressive muscle relaxation (PMR) and those receiving TAU.(309) However, when combined with deep breathing exercises, PMR was associated with lower headache frequency in individuals with chronic TTH.(310) Evidence from two RCTs suggests that PMR improves disability and QoL in individuals with migraine or TTH compared with controls.(309, 310) Despite PMR's minimal harm, low burden, and promising results, the outcome (e.g., lower headache frequency) studied limits the evidence to a *neither for nor against* recommendation for PMR.

There is likely some variation in patient preferences regarding behavioral interventions for headache. Given the complexity of treating and managing headache, the patient focus group noted that patients valued receiving a variety of treatment options, explicitly expressing an interest in non-pharmacological approaches. Though some time commitment is needed to achieve typical treatment dosage in behavioral interventions, for subgroups not interested or able to seek typical primary care treatment modalities (e.g., pregnant or lactating patients, special active duty Service member status limitations), this non-invasive alternative may be worthwhile. Behavioral interventions delivered via telehealth may improve access and widespread dissemination, especially within rural settings. Participants expressed that virtual visits could be helpful and could reduce the burden on patients and providers. When leveraging technology, ensuring patients are adequately trained and have access to the required technology is crucial. Of note, some patients might still be unable to use mobile phones or tablets in specific workplace settings. Further considerations of potential barriers to treatment include limited access to this treatment because of providers' lack of specific training in the treatment of headache through psychological and behavioral modalities, perceived stigma related to mental health-related therapies, and associated caregiver burden or required treatment modifications for individuals with physical or cognitive impairments or both.

Although the systematic evidence review carried out for this CPG update did not capture evidence published before the search window, the Work Group acknowledges that behavioral interventions are historically accepted as standard practice in the treatment of headache, and additional research is less likely to be published because of the known effectiveness in addressing headache. Alongside the evidence presented above, the 2020 VA/DoD Headache CPG included additional support for the use of these interventions.(311-315) Future investigators should consider research studies using rigorous methodologies to increase the quality of evidence (i.e., use of randomization and blinding). Furthermore, future RCTs should consider assessing various modalities of PMR therapy and its effect on several important outcomes, including the impact of behavioral interventions on disease activity (e.g., headache frequency, intensity, duration), QoL and disability, and sleep and mental health symptoms; effectiveness of behavioral interventions as a standalone therapy or combined therapies; potential differences in behavioral treatment modality utilized (e.g., telehealth versus in-person delivery, individual versus group settings); impact of behavioral interventions as preventive or acute management or both; and "dose" or required length of the intervention and the sustainability of desired outcomes.

The Work Group systematically reviewed evidence related to this recommendation (301-310) and considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG.(311-315) Therefore, it is categorized as *Reviewed, New-replaced*. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including variability in the interventions provided, the comparator groups, small sample size, studies underpowered to detect differences in

critical outcomes, lack of blinding of outcome assessors, heterogeneity of headache diagnosis studied, and attrition during the treatment or follow-up period. Based on the current literature reviewed, the benefits of PMR slightly outweighed its potential burden, positive outcomes of PMR were balanced with the potential burden of dedicating time to treatment (e.g., CBT, mindfulness-based therapy), and the potential burden of needing a smartphone device and the time and cost to train on the application slightly outweighed the potential benefits for smartphone application-based heartrate variability monitoring and biofeedback. Patient values and preferences varied for smartphone application-based heartrate variability monitoring relaxation and biofeedback because some patients prefer non-invasive treatments although others do not, and some might lack access to a smartphone. Patient values and preferences varied largely for CBT, mindfulness-based therapy, and PMR because some patients prefer non-invasive, non-pharmacologic treatments, although others do not and might view devoting time to these treatments as a burden. However, none of the therapies listed in the recommendation demonstrated any AEs. Thus, the Work Group made the following recommendation: 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 heartrate variability monitoring
- Cognitive behavioral therapy
- Mindfulness-based therapies
- Progressive muscle relaxation
- Smartphone application-based heartrate variability monitoring

Recommendation

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)

Discussion

Acupuncture

Three SRs (316-318) and four RCTs (319-322) focused on the effectiveness of acupuncture interventions to reduce the number of migraine days per month. Two SRs (317, 323) and one RCT (322) also focused on acupuncture's effect on disability and QoL. Very low–quality evidence suggests that acupuncture decreased the number of migraine days per month.(316, 317, 320-322) One RCT in the acupuncture group found no difference in the number of migraine days between intervention and control groups.(319)

Low- to very low–quality evidence suggests that acupuncture improved disability or QoL scores compared with control groups.(293, 310, 317, 322-327) Evidence from one RCT

found that acupuncture improved disability and QoL scores at 20 weeks follow-up in patients with episodic migraine.(322)

The methodological quality of the studies reviewed presented with significant limitations, including publication bias and incomplete data.(316-318, 322, 323) The included studies had populations specific to southeast Asia, limiting the generalizability to the active duty Service member and Veteran population. Acupuncture points and techniques varied based on the region of training, style, and technique of the practitioners. The sham comparators and acupuncture interventions were also highly variable across the included studies. Sham acupuncture and interventions can demonstrate a large non-specific effect in many pain conditions. Across the studies, sham comparators included needling at a point near a headache-related acupuncture point, needling at an acupuncture point not felt to be typically beneficial for headache, and use of a telescoping needle that did not puncture the skin at a headache-related acupuncture point.(316-318, 322, 323) Although a comparison with other active treatments would have more clearly outlined the efficacy of acupuncture, such studies were not found in the 2023 systematic evidence review. Because multiple outcomes demonstrated that acupuncture did not have a statistically significant difference compared with the sham comparators, the Work Group determined that the evidence failed to clearly define whether acupuncture itself is beneficial or whether non-specific needling resulting in a diffuse noxious inhibitory effect improved headache in the included studies.

Further limiting the strength of evidence, the heterogeneity of acupuncture dosing contributed to the mixed results in the effect of acupuncture. Acupuncture interventions in the SRs required at least one session per week over 6 weeks, with some studies requiring more treatments.(316-318) In the studies reviewed, although acupuncture is generally considered to be safe, the harms of acupuncture were not assessed as outcomes. No AEs were reported in the literature reviewed.

Patient preferences regarding this treatment are varied. The patient focus group expressed interest in CIH therapies while simultaneously minimizing pharmacologic options. Several factors might be burdensome to receive CIH therapies. The need for ongoing treatments, often weekly or more frequently, along with potential financial impact of copays, travel, and work might limit patients seeking this intervention. Needle hesitancy and unfamiliarity with acupuncture might play a role in patient acceptability. VA and DoD have varying credentialing and privileging of acupuncture providers, which might limit access in certain geographic areas. Acupuncture could be a relative contraindication for certain patient populations, including those who are pregnant.

The Work Group's confidence in the quality of the evidence in the use of acupuncture was very low. The body of evidence had limitations, including a small sample size and confounders in the analysis, and the effect size was very small for the most robust outcome. The Work Group determined that the harms were minimal; however, the burdens associated with time for treatment are important to consider. Other

considerations included lack of standardization of acupuncture techniques or sham, inconsistent improvement in headache frequency, number of headache or migraine days per month, medication usage and QoL, and burdens imposed on patients and the medical system. Additionally, patient values and preferences varied significantly.

Dry Needling

Dry needling was reviewed in the 2020 VA/DoD Headache CPG, where evidence from 1 RCT was included comparing dry needling to botulinum toxin (e.g., Botox), trigger point injections, or medication in the treatment of cervicogenic, TTH, and migraine.(328) Low quality evidence supported the dry needling intervention for improved QoL and disability outcomes. Further evidence was reviewed as part of the systematic evidence review for this CPG update, which included an SR of 11 RCTs.(323)

Pourahmadi et al. (2021) reviewed dry needling compared to physical therapy, pharmacological intervention, and injections of medications into the tissue (i.e., lidocaine).(323) Studies reviewed focused on the treatment of cervicogenic, TTH, and migraine. The Work Group's confidence in the quality of the evidence for dry needling remains very low given variations in the NNT and lack of allocation concealment or blinding in most studies. The results favored dry needling for QoL and disability outcomes but not for an overall reduction in pain intensity.

Large variation in patient preference might occur, including a patient's fear of needles, pain, or discomfort at the needling site and the possibility of infection risk or lung puncture. Tissue damage is expected with any invasive intervention. When comparing this risk of injection, the Work Group determined that the use of a sharp, beveled, hollow-core needle has a higher potential for muscle fiber damage than the use of a solid filiform needle (e.g., acupuncture needle) for dry needling. The potential for a transient increase in pain from dry needling alone or injection of botulinum toxin with needling, compared with injection of local anesthetic, should also be considered when choosing an approach. Overall, the Work Group determined the harms were lower with dry needling alone compared with the injection of local anesthetic or botulinum toxin. Additionally, given the potential limited time of its effectiveness, dry needling might require increased time commitment for patients to maintain the intervention's effectiveness for headache. Finally, ensuring that practitioners are well trained and comfortable in the provision of the intervention might be a barrier to its availability at VA and DoD facilities.

Yoga

Two meta-analyses assessed the efficacy of yoga for the treatment of headache or migraine. One meta-analysis, including six RCTs, examined the efficacy and safety of yoga for the treatment of headache.(324) Within this SR, yoga types were described as "yogic postures," "breathing techniques," and "relaxation;" "meditation," "hatha," and "raiyoga." Although evidence suggests that yoga improved headache frequency and

duration, the meta-analysis showed inconsistencies in the evaluation of outcomes (i.e., type of headache versus migraine). Additionally, the number of included RCTs in the study was low, providing inconclusive evidence about the effectiveness of yoga as a treatment. The authors of this SR were unable to delineate the safety of the intervention because none of the studies reviewed addressed the presence or absence of AEs. Another meta-analysis by Long et al. (2022) included six RCTs that examined the effectiveness of yoga for migraine.(326) Yoga type described by Long et al. (2022) identified studies based on mindfulness, "standardized integrative yoga model", "yoga practice", or "yoga therapy". Major limitations of the studies reviewed included the studies' small sample sizes and heterogeneity of the type and dosage of yoga used. Despite the available evidence in the improvement of headache or migraine pain intensity and frequency, the Work Group's level of confidence in recommending yoga is very low based on the quality of evidence presented by the meta-analyses.

In addition to the quality of evidence, the Work Group considered other challenges and barriers in the level of recommendation of yoga for headache or migraine. Patient preferences, values, and degree of physical fitness might vary in the successful implementation of and interest in yoga practices. The acceptance of yoga as a therapeutic intervention or practice depends on one's cultural or spiritual beliefs, which might be seen as both a barrier or a facilitator in the use of yoga for headache or migraine. Others might perceive yoga as a time-consuming and costly intervention, particularly if the effect of yoga on headache or migraine is short-term. Yoga interventions that are affordable are often provided in group settings. However, patients might prefer to complete interventions in isolation rather than in group settings. The role of telehealth might provide further benefits but has yet to be explored in the literature. Furthermore, patients might perceive yoga as a difficult practice to successfully perform because it might require a certain level of physical fitness or flexibility. Many types of yoga often require coaching from an experienced practitioner, making the intervention less feasible. Given the need for an experienced and competent yoga instructor, resources might vary depending on locality or region. Resources might be limited in VA and DoD facilities. Alongside the evidence from the 2023 CPG, additional evidence was reviewed from the 2020 VA/DoD Headache CPG.(277, 278, 329-332)

The Work Group systematically reviewed evidence related to this recommendation, including acupuncture, dry needling, and yoga (293, 310, 316-327), and considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG.(277, 278, 328-332) Therefore, it is categorized as *Reviewed, New-replaced*. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including small sample size,(324, 326) lack of blinding, allocation concealment,(316-323) and heterogeneity in type of intervention and sham comparator provided.(316-322) The burdens of interventions such as acupuncture, dry needling, and yoga slightly outweighed the potential benefits of improving QoL, disability, headache frequency, and intensity. Patient values and preferences varied largely

because some patients might prefer nonpharmacologic interventions, yet others might prefer immediate results. Thus, the Work Group made the following recommendation: There is insufficient evidence to recommend for or against acupuncture, dry needling, or yoga for the treatment and/or prevention of headache.

Recommendation

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)

Discussion

Trigger foods can be assessed through an elimination diet (i.e., all potential trigger foods are eliminated from a diet and then reintroduced deliberately while monitoring the relationship between migraine onset and food intake). Two studies found that individuals who avoided trigger foods or modified their diet for the prevention of migraine had fewer migraine attacks per month, and the total monthly analgesic consumption rate decreased.(333, 334) Participants (n=50) in Ozon et al. (2018) first identified migraine-triggering foods using a questionnaire, then participated in an elimination-based diet for 2 months.(333) Following this dietary change, the groups were divided: one group (n=25) relaxed their diet restrictions, and the other arm (n=25) continued the previously identified restrictions. Both groups continued their medications as prescribed without change. The group that continued with diet restrictions had 1.3 fewer migraines per month at 4 months compared with the group that could relax their diet (p=0.013).(333) Zencirci et al. (2010) (n=50) also separated participants into two groups: one group (n=25) who used medications as identified in the study (metoprolol 120 mg per day, riboflavin 600 mg three times per day, and naproxen sodium 550 mg at the aura or beginning of symptom onset) and a second group (n=25) who used these same medications plus trigger food avoidance based on a provided standard list.(334) Both groups kept daily pain diaries recording headache attack frequency, severity with VAS scores, and need for naproxen therapy. These diaries were assessed every 15 days for 12 months. Participants who combined medications with trigger food avoidance experienced 2.45 fewer migraine periods per month (p=0.007).(334)

The Work Group's confidence in the quality of the evidence was low.(333, 334) The body of evidence had limitations, including self-reporting of trigger foods and a small number of participants (n=50 in each study). The burdens slightly outweighed the potential benefits based on limited data. The burdens associated with elimination of trigger foods for participants include a reduction in QoL for those avoiding desirable foods, disordered eating, social isolation, insufficient nutrition, or difficulty adhering to diet based on socioeconomic challenges. Patient preferences vary greatly because elimination diets require a commitment to lifestyle changes that might be challenging.

In the 2020 VA/DoD Headache CPG, the weak for recommendation specifically focused on education of trigger avoidance. Although the evidence regarding dietary trigger suggests potential benefit, data providing low-quality evidence is limited at this time. The studies did not focus on education, but on dietary changes; thus, the Work Group modified the recommendation from the 2020 CPG to remove the education focus. More research is needed in the safety and effectiveness of any self-directed lifestyle modification and subsequent education provided.

The Work Group considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG.(333, 334) Therefore, this recommendation is categorized as *Not reviewed, Amended*. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations, including small sample size, lack of blinding, and self-reported adherence to intervention. The potential harms of reduction in QoL for individuals avoiding desirable foods, disordered eating, social isolation, insufficient nutrition, or difficulty adhering to diet based on socioeconomic challenges slightly outweighed the benefits of a reduction in headache days and medication usage. Patient values and preferences varied largely because of the burden of lifestyle modifications. Thus, the Work Group made the following recommendation: There is insufficient evidence to recommend for or against dietary trigger avoidance for the prevention of headache.

Recommendation

47. We suggest against immunoglobulin G antibody testing for dietary trigger avoidance for the prevention of headache.
    (Weak against | Not reviewed, Amended)

Discussion

Two studies from the 2020 VA/DoD Headache CPG evaluated a relationship between IgG and food sensitivity and whether lab testing for food hypersensitivity through enzyme-linked immunosorbent assay (ELISA) would be more effective or timely than the traditional elimination diet method or both.(335, 336) The primary outcome measure in both studies was a decrease in total number of headache days.(335, 336) Alpay et al. (2010) (n=30) found a significant difference favoring the elimination diet for decreasing the total number of headache days, but the study had a small sample size and patients were followed for only two 6-week diet-modification periods.(335) Mitchell et al. (2011) (n=167) found no significant difference in the number of headache days between the group following a diet developed based on ELISA findings and the group given a standardized sham diet.(336) This study also had a short follow-up period.

The Work Group's confidence in the quality of the evidence was very low.(335, 336) Few studies evaluated the potential impact of this treatment approach, and they had conflicting findings. The body of evidence had limitations, including small sample size and short follow-up periods.(335, 336) The harms slightly outweighed the benefits

because insufficient data existed to suggest benefit with food trigger avoidance; therefore, obtaining IgG testing in the pursuit of trigger avoidance would be unbeneficial and could cause unnecessary harm. Providers might not know how to use this information and, thus, might refer patients to other specialists, taking up time for the patient and resources or creating an unsupported elimination diet.

Patient values and preferences varied largely because some patients might prefer the more rapid determination of foods to avoid rather than the typical elimination diet process. Additionally, large variation surrounds the use of an elimination diet, which can impact QoL and might be difficult to follow for individuals in different socioeconomic situations. Immunoglobulin G antibody identification might be unavailable in some areas or might require an out-of-pocket expense or a specialist to conduct the test. The results might also be misinterpreted as an inflammatory response and lead to unnecessary lifestyle change for the patient. Given the limited data for this recommendation and inconclusive evidence in Recommendation 46, more research is needed on the safety and effectiveness of an elimination diet before further conclusions can be drawn regarding IgG.

The Work Group considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG.(335, 336) Therefore, this recommendation is categorized as *Not reviewed, Amended*. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including small sample size and short follow-up.(335, 336) The harm of inappropriate use of positive results slightly outweighed the potential benefits of reduction in headache from an IgG directed diet restriction. Patient values and preferences varied largely because of the difficulty with dietary adherence; some patients might want the fast answer for foods to avoid over the typical elimination process. Thus, the Work Group made the following recommendation: We suggest against immunoglobulin G antibody testing for dietary trigger avoidance for the prevention of headache.

Recommendation

48. There is insufficient evidence to recommend for or against any form of neuromodulation for the treatment and/or prevention of migraine:
    - Non-invasive vagus nerve stimulation
    - Supraorbital, or external trigeminal, nerve stimulation
    - Remote electrical neurostimulation
    - External combined occipital and trigeminal neurostimulation
    - Repetitive transcranial magnetic stimulation
    - Transcranial direct current stimulation

    (Neither for nor against | Reviewed, New-replaced)

Discussion

Non-invasive Vagus Nerve Stimulation

Non-invasive vagus nerve stimulation devices have been cited as a nonpharmacologic treatment modality to provide relief for acute migraine and cluster headaches. The data relating to migraines include one SR and two RCTs.(337-339) The evidence reviewed by the Work Group on the use of n-VNS included two different devices targeting the vagus nerve transcutaneously in the neck via a handheld device or the ear via a clip apparatus, such as transauricular vagus nerve stimulation (ta-VNS). The SR by Lai et al. (2020) was reviewed for n-VNS for migraine in the 2020 VA/DoD Headache CPG.(337)

Mixed low-quality evidence relates to the efficacy of cervical n-VNS or ta-VNS for individuals experiencing chronic or episodic migraine headaches.(337-339) For the critical outcome of migraine days per month, the RCT by Najib et al. (2022) (n=113) and two RCTs in the SR by Lai et al. (2020) (n=391) found no difference in migraine or headache days per month when compared with sham for chronic or episodic migraines.(337, 338) For the critical outcome of pain relief, one RCT in the SR by Lai et al. (2020) favored n-VNS for pain relief at 60 minutes (OR: 1.73) when compared with sham.(337) In a small RCT (n=70) comparing ta-VNS versus sham and using a longer protocol (30 minutes versus 2 minutes), Zhang et al. (2021) found a difference in the mean reduction in migraine days and a statistically significant difference in mean pain reduction on the 0-10 VAS (timeframe not reported) for individuals with a diagnosis of chronic migraine.(339) Data on AEs were reported in two RCTs in the SR by Lai et al. (2020) and in the RCT by Najib et al. (2022) with no difference between the n-VNS and sham.(337, 338)

The evidence was also mixed for the important outcomes of reduction in abortive use and functional disability. One RCT (n=143) from the SR by Lai et al. (2020) reported a reduction in abortive medication use for episodic migraine (OR: 0.61), although the RCT by Najib et al. (2022) reported no difference for individuals with episodic or chronic migraine.(337, 338) Similar conflicting evidence was found in measuring functional disability, which was reported by Najib et al. (2022) using both the HIT-6 and MIDAS. (338) These authors found a clinically relevant improvement in the HIT-6 and no difference in MIDAS scores over the same time period when compared with sham.(338) Clinically relevant change on the HIT-6 questionnaire is defined as a between-group MID of -1.5.(340) The small RCT by Zhang et al. (2020) used the Migraine Specific Quality of Life Questionnaire without a significant difference between active and sham interventions.(339)

Likely a large variation in patient preferences exists regarding this treatment. Although the patient focus group expressed a desire for a mix of pharmacologic and non-pharmacologic treatment options, some patients do not prefer the physical sensation of electrical stimulation and might not wish to follow a protocol that involves multiple treatments per day, every day. The ta-VNS device does not appear to be readily available

in the U.S., and placement can be challenging for the cervical n-VNS device. The commercially available n-VNS device has specific protocols and placement that require both provider and the patient training and might require the assistance of a caregiver for patients with physical or cognitive impairments preventing independent use. Additionally, significant contraindications that the provider must be aware of will narrow the pool of eligible patients. Concerns related to environmental waste also arise because the original commercial device contains potentially hazardous materials (e.g., lithium batteries) and must be thrown away after 1 month. Finally, concerns with the business model relate to the device's becoming inoperable after a certain number of days, which then requires multiple steps for the patient to receive a renewal for the device to operate again, causing delays in care and increasing overall cost to the system.

Supraorbital, or External Trigeminal, Nerve Stimulation

Evidence suggests that SON stimulation (also called external trigeminal nerve stimulation) results in inconsistent efficacy for the acute or preventive treatment of migraine. Kuruvilla et al. (2022) found that acute treatment with SON stimulation is favored over sham for pain reduction (25.5% versus 18.3%) and absence of MBS (56.4% versus 43.4%) at 2 hours post-treatment, which was statistically significant for both outcomes.(341) Conversely, a single RCT in the SR by Moisset et al. (2020) found no difference for SON stimulation versus sham for the acute treatment of migraine.(342) Findings from other studies, conducted in a variety of patient populations, have been consistent with this finding.(343)

A single small RCT (n=67) in the SR by Moisset et al. (2020) favored SON stimulation over sham with a moderate effect size (-0.63) for migraine prevention.(342) Another RCT (n=110) in the SR by Moisset et al. (2020) favored SON stimulation plus flunarizine over SON stimulation alone and found no difference between SON stimulation when compared with flunarizine for migraine prevention.(342) This RCT found no difference in acute medication use when comparing SON stimulation to flunarizine for migraine prevention. Evidence also suggests that SON stimulation is associated with more AEs, specifically forehead paresthesias, when compared with sham (3.5% versus 0.4%).(341)

Large variation occurs in patient preferences regarding this treatment because some patients prefer neuromodulation over medication and can treat themselves at home using the device, whereas others might feel uncomfortable sitting with a visible device. Additionally, many patients do not tolerate the stimulation sensations.

This treatment also has resource use considerations because of opportunity costs for both patient and provider training. Furthermore, the SON stimulator device is more expensive than a standard TENS unit. Subgroup considerations include patients presenting with migraine with allodynia who are less likely to tolerate the device sensation and patients with physical or cognitive impairments who might require a caregiver to safely operate the device.

Remote Electrical Neurostimulation

Evidence suggests that remote electrical neurostimulation improves pain when used for the acute treatment of migraine. Two RCTs in an SR by Moisset et al. (2020) found that remote electrical neurostimulation was associated with a greater proportion (RR=2.14) of patients who were pain free at 2 hours compared with sham.(342) No significant AEs were noted in the included studies.

Patient preferences vary largely regarding this treatment. Some patients prefer non-pharmacologic treatments, although others object to using smart devices for headache treatment because of concerns about being tracked. Furthermore, there are resource use considerations because the device has a limited number of uses before shutting off, rendering it non-functional. The device must then be thrown away, which has an environmental impact. The need for bandwidth access and technical literacy poses both equity and feasibility concerns. Additionally, there are some DoD settings where Bluetooth is restricted, impacting feasibility. Subgroup considerations include patients with physical or cognitive impairments who might require a caregiver to safely operate the device.

External Combined Occipital and Trigeminal Neurostimulation

Evidence suggests that acute treatment of migraine with an external combined occipital and trigeminal neurostimulation device results in inconsistent outcomes when compared with sham. An RCT (n=187) by Tepper et al. (2022) found that treatment with the external combined occipital and trigeminal neurostimulation device was associated with improvements in pain freedom and freedom from MBS at 2 hours post-treatment.(344) The finding of pain freedom at 2 hours did not reach statistical significance in another RCT (n=55) by Daniel et al. (2022).(345) Although the RCT by Daniel et al. (2022) did demonstrate that the treatment improved pain intensity, the RCT by Tepper et al. (2022) used a non-validated scale to measure pain improvement, which confounded the interpretation of benefit.(344, 345) Neither of these RCTs demonstrated statistical significance in AEs from the combined neurostimulation device compared with sham treatment.

Patient preferences varied largely regarding this treatment because some patients prefer non-pharmacologic treatment, although other patients might object to being tracked through the device's cloud interface. Additionally, resource use is a concern because the device comes preloaded with a limit of 10 treatments and then requires a prescription for refill. Subgroup considerations include patients who are unable to use a device that tracks through a cloud interface (e.g., deployed active duty Service members) and those with physical or cognitive impairments who might require a caregiver to safely operate the device.

Repetitive Transcranial Magnetic Stimulation

Repetitive transcranial magnetic stimulation (rTMS) has been proposed as a treatment option for several headache disorders, including migraine, PTH, and TTH. For this recommendation, the Work Group reviewed two RCTs by Leahu et al. (2021) (n=65) and Shah et al. (2021) (n=108) as well as an SR by Saltychev et al. (2022), which included eight RCTs.(346-348)

Leahu et al. (2021) compared rTMS with sham rTMS in episodic migraine patients and demonstrated a reduction in the primary, critical outcome of migraine days per month of -3.2 days at 12 weeks.(346) Leahu et al. (2021) found mixed improvement in the secondary outcomes of migraine attacks and headache pain intensity measured by the VAS, with a reduction in migraine attacks from baseline but less profound decreases in headache intensity seen at the 8- and 12-week time points.(346) The strength of evidence for the primary outcome of migraine days per month in this study was moderate.

In a single-blind RCT, Shah et al. (2021) evaluated the effects of high- and low-frequency rTMS compared with sham rTMS for the treatment of chronic migraine.(348) In this study, only high-frequency rTMS demonstrated benefit compared with sham rTMS. Specifically, the study by Shah et al. (2021) demonstrated a reduction in the critical outcome of migraine attacks from 10.83±3.37 in the sham group to 7.015±1.45 in the high-frequency rTMS group at the 4-week endpoint.(348) No difference in migraine attacks was reported in the low-frequency rTMS group at the 4-week endpoint. However, the strength of this evidence was low. For the critical outcome of migraine pain intensity, the benefits of high-frequency rTMS were seen only at the 2-week time point, and again the strength of evidence was moderate. For the important outcome of functional disability, no effect occurred in the high frequency rTMS group at 4 weeks. The strength of evidence for this outcome was very low.(348)

Saltychev et al. (2022) completed an SR of eight RCTs assessing high-frequency rTMS in patients with migraine, including patients with chronic and episodic migraine (at least 4 migraine days per month).(347) The pooled data from eight RCTs demonstrated a reduction in migraine days of 8.09 (95% CI: -11.4 to -4.79). The pooled data from six RCTs, however, demonstrated a reduction of VAS (0-100) by 13.56 points (95% CI: -21.8 to -5.32), which is a less robust response.(347) The strength of evidence for both of these outcomes was moderate.

The Work Group identified study-specific limitations, which contributed to the *Neither for nor against* recommendation strength, including the small size of the RCT by Leahu et al. (2021) as well as the short follow-up period in the RCT by Shah et al. (2021).(346, 348) Saltychev et al. (2022) combined multiple small RCTs that employed different treatment paradigms for migraine headaches, limiting the applicability of these

studies.(347) Additionally, they combined studies of disparate clinical populations with widely varying migraine frequencies.

Despite the study-specific limitations, a significant treatment effect is possible if reproducible in larger trials. This benefit, however, must be weighed against the harms and burdens to the patient. In the case of the rTMS trials reviewed above, the adverse reactions were mild (e.g., headache, auditory symptoms, giddiness), and no serious adverse reactions were reported. However, repeated visits to a treatment facility for the rTMS treatments might be burdensome for patients. The studies evaluated as many as six sessions per week, which could present significant travel burdens because the availability of rTMS is limited.

The Work Group reviewed evidence for the use of rTMS for other headache types, as well. A small (n=30) pilot study on rTMS for TTH by Mattoo et al. (2019) showed some limited benefit at 4 weeks for the critical outcome of headache pain, but the strength of evidence was very low.(349) Additionally, a small (n=20) RCT by Stilling et al. (2020) assessed rTMS for the treatment of PTH but did not evaluate any of the critical outcomes of interest, and the strength of evidence for important outcomes was low.(350) Lastly, all current studies of rTMS for headache disorders have focused treatments on the dorsolateral prefrontal cortex (i.e., the same area of the brain where depression is treated). Although studies report that depression is a criterion for exclusion, the assessment used for identifying patients with depression is unclear, and depression is commonly comorbid with chronic headache disorders. Strong controls for the effect of depression are needed to be certain that rTMS is not simply improving headaches through the treatment of depression.

Large variation in patient preferences occurs regarding this treatment. The patient focus group expressed an interest in non-pharmacologic therapies, but they also noted a preference for virtual care as an option for headache treatment. Repetitive transcranial magnetic stimulation requires an in-person visit to a specialized care location. In addition, many patients are opposed to stimulation of the nervous system electronically or magnetically. Because of the nature of the treatment (magnetic stimulation), there are patient-specific contraindications, including epilepsy, implanted medical devices (e.g., pacemakers or defibrillators), and shrapnel or other embedded metal. Some of these conditions, including epilepsy and embedded shrapnel, might disproportionately impact combat-injured soldiers and Veterans. Further, patients might harbor some biases against using a treatment that also treats psychiatric disorders, such as depression. Additionally, rTMS has significant resource use considerations because the treatment requires a fixed facility with specialized equipment and providers trained to use the equipment. These restrictions limit access for patients in rural or deployed environments. Lastly, as a limited resource, it may be harder for larger systems to implement the treatment.

Transcranial Direct Current Stimulation

The Work Group reviewed the effect of transcranial direct current stimulation (tDCS) compared with sham in the treatment of episodic and chronic migraine.(351-355) The evidence gathered in the current systematic evidence review builds on the SR of four RCTs by Shirahige et al. (2016) that the Work Group reviewed in the 2020 VA/DoD Headache CPG.(356) The Work Group has very low confidence in the quality of the small studies included in the systematic evidence review.(351-355) Therefore, the Work Group was unable to draw firm conclusions about the critical outcomes of interest.

One RCT in the SR by Hong et al. (2022) demonstrated a statistically significant difference in the critical outcome of reduction in migraine days per month for tDCS compared with sham at less than or equal to 1 month (WMD: 2.96; p=0.03).(355) Three RCTs in the SR by Hong et al. (2022) also favored tDCS over sham between 1 and 3 months (WMD: 1.14; p<0.00001), but two RCTs in the SR by Hong et al. (2022) found no difference between tDCS and sham at greater than 3 months.(355) A very small RCT by Hodaj et al. (2022) (n=36) found a statistically significant difference at 3 months after treatment cessation in both absolute change (p=0.036) and percentage change (p=0.011) from baseline in migraine attacks per month for participants with chronic migraine headaches.(354) However, the study found no difference in functional outcomes between groups as measured by the HIT-6, MIDAS, and 12-Item Short Form Health Survey (physical and mental subscales). Another very small RCT by Dalla et al. (2020) (n=45) found a statistically significant difference in the percentage of decrease in headache frequency from baseline (p=0.004), but this difference is averaged over three measurement intervals at 10, 60, and 120 days after treatment initiation.(351) The treatment duration was 5 consecutive days plus two sessions at 30 days. Further, baseline migraine rates were higher in the intervention group. For these reasons, the Work Group questioned the quality of these findings. The population in this RCT was also limited to those who had not tried any previous prophylaxis, thus limiting the generalizability of the findings.

A single, very small RCT (n=20) by De Icco et al. (2021) evaluated tDCS versus sham in addition to a 7-day in-patient detoxification protocol for individuals with concurrent diagnoses of chronic migraine and MOH.(353) This study demonstrated a statistically significant difference in both migraine (p=0.007) and headache (p=0.044) days per month at 1 and 6 months after treatment cessation. No difference in acute medication use or functional outcomes was found at any time interval as measured by the HIT-6, MIDAS, or Migraine-Specific Quality of Life Questionnaire.(353)

In addition to the RCTs by Hodaj et al. (2022) and De Icco et al. (2021), a very small RCT by de Brito et al. (2022) (n=30) with female participants reported on functional outcomes.(352-354) The authors found a statistically significant difference (p=0.032) on the MIDAS with a very small effect size (0.01) at 30 days after treatment compared with

sham.(352) In addition to issues with generalizability, differences in baseline headaches occurred in the active treatment group, which further confounds these results.

Adverse events were narrowly reported. Hodaj et al. (2022) commented that there were "no serious side effects to report."(354) In the SR by Shirahige et al. (2016), the authors found minimal unwanted side effects of sleepiness (OR: 1.32) and headache (OR: 0.48) compared with sham across the four RCTs, but the differences between groups were not statistically significant.(356) An additional NMA included in the 2020 VA/DoD Headache CPG contributes to the evidence base for this recommendation.(357)

Patient preferences are likely to vary largely regarding this treatment. Although the patient focus group expressed a desire for a mix of pharmacologic and non-pharmacologic treatment options, some people do not prefer the physical sensation of electrical stimulation and might not wish to engage in the typically intensive protocols. Resource considerations include provider training on placing electrodes, administering the treatment, and understanding the significant contraindications to the use of this technology. Given these considerations, tDCS is likely unavailable outside specialty settings, which presents possible equity issues for individuals in deployed or highly rural settings. Although the Work Group found home products available for purchase, tDCS is not currently FDA cleared as a medical device. Transcranial direct current stimulation is inadvisable outside a trained specialist's guidance, thus affecting the feasibility of use for the treatment of migraines. Subgroup considerations include those with any of the many contraindications to the use of this device.

The Work Group systematically reviewed evidence related to this recommendation (337-339, 341, 342, 344-348, 350-355) and considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG.(340, 343, 349, 356, 357) Therefore, it is categorized as *Reviewed, New-replaced*. For external combined occipital and trigeminal neurostimulation system, SON stimulation, and tDCS, the Work Group's confidence in the quality of the evidence was very low. For n-VNS, remote electrical neurostimulation, and rTMS, the confidence in the quality of the evidence was low. The body of evidence had some limitations, including that studies funded by the device company also had an author or authors serving on the medical advisory board of the device company itself. Additional limitations included inconsistent outcomes for studies assessing acute migraine treatment and small sample sizes for studies assessing migraine prevention. (341, 342) In addition, variation occurred in the type of VNS device used and in treatment protocols.(337-339) For external combined occipital trigeminal neurostimulation system, n-VNS, rTMS, SON stimulation, and tDCS, the inconsistent benefits were balanced with the low risk of AEs or harm. However, in the case of external combined occipital and trigeminal neurostimulation system, for certain subgroups (i.e., those with contraindicated conditions, physical or cognitive impairment), the Work Group determined that the burdens slightly outweighed the benefits. The benefits of remote electrical neurostimulation for improving pain slightly outweighed the

potential burdens. Patient values and preferences varied largely because some patients prefer non-pharmacologic treatment, although others might have concerns about being tracked through the device's cloud interface, would not tolerate the stimulation, or might lack a smart device or technological literacy. Thus, the Work Group made the following recommendation: There is insufficient evidence to recommend for or against any form of neuromodulation for the treatment and/or prevention of migraine:

- Non-invasive vagus nerve stimulation
- Supraorbital, or external trigeminal, nerve stimulation
- Remote electrical neurostimulation
- External combined occipital and trigeminal neurostimulation
- Repetitive transcranial magnetic stimulation
- Transcranial direct current stimulation

E. Non-pharmacologic Therapy

Recommendation

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)

Discussion

The Work Group reviewed studies on the management of PTH. Overall, the evidence was determined to be of very-low quality, with insufficient evidence to recommend for or against choosing a specific treatment strategy for acute, chronic, or preventive management of PTH. The reviewed studies included two RCTs focusing on acute management and three RCTs on persistent or chronic forms of PTH. The RCTs included evidence from IV analgesics,(358) antiemetic and antihistamine combinations, (359) onabotulinumtoxinA injections,(360) osteopathic manipulation,(361) and neuromodulation.(350) Two RCTs evaluated acute PTH (358, 359) and three RCTs evaluated persistent PTH.(350, 360, 361) Evidence from one RCT (n=160) suggests no difference in headache days 1 week after discharge following IV metoclopramide plus diphenhydramine drip over placebo in patients with acute PTH treated in the ED.(359) Although not a critical outcome, it should be noted that only 10% of the individuals in the treatment group required rescue medication while in the ED before being discharged compared with 90% of the placebo group.(359) A second RCT on acute PTH (n=105) compared IV doses of paracetamol (15mg per kg) with morphine (0.1mg per kg) and ketorolac (30 mg per kg) at 15 and 30 minutes.(358) Evidence from the study suggests a greater reduction in headache severity (based on VAS) from paracetamol compared with morphine and ketorolac at 15 and 30 minutes but no difference between the medications 1 hour after treatment.(358) Both Friedman et al. (2021) (n=160) and Azimi et al. (2022) (n=105) included fairly large sample sizes, but overall they were rated as

low to very low quality of evidence because of serious or very serious study limitations and imprecision.(358, 359) Three RCTs provided evidence regarding therapies for persistent PTH in outpatient settings.(350, 360, 361)

Overall, findings were mixed. More consistent results were found from very low–quality trials evaluating onabotulinumtoxinA (360) and osteopathic manipulative treatment (OMT) (361) than the RCT evaluating neuromodulation.(350) In Zirovich et al. (2021) (n=14) compared onabotulinumtoxinA with placebo and found that the number of headaches per week (2.24 versus 0.16) and the mean decrease in pain intensity (0.06 versus 0.04) were significantly improved over a 16-week period.(360) However, ROB and serious imprecision were noted because of the small sample size (n=14) in the treatment group. Furthermore, the study was determined to have very serious imprecision and serious limitations regarding ROB.(360) In a small RCT (n=10), OMT compared with baseline or TAU OMT was reported to decrease pain severity from baseline, but this study included no comparators and was determined to have very serious limitations and imprecision.(361) Stilling et al. (2020) examined the use of repetitive transcranial magnetic stimulation (rTMS) compared with sham, assessing headache outcomes of change in headache severity, function (HIT-6), and QoL at baseline and 1 month post treatment.(350) Evidence from this RCT suggests rTMS resulted in a greater reduction in headache severity compared with sham therapy after 1 month of treatment.(350) However, the quality of the trial was determined to be poor, and no differences were found regarding functioning or QoL between the groups.

The evidence reviewed included both pharmacologic and non-pharmacologic therapies. Patient preferences vary regarding this treatment. Although some patients might not want to take medication or receive an injection, others from the patient focus group found that the combination of oral medications and other types of therapies were more effective in managing pain. Osteopathic manipulative treatment, rTMS, and onabotulinumtoxinA involve a significant resource burden. Osteopathic manipulative treatment involves an opportunity cost because a trained provider is needed to provide the treatment; rTMS is associated with costs related to multiple in-person therapy sessions requiring a medical device and trained personnel; and onabotulinumtoxinA, although less expensive and more available than the previously mentioned options, requires trained personnel to deliver the relatively expensive series of injections to the patient.

Recognizing patient desire for multimodal treatment options, future studies should evaluate whether specific treatment combinations are more effective for PTH. Additionally, future studies should focus on addressing whether PTH treatment should correspond with the type of primary headache the patient's PTH most resembles or whether subtle differences exist that the provider should consider based on the mechanism of injury. Additionally, some treatments that might be acceptable for persistent PTH might be unbeneficial or inappropriate following the head trauma in the acute phase of PTH (e.g., OMT, onabotulinumtoxinA injections). Given the significant

number of Veterans and active duty Service members with a PTH diagnosis, desperate need exists to determine safe and effective recommendations for these populations. Trials focusing on patients with PTH have poor enrollment and terminate early. Multicenter trials at key locations within DoD and VA healthcare systems might be necessary to adequately assess critical outcomes related to PTH.

The Work Group systematically reviewed evidence related to this recommendation. (350, 358-361) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including small sample size and effect size,(350, 360, 361) confounders in the analysis,(350, 358-361) high attrition,(360) lack of blinding detail,(361) and absence of critical outcomes.(350, 358, 361) The benefits of pharmacologic and nonpharmacologic interventions to reduce headaches and headaches per week, or headache pain severity and use of rescue medication were balanced with the potential harm of AEs, which was small. Patient values and preferences varied because some patients prefer less invasive treatments, such as medications, OMT, and rTMS, versus injections. Thus, the Work Group made the following recommendation: There is insufficient evidence to recommend for or against choosing a specific treatment strategy for posttraumatic headache.

Recommendation

50. There is insufficient evidence to recommend for or against any specific medication over another for the acute treatment of migraine.
(Neither for nor against | Reviewed, New-added)

Discussion

The Work Group reviewed the available evidence for the comparative effectiveness of agents for the acute treatment of migraine. Overall, the evidence retrieved either suggested no difference between the compared agents or showed a small difference with a very low quality of evidence. Most reviewed studies compared agents within a particular class, such as comparing one antiemetic with another. The individual studies tended to be small and the studies with a moderate quality of evidence failed to show a difference between the efficacy of the agents evaluated.

Hodgson et al. (2021) found no difference between chlorpromazine and prochlorperazine in headache severity, photophobia, or phonophobia at 2 hours with moderate-quality evidence.(362) An NMA of six RCTs by Hong et al. (2020) suggested no difference between rimegepant and ubrogepant for the outcomes of pain freedom at 2 hours, freedom from nausea, freedom from photophobia, or freedom from phonophobia at 2 hours, with low-quality evidence.(363) An RCT by Friedman et al. (2020) (n=99) found no difference between GON block and IV metoclopramide for the outcomes of pain freedom and pain relief at 2 hours.(364) Kandil et al. (2021), another RCT (n=71), suggested no difference among IV magnesium, IV prochlorperazine, and

IV metoclopramide for pain at 2 hours.(273) Nurathirah et al. (2022), an SR comprising up to three RCTs, depending on the outcome queried, and Soltani et al. (2021) suggested no difference among IV ketorolac, IV metoclopramide, IV chlorpromazine, and IV prochlorperazine for any critical outcomes related to efficacy for migraine.(365, 366) Nurathirah et al. (2022) also included a very small RCT (n=29) that showed a benefit of ketorolac over sumatriptan for pain intensity at 1 hour with very low–quality evidence.(365) Further, the same SR also evaluated one RCT that suggested benefit of ketorolac over sodium valproate for pain intensity at 1 hour with a low quality of evidence and one RCT that suggested no difference between ketorolac and diclofenac for frequency of AEs at 1 hour in individuals with migraine.(365)

Overall, the quality of evidence for this topic was very low. The SRs identified very few RCTs, which tended to be small and had methodological flaws, limiting the ability to identify differences between treatments. Most of these studies included IV treatments typically used in ED or infusion centers and might be inapplicable to most patients with migraine. The only comparison study identified on newer oral agents was an NMA that found no difference between rimegepant and ubrogepant.(363)

Patient preferences vary little regarding this treatment. The harms and burdens could not be differentiated in this group of treatments because there was little difference among treatment efficacies. Further, other implications were not a large factor considered in the Work Group's development of this recommendation because it covers a very broad group of medications that range in delivery route, care setting, and cost.

The Work Group systematically reviewed evidence related to this recommendation. (273, 362-366) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's overall confidence in the quality of the evidence was very low. The body of evidence had some limitations, including small sample sizes, limited scope of interventions, and lack of differences in most drugs evaluated. There were individual studies that had higher strength of evidence, but they were either well-designed studies that showed no difference in the drugs being evaluated or small trials showing benefit of one agent over another. These interventions when compared with one another failed to show significant benefit of any one agent over any other and were felt to be balanced with the potential harm. Patient values and preferences were similar because the Work Group felt that a significant difference was identified among these interventions. Thus, the Work Group made the following recommendation: There is insufficient evidence to recommend for or against any specific medication over another for the acute treatment of migraine.

Recommendation

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)

Discussion

The comparative evidence for preventive pharmacotherapies is inconsistent, and the current body of evidence does not support the use of any one of the studied preventive pharmacotherapies over another. The systematic evidence review included 11 comparative studies in migraine prevention and one comparative SR in cluster headache prevention. Overall, the quality of the evidence was very low. One RCT comparing topiramate to propranolol for migraine prevention by Mohammadianinejad et al. (2021) did not assess the prespecified critical outcomes for migraine preventive therapies.(367) One RCT by Li et al. (2021) compared topiramate with flunarizine, the latter being a calcium channel blocker unavailable in the U.S.(368)

Migraine Headache

For migraine preventive therapies, some studies compared agents within the therapeutic class. One SR by Wang et al. (2020) and one RCT by Hedayat et al. (2022) compared venlafaxine with other antidepressants, including an SSRI (escitalopram in Wang et al. [2020]) and a TCA (amitriptyline in both studies).(114, 369) Both studies found no difference among these agents in monthly migraine days. Other studies compared across classes. One RCT by Dakhale et al. (2019) compared sodium valproate with propranolol; one RCT by Chowdhury et al. (2022) compared topiramate with propranolol; and one NMA by Overeem et al. (2021) compared all currently available CGRP targeting antibodies with topiramate.(165, 370, 371) Yang et al. (2021) published the most robust NMA comparing all currently available CGRP targeting antibodies, topiramate, and onabotulinumtoxinA.(140) All these studies showed no difference in the head-to-head comparison for the critical outcome of change in monthly migraine or headache days.

Three RCTs suggested superiority of one agent over another for migraine prevention; however, each had either conflicting results with the other studies or significant study design flaws that limited their clinical applicability, or both. Rothrock et al. (2019) compared topiramate with onabotulinumtoxinA and found onabotulinumtoxinA to be superior in the reduction of monthly headache days in patients with chronic migraine.(372) This study was significantly limited by the allowance for patients who did not tolerate topiramate before week 36 to switch to the onabotulinumtoxinA group (which consisted of 80% of the topiramate group). Furthermore, the Yang et al. (2021) NMA also looked at this comparison pair and found no difference in monthly migraine days between the two.(140) The second RCT by Reuter et al. (2022) favored erenumab

over topiramate in the reduction of monthly migraine days.(373) This finding conflicted with the results of the Yang et al. (2021) SR, which demonstrated no difference between the two.(140) Lastly, an RCT by Jyothi et al. (2022) suggested that amitriptyline 10 mg daily was superior to propranolol 20 mg daily in the reduction of monthly headache days in episodic migraine, but both doses studied were subtherapeutic for migraine prevention.(374)

Cluster Headache

One NMA for cluster headache prevention by Pompilio et al. (2021) assessed the difference between verapamil and galcanezumab.(245) Although the surface under the cumulative ranking for probability of effectiveness was higher for galcanazeumab than for verapamil (see Recommendation 28) among those with episodic cluster headache, no statistically significant difference between these two agents in number of cluster headache episodes was found. As a single SR that did include some data from single arm studies, the critical efficacy outcome could be assessed only by RCTs, which were limited by their small sample size.(245)

Because comparative efficacy evidence is either conflicting or demonstrates no difference between preventive pharmacotherapies for headache, other characteristics such as administration, monitoring, and safety should be individually considered to find the best balance of risks versus harms for the individual. The patient focus group also reported that varied combinations of therapy worked for them and noted a preference to discuss therapy options with their provider.

The Work Group systematically reviewed evidence related to this recommendation. (114, 140, 165, 245, 368-374) Therefore, it is categorized as *Reviewed, New-added*. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had several limitations, including small sample size, conflicting critical outcomes, and inconsistent dosing between studies and subtherapeutic dosing. Nevertheless, the Work Group felt that discussing the lack of comparative evidence supporting one preventive therapy over another was important. Finding the right balance of benefits versus risks and harms should be individualized to the patient's specific needs. However, the Work Group determined that the benefits were generally balanced with potential harms and burdens because all the drugs have some level of effectiveness. Patient values and preferences will differ for each individual pharmacotherapy option; however, the values and preferences were very similar in not using a preset algorithmic approach to choosing treatment options. The patient focus group consistently mentioned interest in an individualized approach to treatment. In considering such an approach, health care providers should also discuss the risks and benefits of each pharmacotherapy while considering comorbidities and contraindications. Thus, the Work Group made the following recommendation: 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.

Recommendation

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)

Discussion

This recommendation is an expansion of the 2020 VA/DoD Headache CPG which discussed the combination of pharmacotherapies for the prevention of chronic migraine. The 2020 VA/DoD Headache CPG recommendation reviewed three RCTs and determined that insufficient evidence existed to recommend for or against any specific combination of medical therapy.(375-377) In this iteration, the Work Group broadened the analysis to include combinations of any therapy (i.e., combining pharmacotherapies, enhancing pharmacotherapy with behavioral interventions, neuromodulation, interventional procedures, CIH) for the prevention of any headache type. The Work Group reviewed six RCTs published since 2019 that evaluated combination therapies in addition to reviewing the evidence from the 2020 VA/DoD Headache CPG.(271, 378-382)

Chowdhury et al. (2022) (n=121) evaluated the combination of topiramate and GON block (with lidocaine in isolation versus lidocaine with methylprednisolone) versus topiramate monotherapy for reduction of monthly migraine days.(271) Patients were divided into three groups, and the results found that treatment with combination therapy, either with ($p=0.003$) or without ($p<0.001$) methylprednisolone, had a reduction in monthly migraine days compared with monotherapy. The combination of topiramate with methylprednisolone plus lidocaine had a reduction from 12.9 to 4.0 monthly migraine days, and topiramate plus lidocaine had an improvement from 15 to 4.2 days. In comparison, the topiramate monotherapy group saw an improvement from 14.1 to 6.7 migraine days per month. Neither patients nor assessors were blinded in this study. This RCT was the only one reviewing this combination; thus, although benefit was suggested, insufficient evidence was available to recommend in its favor.(271)

The use of atorvastatin in combination with another oral therapy was evaluated in two different studies. Ganji et al. (2021) (n=68) was a prospective, randomized triple-blinded study evaluating the combination of sodium valproate 500 mg alone (with placebo) versus in combination with atorvastatin 20 mg.(378) The study evaluated the frequency of migraine attack. The combination therapy showed a reduction in the primary outcome compared with control ($p=0.0001$). Sherafat et al. (2022) looked at atorvastatin 40 mg plus nortriptyline 25 mg versus nortriptyline with placebo.(382) The study (n=142) favored combination therapy for reduction in headache frequency ($p=0.007$) at 24 weeks (but no statistical difference at 4 and 14 weeks). QoL favored combination therapy at 14 and 24 weeks ($p=0.001$). Notably, of the 142 enrolled participants allocated into treatment groups, only 68 completed the study, and an intention to treat analysis was not performed.

An RCT (n=83) published by Kalita et al. (2021) suggested benefit of rTMS plus amitriptyline over rTMS monotherapy.(380) The rTMS therapy was 10 hertz over the left frontal cortex with 60 pulses per session and three sessions per month. The primary outcome was the percentage of patients with more than 50% reduction in monthly headache days at 3 months and favored the combination group (p<0.001). In this study, more than one-half of the patients in the monotherapy group switched to combination therapy, and there was no placebo group.

Jiang et al. (2019) compared flunarizine 5 mg daily monotherapy versus flunarizine 5 mg in combination with transcutaneous supraorbital nerve stimulation (n=154),(379) delivered at 20 minutes daily. Only patients who completed two-thirds of the treatment time were included at the end of the study. The results favored combination therapy for reduction in monthly migraine days (p=0.041) and for the percentage of patients with at least 50% reduction in monthly migraine days (p=0.001) at 3 months. Notably, flunarizine is unavailable in the U.S.

Finally, Mehta et al. (2021) (n=61) allocated patients to usual pharmacotherapy versus medication plus yoga or physical therapy.(381) Headache frequency at 3 months favored the combination of yoga or physical therapy with pharmacotherapy (p=0.0043), but no difference was found in HIT-6 scores at 3 months. The study relied on patient self-reporting of treatment adherence and had no blinding of outcome assessors.

Overall, confidence in the quality of the evidence was very low because of low sample sizes, lack of clarity regarding randomization, allocation concealment, blinding of different parties, high attrition and patient crossover rates, and lack of intention to treat analysis.(271, 378-382) Each study evaluated a different combination, so replicated trials would be required to confirm the treatment benefits.

The Work Group determined that harms slightly outweighed benefits because of poor-quality evidence suggesting benefit with known side effects and burdens to treatment. Although atorvastatin, topiramate, propranolol, and amitriptyline are frequently prescribed, they have substantial side-effect burden without clear data suggesting combination therapy results in further benefit. Additionally, therapies such as yoga, neurostimulation, magnetic stimulation, and nerve blocks can be burdensome because of the time commitment and discomfort of the procedure or treatment.

Some variability occurs in patient preferences in this case because of the number of different therapy types encompassed in this recommendation. Depending on the type of combination therapy involved, patients might have an aversion to needles, prefer to avoid additional medications, or lack available time for treatments. Certain types of therapy, such as procedural and stimulation devices, might also be unavailable to all patients. Importantly, the patient focus group noted the importance of combination therapy in their treatment, highlighting the need for further research in this area.

The Work Group systematically reviewed evidence related to this recommendation (271, 378-382) and considered the assessment of the evidence put forth in the 2020 VA/DoD Headache CPG.(375-377) Therefore, it is categorized as *Reviewed, New-replaced*. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including small sample size, high attrition, unblinded groups, and lack of intention to treat analysis.(271, 375-382) The harms of combination therapy slightly outweighed the potential benefit of reduction in number of headache days and percentage of patients with greater than 50% improvement in headache frequency. Patient values and preferences varied because multiple treatment modalities might be overwhelming to patients who want to limit medication intake or have limited time to engage in non-pharmacologic therapies. Thus, the Work Group made the following recommendation: There is insufficient evidence to recommend for or against any specific combination of therapies for the prevention of headache.

X. Research Priorities

During the development of the 2023 VA/DoD Headache CPG, the Work Group identified topics needing additional research, including areas requiring stronger evidence to support current recommendations and research exploring new areas to guide future CPGs.

The Work Group identified areas in which well-designed studies, preferably in the population of interest (i.e., active duty Service members, Veterans), are needed. These areas are ones that require stronger evidence to support current recommendations as well as those that require evidence to inform new recommendations for future CPGs. Overall, themes noted across recommendations are that a majority of acute and prevention treatment studies focused on migraine followed by TTH. A smaller body of science related to interventions for PTH remains, as evident by the lack of FDA-approved and cleared acute or preventive treatments for this important headache condition.

Additionally, understanding health disparities as they relate to headache care has largely been unexplored. Men are historically underrepresented in headache research, including clinical trials and epidemiological work. Marginalized and underserved groups also seem to bear disproportionate burden of migraine, including Hispanics and Latinos, people with low socioeconomic status, and persons living in rural areas.(43-45) These groups are underrepresented in headache and migraine research. Since the 2020 VA/DoD Headache CPG was published, evidence has been emerging regarding the efficacy of select pharmacotherapies in patient groups historically poorly represented in headache and migraine trials; however, the approach to these studies was to examine medications within different countries (see Recommendation 5).

The unit of randomization for clinical trials examined for this CPG has almost, if not exclusively, been at the patient level (e.g., a patient is randomized to one drug, perhaps at varying doses, compared with placebo). Different trial designs exist where the unit of randomization can occur at the clinic, medical center, or community level. Pragmatic

trials are intended to test the effectiveness (rather than efficacy) of an intervention in real-world, clinical practice settings, rather than whether an intervention works in ideal situations.(383) These types of study designs might better address whether pharmacologic and nonpharmacologic interventions work in real-life settings.

Given the explosion of acute and preventive headache therapeutics in recent years, more comparative effectiveness studies are needed between combinations of pharmacologic and non-pharmacologic modalities, including trials where one type of therapy is compared with the same type in combination with an adjunct therapy (e.g., in migraine prevention, CGRP-inhibitor compared with a CGRP-inhibitor and behavioral intervention).

Specific headache types warrant more research. Additional studies into PTH and MOH should consider the possibility of combinations of therapies. Studies where treatment is tailored to the PTH phenotype (e.g., migrainous) should be pursued.

When considering more specific recommendations for research priorities, the Work Group identified the following additional important topics for future research.

A. Pharmacotherapies

Broadly, future research should be conducted on the potential roles for older pharmacotherapies in the management of headache diseases other than migraine (e.g., role of ARBs in PTH) as well as additional comparative effectiveness clinical trials. Much of the comparative effectiveness data that informed the comparative effectiveness recommendations for acute and preventive migraine therapies was drawn from NMAs rather than RCTs. Other areas of potential research interest include evaluating specific abortive pharmacotherapies for situational prophylaxis (e.g., menstrual migraine, periods of increased duress). Also, examination of longer-term safety data of newer abortive and preventive therapies when used among individuals of childbearing age and those already pregnant should be continued.

B. Injections, Infusions, and Procedures

The Work Group identified heterogeneity among protocols and treatment regimens across this group of interventions. For example, studies examining GON block for acute treatment and prevention of migraine noted various combinations and doses of steroids and anesthetics used in the injection. Standardization across protocols as well as dose finding studies are important research priorities.(384)

C. Neuromodulation

Another priority is comparative effectiveness studies of neuromodulation devices to one another and to other acute and preventive therapies. One post-hoc analysis comparing REN to standard of care acute pharmacotherapies for chronic migraine found no statistically significant differences between REN and standard pharmacotherapies for obtaining single-treatment pain relief, single-treatment pain freedom, or pain freedom

consistency.(385) Another research priority includes testing neuromodulation in PTH as well as studying an approach that combines treatment of headache outcomes along with outcomes pertinent to co-occurring conditions that can be treated simultaneously with a single neuromodulatory device (e.g., non-invasive vagal nerve stimulation among patients with PTH and PTSD compared with PTH without PTSD).

D. Behavioral Interventions

Although the systematic evidence review carried out for this CPG update did not capture evidence published before the search window, the Work Group acknowledges that behavioral interventions (e.g., biofeedback, heart rate variability monitoring, CBT, mindfulness-based therapies, and progressive muscle relaxation) are historically accepted as standard practice in the treatment of headache, and additional research is less likely to be published because of their well-known effectiveness in addressing headache. Future research priorities might include the need for high-quality, randomized, blinded, controlled trials assessing the

- Impact of behavioral interventions on disease activity (e.g., headache frequency, intensity, duration), acute and preventive medication use, QoL and disability, and other important outcomes, such as sleep and mental health symptoms;
- Effectiveness of behavioral interventions as standalone or combined therapies (e.g., PMR alone versus in combination with pharmacotherapy or a component of other behavioral interventions, such as CBT or biofeedback);
- Potential differences in behavioral treatment modality used (e.g., telehealth versus in-person delivery, individual versus group settings);
- Impact of behavioral interventions as preventive or acute management treatment or both; and
- “Dose” or required length of the intervention and the sustainability of desired outcomes and maintenance of treatment benefits over time.

E. Rehabilitation Approaches

More research is needed on the impact of rehabilitation therapies and the multiple modalities under that umbrella on TTH, migraine, and other types of headaches because these treatments present an opportunity for non-pharmacologic intervention, which might be even more true among patients with headaches and comorbidities such as TBI and lower back pain.

F. Complementary and Integrative Health (Including Nutraceuticals)

Despite the popularity of various complementary and integrative treatments (e.g., acupuncture, dry needling, yoga), trials evaluating efficacy are minimal and have serious methodologic flaws. Future research priorities might include the need for high-

quality, randomized, blinded, controlled trials that operationalize the type of technique used and the comparator group assessed, such as those that assess the

- Impact of complementary and integrative treatments on disease activity (e.g., headache frequency, intensity, duration), acute and preventive medication use, QoL and disability, and other important outcomes, such as sleep and mental health symptoms;
- Effectiveness of acupuncture versus an active control (i.e., not with sham), such as dry needling;
- Effects of full body acupuncture compared with auricular acupuncture for various headache disorders;
- Impact of CIH modalities as preventive or acute management treatment or both;
- Dose or required length of the intervention and the sustainability of desired outcomes and maintenance of treatment benefits over time for acupuncture, dry needling, and yoga studies;
- Safety and effectiveness of self-directed lifestyle modification and use of an elimination diet; and
- Effectiveness and tolerability of peppermint oil or extracts, CoQ10, feverfew, melatonin, omega-3, vitamin B2, or vitamin B6 for the prevention and treatment of headache and vitamin B2 in pregnant patients with headache.

Appendix A: Guideline Development Methodology

A. Developing Key Questions to Guide the Systematic Evidence Review

To guide this CPG's systematic evidence review, the Work Group drafted 12 KQs on clinical topics of the highest priority for the VA and DoD populations. The KQs followed the population, intervention, comparison, outcome, timing, and setting (PICOTS) framework, as established by the Agency for Healthcare Research and Quality (AHRQ). Table A-1 lists and describes the PICOTS elements.

Table A-1. PICOTS (386)

PICOTS Element	Description
Population or Patients	Patients of interest. It includes the condition or conditions, populations or sub-populations, disease severity or stage, co-occurring conditions and other patient characteristics or demographics.
Intervention or Exposure	Treatment (e.g., drug, surgery, lifestyle changes), approach (e.g., doses, frequency, methods of administering treatments), or diagnostic or screening test or both used with the patient or population.
Comparator	Treatment or treatments (e.g., placebo, different drugs) or approach or approaches (e.g., different dose, different frequency, standard of care) being compared with the intervention or exposure of interest described above.
Outcomes	Results of interest (e.g., mortality, morbidity, QoL, complications). Outcomes can include short, intermediate, and long-term outcomes.
Timing, if Applicable	Duration or follow-up of interest for the particular patient intervention and outcome to occur (or not occur).
Setting, if Applicable	Setting or context of interest. Setting can be a location (e.g., primary, specialty, inpatient care) or a type of practice.

Abbreviations: PICOTS: population, intervention, comparison, outcome, timing, and setting

Because of resource constraints, all KQs of interest to the Work Group could not be included in the systematic evidence review. Thus, the Work Group selected the 12 highest priority KQs for inclusion (see Table A-2).

Using the GRADE approach, the Work Group rated each outcome on a 1-9 scale (7-9, critical for decision making; 4-6, important, but not critical, for decision making; and 1-3, of limited importance for decision making). Critical and important outcomes were included in the evidence review (see Outcomes); however, only critical outcomes were used to determine the overall quality of evidence (see Determining Recommendation Strength and Direction).

a. Populations

Key Question	Population
1, 2, 4, 5	Adults with the primary headache disorders of: a) cluster headache, b) migraine, and c) tension-type headache
3	Adults diagnosed with posttraumatic headache
6-11	Adults with headache
12	Adults with suspected/confirmed medication overuse headache

b. Interventions

Key Question	Intervention(s)
1	• Angiotensin-converting Enzyme (ACE) Inhibitors ♦ Benazepril ♦ Captopril ♦ Enalapril ♦ Fosinopril ♦ Lisinopril ♦ Moexipril ♦ Perindopril ♦ Quinapril ♦ Ramipril ♦ Trandolapril • Angiotensin II Receptor Blockers (ARBs) ♦ Azilsartan ♦ Candesartan ♦ Eprosartan ♦ Irbesartan ♦ Losartan ♦ Olmesartan ♦ Telmisartan ♦ Valsartan • Antidepressants ♦ Amitriptyline ♦ Citalopram ♦ Desipramine ♦ Doxepin ♦ Duloxetine ♦ Escitalopram ♦ Fluoxetine ♦ Fluvoxamine ♦ Imipramine ♦ Mirtazapine ♦ Nortriptyline ♦ Paroxetine ♦ Protriptyline ♦ Sertraline ♦ SNRIs ♦ SSRIs ♦ Tricyclic antidepressants ♦ Venlafaxine • Antiepileptic Agents ♦ Divalproex Sodium ♦ Gabapentin ♦ Levetiracetam ♦ Lamotrigine ♦ Pregabalin ♦ Sodium Valproate ♦ Topiramate ♦ Zonisamide • Beta-Blockers ♦ Atenolol ♦ Metoprolol ♦ Nadolol ♦ Propranolol ♦ Timolol

Key Question	Intervention(s)
1 (cont.)	• Non-beta Blocker Antihypertensives ♦ Candesartan ♦ Flunarizine ♦ Lisinopril ♦ Nifedipine ♦ Nimodipine • Verapamil • Botulinum Toxins ♦ AbobotulinumtoxinA(Dysport ®) ♦ IncobotulinumtoxinA (Xeomin ®) ♦ OnabotulinumtoxinA (Botox ®) ♦ RimabotulinumtoxinB (myobloc) • CGRP Inhibitors ♦ Atogepant ♦ Eptinezumab-jjmr ♦ Erenumab-aooe ♦ Fremanezumab-vfrm ♦ Galcanezumab-gnlm ♦ Rimegepant • Long-acting Dihydropyridine (DHP) Calcium Channel Blockers (CCBs) ♦ Amlodipine ♦ Felodipine ♦ Nicardipine SR ♦ Nifedipine SR (XL, CC) ♦ Nisoldipine ER • Nerve blocks ♦ Auriculotemporal ♦ Cervical Epidural ♦ Cervical Medial Branch ♦ Occipital ♦ Sphenopalatine ♦ Stellate Ganglion Block ♦ Supraorbital • Other ♦ Cyproheptadine ♦ Memantine
2	• See list of medications under KQ 1 above
3	• Pharmacologic and nonpharmacologic interventions
4	• Antiemetic Agents ♦ Chlorpromazine ♦ Ondansetron ♦ Prochlorperazine ♦ Promethazine ♦ Reglan/metoclopramide • Antiepileptic Agent: Depacon – sodium valproate / valproic acid /divalproex sodium • CGRP Inhibitors ♦ Rimegepant ♦ Ubrogepant • Combination Agents ♦ Acetaminophen / caffeine ♦ Acetaminophen / isometheptene / dichloralphenazone ♦ Aspirin / acetaminophen / caffeine ♦ Butalbital / acetaminophen / caffeine ♦ Butalbital / aspirin / caffeine • IV steroids (SOluMedrol)

Key Question	Intervention(s)
4 (cont.)	• Nerve blocks ♦ Auriculotemporal ♦ Cervical Epidural ♦ Cervical Medial Branch ♦ Occipital ♦ Sphenopalatine ♦ Stellate Ganglion Block ♦ Supraorbital • Occipital or other nerve blocks • Other ♦ Butorphanol *Stadol ♦ Caffeine ♦ Dihydroergotamine ♦ Ergotamine ♦ Intranasal lidocaine ♦ IV magnesium ♦ Ketamine ♦ Opioids o Fioricet o Oxycodone o Percocet o Tramadol o Vicodin ♦ Tizanidine • Over-the-counter Agents ♦ Acetaminophen ♦ Acetaminophen/aspirin/caffeine ♦ Acetaminophen/caffeine • Serotonin 5-HT Receptor Agonists ♦ Almotriptan ♦ Eletriptan ♦ Frovatriptan ♦ Lasmiditan ♦ Naratriptan ♦ Rizatriptan ♦ Sumatriptan ♦ Sumatriptan/naproxen sodium ♦ Zolmitriptan • Simple Analgesics / Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) ♦ Acetaminophen ♦ Aspirin ♦ Celecoxib/Celebrex ♦ Dexketoprofen ♦ Etodolac ♦ Ibuprofen ♦ Indomethacin ♦ Ketorolac Injection ♦ Naproxen ♦ Oral diclofenac (cambia) ♦ Other NSAIDs ♦ Salsalate ♦ Sulindac ♦ Nabumetone ♦ Diflunisal ♦ Ketorolac ♦ Meloxicam ♦ Piroxicam ♦ Choline mg
5	• See list of medications for KQ 4 above
6	• Invasive Neuromodulation ♦ Botulinum toxin ♦ Chemodenervation ♦ Cold laser ♦ Cervical facet injections ♦ Closure of right-to-left cardiac shunt ♦ Greater occipital nerve invasive electrical stimulation ♦ Implanted stimulators

Key Question	Intervention(s)
6 (cont.)	• Invasive Neuromodulation (cont.) ♦ Neurotomy procedures o Chemical ablation/neurolysis o Cold ablation o Radiofrequency ablation o Radiofrequency stimulation ♦ Pulsed radiofrequency ♦ Trigger point injections
7	• Acupressure • Acupuncture • Battlefield acupuncture (BFA) • Biofeedback including diaphragmatic breathing, guided imagery • Breathing exercises • Combined therapies • Light Therapy • Massage • Meditation • Mindfulness • Progressive muscle relaxation • Qi gong • Relaxation therapy • Stress management • Tai chi • Thermazone • Tinted glasses • Yoga
8	• Behavioral management • Behavioral therapy • Biofeedback including diaphragmatic breathing, guided imagery • CBT • Combined therapy approaches • Desensitizing triggers • MBCT • MBSR (mindfulness-based stress reduction)
9	• Non-invasive neuromodulation ♦ Alpha stimulation ♦ Occipital nerve stimulation ♦ Percutaneous electrical nerve stimulation ♦ Non-invasive vagus nerve stimulation (nVNS; gammaCore) ♦ Remote electrical neuromodulation (REN; Nerivio Migra) ♦ Remote TENS ♦ Single pulse transcranial magnetic stimulation (sTMS; eNeura) ♦ Transcutaneous supraorbital nerve stimulation (t-SNS) o Cefaly o Relivion (t-SNS + ONS) ♦ Transcranial direct current stimulation ♦ Transcranial magnetic stimulation (of the: primary motor cortex – M1, dorsolateral prefrontal cortex and vertex) ♦ Transcutaneous electrical nerve stimulation (TENS) ♦ Transcutaneous occipital nerve stimulation (ONS; Relivion) ♦ Trigeminal nerve stimulation (Cefaly) ♦ Vibrating headbands

Key Question	Intervention(s)
10	• Any medication under KQ 1, in combination with ♦ Behavioral therapy ♦ Biofeedback ♦ CBT/other therapies that use cognitive behavior elements • Any combined therapy approach
11	• Presence of one of the following co-occurring conditions: ♦ Chronic Pain/Chronic Overlapping Pain Conditions (including IBS)/Other chronic pain, including: Fibromyalgia, TMD, Lower back pain, Neck pain, and Arthritis ♦ Mental Health Conditions (Depression/anxiety/stress-related disorders or PTSD/mood disorders) ♦ Sleep disorders ♦ Military Exposures – TBI, Military Sexual Trauma ♦ Vascular Risk Factors (Metabolic Syndrome/Obesity/Diabetes/Hypertension) ♦ Vascular Disease: Cerebrovascular and Cardiovascular Disease
12	Remove 'offending' medication/ withdrawal use or withdrawing and replacing medication

c. Comparators

Key Question	Comparator(s)	
1	• Placebo	• Usual care
2	• Other medications from KQ 1 list	
3	• Placebo	• Usual care
4	• TAU • Waitlist • Placebo	• Active control conditions (e.g., another psychotherapy) (active control conditions or placebo should be prioritized over wait-list/TAU)
5	• Other medications from KQ 4 list	
6	• TAU	• Conservative/outpatient treatment
7	• Pharmacological therapy • Active control	• Sham • Placebo
8	• Pharmacological therapy • Active control	• Sham • Placebo
9	• Placebo • Sham control	• Other approaches to treatment and prevention
10	• Pharmacotherapy intervention only	• Behavioral intervention only
11	• Absence of co-occurring conditions	
12	• No intervention/continue to treat symptomatically	• Add prophylactic treatment

d. Outcomes

KQ	Critical Outcomes(s)	Important Outcomes
1, 2	• Change in headache and migraine days (e.g., change in mean monthly headache days from baseline, change in mean monthly migraine days from baseline, change in number of moderate/severe headache days)	• Adverse events (e.g., serious adverse events, treatment emergent adverse events) • Disability/QoL outcomes (e.g., Activity Impairment in Migraine-Diary, Migraine Interictal Burden Scale [MIBS], MIDAS-A [days], HIT-6, MSQ, MSID, Migraine Physical Function Impact Diary [MPFID], Headache Disability Index [HDI], Headache Scale, SF-36) • Change in acute headache treatment days/abortive medication use from baseline, change in migraine specific medication days from baseline • Conversion from chronic to episodic headache (15-day threshold) • Headache attack intensity/headache intensity (e.g., MIDAS-B [Intensity]) • Responder rates (at different time points) ♦ 50% responder rate ♦ 75% responder rate ♦ 100% responder rate
3	• Change in headache and migraine days (e.g., change in mean monthly headache days from baseline, change in mean monthly migraine days from baseline, change in number of moderate/severe headache days) • Change in acute headache treatment days/abortive medication use from baseline, change in migraine specific medication days from baseline • Time to pain freedom ♦ 2-hours post-treatment • Time to freedom from “most bothersome symptom” (cardinal symptoms of photophobia, phonophobia, nausea/vomiting) ♦ 2-hours post-treatment	• Disability/QoL outcomes (e.g., Activity Impairment in Migraine-Diary, Migraine Interictal Burden Scale [MIBS], MIDAS-A [days], HIT-6, MSQ, MSID, Migraine Physical Function Impact Diary [MPFID], Headache Disability Index [HDI], Headache Scale, SF-36) • Headache/migraine intensity ♦ 2-hours post-treatment • Responder rates (at different time points) ♦ 50% responder rate ♦ 75% responder rate ♦ 100% responder rate
4, 5	• Headache/migraine intensity ♦ 2-hours post-treatment • Time to pain freedom ♦ 2-hours post-treatment • Time to freedom from “most bothersome symptom” (cardinal symptoms of photophobia, phonophobia, nausea/vomiting) ♦ 2-hours post-treatment	• Adverse events (e.g., serious adverse events, treatment emergent adverse events) • Side effects

KQ	Critical Outcomes(s)	Important Outcomes
6	• Headache/migraine intensity ♦ 2-hours post-treatment • Change in headache and migraine days (e.g., change in mean monthly headache days from baseline, change in mean monthly migraine days from baseline, change in number of moderate/severe headache days) • Time to pain freedom ♦ 2-hours post-treatment • Time to freedom from "most bothersome symptom" (cardinal symptoms of photophobia, phonophobia, nausea/vomiting) ♦ 2-hours post-treatment	• Adverse events (e.g., serious adverse events, treatment emergent adverse events) • Change in acute headache treatment days/abortive medication use from baseline, change in migraine specific medication days from baseline • Responder rates (at different time points) ♦ 50% responder rate ♦ 75% responder rate ♦ 100% responder rate
7	• Change in headache and migraine days (e.g., change in mean monthly headache days from baseline, change in mean monthly migraine days from baseline, change in number of moderate/severe headache days) • Disability/QoL outcomes (e.g., Activity Impairment in Migraine-Diary, Migraine Interictal Burden Scale [MIBS], MIDAS-A [days], HIT-6, MSQ, MSID, Migraine Physical Function Impact Diary [MPFID], Headache Disability Index [HDI], Headache Scale, SF-36)	• Change in acute headache treatment days/abortive medication use from baseline, change in migraine specific medication days from baseline • Conversion from chronic to episodic headache (15-day threshold) • Mental health measures (e.g., PHQ-9, PCL-5, GAD-7) • Headache/migraine intensity ♦ 2-hours post-treatment • Headache attack intensity/headache intensity (e.g., MIDAS-B [Intensity])
8	• Change in headache and migraine days (e.g., change in mean monthly headache days from baseline, change in mean monthly migraine days from baseline, change in number of moderate/severe headache days) • Disability/QoL outcomes (e.g., Activity Impairment in Migraine-Diary, Migraine Interictal Burden Scale [MIBS], MIDAS-A [days], HIT-6, MSQ, MSID, Migraine Physical Function Impact Diary [MPFID], Headache Disability Index [HDI], Headache Scale, SF-36) • Change in acute headache treatment days/abortive medication use from baseline, change in migraine specific medication days from baseline	• Conversion from chronic to episodic headache (15-day threshold) • Mental health measures (e.g., PHQ-9, PCL-5, GAD-7) • Headache attack intensity/headache intensity (e.g., MIDAS-B [Intensity]) • Responder rates (at different time points) ♦ 50% responder rate ♦ 75% responder rate ♦ 100% responder rate

KQ	Critical Outcomes(s)	Important Outcomes
9	• Change in headache and migraine days (e.g., change in mean monthly headache days from baseline, change in mean monthly migraine days from baseline, change in number of moderate/severe headache days) • Change in acute headache treatment days/abortive medication use from baseline, change in migraine specific medication days from baseline • Adverse events (e.g., serious adverse events, treatment emergent adverse events) • Headache/migraine intensity ♦ 2-hours post-treatment • Time to pain freedom ♦ 2-hours post-treatment • Time to freedom from “most bothersome symptom” (cardinal symptoms of photophobia, phonophobia, nausea/vomiting) ♦ 2-hours post-treatment	• Disability/QoL outcomes (e.g., Activity Impairment in Migraine-Diary, Migraine Interictal Burden Scale [MIBS], MIDAS-A [days], HIT-6, MSQ, MSID, Migraine Physical Function Impact Diary [MPFID], Headache Disability Index [HDI], Headache Scale, SF-36)
10	• Change in headache and migraine days (e.g., change in mean monthly headache days from baseline, change in mean monthly migraine days from baseline, change in number of moderate/severe headache days)	• Disability/QoL outcomes (e.g., Activity Impairment in Migraine-Diary, Migraine Interictal Burden Scale [MIBS], MIDAS-A [days], HIT-6, MSQ, MSID, Migraine Physical Function Impact Diary [MPFID], Headache Disability Index [HDI], Headache Scale, SF-36) • Responder rates (at different time points) ♦ 50% responder rate ♦ 75% responder rate ♦ 100% responder rate • Change in acute headache treatment days/abortive medication use from baseline, change in migraine specific medication days from baseline • Conversion from chronic to episodic headache (15-day threshold) • Headache attack intensity/headache intensity (e.g., MIDAS-B [Intensity]) • Mental health measures (e.g., PHQ-9, PCL-5, GAD-7)

KQ	Critical Outcomes(s)	Important Outcomes
11	• Disability/QoL outcomes (e.g., Activity Impairment in Migraine-Diary, Migraine Interictal Burden Scale [MIBS], MIDAS-A [days], HIT-6, MSQ, MSID, Migraine Physical Function Impact Diary [MPFID], Headache Disability Index [HDI], Headache Scale, SF-36) • Difference in headache and migraine days (e.g., change in mean monthly headache days from baseline, change in mean monthly migraine days from baseline, change in number of moderate/severe headache days) • Headache attack intensity/headache intensity (e.g., MIDAS-B [Intensity])	• Difference in acute headache treatment days/abortive medication use from baseline, change in migraine specific medication days from baseline • Mental health measures (e.g., PHQ-9, PCL-5, GAD-7) • Responder rates (at different time points) ♦ 50% responder rate ♦ 75% responder rate ♦ 100% responder rate • Conversion from chronic to episodic headache (15-day threshold)
12	• Change in headache and migraine days (e.g., change in mean monthly headache days from baseline, change in mean monthly migraine days from baseline, change in number of moderate/severe headache days) • Change in acute headache treatment days/abortive medication use from baseline, change in migraine specific medication days from baseline	• Disability/QoL outcomes (e.g., Activity Impairment in Migraine-Diary, Migraine Interictal Burden Scale [MIBS], MIDAS-A [days], HIT-6, MSQ, MSID, Migraine Physical Function Impact Diary [MPFID], Headache Disability Index [HDI], Headache Scale, SF-36) • Conversion from chronic to episodic headache (15-day threshold) • Responder rates (at different time points) ♦ 50% responder rate ♦ 75% responder rate ♦ 100% responder rate • Headache attack intensity/headache intensity (e.g., MIDAS-B [Intensity]) • Mental health measures (e.g., PHQ-9, PCL-5, GAD-7)

Timing: For KQs 1 and 2, the minimum treatment duration is 2 months. There was no minimum treatment duration or follow-up requirement for any other KQs.

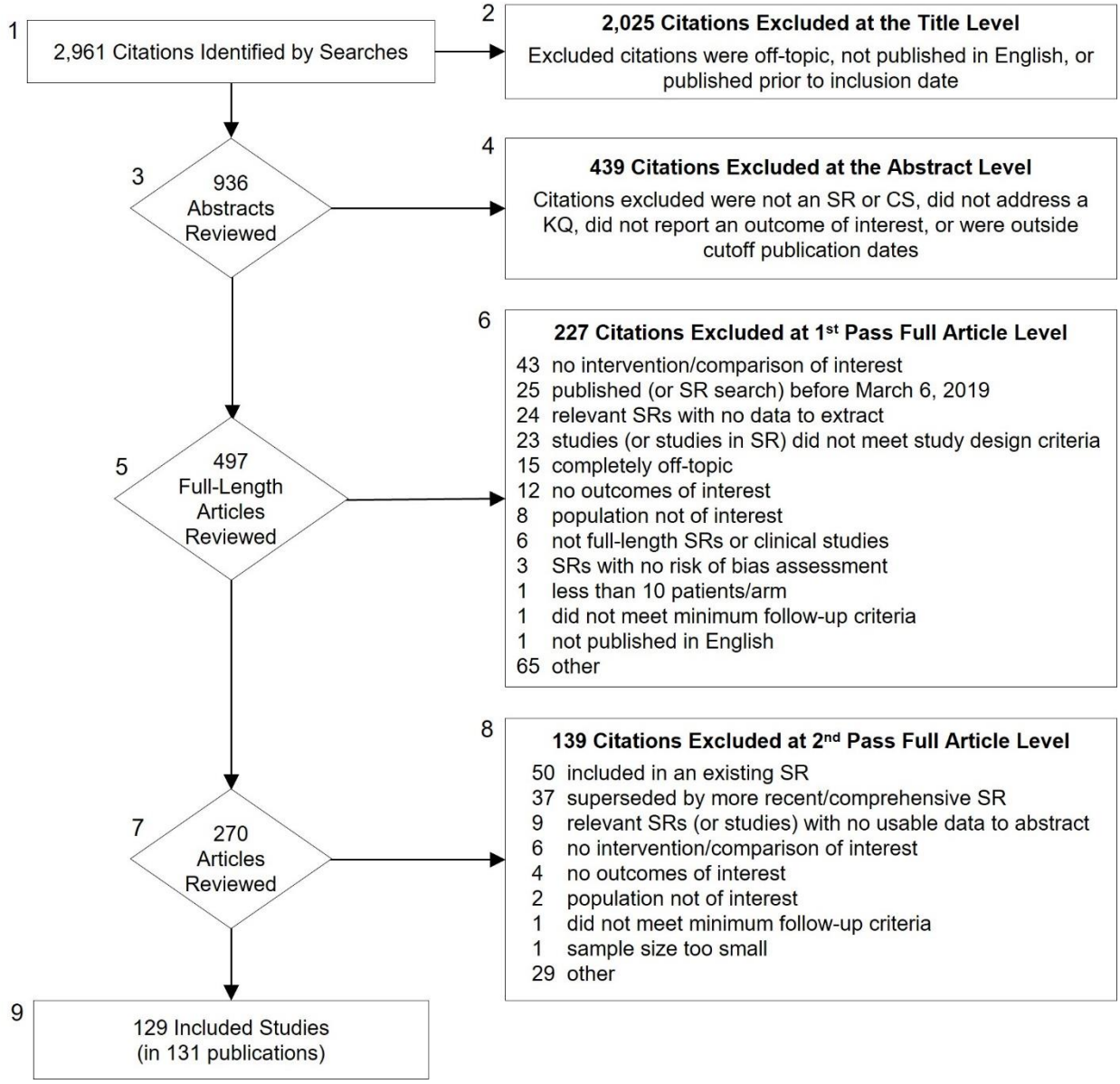
Settings: For KQs 1-6 and 12, any of the following settings (outpatient, clinic, inpatient, emergency department, infusion centers, virtual/telehealth). For KQs 7-11, the relevant settings are outpatient and virtual/telehealth.

B. Conducting the Systematic Review

Based on the Work Group's decisions regarding the CPG's scope, KQs, and PICOTS statements, the Lewin Team produced a systematic evidence review protocol before conducting the review. The protocol detailed the KQs, PICOTS criteria, methodology to be used during the systematic evidence review, and the inclusion and exclusion criteria to be applied to each potential study, including study type and sample size. The Work Group reviewed and approved the protocol.

Figure A-1 below outlines the systematic evidence review's screening process (see also the General Criteria for Inclusion in Systematic Review. In addition, Table A-2 indicates the number of studies that addressed each of the questions.

Figure A-1. Study Flow Diagram



Alternative Text Description of Study Flow Diagram

Figure A-1. Study Flow Diagram is a flow chart with nine labeled boxes linked by arrows that describe the literature review inclusion-exclusion process. Arrows point down to boxes that describe the next literature review step and arrows point right to boxes that

describe the excluded citations at each step (including the reasons for exclusion and the numbers of excluded citations).

1. Box 1: 2,961 Citations Identified by Searches
    a. Right to Box 2: 2,025 Citations Excluded at the Title Level
        i. Citations excluded at this level were off-topic, not published in English, or published prior to inclusion date.
    b. Down to Box 3
2. Box 3: 936 Abstracts Reviewed
    a. Right to Box 4: 439 Citations Excluded at the Abstract Level
        i. Citations excluded at this level were not an SR or CS, did not address a KQ, did not report an outcome of interest, or were outside cutoff publication dates.
    b. Down to Box 5
3. Box 5: 497 Full-Length Articles Reviewed
    a. Right to Box 6: 227 Citations Excluded at 1st Pass Full-Article Level
        i. 43 no intervention/comparison of interest, 25 published (or SR search) before March 6, 2019, 24 relevant SR with no data to extract, 23 studies (or studies in SR) did not meet study design criteria, 15 completely off-topic, 12 no outcomes of interest, 8 population not of interest, 6 not full-length SRs or clinical studies, 3 SRs with no risk of bias assessment, 1 less than 10 patients/arm, 1 did not meet minimum follow-up criteria, 1 not published in English, 65 other.
    b. Down to Box 7
4. Box 7: 270 Articles Reviewed
    a. Right to Box 8: 139 Citations Excluded at 2nd Pass Full-Article Level
        i. 50 included in an existing SR, 37 superseded by more recent/comprehensive SR, 9 relevant SRs or studies with no usable data to abstract, 6 no intervention/comparison of interest, 4 no outcomes of interest, 2 population not of interest, 1 did not meet minimum follow-up criteria, 1 sample size too small, 29 other.
    b. Down to Box 9: 129 included studies (in 131 publications)

Table A-2. Evidence Base for KQs

KQ Number	KQ	Number and Study Type
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 acute, chronic, or preventive management of posttraumatic headache?	5 RCTs
4	What is the safety and effectiveness of acute prescription and non-prescription 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 acute prescription and non-prescription pharmacologic agents in the treatment 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 acute 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 non-invasive 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 CIH) 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)**

Abbreviations: RCT: randomized controlled trial; SR: systematic review

a. General Criteria for Inclusion in Systematic Evidence Review

- RCTs or systematic reviews published on or after March 6, 2019 to August 16, 2022. If multiple systematic reviews addressed a key question, we selected the

most recent and/or comprehensive review. Systematic reviews were supplemented with RCTs published subsequent to the systematic review.

- Studies had to be published in English.
- Publication must have been a full clinical study or systematic review; abstracts alone were not included. Similarly, letters, editorials, and other publications that were not full-length clinical studies were not accepted as evidence.
- Systematic reviews must have searched MEDLINE or EMBASE for eligible publications, performed a risk of bias assessment of included studies, and assessed the quality of evidence using a recognizable rating system, such as GRADE or something compatible (e.g., the Strength of Evidence grading used by the Evidence-based Practice Centers of the Agency for Healthcare Research and Quality). If an existing review did not assess the overall quality of the evidence, evidence from the review must have been reported in a manner that allowed us to judge the overall risk of bias, consistency, directness, and precision of evidence. We did not use an existing review as evidence if we were unable to assess the overall quality of the evidence in the review.
- Study must have enrolled at least 20 patients (10 per study group for treatment studies, 20 total patients for diagnostic studies); Small sample size is associated with increased risk of bias and we downgrade small studies in the GRADE domain of precision: one downgrade for imprecision of a single study with <200 patients per study arm.
- Newer Cochrane reviews already take into account small sample-size in their estimation of risk of bias. In these cases, where sample size has already contributed to the assessment of the evidence, we did not downgrade those data a second time.
- Study must have reported on an outcome of interest.
- Study must have enrolled a patient population in which at least 80% of patients were diagnosed with headache (or a type of headache specified in the KQ) and were age 18 years or older. If the percentage was less than 80%, then data must have been reported separately for this patient subgroup.

b. Key Question Specific Criteria for Inclusion in Systematic Evidence Review

- For KQs 1-10 and 12, acceptable study designs included systematic reviews of randomized controlled trials (RCTs) and individual RCTs not evaluated in systematic reviews If no relevant studies with these designs were found for a given KQ or sub-question, prospective nonrandomized comparative studies were evaluated for inclusion.
- For KQ 11, acceptable study designs included systematic reviews, RCTs or prospective cohort studies that statistically compared outcomes for patients with headache and a co-occurring medical or mental health condition to patients with

headache without the identified co-occurring medical or mental health condition. Large retrospective database studies (500 patients minimum) that performed multivariate statistical analyses of the effect of co-occurring conditions on patient outcomes were also acceptable.

c. Literature Search Strategy

Information regarding the bibliographic databases, date limits, and platform, provider, or both can be found in Table A-3. See Appendix J for additional information on the search strategies, including topic-specific search terms and search strategies.

Table A-3. Bibliographic Database Information

Name		Date Limits	Platform/Provider
Bibliographic Databases	Embase (Excerpta Medica) and MEDLINE	March 6, 2019 through August 16, 2022	Elsevier
	PsycINFO	March 6, 2019 through August 16, 2022	OVID
	PubMed (In-process, Publisher, and PubMedNotMedline records)	January 1, 2016 through May 1, 2022	National Library of Medicine
Gray Literature Resources	Agency for Healthcare Research and Quality (AHRQ)	March 6, 2019 through August 16, 2022	AHRQ

d. Rating the Quality of Individual Studies and the Body of Evidence

The Lewin Team assessed the methodological risk of bias of individual diagnostic, observational, and interventional studies using the U.S. Preventive Services Task Force (USPSTF) method. Each study is assigned a rating of *Good*, *Fair*, or *Poor* based on a set of criteria that vary depending on study design. Detailed lists of criteria and definitions appear in Appendix VI of the USPSTF procedure manual.(387)

Next, the Lewin Team assessed the overall quality of the body of evidence for each critical and important outcome using the GRADE approach. This approach considers the following factors: overall study quality (or overall risk of bias or study limitations), consistency of evidence, directness of evidence, and precision of evidence. The overall quality of the body of evidence is rated as *High*, *Moderate*, *Low*, and *Very Low*.

C. Developing Evidence-Based Recommendations

In consultation with the VA Office of Quality and Patient Safety and the Clinical Quality Improvement Program, Defense Health Agency, the Lewin Team convened a 3.5 day in-person recommendation development meeting from December 12 – 15, 2022, to develop this CPG's evidence-based recommendations. Two weeks before the meeting, the Lewin Team finalized the systematic evidence review and distributed the report to the Work Group; findings were also presented during the recommendation development meeting.

Led by the Champions, the Work Group interpreted the systematic evidence review's findings and developed this CPG's recommendations. The strength and direction of each recommendation were determined by assessing the quality of the overall evidence base, the associated benefits and harms, patient values and preferences, and other implications (see Determining Recommendation Strength and Direction).

a. Determining Recommendation Strength and Direction

Per GRADE, each recommendation's strength and direction is determined by the following four domains.(71) Information on each domain, questions to consider, and the resulting judgment can be found in Table A-4.

1. Confidence in the Quality of the Evidence

Confidence in the quality of the evidence reflects the quality of the body of evidence supporting a recommendation (see Rating the Quality of Individual Studies and the Body of Evidence). The options for this domain include *High*, *Moderate*, *Low*, or *Very Low*. These four ratings are a direct reflection of the GRADE ratings for each relevant critical outcome in the evidence review (see Outcomes). Per GRADE, if the quality of evidence differs across the relevant critical outcomes, the lowest quality of evidence for any of the critical outcomes determines the overall quality of the evidence for a recommendation.(2, 73)

The recommendation strength generally aligns with the confidence in the quality of evidence. For example, *Strong* recommendations are typically supported by *High* or *Moderate* quality evidence. However, GRADE permits *Low* or *Very Low* quality evidence to support a *Strong* recommendation in certain instances (e.g., life-threatening situation).(71)

2. Balance of Desirable and Undesirable Outcomes

The balance of desirable and undesirable outcomes (i.e., benefits and harms) refers to the relative magnitudes or tradeoffs of anticipated benefits (e.g., increased longevity, reduced morbidity, improved QoL, decreased resource use) and harms (e.g., decreased longevity, increased complications, impaired QoL). The options for this domain include *benefits outweigh harms/burdens*, *benefits slightly outweigh harms/burdens*, *benefits and harms/burdens are balanced*, *harms/burdens slightly outweigh benefits*, and *harms/burdens outweigh benefits*. This domain assumes most providers will offer patients an intervention if its advantages exceed the harms. The Work Group's understanding of the benefits and harms associated with the recommendation influenced the recommendation's strength and direction.

3. Patient Values and Preferences

Patient values and preferences is an overarching term that includes patients' perspectives, beliefs, expectations, and goals for health and life as they might apply to the intervention's potential benefits, harms, costs, limitations, and inconvenience. The

options for this domain include *similar values*, *some variation*, and *large variation*. For instance, there might be *some variation* in patient values and preferences for a recommendation on the use of acupuncture because some patients might dislike needles. When patient values seem homogeneous, this domain might increase the recommendation's strength. Alternatively, when patient values seem heterogeneous, this domain might decrease a recommendation's strength. As part of this domain, the Work Group considered the findings from the patient focus group carried out as part of this CPG update (see Appendix D).

4. Other Implications

Other implications encompass the potential consequences or other impacts that might affect the strength or direction of the recommendation. The options for this domain, for example, include resource use, equity, acceptability, feasibility, and subgroup considerations. The following are example implications related to equity and subgroup considerations, respectively: some of the indicated population might be geographically remote from an intervention (e.g., complex radiological equipment); a drug might be contraindicated in a subgroup of patients.

Table A-4. GRADE Evidence to Recommendation Framework

Decision Domain	Questions to Consider	Judgment
Confidence in the quality of the evidence	• Among the designated critical outcomes, what is the lowest quality of relevant evidence? • How likely is further research to change the confidence in the estimate of effect?	• High • Moderate • Low • Very Low
Balance of desirable and undesirable outcomes	• What is the magnitude of the anticipated desirable outcomes? • What is the magnitude of the anticipated undesirable outcomes? • Given the best estimate of typical values and preferences, are you confident that benefits outweigh harms/burdens or vice versa?	• Benefits outweigh harms/ burdens • Benefits slightly outweigh harms/burdens • Benefits and harms/ burdens are balanced • Harms/burdens slightly outweigh benefits • Harms/burdens outweigh benefits
Patient values and preferences	• What are the patients' values and preferences? • Are values and preferences similar across the target population? • Are you confident about typical values and preferences?	• Similar values • Some variation • Large variation

Decision Domain	Questions to Consider	Judgment
Other implications (e.g., resource use, equity, acceptability, feasibility, subgroup considerations)	• What are the costs per resource unit? • Is this intervention generally available? • What is the variability in resource requirements across the target population and settings? • Are the resources worth the expected net benefit from the recommendation? • Is this intervention and its effects worth withdrawing or not allocating resources from other interventions?	Various considerations

b. Recommendation Categorization

A summary of the recommendation categories and definitions is available in Table 4.

1. Categorizing Recommendations with an Updated Review of the Evidence

Reviewed refers to recommendations on topics included in this CPG's systematic evidence review. *Reviewed*, *New-added* recommendations are original, new recommendations (i.e., not included in the previous CPG). These recommendations are based entirely on evidence included in the current CPG's systematic evidence review.

Reviewed, *New-replaced* recommendations were in the previous CPG but revised based on the updated evidence review. These recommendations may have clinically relevant edits. *Reviewed*, *Not changed* recommendations were carried forward from the previous CPG unchanged. *Reviewed*, *Amended* recommendations were carried forward from the previous CPG with a nominal change. This allowed for the recommendation language to reflect GRADE approach and any other not clinically meaningful edits deemed necessary. These recommendations can be based on a combination of evidence included in the current CPG's systematic evidence review and the evidence base that supported the recommendation in the previous CPG.

Reviewed, *Deleted* refers to recommendations from the previous CPG that were deleted after a review of the evidence. This may occur if the evidence supporting the recommendation is outdated (e.g., there is no longer a basis to recommend use of an intervention and/or new evidence suggests a shift in care), rendering the recommendation obsolete.

2. Categorizing Recommendations without an Updated Review of the Evidence

There were also cases in which it was necessary to carry forward recommendations from the previous CPG without an updated review of the evidence. Given time and resource constraints, the systematic evidence review carried out for this CPG update could not cover all available evidence on headache; therefore, its KQs focused on new or updated research or areas not covered in the previous CPG.

For areas in which the relevant evidence was not changed and for which recommendations made in the previous CPG were still relevant, recommendations could have been carried forward to the updated CPG without an updated review of the evidence. The evidence supporting these recommendations was thus also carried forward from the previous CPG. These recommendations were categorized as *Not reviewed*. If evidence had not been reviewed, recommendations could have been categorized as *Not changed*, *Amended*, or *Deleted*. *Not reviewed*, *Not changed* recommendations were carried forward from the previous CPG unchanged. *Not reviewed*, *Amended* recommendations were carried forward from the previous CPG with a nominal change. *Not reviewed*, *Deleted* recommendations were determined by the Work Group to not be relevant. A recommendation may not be relevant if it, for example, pertained to a topic (e.g., population, care setting, treatment) outside of the updated CPG's scope or if it was determined to be common practice.

The recommendation categories for the current CPG are noted in the Recommendations. The recommendation categories from the 2020 VA/DoD Headache CPG are noted in Appendix F.

D. Drafting and Finalizing the Guideline

The Work Group wrote, reviewed, and edited three drafts of the CPG using an iterative review process to solicit feedback on and make revisions to the CPG. The first and second drafts were posted online for 20 and 14 business days, respectively, for the Work Group to provide feedback. Draft 3 was made available for a 14-day peer review and comment (see External Peer Review). The Work Group reviewed all feedback submitted during each review period and made appropriate revisions to the CPG. Following the Draft 3 review and comment period, the Work Group reviewed external feedback and created a final draft of the CPG. The Champions then presented the CPG to the VA/DoD EBPWG for approval. The Work Group considered the VA/DoD EBPWG's feedback and revised the CPG, as appropriate, to create the final version. To accompany the CPG, the Work Group produced toolkit products, including a provider summary, pocket card, and patient summary. The VA/DoD EBPWG approved the final CPG and toolkit products in September 2023.

Appendix B: The International Classification of Headache Disorders, 3rd Edition

A. Full criteria

The criteria for the common primary and secondary headaches syndromes addressed in this guideline are listed below. Please see the full ICHD-3 for more details: https://ichd-3.org/.

1.1 Migraine without aura

Previously used terms:

Common migraine; hemicrania simplex.

Description:

Recurrent headache disorder manifesting in attacks lasting 4-72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia.

Diagnostic criteria:

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

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[a] One or a few migraine attacks may be difficult to distinguish from symptomatic migraine-like attacks. Furthermore, the nature of a single or a few attacks may be difficult to understand. Therefore, at least five attacks are required. Individuals who otherwise meet criteria for 1.1 Migraine without aura but have had fewer than five attacks should be coded 1.5.1 Probable migraine without aura.

[b] When the patient falls asleep during migraine and wakes up without it, duration of the attack is reckoned until the time of awakening.

[c] In children and adolescents (aged under 18 years), attacks may last 2-72 hours (the evidence for untreated durations of less than two hours in children has not been substantiated).

1.2 Migraine with aura

Previously used terms:

Classic or classical migraine; ophthalmic, hemiparaesthetic, hemiplegic or aphasic migraine; migraine accompagnée; complicated migraine.

Description:

Recurrent attacks, lasting minutes, of unilateral fully-reversible visual, sensory or other central nervous system symptoms that usually develop gradually and are usually followed by headache and associated migraine symptoms.

Diagnostic criteria:

A. At least two attacks fulfilling criteria B and C

B. One or more of the following fully reversible aura symptoms:
    1. Visual
    2. Sensory
    3. Speech and/or language
    4. Motor
    5. Brainstem
    6. Retinal

C. At least three of the following six characteristics:
    1. At least one aura symptom spreads gradually over ≥5-minutes
    2. Two or more aura symptoms occur in succession
    3. Each individual aura symptom lasts 5-60 minutes[a]
    4. At least one aura symptom is unilateral[b]
    5. At least one aura symptom is positive[c]
    6. The aura is accompanied, or followed within 60-minutes, by headache

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

1.3 Chronic migraine

Description:

Headache occurring on 15 or more days/month for more than 3-months, which, on at least 8 days/month, has the features of migraine headache.

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[a] When for example three symptoms occur during an aura, the acceptable maximal duration is 3×60 minutes. Motor symptoms may last up to 72 hours.
[b] Aphasia is always regarded as a unilateral symptom; dysarthria may or may not be.
[c] Scintillations and pins and needles are positive symptoms of aura.

Diagnostic criteria:

A. Headache (migraine-like or tension-type-like[d]) on ≥15-days/month for >3-months, and fulfilling criteria B and C

B. Occurring in a patient who has had at least five attacks fulfilling criteria B-D for 1.1 *Migraine without aura* and/or criteria B and C for 1.2 *Migraine with aura*

C. On ≥8-days/month for >3-months, fulfilling any of the following[e]:

   1. Criteria C and D for 1.1 *Migraine without aura*
   2. Criteria B and C for 1.2 *Migraine with aura*
   3. Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative

D. Not better accounted for by another ICHD-3 diagnosis[f,g,h].

2.1 Infrequent episodic tension-type headache

Description:

Infrequent episodes of headache, typically bilateral, pressing or tightening in quality and of mild to moderate intensity, lasting minutes to days. The pain does not worsen with routine physical activity and is not associated with nausea, although photophobia or phonophobia may be present.

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[d] The reason for singling out 1.3 Chronic migraine from types of episodic migraine is that it is impossible to distinguish the individual episodes of headache in patients with such frequent or continuous headaches. In fact, the characteristics of the headache may change not only from day to day but even within the same day. Such patients are extremely difficult to keep medication-free in order to observe the natural history of the headache. In this situation, attacks with and those without aura are both counted, as are both migraine-like and tension-type-like headaches (but not secondary headaches).

[e] Characterization of frequently recurring headache generally requires a headache diary to record information on pain and associated symptoms day-by-day for at least one month.

[f] Because tension-type-like headache is within the diagnostic criteria for 1.3 Chronic migraine, this diagnosis excludes the diagnosis of 2. Tension-type headache or its types.

[g] 4.10 New daily persistent headache may have features suggestive of 1.3 Chronic migraine. The latter disorder evolves over time from 1.1 Migraine without aura and/or 1.2 Migraine with aura; therefore, when these criteria A-C are fulfilled by headache that, unambiguously, is daily and unremitting from <24 hours after its first onset, code as 4.10 New daily persistent headache. When the manner of onset is not remembered or is otherwise uncertain, code as 1.3 Chronic migraine.

[h] The most common cause of symptoms suggestive of chronic migraine is medication overuse, as defined under 8.2 Medication-overuse headache. Around 50% of patients apparently with 1.3 Chronic migraine revert to an episodic migraine type after drug withdrawal; such patients are in a sense wrongly diagnosed as 1.3 Chronic migraine. Equally, many patients apparently overusing medication do not improve after drug withdrawal; the diagnosis of 8.2 Medication-overuse headache may be inappropriate for these (assuming that chronicity induced by drug overuse is always reversible). For these reasons, and because of the general rule to apply all relevant diagnoses, patients meeting criteria for 1.3 Chronic migraine and for 8.2 Medication-overuse headache should be coded for both. After drug withdrawal, migraine will either revert to an episodic type or remain chronic, and should be re-diagnosed accordingly; in the latter case, the diagnosis of 8.2 Medication-overuse headache may be rescinded.

Diagnostic criteria:

A. At least 10 episodes of headache occurring on <1-day/month on average (<12-days/year) and fulfilling criteria B-D
B. Lasting from 30-minutes to 7-days
C. At least two of the following four characteristics:
    1. Bilateral location
    2. Pressing or tightening (non-pulsating) quality
    3. Mild or moderate intensity
    4. Not aggravated by routine physical activity such as walking or climbing stairs
D. Both of the following:
    1. No nausea or vomiting
    2. No more than one of photophobia or phonophobia
E. Not better accounted for by another ICHD-3 diagnosis.[i]

2.2 Frequent episodic tension-type headache

Description:

Frequent episodes of headache, typically bilateral, pressing or tightening in quality and of mild to moderate intensity, lasting minutes to days. The pain does not worsen with routine physical activity and is not associated with nausea, although photophobia or phonophobia may be present.

Diagnostic criteria:

A. At least 10 episodes of headache occurring on 1-14 days/month on average for >3-months (≥12 and <180-days/year) and fulfilling criteria B-D
B. Lasting from 30-minutes to 7-days
C. At least two of the following four characteristics:
    1. Bilateral location
    2. Pressing or tightening (non-pulsating) quality
    3. Mild or moderate intensity
    4. Not aggravated by routine physical activity such as walking or climbing stairs

[i] When headache fulfils criteria for both 1.5 Probable migraine and 2.1 Infrequent episodic tension-type headache, code as 2.1 Infrequent episodic tension-type headache (or as either subtype of it for which the criteria are fulfilled) under the general rule that definite diagnoses always trump probable diagnoses.

D. Both of the following:
    1. No nausea or vomiting
    2. No more than one of photophobia or phonophobia
E. Not better accounted for by another ICHD-3 diagnosis.[j]

2.3 Chronic tension-type headache

Coded elsewhere.

3.1 Cluster headache

Previously used terms:

Ciliary neuralgia; erythromelalgia of the head; erythroprosopalgia of Bing; hemicrania angioparalytica; hemicrania neuralgiformis chronica; histaminic cephalalgia; Horton's headache; Harris-Horton's disease; migrainous neuralgia (of Harris); petrosal neuralgia (of Gardner); Sluder's neuralgia; sphenopalatine neuralgia; vidian neuralgia.

Description:

Attacks of severe, strictly unilateral pain, which is orbital, supraorbital, temporal, or in any combination of these sites, lasting 15-180 minutes and occurring from once every other day to eight times a day. The pain is associated with ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, ptosis and/or eyelid edema, and/or with restlessness or agitation.

Diagnostic criteria:

A. At least five attacks fulfilling criteria B-D
B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes (when untreated)[k]
C. Either or both of the following:
    1. At least one of the following symptoms or signs, ipsilateral to the headache:
        - Conjunctival injection and/or lacrimation
        - Nasal congestion and/or rhinorrhoea
        - Eyelid oedema
        - Forehead and facial sweating

[j] When headache fulfils criteria for both 1.5 Probable migraine and 2.2 Frequent episodic tension-type headache, code as 2.2 Frequent episodic tension-type headache (or as either subtype of it for which the criteria are fulfilled) under the general rule that definite diagnoses always trump probable diagnoses.

[k] During part, but less than half, of the active time-course of 3.1 Cluster headache, attacks may be less severe and/or of shorter or longer duration.

- Miosis and/or ptosis

2. A sense of restlessness or agitation

D. Occurring with a frequency between one every other day and 8 per day[l]

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

4.10 New daily persistent headache

Previously used terms:

Chronic headache with acute onset; de novo chronic headache.

Description:

Persistent headache, daily from its onset, which is clearly remembered. The pain lacks characteristic features, and may be migraine-like or tension-type-like, or have elements of both.

Diagnostic criteria:

A. Persistent headache fulfilling criteria B and C

B. Distinct and clearly-remembered onset, with pain becoming continuous and unremitting within 24 hours

C. Present for >3 months

D. Not better accounted for by another ICHD-3 diagnosis[m,n,o,p]

[l] During part, but less than half, of the active time-course of 3.1 Cluster headache, attacks may be less frequent.

[m] 4.10 New daily persistent headache is unique in that headache is daily from onset, and very soon unremitting, typically occurring in individuals without a prior headache history. Patients with this disorder invariably recall and can accurately describe such an onset; if they cannot do so, another diagnosis should be made. Nevertheless, patients with prior headache (1. Migraine or 2. Tension-type headache) are not excluded from this diagnosis, but they should not describe increasing headache frequency prior to its onset. Similarly, patients with prior headache should not describe exacerbation associated with or followed by medication overuse.

[n] 4.10 New daily persistent headache may have features suggestive of either 1. Migraine or 2. Tension-type headache. Even though criteria for 1.3 Chronic migraine and/or 2.3 Chronic tension-type headache may also be fulfilled, the default diagnosis is 4.10 New daily persistent headache whenever the criteria for this disorder are met. In contrast, when the criteria for both 4.10 New daily persistent headache and 3.4 Hemicrania continua are met, then the latter is the default diagnosis

[o] Abortive drug use may exceed the limits defined as causative of 8.2 Medication-overuse headache. In such cases, the diagnosis of 4.10 New daily persistent headache cannot be made unless the onset of daily headache clearly predates the medication overuse. When this is so, both diagnoses, 4.10 New daily persistent headache and 8.2 Medication-overuse headache, should be given.

[p] In all cases, other secondary headaches such as 5.1 Acute headache attributed to traumatic injury to the head, 7.1 Headache attributed to increased cerebrospinal fluid pressure and 7.2 Headache attributed to low cerebrospinal fluid pressure should be ruled out by appropriate investigations.

5.1 Acute headache attributed to traumatic injury to the head

Description:

Headache of less than 3 months' duration caused by traumatic injury to the head and/or neck.

Diagnostic criteria:

A. Any headache fulfilling criteria C and D

B. Traumatic injury to the head[q] has occurred

C. Headache is reported to have developed within 7 days after one of the following:

   1. the injury to the head
   2. regaining of consciousness following the injury to the head
   3. discontinuation of medication(s) impairing ability to sense or report headache following the injury to the head

D. Either of the following:

   1. headache has resolved within 3 months after its onset
   2. headache has not yet resolved but 3 months have not yet passed since its onset

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

5.1.1 Acute headache attributed to moderate or severe traumatic injury to the head

Diagnostic criteria:

A. Headache fulfilling criteria for 5.1 *Acute headache attributed to traumatic injury to the head*

B. Injury to the head associated with at least one of the following:

   1. loss of consciousness for >30 minutes
   2. Glasgow Coma Scale (GCS) score <13
   3. post-traumatic amnesia lasting >24 hours[r]
   4. alteration in level of awareness for >24 hours
   5. imaging evidence of a traumatic head injury such as skull fracture, intracranial hemorrhage and/or brain contusion.

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[q] Traumatic injury to the head is defined as a structural or functional injury resulting from the action of external forces upon the head. These include impact between the head and an object, penetration of the head by a foreign body, forces generated from blasts or explosions, and other forces yet to be defined.

[r] The duration of post-traumatic amnesia is defined as the time between head injury and resumption of normal continuous recall of events.

5.1.2 Acute headache attributed to mild traumatic injury to the head

Diagnostic criteria:

A. Headache fulfilling criteria for 5.1 *Acute headache attributed to traumatic injury to the head*

B. Injury to the head fulfilling both of the following:

1. associated with none of the following:
    - loss of consciousness for >30 minutes
    - Glasgow Coma Scale score <13
    - post-traumatic amnesia lasting >24 hours[s]
    - altered level of awareness for >24 hours
    - imaging evidence of a traumatic head injury such as skull fracture, intracranial haemorrhage and/or brain contusion
2. associated with one or more of the following symptoms and/or signs:
    - transient confusion, disorientation or impaired consciousness
    - loss of memory for events immediately before or after the head injury
    - two or more of the following symptoms suggestive of mild traumatic brain injury:
        - nausea
        - vomiting
        - visual disturbances
        - dizziness and/or vertigo
        - gait and/or postural imbalance
        - impaired memory and/or concentration.

5.2 Persistent headache attributed to traumatic injury to the head

Coded elsewhere:

Trauma due to acceleration/deceleration movements of the head, with flexion/extension of the neck, is classified as whiplash. Persistent headache attributed to such trauma is coded as 5.4 *Persistent headache attributed to whiplash*. Persistent headache attributed to surgical craniotomy performed for reasons other than traumatic head injury is coded as 5.6 *Persistent headache attributed to craniotomy*.

[s] The duration of post-traumatic amnesia is defined as the time between head injury and resumption of normal continuous recall of events.

Description:

Headache of more than 3 months' duration caused by traumatic injury to the head.

Diagnostic criteria:

A. Any headache fulfilling criteria C and D

B. Traumatic injury to the head[t] has occurred

C. Headache is reported to have developed within 7 days after one of the following:

   1. the injury to the head
   2. regaining of consciousness following the injury to the head
   3. discontinuation of medication(s) impairing ability to sense or report headache following the injury to the head

D. Headache persists for >3 months after its onset

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

5.2.1 Persistent headache attributed to moderate or severe traumatic injury to the head

Diagnostic criteria:

A. Headache fulfilling criteria for 5.2 *Persistent headache attributed to traumatic injury to the head*

B. Injury to the head associated with at least one of the following:

   1. loss of consciousness for >30 minutes
   2. Glasgow Coma Scale score <13
   3. post-traumatic amnesia lasting >24 hours[v]
   4. alteration in level of awareness for >24 hours
   5. imaging evidence of a traumatic head injury such as skull fracture, intracranial hemorrhage and/or brain contusion.

[t] Traumatic injury to the head is defined as a structural or functional injury resulting from the action of external forces upon the head. These include impact between the head and an object, penetration of the head by a foreign body, forces generated from blasts or explosions, and other forces yet to be defined.

[u] When headache following head injury becomes persistent, the possibility of 8.2 Medication-overuse headache needs to be considered

[v] The duration of post-traumatic amnesia is defined as the time between head injury and resumption of normal continuous recall of events.

5.2.2 Persistent headache attributed to mild traumatic injury to the head

Diagnostic criteria:

A. Headache fulfilling criteria for 5.2 Persistent headache attributed to traumatic injury to the head

B. Head injury fulfilling both of the following:

1. associated with none of the following:
    - loss of consciousness for >30 minutes
    - Glasgow Coma Scale score <13
    - post-traumatic amnesia lasting >24 hours[w]
    - altered level of awareness for >24 hours
    - imaging evidence of a traumatic head injury such as skull fracture, intracranial hemorrhage and/or brain contusion
2. associated with one or more of the following symptoms and/or signs:
    - transient confusion, disorientation or impaired consciousness
    - loss of memory for events immediately before or after the head injury
    - two or more of the following symptoms suggestive of mild traumatic brain injury:
        - nausea
        - vomiting
        - visual disturbances
        - dizziness and/or vertigo
        - gait and/or postural imbalance
        - impaired memory and/or concentration

5.3 Acute headache attributed to whiplash[x]

Description:

Headache of less than 3 months' duration caused by whiplash.

[w] The duration of post-traumatic amnesia is defined as the time between head injury and resumption of normal continuous recall of events.

[x] Whiplash is defined as sudden and inadequately restrained acceleration/deceleration movements of the head with flexion/extension of the neck. Whiplash may occur after either high or low impact forces.

Diagnostic criteria:

A. Any headache fulfilling criteria C and D

B. Whiplash, associated at the time with neck pain and/or headache, has occurred

C. Headache has developed within 7 days after the whiplash

D. Either of the following:

   1. headache has resolved within 3 months after its onset
   2. headache has not yet resolved but 3 months have not yet passed since its onset

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

Note: Whiplash is defined as sudden and inadequately restrained acceleration/ deceleration movements of the head with flexion/extension of the neck. Whiplash may occur after either high or low impact forces.

5.4 Persistent headache attributed to whiplash

Description:

Headache of more than 3 months' duration caused by whiplash.

Diagnostic criteria:

A. Any headache fulfilling criteria C and D

B. Whiplash[y], associated at the time with neck pain and/or headache, has occurred

C. Headache developed within 7 days after the whiplash

D. Headache persists for >3 months after its onset

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

8.2 Medication Overuse Headache

Previously used terms:

Drug-induced headache; medication-misuse headache; rebound headache.

Coded elsewhere:

Patients with a pre-existing primary headache who, in association with medication overuse, develop a new type of headache or a significant worsening of their pre-existing headache that, in either case, meets the criteria for 8.2 Medication-overuse headache (or one of its subtypes) should be given both this diagnosis and the diagnosis of the pre-

[y] Whiplash is defined as sudden and inadequately restrained acceleration/deceleration movements of the head with flexion/extension of the neck. Whiplash may occur after either high or low impact forces.

[z] When headache following whiplash becomes persistent, the possibility of 8.2 Medication-overuse headache needs to be considered.

existing headache. Patients who meet criteria for both 1.3 Chronic migraine and 8.2 Medication-overuse headache should be given both diagnoses.

Description:

Headache occurring on 15 or more days/month in a patient with a pre-existing primary headache and developing as a consequence of regular overuse of acute or symptomatic headache medication (on 10 or more or 15 or more days/month, depending on the medication) for more than 3 months. It usually, but not invariably, resolves after the overuse is stopped.

Diagnostic criteria:

A. Headache occurring on ≥15-days/month in a patient with a pre-existing headache disorder.

B. Regular overuse for >3-months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache.[aa,bb,cc]

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

Previously used terms: Rebound headache, medication-misuse headache, drug-induced headache

11.2.1 Cervicogenic headache

Coded elsewhere:

Headache causally associated with cervical myofascial pain sources (myofascial trigger points) may, when it meets other criteria, be coded as 2.1.1 *Infrequent episodic tension-type headache associated with pericranial tenderness*, 2.2.1 *Frequent episodic tension-type headache associated with pericranial tenderness* or 2.3.1 *Chronic tension-type headache associated with pericranial tenderness*. A11.2.5 *Headache attributed to cervical myofascial pain* is an Appendix diagnosis awaiting evidence that this type of headache is more closely related to other cervicogenic headaches than to 2. *Tension-*

[aa] Patients should be coded for one or more subtypes of 8.2 Medication-overuse headache according to the specific medication(s) overused and the criteria for each below. For example, a patient who fulfils the criteria for 8.2.2 Triptan-overuse headache and the criteria for one of the subforms of 8.2.3 Non-opioid analgesic-overuse headache should receive both these codes. The exception occurs when patients overuse combination-analgesic medications, who are coded 8.2.5 Combination-analgesic-overuse headache and not according to each constituent of the combination-analgesic medication.

[bb] Patients who use multiple drugs for acute or symptomatic treatment of headache may do so in a manner that constitutes overuse even though no individual drug or class of drug is overused; such patients should be coded 8.2.6 Medication-overuse headache attributed to multiple drug classes not individually overused.

[cc] Patients who are clearly overusing multiple drugs for acute or symptomatic treatment of headache but cannot give an adequate account of their names and/or quantities are coded 8.2.7 Medication-overuse headache attributed to unspecified or unverified overuse of multiple drug classes until better information is available. In almost all cases, this necessitates diary follow-up.

type headache. Clearly, there are many cases which overlap these two categories, for which diagnosis can be challenging.

Description:

Headache caused by a disorder of the cervical spine and its component bony, disc and/or soft tissue elements, usually but not invariably accompanied by neck pain.

Diagnostic criteria:

A. Any headache fulfilling criterion C

B. Clinical and/or imaging evidence[dd] of a disorder or lesion within the cervical spine or soft tissues of the neck, known to be able to cause headache[ee]

C. Evidence of causation demonstrated by at least two of the following:

   1. Headache has developed in temporal relation to the onset of the cervical disorder or appearance of the lesion
   2. headache has significantly improved or resolved in parallel with improvement in or resolution of the cervical disorder or lesion
   3. cervical range of motion is reduced and headache is made significantly worse by provocative maneuvers
   4. headache is abolished following diagnostic blockade of a cervical structure or its nerve supply

D. Not better accounted for by another ICHD-3 diagnosis.[ff,gg,hh]

[dd] Imaging findings in the upper cervical spine are common in patients without headache; they are suggestive but not firm evidence of causation.

[ee] Tumours, fractures, infections and rheumatoid arthritis of the upper cervical spine have not been formally validated as causes of headache, but are accepted to fulfil criterion B in individual cases. Cervical spondylosis and osteochondritis may or may not be valid causes fulfilling criterion B, again depending on the individual case.

[ff] When cervical myofascial pain is the cause, the headache should probably be coded under 2. Tension-type headache; however, awaiting further evidence, an alternative diagnosis of A11.2.5 Headache attributed to cervical myofascial pain is in the Appendix.

[gg] Headache caused by upper cervical radiculopathy has been postulated and, considering the now well-understood convergence between upper cervical and trigeminal nociception, this is a logical cause of headache. Pending further evidence, this diagnosis is in the Appendix as A11.2.4 Headache attributed to upper cervical radiculopathy.

[hh] Features that tend to distinguish 11.2.1 Cervicogenic headache from 1. Migraine and 2. Tension-type headache include side-locked pain, provocation of typical headache by digital pressure on neck muscles and by head movement, and posterior-to-anterior radiation of pain. However, while these may be features of 11.2.1 Cervicogenic headache, they are not unique to it and they do not necessarily define causal relationships. Migrainous features such as nausea, vomiting and photo/phonophobia may be present with 11.2.1 Cervicogenic headache, although to a generally lesser degree than in 1. Migraine, and may differentiate some cases from 2. Tension-type headache.

Appendix C: Treatment Options for Headache in General

The following table contains general information regarding treatment options for headache.

Table C-1. Treatment Options for Headache in General

Type	Treatment	Notes
Non-pharmacologic Therapy	Acupuncture	• Evidence suggests small or inconsistent benefits for migraine and TTH in comparison with sham acupuncture • No statistically significant differences when compared with beta-blockers, valproic acid, or CCBs, which are also reviewed in this CPG
	CBT, biofeedback, or mindfulness-based therapy	• Although CBT, biofeedback, and mindfulness approaches are commonly used, there was insufficient evidence in this CPG's systematic evidence review to support a recommendation
	Dietary trigger avoidance	• The evidence regarding dietary trigger avoidance is limited
	Dry needling	• Evidence of dry needling compared with no treatment was limited
	Immunoglobulin G antibody testing	• There was insufficient evidence in this CPG's systematic evidence review to support a recommendation
Pharmacotherapy – Preventive	Fluoxetine or venlafaxine	• There was insufficient evidence in this CPG's systematic evidence review to support a recommendation
	IV metoclopramide, IV prochlorperazine, or intranasal lidocaine	• There was insufficient evidence in this CPG's systematic evidence review to support a recommendation

[a] For the full recommendation language, see Recommendations.

See Appendix G for pharmacotherapy dosing tables for Headache.

Abbreviations: CBT: cognitive behavioral therapy; CCB: calcium channel blocker; CPG: clinical practice guideline; IV: intravenous; SPG: sphenopalatine ganglion; TTH: tension-type headache

Appendix D: Patient Focus Group Methods and Findings

A. Methods

VA and DoD Leadership recruited nine participants for the focus group, with support from the Champions and other Work Group members, as needed. Although participant recruitment focused on eliciting a range of perspectives likely relevant and informative in the CPG development process, the patient focus group participants were not intended to be a representative sample of VA and DoD patients. The participants were not incentivized for participation or reimbursed for travel expenses. The Work Group, with support from the Lewin Team, identified topics on which patient input was important to consider in developing the CPG. The Lewin Team developed, and the Work Group approved, a patient focus group guide covering these topics. The focus group facilitator led the discussion, using the guide to elicit patient perspectives about their treatment and overall care. Given the limited time and the range of interests of the focus group participants, not all questions were addressed.

B. Patient Focus Group Findings

a. Participants noted that performing thorough diagnostic tests (e.g., MRI, CT) earlier in the process would allow for more accurate diagnoses and assist with developing effective treatment plans

- Participants wished to receive timely diagnostic tests to obtain accurate diagnoses and appropriate care.
- Participants noted that pain is multifactorial, and failure to recognize underlying causes of their headache impacted the effectiveness of their treatment plans.

b. Participants stated that combinations of treatments were effective in managing their headache; although participants indicated that medication was useful, many found that other types of therapies (e.g., physical therapy, Botox, acupuncture, biofeedback) were important components in their treatment.

- Participants shared their experience with using oral medications as well as combinations of oral medications and other types of therapies to manage their pain.
- Participants emphasized that providers should seek and understand the evidence on newer therapies, discuss these options with patients, and leverage these therapies when appropriate.
- Participants valued informed communication with providers regarding their treatment plans.

c. Participants shared that more education about headaches was needed for patients, primary care providers, and military commanders; for patients, such education would assure a better understanding of headache type, self-management, and treatment options.

- Participants expressed a need for greater patient education and information sharing from providers to patients.
- Participants stated that military commanders should be more informed about headaches and more involved in their service members' headache management.

d. Participants noted mixed preferences for in-person versus virtual options for receiving their headache care; they expressed that in-person visits were necessary for initial evaluations.

- Participants shared that in-person visits are critical for initial evaluations and developing treatment plans.
- Participants indicated that virtual visits could be useful for follow-up appointments or prescription refills and that they could potentially reduce burden on both patients and providers.

e. Participants expressed that continuity of care, care coordination, access to specialty providers, and consistency in care teams would improve care delivery and satisfaction.

- Participants noted concerns with having to repeatedly change providers and expressed a desire for more consistent care.
- Participants described challenges in coordinating care across primary care and specialty care providers (e.g., needing to obtain referrals to specialists for medication prescriptions).
- Participants discussed their experiences with care across VA/DoD health care systems and the private sector.

Appendix E: Evidence Table

Table E-1. 2023 Headache Evidence Table[a,b,c,d,e,f]

#	Recommendation	2020 Strength of Recommendation	Evidence	2023 Strength of Recommendation	2023 Recommendation Category
1.	We suggest 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 (greater than or equal to 7 days per month) • Migraine diagnosis • Medication use: frequent use of anxiolytics, analgesics (for any condition, including use of opioids or non-opioid analgesics for acute treatment of migraine), or sedative hypnotics • History of anxiety or depression, especially in combination with musculoskeletal complaints or gastrointestinal complaints • Physical inactivity • Sick leave of greater than 2 weeks in the last year • Self-reported whiplash • Smoking (tobacco use)	Weak for	(102-106)	Weak for	Not reviewed, Amended

[a] 2020 CPG Recommendation # column: This indicates the recommendation number of the recommendation in the 2020 VA/DoD Headache CPG.
[b] 2020 CPG Recommendation Text column: This contains the wording of each recommendation from the 2020 VA/DoD Headache CPG.
[c] 2020 CPG Strength of Recommendation column: The 2020 VA/DoD Headache CPG used the GRADE approach to determine the strength of each recommendation.
[d] 2020CPG Recommendation Category column: This is the recommendation category assigned during the development of the 2020VA/DoD Headache CPG. Refer to the Recommendation Categorization section for more information on the description of the categorization process and the definition of each category.
[e] 2023 CPG Recommendation Category column: This is the recommendation category assigned during the development of the 2023 VA/DoD Headache CPG. Refer to the Recommendation Categorization section for more information on the description of the categorization process and the definition of each category.
[f] 2023 CPG Recommendation # column: For recommendations that were carried forward to the 2020VA/DoD Headache CPG, this column indicates the new recommendation(s) to which they correspond.

#	Recommendation	2020 Strength of Recommendation	Evidence	2023 Strength of Recommendation	2023 Recommendation Category
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	(107-113)	Neither for nor against	Not reviewed, Amended
3.	There is insufficient evidence to recommend for or against fluoxetine or venlafaxine for the prevention of headache.	Neither for nor against	(114-116) **Additional Reference** (117)	Neither for nor against	Reviewed, Not changed
4.	We recommend candesartan or telmisartan for the prevention of episodic migraine.	Strong for	(116, 118-120)	Strong for	Reviewed, New-replaced
5.	We recommend erenumab, fremanezumab, or galcanezumab for the prevention of episodic or chronic migraine.	Weak for	(121-140) **Additional References** (141-148)	Strong for	Reviewed, New-replaced
6.	We suggest intravenous eptinezumab for the prevention of episodic or chronic migraine.	NA	(149, 150, 152-154) **Additional References** (151, 155-160)	Weak for	Reviewed, New-added
7.	We suggest lisinopril for the prevention of episodic migraine.	Weak for	(388) **Additional Reference** (161)	Weak for	Reviewed, Not changed
8.	We suggest oral magnesium for the prevention of migraine.	Weak for	(107, 162, 163) **Additional Reference** (164)	Weak for	Not reviewed, Not changed
9.	We suggest topiramate for the prevention of episodic and chronic migraine.	Weak for	(140, 165-167) **Additional Reference** (168)	Weak for	Reviewed, New-replaced
10.	We suggest propranolol for the prevention of migraine.	Weak for	(167)	Weak for	Reviewed, Not changed

#	Recommendation	2020 Strength of Recommendation	Evidence	2023 Strength of Recommendation	2023 Recommendation Category
11.	We suggest valproate for the prevention of episodic migraine.	Neither for nor against	(116, 166) **Additional References** (153, 169-177, 179-182)	Weak for	Reviewed, New-replaced
12.	We suggest memantine for the prevention of episodic migraine.	NA	(183) **Additional References** (184, 185)	Weak for	Reviewed, New-added
13.	We suggest atogepant for the prevention of episodic migraine.	NA	(186)	Weak for	Reviewed, New-added
14.	We suggest onabotulinumtoxinA injection for the prevention of chronic migraine.	Weak for	(140, 187, 188)	Weak for	Reviewed, Not changed
15.	We suggest against abobotulinumtoxinA or onabotulinumtoxinA injection for the prevention of episodic migraine.	Weak against	(188)	Weak against	Reviewed, Not changed
16.	There is insufficient evidence to recommend for or against rimegepant for the prevention of episodic migraine.	NA	(189)	Neither for nor against	Reviewed, New-added
17.	We suggest against the use of gabapentin for the prevention of episodic migraine.	Neither for nor against	(166) **Additional Reference** (190)	Weak against	Reviewed, New-replaced
18.	There is insufficient evidence to recommend for or against levetiracetam for the prevention of episodic migraine.	NA	(191) **Additional References** (192-203)	Neither for nor against	Reviewed, New-added

#	Recommendation	2020 Strength of Recommendation	Evidence	2023 Strength of Recommendation	2023 Recommendation Category
19.	We recommend eletriptan, frovatriptan, rizatriptan, sumatriptan (oral or subcutaneous), the combination of sumatriptan and naproxen, or zolmitriptan (oral or intranasal) for the acute treatment of migraine.	Strong for (sumatriptan (oral or subcutaneous), the combination of sumatriptan/naproxen, or zolmitriptan (oral or intranasal) Weak for (frovatriptan or rizatriptan)	(204-209) **Additional References** (210-213)	Strong for	Reviewed, New-replaced
20.	We recommend aspirin/acetaminophen/caffeine for the acute treatment of migraine.	NA	(214)	Strong for	Reviewed, New-added
21.	We suggest acetaminophen, aspirin, ibuprofen, or naproxen for the acute treatment of migraine.	Weak for	(215-222)	Weak for	Reviewed, Amended
22.	We suggest rimegepant or ubrogepant for the acute treatment of migraine.	NA	(223-226)	Weak for	Reviewed, New-added
23.	We suggest against intravenous ketamine for the acute treatment of migraine.	Weak against	(227) **Additional References** (228, 229)	Weak against	Reviewed, Amended
24.	There is insufficient evidence to recommend for or against lasmiditan for the acute treatment of migraine.	NA	(230-234) **Additional References** (235, 236)	Neither for nor against	Reviewed, New-added
25.	We suggest amitriptyline for the prevention of chronic tension-type headache.	Weak for	(237) **Additional References** (238, 239)	Weak for	Reviewed, Not changed
26.	We suggest against botulinum/neurotoxin injection for the prevention of chronic tension-type headache.	Weak against	(240, 241)	Weak against	Reviewed, Not changed
27.	We suggest ibuprofen (400 mg) or acetaminophen (1,000 mg) for the acute treatment of tension-type headache.	Weak for	(242-244)	Weak for	Reviewed, Not changed

#	Recommendation	2020 Strength of Recommendation	Evidence	2023 Strength of Recommendation	2023 Recommendation Category
28.	We suggest galcanezumab for the prevention of episodic cluster headache.	Weak for	(124, 245) **Additional References** (148, 246)	Weak for	Reviewed, Not changed
29.	We suggest against galcanezumab for the prevention of chronic cluster headache.	NA	(248) **Additional References** (148, 247, 249)	Weak against	Reviewed, New-added
30.	There is insufficient evidence to recommend for or against verapamil for the prevention of episodic or chronic cluster headache.	NA	(245) **Additional References** (124, 250, 251)	Neither for nor against	Reviewed, New-added
31.	We suggest subcutaneous sumatriptan (6 mg) or intranasal zolmitriptan (10 mg) for the acute treatment of cluster headache.	Neither for nor against	(252) **Additional References** (253, 254)	Weak for	Reviewed, New-replaced
32.	We suggest the use of normobaric oxygen therapy for the acute treatment of cluster headache.	Neither for nor against	(252, 255-257)	Weak for	Not reviewed, Amended
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	(258-263)	Neither for nor against	Reviewed, New-replaced
34.	We suggest greater occipital nerve block for the acute treatment of migraine.	Weak for	(264-267) **Additional References** (268, 269)	Weak for	Reviewed, Not changed
35.	There is insufficient evidence to recommend for or against greater occipital nerve block for the prevention of chronic migraine.	NA	(187, 270, 271) **Additional References** (268, 269)	Neither for nor against	Reviewed, New-added

#	Recommendation	2020 Strength of Recommendation	Evidence	2023 Strength of Recommendation	2023 Recommendation Category
36.	There is insufficient evidence to recommend for or against supra orbital nerve block for acute treatment of migraine.	NA	(267)	Neither for nor against	Reviewed, New-added
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 acute treatment of headache.	Weak for (intravenous magnesium) Neither for nor against (intravenous metoclopramide, intravenous prochlorperazine, or intranasal lidocaine)	(162, 231, 272-274) **Additional References** (275, 276)	Neither for nor against	Reviewed, New-replaced
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	(277, 278)	Neither for nor against	Reviewed, New-replaced
39.	We suggest against an implantable sphenopalatine ganglion stimulator for the treatment of cluster headache.	NA	(279)	Weak against	Reviewed, New-added
40.	We suggest against patent foramen ovale closure for the treatment or prevention of migraine.	NA	(280, 281)	Weak against	Reviewed, New-added
41.	We suggest non-invasive vagus nerve stimulation for the acute treatment of episodic cluster headache.	Weak for	(282, 283)	Weak for	Reviewed, Not changed
42.	We suggest physical therapy for the management of tension-type, migraine, or cervicogenic headache.	Weak for	(284-293) **Additional Reference** (294)	Weak for	Reviewed, New-replaced
43.	We suggest aerobic exercise or progressive strength training for the prevention of tension-type and migraine headache.	Weak for	(295-300) **Additional Reference** (294)	Weak for	Not reviewed, Amended

#	Recommendation	2020 Strength of Recommendation	Evidence	2023 Strength of Recommendation	2023 Recommendation Category
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 heartrate variability monitoring • Cognitive behavioral therapy • Mindfulness-based therapies • Progressive muscle relaxation	Neither for nor against (Biofeedback, Cognitive behavioral therapy) Weak for (Mindfulness-based therapies)	(301-315)	Neither for nor against	Reviewed, New-replaced
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	(277, 278, 293, 310, 316-332)	Neither for nor against	Reviewed, New-replaced
46.	There is insufficient evidence to recommend for or against dietary trigger avoidance for the prevention of headache.	Weak for	(333, 334)	Neither for nor against	Not reviewed, Amended
47.	We suggest against immunoglobulin G antibody testing for dietary trigger avoidance for the prevention of headache.	Neither for nor against	(335, 336)	Weak against	Not reviewed, Amended
48.	There is insufficient evidence to recommend for or against any form of neuromodulation for the treatment and/or prevention of migraine: • Non-invasive 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	(337-357)	Neither for nor against	Reviewed, New-replaced
49.	There is insufficient evidence to recommend for or against choosing a specific treatment strategy for posttraumatic headache.	NA	(350, 358-361)	Neither for nor against	Reviewed, New-added

#	Recommendation	2020 Strength of Recommendation	Evidence	2023 Strength of Recommendation	2023 Recommendation Category
50.	There is insufficient evidence to recommend for or against any specific medication over another for the acute treatment of migraine.	NA	(273, 362-366)	Neither for nor against	Reviewed, New-added
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.	NA	(114, 140, 165, 245, 368-374)	Neither for nor against	Reviewed, New-added
52.	There is insufficient evidence to recommend for or against any specific combination of therapies for the prevention of headache.	Neither for nor against	(271, 375-382)	Neither for nor against	Reviewed, New-replaced

Appendix F: 2020 Recommendation Categorization Table

Table F-1. 2020 VA/DoD Headache CPG Recommendation Categorization Table[a,b,c,d,e,f]

2020 CPG Recommendation #	2020 CPG Recommendation Text	2020 CPG Strength of Recommendation	2020 CPG Recommendation Category	2023 CPG Recommendation Category	2023 CPG Recommendation #
1.	We suggest providers assess the following risk factors for medication overuse headache in patients with headache: • Medication use: frequent use of anxiolytics, analgesics, or sedative hypnotics • Physical inactivity • Self-reported whiplash • History of anxiety or depression with or without musculoskeletal complaints and/or gastrointestinal complaints • Sick leave of greater than two weeks in the last year • Smoking	Weak for	Reviewed, New-added	Not reviewed, Amended	1
2.	There is insufficient evidence to recommend for or against any specific strategy or healthcare setting for the withdrawal of medication in the treatment of medication overuse headache.	Neither for nor against	Reviewed, New-added	Reviewed, New-replaced	33

[a] 2020 CPG Recommendation # column: This indicates the recommendation number of the recommendation in the 2020 VA/DoD Headache CPG.
[b] 2020 CPG Recommendation Text column: This contains the wording of each recommendation from the 2020 VA/DoD Headache CPG.
[c] 2020 CPG Strength of Recommendation column: The 2020 VA/DoD Headache CPG used the GRADE approach to determine the strength of each recommendation.
[d] 2020CPG Recommendation Category column: This is the recommendation category assigned during the development of the 2020VA/DoD Headache CPG. Refer to the Recommendation Categorization section for more information on the description of the categorization process and the definition of each category.
[e] 2023 CPG Recommendation Category column: This is the recommendation category assigned during the development of the 2023 VA/DoD Headache CPG. Refer to the Recommendation Categorization section for more information on the description of the categorization process and the definition of each category.
[f] 2023 CPG Recommendation # column: For recommendations that were carried forward to the 2020VA/DoD Headache CPG, this column indicates the new recommendation(s) to which they correspond.

2020 CPG Recommendation #	2020 CPG Recommendation Text	2020 CPG Strength of Recommendation	2020 CPG Recommendation Category	2023 CPG Recommendation Category	2023 CPG Recommendation #
3.	We suggest physical therapy for the management of tension-type headache.	Weak for	Reviewed, New-added	Reviewed, New-replaced	42
4.	We suggest aerobic exercise or progressive strength training for the management of headache.	Weak for	Reviewed, New-added	Not reviewed, Amended	43
5.	We suggest mindfulness-based therapies for the treatment of headache.	Weak for	Reviewed, New-added	Reviewed, New-replaced	44
6.	We suggest education regarding dietary trigger avoidance for the prevention of migraine.	Weak for	Reviewed, New-added	Not reviewed, Amended	46
7.	We suggest non-invasive vagus nerve stimulation for the acute treatment of episodic cluster headache.	Weak for	Reviewed, New-added	Reviewed, Not changed	41
8.	There is insufficient evidence to recommend for or against acupuncture for the treatment of headache.	Neither for nor against	Reviewed, New-added	Reviewed, New-replaced	45
9.	There is insufficient evidence to recommend for or against dry needling for the treatment of headache.	Neither for nor against	Reviewed, New-added	Reviewed, New-replaced	45
10.	There is insufficient evidence to recommend for or against pulsed radiofrequency or sphenopalatine ganglion block for the treatment of headache.	Neither for nor against	Reviewed, New-added	Reviewed, New-replaced	38
11.	There is insufficient evidence to recommend for or against cognitive behavioral therapy or biofeedback for the treatment of headache.	Neither for nor against	Reviewed, New-added	Reviewed, New-replaced	44
12.	There is insufficient evidence to recommend for or against an elimination diet based on immunoglobulin G antibody test results for the prevention of headache.	Neither for nor against	Reviewed, New-added	Not reviewed, Amended	47

2020 CPG Recommendation #	2020 CPG Recommendation Text	2020 CPG Strength of Recommendation	2020 CPG Recommendation Category	2023 CPG Recommendation Category	2023 CPG Recommendation #
13.	There is insufficient evidence to recommend for or against the following for headache: • Transcranial magnetic stimulation • Transcranial direct current stimulation • External trigeminal nerve stimulation • Supraorbital electrical stimulation	Neither for nor against	Reviewed, New-added	Reviewed, New-added	49
14.	We recommend candesartan or telmisartan for the prevention of episodic or chronic migraine.	Strong for	Reviewed, New-added	Reviewed, New-replaced	4
15.	We suggest erenumab, fremanezumab, or galcanezumab for the prevention of episodic or chronic migraine.	Weak for	Reviewed, New-added	Reviewed, New-replaced	5
16.	We suggest lisinopril for the prevention of episodic migraine.	Weak for	Reviewed, New-added	Reviewed, Not changed	7
17.	We suggest oral magnesium for the prevention of migraine.	Weak for	Reviewed, New-added	Not reviewed, Not changed	8
18.	We suggest topiramate for the prevention of episodic migraine.	Weak for	Reviewed, New-added	Reviewed, New-replaced	9
19.	We suggest propranolol for the prevention of migraine.	Weak for	Reviewed, New-added	Reviewed, Not changed	10
20.	We suggest onabotulinumtoxinA injection for the prevention of chronic migraine.	Weak for	Reviewed, New-added	Reviewed, Not changed	14
21.	We suggest against abobotulinumtoxinA or onabotulinumtoxinA injection for the prevention of episodic migraine.	Weak against	Reviewed, New-added	Reviewed, Not changed	15
22.	There is insufficient evidence to recommend for or against gabapentin for the prevention of episodic migraine.	Neither for nor against	Reviewed, New-added	Reviewed, New-replaced	17
23.	There is insufficient evidence to recommend for or against nimodipine or nifedipine for the prevention of episodic migraine.	Neither for nor against	Reviewed, New-added	Not reviewed, Deleted	N/A

2020 CPG Recommendation #	2020 CPG Recommendation Text	2020 CPG Strength of Recommendation	2020 CPG Recommendation Category	2023 CPG Recommendation Category	2023 CPG Recommendation #
24.	There is insufficient evidence to recommend for or against coenzyme Q10, feverfew, melatonin, omega-3, vitamin B2, or vitamin B6 for the prevention of migraine.	Neither for nor against	Reviewed, New-added	Not reviewed, Amended	2
25.	There is insufficient evidence to recommend for or against combination pharmacotherapy for the prevention of migraine.	Neither for nor against	Reviewed, New-added	Reviewed, New-replaced	52
26.	We recommend sumatriptan (oral or subcutaneous), the combination of sumatriptan/naproxen, or zolmitriptan (oral or intranasal) for the acute treatment of migraine.	Strong for	Reviewed, New-added	Reviewed, New-replaced	19
27.	We suggest frovatriptan or rizatriptan for the acute treatment of migraine.	Weak for	Reviewed, New-added	Reviewed, New-replaced	19
28.	We suggest triptans instead of opioids or non-opioid analgesics to lower the risk of medication overuse headache for the acute treatment of migraine.	Weak for	Reviewed, New-added	Not reviewed, Amended	1
29.	We suggest ibuprofen, naproxen, aspirin, or acetaminophen for the acute treatment of migraine.	Weak for	Reviewed, New-added	Reviewed, Amended	21
30.	We suggest greater occipital nerve block for the acute treatment of migraine.	Weak for	Reviewed, New-added	Reviewed, Not changed	34
31.	We suggest intravenous magnesium for the acute treatment of migraine.	Weak for	Reviewed, New-added	Reviewed, New-replaced	37
32.	We suggest amitriptyline for the prevention of chronic tension-type headache.	Weak for	Reviewed, New-added	Reviewed, Not changed	25
33.	We suggest against botulinum/neurotoxin injection for the prevention of chronic tension-type headache.	Weak against	Reviewed, New-added	Reviewed, Not changed	26
34.	We suggest ibuprofen (400 mg) or acetaminophen (1,000 mg) for the acute treatment of tension-type headache.	Weak for	Reviewed, New-added	Reviewed, Not changed	28
35.	We suggest galcanezumab for the prevention of episodic cluster headache.	Weak for	Reviewed, New-added	Reviewed, Not changed	28

2020 CPG Recommendation #	2020 CPG Recommendation Text	2020 CPG Strength of Recommendation	2020 CPG Recommendation Category	2023 CPG Recommendation Category	2023 CPG Recommendation #
36.	There is insufficient evidence to recommend for or against any particular medication for the acute treatment of cluster headache.	Neither for nor against	Reviewed, New-added	Reviewed, New-replaced	31
37.	There is insufficient evidence to recommend for or against oxygen therapy for the acute treatment of primary headache.	Neither for nor against	Reviewed, New-added	Not reviewed, Amended	32
38.	There is insufficient evidence to recommend for or against valproate for the prevention of headache.	Neither for nor against	Reviewed, New-added	Reviewed, New-replaced	11
39.	There is insufficient evidence to recommend for or against fluoxetine or venlafaxine for the prevention of headache.	Neither for nor against	Reviewed, New-added	Reviewed, Not changed	3
40.	We suggest against intravenous ketamine for the acute treatment of headache.	Weak against	Reviewed, New-added	Reviewed, Amended	23
41.	There is insufficient evidence to recommend for or against intravenous metoclopramide, intravenous prochlorperazine, or intranasal lidocaine for the acute treatment of headache.	Neither for nor against	Reviewed, New-added	Reviewed, New-replaced	37
42.	There is insufficient evidence to recommend for or against prescription or nonprescription pharmacologic agents for the treatment of secondary headache.	Neither for nor against	Reviewed, New-added	Not reviewed, Deleted	N/A

Appendix G: Pharmacotherapy

The following tables summarize pharmacotherapy options for preventive and abortive treatment. Refer to each drug's prescribing information for full details.

Table G-1. Pharmacotherapy – Preventive Dosing Information

Type	Drug	Initial Dose	Usual Range	Comments
Beta-Adrenergic Antagonists	Atenolol	50 mg/day	50–200 mg/day	• Dose should be titrated and maintained for at least 3 months before assessment of response.
	Metoprolol tartrate and metoprolol succinate	100 mg/day in divided doses	100–200 mg/day in divided doses	
	Nadolol	40–80 mg/day	80–240 mg/day	
	Propranolol	40 mg/day in divided doses	40–160 mg/day in divided doses	
	Timolol	20 mg/day in divided doses	20–60 mg/day in divided doses	
Antidepressants	Amitriptyline	10 mg at bedtime	20–50 mg at bedtime	• Use slow titration to reduce sedation.
	Nortriptyline	10 mg daily or at bedtime	20–50 mg daily or at bedtime	• Use slow titration to reduce sedation.
	Venlafaxine	37.5 mg/day	75–150 mg/day	• Titrate dose weekly, as tolerated.
Anticonvulsants	Topiramate	25 mg/day	50–200 mg/day in divided doses	• Increase by 25 mg/week.
	Valproic acid/ divalproex sodium	250–500 mg/day in divided doses or daily for extended release	500–1,500 mg/day in divided doses or daily for extended release	• May monitor levels if adherence is an issue

Type	Drug	Initial Dose	Usual Range	Comments
Calcitonin Gene-Related Peptide Inhibitors	Eptinezumab-jjmr	100 mg IV every 3 months	up to 300 mg IV every 3 months	• Might contain polysorbate 80 (also known as Tweens), which can cause hypersensitivity reactions. • Avoid use in patients with recent cardiovascular or cerebrovascular ischemic events.
	Erenumab-aooe	70 mg SQ monthly	70–140 mg SQ monthly	
	Fremanezumab-vfrm	225 mg SQ monthly	225 mg SQ monthly or 675 mg SQ every 3 months	
	Galcanezumab-gnlm	240 mg SQ one-time loading dose (migraine), 300 mg SQ (cluster)	Maintenance dose for migraine is 120mg SQ monthly. Use in cluster should continue at 300mg SQ monthly until end of cluster period.	
	Atogepant	10–60 mg/day	10–60 mg/day	
	Rimegepant	75 mg every other day	75 mg every other day	• Avoid strong CYP3A4 inhibitors, strong or moderate CYP3A4 inducers, p-glycoprotein inhibitors. • Approved for both acute and preventive treatment (maximum daily dose is 75 mg)
Triptans	Frovatriptan	2.5 mg/day or 5 mg/day in divided doses	Same as initial dose	• Use intermittently for short-term prevention of menstrually associated migraines. Daily or prolonged use might lead to medication overuse headache.
	Naratriptan	2 mg/day in divided doses	Same as initial dose	
	Zolmitriptan	5–7.5 mg/day in divided doses	Same as initial dose	
Miscellaneous	Histamine	1–10 mg two times/week	Same as initial dose	• Might cause transient itching and burning at injection site
	Magnesium	400 mg/day	800 mg/day in divided doses	• Might be more helpful in migraine with aura and menstrual migraine
	MIG-99 (feverfew)	10–100 mg/day in divided doses	Same as initial dose	• Withdrawal might be associated with increased headaches.
	Riboflavin	400 mg/day in divided doses	400 mg/day in divided doses	• Benefit only after 3 months

Abbreviations: mg: milligrams; SQ: subcutaneously

Table G-2. Pharmacotherapy – Abortive Dosing Information

Type	Drug	Usual Dose	Comments
Analgesics	Acetaminophen	1,000 mg at onset; repeat every 4–6 hours, as needed.	• Maximum daily dose is 4 g; lower dosage in individuals with risk factors. Consult prescribing information for further detail.
	Acetaminophen 250 mg/ aspirin 250 mg/caffeine 65 mg	2 tablets at onset and every 6 hours	• Available OTC
Nonsteroidal Anti-inflammatory Drugs	Aspirin	500–1,000 mg every 4–6 hours	• Maximum daily dose is 4 g.
	Diclofenac	50–100 mg at onset; can repeat 50 mg in 8 hours	• Avoid doses >150 mg/day.
	Ibuprofen	200–800 mg every 6 hours	• Avoid doses >2.4 g/day.
	Naproxen sodium	550–825 mg at onset; can repeat 220 mg in 3–4 hours	• Avoid doses >1.375 g/day.
	Celecoxib oral solution	120 mg as a single dose	• Maximum dose is 120 mg per 24 hours.
Ergotamine Tartrate	Oral tablet (1 mg) with caffeine 100 mg	2 mg at onset; then 1–2 mg every 30 minutes, as needed	• Maximum dose is 6 mg/day or 10 mg/week. • Consider pretreatment with an antiemetic.
	Sublingual tablet (2 mg)	2 mg sublingual tablet at the first sign of an attack; then 2 mg sublingual tablet after 30 minutes, if needed If the additional dose is well tolerated, the initial dose may be increased at the next attack, up to a maximum initial dose of 4 mg ergotamine.	• Do not exceed 3 tablets (6 mg ergotamine)/24 hours per any 1 attack.
	Rectal suppository (2 mg) with caffeine 100 mg	Insert ½–1 suppository at onset; repeat after 1 hour as needed.	• Maximum dose is 4 mg/day or 10 mg/week. • Consider pretreatment with an antiemetic.

Type	Drug	Usual Dose	Comments
Dihydroergotamine	Injection 1 mg/mL	0.25–1 mg at onset IM, IV, or subcutaneous; repeat every hour as needed.	• Maximum dose is 3 mg/day or 6 mg/week.
	Nasal spray 4 mg/mL	1 spray (0.5 mg) in each nostril at onset; repeat sequence 15 minutes later (total dose is 2 mg or 4 sprays). 1 spray (0.725 mg) into each nostril (total of 2 sprays per dose); may repeat, as needed, after ≥1 hour for a total of 4 sprays (2 doses)	• Maximum dose is 3 mg/day (Migranal®). • Maximum dose is 4 sprays (2 doses) per 24 hours; 6 sprays (3 doses) per 7 days (Trudhesa®). • Prime sprayer four times before using. • Do not tilt head back or inhale through nose while spraying. • Discard open ampules after 8 hours.
Triptans	Zolmitriptan	2.5 or 5 mg at onset as regular or orally disintegrating tablet; can repeat after 2 hours, if needed	• Optimal dose is 2.5 mg. • Maximum dose is 10 mg/day. • Taken in the perimenstrual period to prevent menstrual migraine
	Almotriptan	6.25 or 12.5 mg at onset; can repeat after 2 hours, if needed	• Optimal dose is 12.5 mg. • Maximum daily dose is 25 mg.
	Eletriptan	20 or 40 mg at onset; can repeat after 2 hours, if needed	• Maximum single dose is 40 mg. • Maximum daily dose is 80 mg.
	Frovatriptan	2.5 or 5 mg at onset; can repeat in 2 hours, if needed	• Optimal dose is 2.5–5 mg. • Maximum daily dose is 7.5 mg (3 tablets).
	Sumatriptan injection	6 mg subcutaneous at onset; can repeat after 1 hour, if needed	• Maximum daily dose is 12 mg.
	Naratriptan	1 or 2.5 mg at onset; can repeat after 4 hours, if needed	• Optimal dose is 2.5 mg. • Maximum daily dose is 5 mg.
	Zolmitriptan nasal spray	5 mg (1 spray) at onset; can repeat after 2 hours, if needed	• Maximum daily dose is 10 mg. • Administer one spray in one nostril.
	Sumatriptan nasal	Spray: 5, 10, or 20 mg at onset; can repeat after 2 hours, if needed Powder: 11 mg in each nostril	• Optimal dose is 20 mg. • Maximum daily dose is 40 mg and 44 mg for powder. • Single-dose device delivering 5 or 20 mg • Administer 1 spray in one nostril.

Type	Drug	Usual Dose	Comments
Triptans (cont.)	Sumatriptan oral tablets	25, 50, 85, or 100 mg at onset; can repeat after 2 hours, if needed	• Optimal dose is 50–100 mg. • Maximum daily dose is 200 mg. • Combination product with naproxen, 85 mg/500 mg
	Rizatriptan	5 or 10 mg at onset as regular or orally disintegrating tablet; can repeat after 2 hours, if needed	• Optimal dose is 10 mg. • Maximum daily dose is 30 mg. • Onset of effect is similar with standard and orally disintegrating tablets. • Use 5 mg dose (15 mg/day maximum) in patients receiving propranolol.
Calcitonin Gene-Related Peptides Inhibitors	Rimegepant	75 mg orally disintegrating tablet	• Maximum daily dose is 75 mg. • Avoid strong CYP3A4 inhibitors, strong or moderate CYP3A4 inducers, p-glycoprotein inhibitors. • Approved for both acute and preventive treatment
	Ubrogepant	50–100 mg as a single dose; may repeat in ≥2-hours	• Up to 200 mg/24 hours, contraindicated with strong CYP3A4 inhibitors; dose adjustment in moderate renal impairment and severe (Child Pugh Class C) hepatic impairment
	Zavegepant*	10 mg (1 spray) in one nostril as a single dose; maximum 10 mg (1 spray) per 24 hours	• Intranasal delivery • Avoid in severe (Child Pugh Class C) hepatic impairment and creatinine clearance fewer than 30 mL/min. • Avoid OATP1B3 and NTCP inhibitors and inducers. • Intranasal decongestants might decrease absorption. If use is necessary, separate from zavegepant by at least 1 hour.

Type	Drug	Usual Dose	Comments
Selective 5-HT 1F Receptor Agonist	Lasmiditan	50 mg, maximum of one dose per 24 hours	• 50–200 mg per 24 hours as a single dose • DEA Schedule V drug, may not drive for 8 hours after dose
Miscellaneous	Metoclopramide	10 mg IV at onset	• Useful for acute relief in the office or ED setting
	Prochlorperazine	10 mg IV or IM at onset	

*Zavegepant was approved by the FDA after the timeframe of literature review for this clinical practice guideline. Thus, there are no recommendations for zavegepant; however, it is included in this pharmacotherapy table as a recently approved abortive migraine treatment option.

Abbreviations: CYP3A4: cytochrome P450 3A4; ED: emergency department; IM: intramuscular; IV: intravenous; mg: milligrams; mL: milliliter; NTCP: sodium taurocholate co-transporting polypeptide; OATP1B3: organic anion transporter family 1B3; OTC: over-the-counter.

Appendix H: Glossary

Category	Term	Definition
Headache Definitions	Cervicogenic Headache	A common secondary headache disorder. Defined by the ICHD-3 as "Headache caused by a disorder of the cervical spine and its component bony, disc and/or soft tissue elements, usually but not invariably accompanied by neck pain." See Appendix B for full criteria.
	ICHD-3	The ICDH-3 outlines standardized diagnostic criteria for primary and secondary headache disorders as well as neuropathies and facial pains. Additional information can be found here: https://ichd-3.org/.
	MOH	A common secondary headache disorder. Defined by the ICHD-3 as "Headache occurring on 15 or more days/month in a patient with a preexisting primary headache and developing as a consequence or regular overuse of acute or symptomatic headache medication (on 10 or more of 15 or more days/month, depending on the medication) for more than 3 months. It usually, but not invariably, resolves after the overuse is stopped." See Sidebar 5 and Appendix B for additional details.
	PTH	A common secondary headache disorder. Defined by the ICHD-3 as occurring when "a new headache occurs for the first time on close temporal relationship to trauma or injury to the head and/or neck." Might present with symptoms like migraine, TTH, TACs, or other primary headache disorders. See Appendix B for additional details.
	Primary Headache Disorder	Occurs when headache is not attributable to an underlying disease or condition. Examples of primary headache conditions include migraine, TTH, and TACs. See Table 1, Sidebar 2, and Sidebar 3 for additional information.
	Secondary Headache Disorder	Occurs when headache can be attributable to an underlying disease or condition. Examples include MOH, PTH, and cervicogenic headache. See Sidebar 2 and Sidebar 3 for additional information.
	TTH	The most common type of primary headache disorder. According to the ICHD-3, TTH is "typically bilateral, pressing or tightening in quality and of mild to moderate intensity, lasting minutes to days. The pain does not worsen with routine physical activity and is not associated with nausea, although photophobia and phonophobia might be present." See Table 1, and Sidebar 2 for additional information.
	TAC	An uncommon though severe type of primary headache disorder. According to the ICHD-3, TACs "share the clinical features of unilateral headache and, usually, prominent cranial parasympathetic autonomic features, which are lateralized and ipsilateral to the headache." See Table 1, and Sidebar 2 for additional information.
Headache Assessments	Absenteeism	Absence from work due to disability.
	AUDIT-C	A three-question screen for active alcohol use disorders.
	CAGE	A four-question screen for alcohol use disorders that asks whether one has ever thought about **C**utting down on their drinking, whether they are **A**nnoyed by criticism for their drinking, if they ever feel **G**uilty about their drinking, and if they ever take an **E**arly morning, or "eye-opener" drink.
	GAD	Screen used within primary care to identify individuals with probable GAD, comes as both the GAD-2 and GAD-7.
	HIT-6	Used to assess the impact that headache has on a person's life, with responses for each of the six questions ranging from "never" to "always."

Category	Term	Definition
Headache Assessments (cont.)	ID Migraine	This three-question screening tool for migraine asks (yes/no) whether someone feels nauseated/sick to their stomach, if light bothers them during a headache, and if headaches limit one's ability to work, study, or do what is needed. Patients answering 2 of 3 of these questions in the affirmative have a 75% chance of having migraine.
	MIDAS	Standardized assessment of the disability associated with migraine. MIDAS grades range from little or no disability to severe disability.
	MSQL	A 25-item scale used to assess the QoL among those living with migraine.
	PC-PTSD	Five-item screen that can be used to identify individuals with probable PTSD within primary care settings.
	PHQ	Screen used within primary care to identify individuals with depression; comes as both the PHQ-2 and PHQ-9.
	Presenteeism	Loss of productivity due to disability that occurs when a sick individual goes to work.
	Stigma	Negative and dismissive attitudes experienced by those living with a specific condition. Stigma has been associated with lower QoL and greater impact of headache in one's life.
	SNOOP(4)E	Assessment for "red flags" found on the headache history and physical examination. Systemic, neurologic, onset sudden, onset after 50, pattern change, precipitated, postural, papilledema, exertion. See Sidebar 1 for more information.
	STOP-BANG	Commonly used screen for obstructive sleep apnea. Includes the following components: snoring history, tired during the day, observed stop breathing while sleep, high blood pressure, BMI more than 35 kg/m^2, age more than 50 years, neck circumference more than 40 cm, and male sex. See Sidebar 1 for more information. Online resources are also available to help calculate this score (https://www.mdcalc.com/calc/3992/stop-bang-score-obstructive-sleep-apnea).
Headache Interventions	Active Rehabilitation Approaches	Includes exercise and stretching therapies in which the patient is the primary mover of the therapy. This is in comparison with passive approaches, which include manual therapy, manipulation, cryotherapy, and dry needling. Active approaches can be used as a standalone treatment or in combination with other active as well as passive approaches.
	Behavioral Interventions	A non-pharmacologic approach to headache management where interventions are intended to understand and change behaviors, with the intention of aiding in changing the behavior of individuals and improving health outcomes. These interventions include biofeedback, CBT, mindfulness-based therapies, PMR, and smartphone application-based heartrate variability monitoring.
	Biofeedback	Uses specialized equipment to help patients gain self-awareness skills by monitoring their physiological responses to improve body self-regulation.
	CBT	A structured, goal-oriented form of treatment that focuses on thought-based (cognitive) and action-based (behavioral) intervention components to facilitate treatment of various psychological as well as physiological symptoms, such as headache.

Category	Term	Definition
Headache Interventions (cont.)	CGRP Inhibition	CGRP is a potent vasodilator. Inhibition of the CGRP pathway can be accomplished through mAbs or small molecule receptor antagonists (gepants) and associated with prevention of migraine.
	Mindfulness-Based Therapies	Facilitate the process of intentional awareness in a non-judgmental manner. They often include meditation, relaxation, mindfulness-based stress reduction, mindfulness-based cognitive therapy, and acceptance-based approaches, among others.
	GON	GON block involved injection of an anesthetic agent (with or without steroids) near the GON with the intention of reducing inflammation and reliving pain.
	Neuromodulation	Refers to the process by which the central or peripheral nervous system is stimulated via energy (typically electric or magnetic) with the intention of regulating neural pathways and ameliorating pain and possibly other symptoms associated with headache. Neuromodulation can include via the following: n-VNS; SON, or external trigeminal nerve, stimulation; remote electrical neurostimulation; external combined occipital and trigeminal neurostimulation system; rTMS; and tDCS.
	PMR Therapy	A relaxation technique that encompasses tensing and relaxing individual muscle groups.
	Pulsed Radiofrequency	A minimally invasive treatment for the management of headache, typically performed in the upper cervical nerves and involves direct delivery of energy into nerves that might be responsible for pain.
	Smartphone Application-Based Heartrate Variability Monitoring	Mobile devices can be used to assess heart rate variability or the amount of time a person's heartbeat fluctuates.
	SON	A procedure where local anesthetic is injected locally medially and laterally along the orbital rim.
	SPG Block	A procedure where local anesthetic is delivered topically or injected into the area of the SPG.
	SPG Stimulation	SPG stimulation accomplished via an implantable stimulator.

Abbreviations: AUDIT-C: Alcohol Use Disorders Identification Test-Concise; CAGE: Cutting down on their drinking, whether they are Annoyed by criticism for their drinking, if they ever feel Guilty about their drinking, and if they ever take an Early morning, or "eye-opener," drink; CBT: cognitive behavioral therapy; CGRP: calcitonin gene-related peptide; GAD: generalized anxiety disorder; GON: greater occipital nerve block; HIT-6: Headache Impact Test, 6th edition; ICHD-3: International Classification of Headache Disorders, 3rd edition; mAbs: monoclonal antibodies; MIDAS: Migraine Disability Assessment Test; MOH: medication overuse headache; MSQL: Migraine Specific Quality of Life; n-VNS: non-invasive vagus nerve stimulation; PC-PTSD: Primary Care-Post Traumatic Stress Disorder; PHQ: Patient Health Questionnaire; PMR: progressive muscle relaxation; PTH: posttraumatic headache; QoL: quality of life; rTMS: repetitive transcranial magnetic stimulation; SNOOP(4)E: Systemic, Neurologic, Onset sudden, Onset after 50, Pattern change, Precipitated, Postural, Papilledema, Exertion; SON: supraorbital nerve; SPG: sphenopalatine ganglion; STOP-BANG: Snoring history, Tired during the day, Observed stop breathing while sleep, High blood pressure, BMI more than 35 kg/m2, Age more than 50 years, Neck circumference more than 40 cm, and male Sex; TAC: trigeminal autonomic cephalalgias; tDCS: transcranial direct current stimulation; TTH: tension-type headache

Appendix I: Participant List

CDR (Ret) Jane Abanes, PhD, DNP, MSN/Ed, PMHCNS, PMHNP-BC, RN
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Appendix J: Literature Review Search Terms and Strategy

Table J-1. EMBASE and MEDLINE in EMBASE.com Syntax

KQ #	Set #	Description	EMBASE Search String
KQ 1, KQ 2, KQ 4, KQ 5, KQ 6, KQ 10	#1	Cluster headache, migraine, tension-type headache	"cluster headache"/exp OR "migraine"/exp OR "tension headache"/exp OR (((cluster OR tension) NEXT/2 headache*) OR migrain* OR ((essential OR idiopathic OR "muscle contraction" OR neurological OR psychogenic OR stress) NEXT/1 headache*)):ti,ab,kw
	#2	General headache	"headache and facial pain"/mj/exp OR headache*:ti
	#3	Primary headache (other than cluster, migraine, tension)	"chronic daily headache"/exp OR "chronic headache"/de OR "cough headache"/de OR "episodic headache"/de OR "exertional headache"/de OR "hemicrania continua"/exp OR "hypnic headache"/de OR "nummular headache"/de OR "primary headache"/exp OR "recurrent headache"/de OR "stabbing headache"/de OR "thunderclap headache"/de OR "trigeminal autonomic cephalalgia"/exp OR (((chronic OR compression OR cough OR daily OR episodic OR exercise OR exertional OR hypnic OR neuralgiform OR nummular OR persistent) NEXT/2 headache*) OR "hemicrania continua" OR "paroxysmal hemicrania" OR (primary NEAR/2 headache*) OR SUNA OR SUNCT OR "trigeminal autonomic cephalalgia*"):ti,ab,kw
	#4	Secondary headache (other than post-traumatic or medication overuse)	"secondary headache"/exp OR "vascular headache"/de OR (((cervicogenic OR musculoskeletal OR secondary OR vascular) NEAR/2 headache*) OR "occipital neuralgia*"):ti,ab,kw
	#5	Combine population sets	#1 OR #2 OR #3 OR #4
	#6	Broad descriptive pharmacologic terms (acute, prophylactic)	"antimigraine agent"/mj/exp OR (abort* OR (acute NEXT/2 (therap* OR treatment*)) OR agent OR agents OR "anti migrain*" OR antimigrain* OR drug OR drugs OR medication* OR medicine* OR pharmacologic* OR prevent* OR prophyla* OR therapeutic* OR treat*):ti
	#7	Angiotensin-converting enzyme (ACE) inhibitors (prophylactic)	"dipeptidyl carboxypeptidase inhibitor"/mj/exp OR ("ACE inhibitor*" OR "angiotensin-converting enzyme inhibitor*" OR benazepril OR captopril OR enalapril OR fosinopril OR lisinopril OR moexipril OR perindopril OR quinapril OR ramipril OR trandolapril):ti
	#8	Angiotensin II receptor blockers (ARBS) (prophylactic)	"angiotensin receptor antagonist"/mj/exp OR ((angiotensin NEXT/2 receptor NEXT/1 (antagonist* OR block*)) OR (azilsartan OR candesartan OR eprosartan OR irbesartan OR losartan OR olmesartan OR telmisartan OR valsartan)):ti

KQ #	Set #	Description	EMBASE Search String
KQ 1, KQ 2, KQ 4, KQ 5, KQ 6, KQ 10 (cont.)	#9	Antidepressant agents (prophylactic)	"antidepressant agent"/mj/exp OR (amitriptyline OR "anti-depressant*" OR "anti depressive*" OR antidepressant* OR antidepressive* OR amitriptyline OR citalopram OR desipramine OR doxepin OR duloxetine OR escitalopram OR fluoxetine OR fluvoxamine OR imipramine OR mirtazapine OR nortriptyline OR paroxetine OR protriptyline OR (serotonin NEXT/3 (antagonist* OR inhibitor*)) OR sertraline OR SNRI* OR SSRI* OR tricyclic* OR tetracyclic* OR venlafaxine):ti
	#10	Antiemetic agents (acute)	"antiemetic agent"/mj/exp OR ("anti naus*" OR antinaus* OR "anti emetic*" OR antiemetic* OR chlorpromazine OR metoclopramide OR ondansetron OR prochlorperazine OR promethazine):ti
	#11	Antiepileptic agents (acute, prophylactic)	"anticonvulsive agent"/exp/mj OR ("anti convuls*" OR anticonvuls* OR "anti epileptic*" OR antiepileptic* OR "anti seizure" OR antiseizure OR depakote* OR divalpro* OR gabapentin OR levetiracetam OR lamotrigine OR pregabalin OR topiramate OR valproate OR valproic OR zonisamide):ti
	#12	Beta blockers (prophylactic)	"beta adrenergic receptor blocking agent"/exp/mj OR ((beta NEXT/2 (antagonist* OR block*)) OR atenolol OR metoprolol OR nadolol OR propranolol OR timolol):ti
	#13	Botulinum toxins (prophylactic, invasive neuromodulation)	"botulinum toxin A"/mj OR "botulinum toxin B"/mj OR "chemodenervation"/de OR "neurotoxin"/mj OR (abobotulinum* OR "botulinum toxin*" OR "chemo-denervation" OR chemodenervation OR incobotulinum* OR neurotoxin* OR onabotulinum* OR OBTA OR rimabotulinum*):ti OR (botox* OR dysport* OR myobloc* OR xeomin*):ti,tn
	#14	Calcitonin gene related peptide receptor (CGRP) inhibitors (acute, prophylactic)	"calcitonin gene related peptide receptor antagonist"/mj/exp OR ("anti CGRP" OR antiCGRP OR (("calcitonin gene related peptide" OR CGRP) NEXT/2 (antagonist* OR block* OR inhibit* OR "monoclonal antibod*")) OR atogepant OR eptinezumab* OR erenumab* OR fremanezumab* OR galcanezumab* OR rimegepant OR ubrogepant):ti
	#15	Combination agents (acute)	"antipyretic analgesic agent"/mj/exp OR "acetylsalicylic acid plus caffeine plus paracetamol"/mj OR "butalbital plus caffeine plus paracetamol"/mj OR "combination drug therapy"/mj OR "dichloralphenazone plus isometheptene mucate plus paracetamol"/mj OR "drug combination"/mj OR (combin* OR ((acetaminophen OR paracetamol) AND (butalbital OR caffeine)) OR (("acetylsalicylic acid" OR aspirin) AND (butalbital OR caffeine)) OR ((acetaminophen OR paracetamol) AND isometheptene AND dichloralphenazone)):ti

KQ #	Set #	Description	EMBASE Search String
KQ 1, KQ 2, KQ 4, KQ 5, KQ 6, KQ 10 (cont.)	#16	Injections and intravenous treatments – controlled terms (prophylactic, invasive)	"dexamethasone"/mj OR "dihydroergotamine"/mj OR "diphenhydramine"/mj OR "eptinezumab"/mj OR "erenumab"/mj OR "fremanezumab"/mj OR "galcanezumab"/mj OR "hydromorphone"/mj OR "infusion"/de OR "infusion fluid"/exp OR "injection"/exp OR "intramuscular drug administration"/de OR "intravenous drug administration"/de OR "ketorolac"/mj OR "magnesium"/mj OR "magnesium sulfate"/mj OR "methylprednisolone sodium succinate"/mj OR "metoclopramide"/mj OR "parenteral drug administration"/de OR "prochlorperazine"/mj OR "steroid"/mj OR "subcutaneous drug administration"/de OR "sumatriptan"/mj OR "trigger point injection"/de
	#17	Injections and intravenous treatments – text words (prophylactic, invasive)	("anti naus*" OR antinaus* OR "anti-emetic*" OR antiemetic* OR "cervical facet" OR dexamethasone OR dihydroergotamine OR diphenhydramine OR eptinezumab OR erenumab OR fremanezumab OR fluid* OR galcanezumab OR hydromorphone OR ketorolac OR magnesium OR metoclopramide OR prochlorperazine OR steroid* OR sumatriptan OR "trigger point*" OR valproate OR infus* OR inject* OR intramuscular* OR intravenous* OR IV OR parenteral OR subcutaneous*):ti
	#18	Long-acting dihydropyridine (DHP) calcium channel blockers (CCBs) (prophylactic)	"dihydropyridine derivative"/mj/exp OR ((dihydropyridine AND ("long acting" OR "calcium channel")) OR amlodipine OR felodipine OR nicardipine OR nifedipine OR nisoldipine):ti
	#19	Nerve blocks (invasive)	"nerve block"/mj/exp OR ((nerve NEXT/2 block*) OR ((auriculotemporal OR "auriculo-temporal" OR cervical OR ganglion OR "medial branch" OR occipital OR peripheral OR sphenopalatine OR stellate OR supraorbital OR "supra-orbital") NEXT/3 (epidural* OR block*))):ti
	#20	Non-beta blocker antihypertensives (prophylactic)	"calcium antagonist"/mj/exp OR "calcium channel blocking agent"/mj/exp OR ("anti hypertensive*" OR antihypertensive* OR (calcium NEXT/2 (block* OR antagonist*)) OR flunarizine OR nimodipine OR verapamil):ti
	#21	Opioids (acute)	"butalbital plus caffeine plus paracetamol"/mj OR "hydrocodone bitartrate plus paracetamol"/mj OR "narcotic analgesic agent"/mj/exp OR "opiate"/mj OR "opiate agonist"/mj/exp OR "oxycodone plus paracetamol"/mj OR (((acetaminophen OR paracetamol) AND (butalbital OR caffeine OR hydrocodone OR oxycodone)) OR morphine* OR opiate* OR opioid* OR narcotic* OR tramadol):ti OR (fioricet* OR percocet* OR vicodin*):ti,tn
	#22	Serotonin 5-HT receptor agonists (acute)	"serotonin agonist"/mj/exp OR (almotriptan OR eletriptan OR frovatriptan OR lasmiditan OR naratriptan OR rizatriptan OR (serotonin NEXT/3 agonist*) OR sumatriptan OR zolmitriptan):ti

KQ #	Set #	Description	EMBASE Search String
KQ 1, KQ 2, KQ 4, KQ 5, KQ 6, KQ 10 (cont.)	#23	Simple analgesics / Non-steroidal anti-inflammatory drugs (NSAIDs) (acute)	"acetylsalicylic acid"/mj/exp OR "nonsteroid antiinflammatory agent"/mj/exp OR "paracetamol"/mj/exp OR "salicylic acid derivative"/mj/exp OR (acetaminophen OR "acetylsalicylic acid" OR analgesic* OR aspirin OR celecoxib OR "choline mg" OR "choline magnesium trisalicylate" OR dexketoprofen OR diflunisal OR etodolac OR ibuprofen OR indomethacin OR ketorolac OR meloxicam OR nabumetone OR naproxen OR (("non-steroidal" OR nonsteroidal) NEXT/1 ("anti-inflammator*" OR antiinflammator*)) OR NSAID* OR "oral diclofenac" OR paracetamol OR piroxicam OR salsalate OR sulindac):ti
	#24	Other prophylactic/preventive pharmacologic therapies specified by workgroup	"cyproheptadine"/mj OR "memantine"/mj OR ("anti histamin*" OR antihistamin* OR cyproheptadine OR memantine OR (("n-methyl-d-aspartate" OR NMDA) NEXT/2 antagonist*)):ti
	#25	Other acute/abortive pharmacologic therapies specified by the workgroup	"butorphanol tartrate"/mj/exp OR "caffeine"/mj OR "dihydroergotamine"/mj/exp OR "ergotamine"/mj OR "ketamine"/mj OR ("intranasal drug administration"/de AND lidocaine/mj) OR "tizanidine"/mj OR ("butorphanol tartrate" OR caffeine OR dihydroergotamine OR ergotamine OR (("intra nasal" OR intranasal) NEAR/3 lidocaine) OR ketamine OR tizanidine):ti
	#26	Combine intervention sets	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25
	#27	Combine population and intervention sets	#5 AND #26
	Apply standard exclusion and inclusion filters		See end of table
	Limit to systematic reviews, meta-analyses, and randomized controlled trials		See end of table
KQ 3	#1	Post-traumatic headache	("posttraumatic headache"/exp OR ("head and neck injury"/mj/exp AND "headache and facial pain"/mj/exp) OR ((concuss* OR craniotom* OR injur* OR postconcuss* OR posttrauma* OR trauma* OR whiplash) NEAR/3 (headache* OR migrain*)):ti,ab,kw) NOT "pre injury":ti
	#2	Broad descriptive pharmacologic terms (acute, prophylactic)	"antimigraine agent"/mj/exp OR (abort* OR (acute NEXT/2 (therap* OR treatment*)) OR agent OR agents OR "anti migrain*" OR antimigrain* OR drug OR drugs OR medication* OR medicine* OR pharmacologic* OR prevent* OR prophyla* OR therapeutic* OR treat*):ti
	#3	Angiotensin-converting enzyme (ACE) inhibitors (prophylactic)	"dipeptidyl carboxypeptidase inhibitor"/mj/exp OR ("ACE inhibitor*" OR "angiotensin-converting enzyme inhibitor*" OR benazepril OR captopril OR enalapril OR fosinopril OR lisinopril OR moexipril OR perindopril OR quinapril OR ramipril OR trandolapril):ti

KQ #	Set #	Description	EMBASE Search String
KQ 3 (cont.)	#4	Angiotensin II receptor blockers (ARBS) (prophylactic)	"angiotensin receptor antagonist"/mj/exp OR ((angiotensin NEXT/2 receptor NEXT/1 (antagonist* OR block*)) OR (azilsartan OR candesartan OR eprosartan OR irbesartan OR losartan OR olmesartan OR telmisartan OR valsartan)):ti
	#5	Antidepressant agents (prophylactic)	"antidepressant agent"/mj/exp OR (amitriptyline OR "anti-depressant*" OR "anti depressive*" OR antidepressant* OR antidepressive* OR amitriptyline OR citalopram OR desipramine OR doxepin OR duloxetine OR escitalopram OR fluoxetine OR fluvoxamine OR imipramine OR mirtazapine OR nortriptyline OR paroxetine OR protriptyline OR (serotonin NEXT/3 (antagonist* OR inhibitor*)) OR sertraline OR SNRI* OR SSRI* OR tricyclic* OR tetracyclic* OR venlafaxine):ti
	#6	Antiemetic agents (acute)	"antiemetic agent"/mj/exp OR ("anti naus*" OR antinaus* OR "anti emetic*" OR antiemetic* OR chlorpromazine OR metoclopramide OR ondansetron OR prochlorperazine OR promethazine):ti
	#7	Antiepileptic agents (acute, prophylactic)	"anticonvulsive agent"/exp/mj OR ("anti convuls*" OR anticonvuls* OR "anti epileptic*" OR antiepileptic* OR "anti seizure" OR antiseizure OR depakote* OR divalpro* OR gabapentin OR levetiracetam OR lamotrigine OR pregabalin OR topiramate OR valproate OR valproic OR zonisamide):ti
	#8	Beta blockers (prophylactic)	"beta adrenergic receptor blocking agent"/exp/mj OR ((beta NEXT/2 (antagonist* OR block*)) OR atenolol OR metoprolol OR nadolol OR propranolol OR timolol):ti
	#9	Botulinum toxins (prophylactic, invasive neuromodulation)	"botulinum toxin A"/mj OR "botulinum toxin B"/mj OR "chemodenervation"/de OR "neurotoxin"/mj OR (abobotulinum* OR "botulinum toxin*" OR "chemo-denervation" OR chemodenervation OR incobotulinum* OR neurotoxin* OR onabotulinum* OR OBTA OR rimabotulinum*):ti OR (botox* OR dysport* OR myobloc* OR xeomin*):ti,tn
	#10	Calcitonin gene related peptide receptor (CGRP) inhibitors (acute, prophylactic)	"calcitonin gene related peptide receptor antagonist"/mj/exp OR ("anti CGRP" OR antiCGRP OR (("calcitonin gene related peptide" OR CGRP) NEXT/2 (antagonist* OR block* OR inhibit* OR "monoclonal antibod*")) OR atogepant OR eptinezumab* OR erenumab* OR fremanezumab* OR galcanezumab* OR rimegepant OR ubrogepant):ti
	#11	Combination agents (acute)	"antipyretic analgesic agent"/mj/exp OR "acetylsalicylic acid plus caffeine plus paracetamol"/mj OR "butalbital plus caffeine plus paracetamol"/mj OR "combination drug therapy"/mj OR "dichloralphenazone plus isometheptene mucate plus paracetamol"/mj OR "drug combination"/mj OR (combin* OR ((acetaminophen OR paracetamol) AND (butalbital OR caffeine)) OR (("acetylsalicylic acid" OR aspirin) AND (butalbital OR caffeine)) OR ((acetaminophen OR paracetamol) AND isometheptene AND dichloralphenazone)):ti

KQ #	Set #	Description	EMBASE Search String
KQ 3 (cont.)	#12	Injections and intravenous treatments – Controlled terms (prophylactic, neuromodulation)	"dexamethasone"/mj OR "dihydroergotamine"/mj OR "diphenhydramine"/mj OR "eptinezumab"/mj OR "erenumab"/mj OR "fremanezumab"/mj OR "galcanezumab"/mj OR "hydromorphone"/mj OR "infusion"/de OR "infusion fluid"/exp OR "injection"/exp OR "intramuscular drug administration"/de OR "intravenous drug administration"/de OR "ketorolac"/mj OR "magnesium"/mj OR "magnesium sulfate"/mj OR "methylprednisolone sodium succinate"/mj OR "metoclopramide"/mj OR "parenteral drug administration"/de OR "prochlorperazine"/mj OR "steroid"/mj OR "subcutaneous drug administration"/de OR "sumatriptan"/mj OR "trigger point injection"/de
	#13	Injections and intravenous treatments – Text words (prophylactic, neuromodulation)	("anti naus*" OR antinaus* OR "anti-emetic*" OR antiemetic* OR "cervical facet" OR dexamethasone OR dihydroergotamine OR diphenhydramine OR eptinezumab OR erenumab OR fremanezumab OR fluid* OR galcanezumab OR hydromorphone OR ketorolac OR magnesium OR metoclopramide OR prochlorperazine OR steroid* OR sumatriptan OR "trigger point*" OR valproate OR infus* OR inject* OR intramuscular* OR intravenous* OR IV OR parenteral OR subcutaneous*):ti
	#14	Long-acting dihydropyridine (DHP) calcium channel blockers (CCBs) (prophylactic)	"dihydropyridine derivative"/mj/exp OR ((dihydropyridine AND ("long acting" OR "calcium channel")) OR amlodipine OR felodipine OR nicardipine OR nifedipine OR nisoldipine):ti
	#15	Nerve blocks (neuromodulation)	"nerve block"/mj/exp OR ((nerve NEXT/2 block*) OR ((auriculotemporal OR "auriculo-temporal" OR cervical OR ganglion OR "medial branch" OR occipital OR peripheral OR sphenopalatine OR stellate OR supraorbital OR "supra-orbital") NEXT/3 (epidural* OR block*))):ti
	#16	Non-beta blocker antihypertensives (prophylactic)	"calcium antagonist"/mj/exp OR "calcium channel blocking agent"/mj/exp OR ("anti hypertensive*" OR antihypertensive* OR (calcium NEXT/2 (block* OR antagonist*)) OR flunarizine OR nimodipine OR verapamil):ti
	#17	Opioids (acute)	"butalbital plus caffeine plus paracetamol"/mj OR "hydrocodone bitartrate plus paracetamol"/mj OR "narcotic analgesic agent"/mj/exp OR "opiate"/mj OR "opiate agonist"/mj/exp OR "oxycodone plus paracetamol"/mj OR (((acetaminophen OR paracetamol) AND (butalbital OR caffeine OR hydrocodone OR oxycodone)) OR morphine* OR opiate* OR opioid* OR narcotic* OR tramadol):ti OR (fioricet* OR percocet* OR vicodin*):ti,tn
	#18	Serotonin 5-HT receptor agonists (acute)	"serotonin agonist"/mj/exp OR (almotriptan OR eletriptan OR frovatriptan OR lasmiditan OR naratriptan OR rizatriptan OR (serotonin NEXT/3 agonist*) OR sumatriptan OR zolmitriptan):ti

KQ #	Set #	Description	EMBASE Search String
KQ 3 (cont.)	#19	Simple analgesics / Non-steroidal anti-inflammatory drugs (NSAIDs) (acute)	"acetylsalicylic acid"/mj/exp OR "nonsteroid antiinflammatory agent"/mj/exp OR "paracetamol"/mj/exp OR "salicylic acid derivative"/mj/exp OR (acetaminophen OR "acetylsalicylic acid" OR analgesic* OR aspirin OR celecoxib OR "choline mg" OR "choline magnesium trisalicylate" OR dexketoprofen OR diflunisal OR etodolac OR ibuprofen OR indomethacin OR ketorolac OR meloxicam OR nabumetone OR naproxen OR (("non-steroidal" OR nonsteroidal) NEXT/1 ("anti-inflammator*" OR antiinflammator*)) OR NSAID* OR "oral diclofenac" OR paracetamol OR piroxicam OR salsalate OR sulindac):ti
	#20	Other prophylactic/preventive pharmacologic therapies specified by workgroup	"cyproheptadine"/mj OR "memantine"/mj OR ("anti histamin*" OR antihistamin* OR cyproheptadine OR memantine OR (("n-methyl-d-aspartate" OR NMDA) NEXT/2 antagonist*)):ti
	#21	Other acute/abortive pharmacologic therapies specified by the workgroup	"butorphanol tartrate"/mj/exp OR "caffeine"/mj OR "dihydroergotamine"/mj/exp OR "ergotamine"/mj OR "ketamine"/mj OR ("intranasal drug administration"/de AND lidocaine/mj) OR "tizanidine"/mj OR ("butorphanol tartrate" OR caffeine OR dihydroergotamine OR ergotamine OR (("intra nasal" OR intranasal) NEAR/3 lidocaine) OR ketamine OR tizanidine):ti
	#22	Broad, descriptive terms (invasive and noninvasive)	"neuromodulation"/mj OR ("neuro modulat*" OR neuromodulat*):ti
	#23	Broad, descriptive terms (invasive)	(invasive NEXT/3 (neurostimulat* OR stimulat*)):ti
	#24	Cold laser (invasive)	"low level laser therapy"/de OR ("cold ablation" OR "low level laser*" OR photobiomodulation):ti,ab,kw
	#25	Deep brain stimulation, Greater occipital nerve invasive electrical stimulation, and Sphenopalatine ganglion stimulation (invasive)	"brain depth stimulation"/de OR ("deep brain stimulat*" OR (occipital AND (neurostimulat* OR stimulat*) AND (electric* OR greater OR invasive*)) OR "sphenopalatine ganglion stimulat*"):ti,ab,kw
	#26	Implanted stimulators (invasive)	"implantable neurostimulator"/exp OR ((implant* NEXT/3 ("neuro modulat*" OR neuromodulat* OR "neuro stimulat*" OR neurostimulat* OR stimulat*)) OR "peripheral nerve stimulat*" OR ("peripheral nerve" NEXT/2 "field stimulat*")):ti,ab,kw
	#27	Neurotomy procedures (invasive)	"ablation therapy"/exp OR "neurolysis"/de OR "neurotomy"/de OR (((chemical OR cold OR "radio-frequency" OR radiofrequency) NEXT/1 ablation) OR neurolysis OR neurotomy):ti,ab,kw
	#28	Pulsed radiofrequency (invasive)	"pulsed radiofrequency"/de OR "pulsed radiofrequency treatment"/de OR "radiofrequency therapy"/de OR ((pulsed NEXT/1 ("radio frequency" OR radiofrequency)) OR (("radio frequency" OR radiofrequency) NEXT/1 stimulat*)):ti,ab,kw

KQ #	Set #	Description	EMBASE Search String
KQ 3 (cont.)	#29	Surgical procedures	"atrial septal occluder"/de OR decompression/de OR "decompression surgery"/de OR "microvascular decompression"/de OR "nerve decompression"/de OR "patent foramen ovale closure"/de OR (("atrial septal defect*" OR "patent foramen ovale" OR "right to left shunt*") AND (clos* OR occlu*)):ti,ab,kw OR (decompression OR surg):ti
	#30	Broad, descriptive terms (non-invasive)	(("minimally invasive" OR "non invasive" OR noninvasive) NEXT/3 (neurostimulat* OR stimulat*)):ti
	#31	Non-invasive neuromodulation - controlled terms (non-invasive)	"cranial electrotherapy stimulator"/de OR "electroacupuncture"/de OR "occipital nerve stimulation"/de OR "neuromodulation"/de OR "repetitive peripheral magnetic stimulation"/de OR "transcranial direct current stimulation"/de OR "transcranial direct current stimulator"/de OR "transcranial electrical stimulation"/de OR "transcranial electrical stimulator"/exp OR "transcranial magnetic stimulation"/exp OR "transcutaneous electrical nerve stimulation"/de OR "transcutaneous electrical nerve stimulator"/exp OR "trigeminal nerve stimulation"/de OR "vagus nerve stimulation"/de OR "vagus nerve stimulator"/de
	#32	Non-invasive neuromodulation - Text words (non-invasive)	(((cranial OR transcranial) NEXT/2 (electric* OR electro* OR stimulat*)) OR "electro acupuncture" OR electroacupuncture OR (("non-invasive" OR noninvasive) NEXT/3 ("nerve stimulat*" OR "neuro modulat*" OR neuromodulat* OR "neuro stimulat*" OR neurostimulat*)) OR ((mastoid OR occipital OR "supra-orbital" OR supraorbital OR trigeminal OR vagal OR vagus) NEXT/4 (neurostimulat* OR stimulat*)) OR "percutaneous electric* nerve stimulat*" OR "remote electric* neuromodulat*" OR "repetitive peripheral magnetic stimulat*" OR "transcranial direct current stimulat*" OR "transcranial magnetic stimulat*" OR (transcutaneous NEXT/2 "nerve stimulat*") OR (vibrating NEXT/1 ("head band*" OR headband*))):ab,ti,kw OR (DCS OR tDCS OR ONS OR tONS OR "nerve stimulat*" OR REN OR SNS OR tSNS OR TENS OR TMS OR sTMS OR TNS OR eTNS OR VNS OR nVNS):ti OR ("alpha stim*" OR alphastim*):ti,ab,kw,dn
	#33	Non-invasive neuromodulation - commercial devices (noninvasive)	(cefaly* OR eneura* OR gammacore* OR nerivio* OR relivion* OR "stms mini*"):ab,ti,kw,dn,df
	#34	Complementary integrative health interventions - controlled terms	"acupressure device"/de OR "acupuncture"/de OR "acupuncture point"/exp OR "alternative medicine"/exp OR "biofeedback"/de OR "breathing exercise"/exp OR "diaphragmatic breathing"/de OR "green light"/de OR "green light exposure"/de OR "guided imagery"/de OR "light exposure"/de OR "massage"/exp OR "meditation"/exp OR "mindfulness"/exp OR "phototherapy"/exp OR "qigong"/de OR "relaxation training"/de OR "stress management"/de OR "tai chi"/de OR "white light"/de OR "yoga"/exp

KQ #	Set #	Description	EMBASE Search String
KQ 3 (cont.)	#35	Complementary integrative health interventions - text words	("acu point*" OR acupoint* OR acupressure OR acupuncture OR biofeedback OR "breathing exercise*" OR "breathing technique*" OR ((deep OR diaphragmatic) NEXT/1 breathing) OR "green light" OR "guided imagery" OR "light exposure" OR "light therapy" OR massag* OR meditat* OR "mind-body" OR mindful* OR "myofascial release" OR "non pharmacologic*" OR "nonpharmacologic*" OR photodynamic OR phototherapy OR "progressive muscle relaxation" OR "qi gong" OR qigong OR "relaxation therap*" OR "relaxation training" OR (stress NEAR/2 manag*) OR "tai chi" OR taichi OR "tai ji" OR taiji* OR "thermal therapy" OR thermazone* OR "tinted glasses" OR yoga OR yogic):ab,ti,kw OR ((alternative OR complementary OR integrative) NEXT/3 (approach* OR intervention* OR manag* OR medical OR medicine* OR technique* OR therap* OR treat*)):ti
	#36	Behavioral health approaches - controlled terms	"acceptance and commitment therapy"/de OR "behavior therapy"/de OR "breathing exercise"/exp OR "biofeedback"/de OR "cognitive behavioral therapy"/exp OR "compassion focused therapy"/de OR "diaphragmatic breathing"/de OR "guided imagery"/de OR "mindfulness based cognitive therapy"/de OR "mindfulness-based stress reduction"/de OR "psychotherapy"/exp OR "relaxation training"/de
	#37	Behavioral health approaches - text words	("acceptance and commitment" OR (behav* NEXT/2 (approach* OR health OR intervention* OR manag* OR technique* OR therap* OR treat*)) OR biofeedback OR "breathing exercise*" OR "breathing technique*" OR "cognitive behav*" OR combin* OR "compassion focused therapy" OR ((deep OR diaphragmatic) NEXT/1 breathing) OR desensiti* OR dialectical OR "educational intervention*" OR "guided imagery" OR (manag* NEAR/3 trigger*) OR "mind body" OR (mindful* NEXT/2 ("cognitive therapy" OR "stress reduction")) OR "progressive muscle relaxation" OR psychotherap*):ti,ab,kw OR (cbt OR intervention* OR manag* OR mbct OR mbsr OR psychological OR trigger*):ti
	#38	Combine intervention sets	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37
	#39	Combine population and intervention sets	#1 AND #38
	Apply standard exclusion and inclusion filters		See end of table
	Limit to systematic reviews, meta-analyses, and randomized controlled trials		See end of table

KQ #	Set #	Description	EMBASE Search String
KQ 6	#1	Cluster headache, migraine, tension-type headache	"cluster headache"/exp OR "migraine"/exp OR "tension headache"/exp OR (((cluster OR tension) NEXT/2 headache*) OR migrain* OR ((essential OR idiopathic OR "muscle contraction" OR neurological OR psychogenic OR stress) NEXT/1 headache*)):ti,ab,kw
	#2	General headache	"headache and facial pain"/mj/exp OR headache*:ti
	#3	Primary headache (other than cluster, migraine, tension)	"chronic daily headache"/exp OR "chronic headache"/de OR "cough headache"/de OR "episodic headache"/de OR "exertional headache"/de OR "hemicrania continua"/exp OR "hypnic headache"/de OR "nummular headache"/de OR "primary headache"/exp OR "recurrent headache"/de OR "stabbing headache"/de OR "thunderclap headache"/de OR "trigeminal autonomic cephalalgia"/exp OR (((chronic OR compression OR cough OR daily OR episodic OR exercise OR exertional OR hypnic OR neuralgiform OR nummular OR persistent) NEXT/2 headache*) OR "hemicrania continua" OR "paroxysmal hemicrania" OR (primary NEAR/2 headache*) OR SUNA OR SUNCT OR "trigeminal autonomic cephalalgia*"):ti,ab,kw
	#4	Secondary headache (other than post-traumatic or medication overuse)	"secondary headache"/exp OR "vascular headache"/de OR (((cervicogenic OR musculoskeletal OR secondary OR vascular) NEAR/2 headache*) OR "occipital neuralgia*"):ti,ab,kw
	#5	Combine population sets	#1 OR #2 OR #3 OR #4
	#6	Broad, descriptive terms (invasive and noninvasive)	"neuromodulation"/mj OR ("neuro modulat*" OR neuromodulat*):ti
	#7	Broad, descriptive terms (invasive)	(invasive NEXT/3 (neurostimulat* OR stimulat*)):ti
	#8	Cold laser (invasive)	"low level laser therapy"/de OR ("cold ablation" OR "low level laser*" OR photobiomodulation):ti,ab,kw
	#9	Deep brain stimulation, Greater occipital nerve invasive electrical stimulation, and Sphenopalatine ganglion stimulation (invasive)	"brain depth stimulation"/de OR ("deep brain stimulat*" OR (occipital AND (neurostimulat* OR stimulat*) AND (electric* OR greater OR invasive*)) OR "sphenopalatine ganglion stimulat*"):ti,ab,kw
	#10	Implanted stimulators (invasive)	"implantable neurostimulator"/exp OR ((implant* NEXT/3 ("neuro modulat*" OR neuromodulat* OR "neuro stimulat*" OR neurostimulat* OR stimulat*)) OR "peripheral nerve stimulat*" OR ("peripheral nerve" NEXT/2 "field stimulat*")):ti,ab,kw
	#11	Neurotomy procedures (invasive)	"ablation therapy"/exp OR "neurolysis"/de OR "neurotomy"/de OR (((chemical OR cold OR "radio-frequency" OR radiofrequency) NEXT/1 ablation) OR neurolysis OR neurotomy):ti,ab,kw
	#12	Pulsed radiofrequency (invasive)	"pulsed radiofrequency"/de OR "pulsed radiofrequency treatment"/de OR "radiofrequency therapy"/de OR ((pulsed NEXT/1 ("radio frequency" OR radiofrequency)) OR (("radio frequency" OR radiofrequency) NEXT/1 stimulat*)):ti,ab,kw

KQ #	Set #	Description	EMBASE Search String
KQ 6 (cont.)	#13	Surgical procedures	"atrial septal occluder"/de OR decompression/de OR "decompression surgery"/de OR "microvascular decompression"/de OR "nerve decompression"/de OR "patent foramen ovale closure"/de OR (("atrial septal defect*" OR "patent foramen ovale" OR "right to left shunt*") AND (clos* OR occlu*)):ti,ab,kw OR (decompression OR surg):ti
	#14	Broad, descriptive terms (non-invasive)	(("minimally invasive" OR "non invasive" OR noninvasive) NEXT/3 (neurostimulat* OR stimulat*)):ti
	#15	Non-invasive neuromodulation - controlled terms	"cranial electrotherapy stimulator"/de OR "electroacupuncture"/de OR "occipital nerve stimulation"/de OR "neuromodulation"/de OR "repetitive peripheral magnetic stimulation"/de OR "transcranial direct current stimulation"/de OR "transcranial direct current stimulator"/de OR "transcranial electrical stimulation"/de OR "transcranial electrical stimulator"/exp OR "transcranial magnetic stimulation"/exp OR "transcutaneous electrical nerve stimulation"/de OR "transcutaneous electrical nerve stimulator"/exp OR "trigeminal nerve stimulation"/de OR "vagus nerve stimulation"/de OR "vagus nerve stimulator"/de
	#16	Non-invasive neuromodulation - text words	(((cranial OR transcranial) NEXT/2 (electric* OR electro* OR stimulat*)) OR "electro acupuncture" OR electroacupuncture OR (("non-invasive" OR noninvasive) NEXT/3 ("nerve stimulat*" OR "neuro modulat*" OR neuromodulat* OR "neuro stimulat*" OR neurostimulat*)) OR ((mastoid OR occipital OR "supra-orbital" OR supraorbital OR trigeminal OR vagal OR vagus) NEXT/4 (neurostimulat* OR stimulat*)) OR "percutaneous electric* nerve stimulat*" OR "remote electric* neuromodulat*" OR "repetitive peripheral magnetic stimulat*" OR "transcranial direct current stimulat*" OR "transcranial magnetic stimulat*" OR (transcutaneous NEXT/2 "nerve stimulat*") OR (vibrating NEXT/1 ("head band*" OR headband*))):ab,ti,kw OR (DCS OR tDCS OR ONS OR tONS OR "nerve stimulat*" OR REN OR SNS OR tSNS OR TENS OR TMS OR sTMS OR TNS OR eTNS OR VNS OR nVNS):ti OR ("alpha stim*" OR alphastim*):ti,ab,kw,dn
	#17	Non-invasive neuromodulation - commercial devices	(cefaly* OR eneura* OR gammacore* OR nerivio* OR relivion* OR "stms mini*"):ab,ti,kw,dn,df
	#18	Combine intervention sets	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
	#19	Combine population and intervention sets	#5 AND #18
	Apply standard exclusion and inclusion filters		See end of table
	Limit to systematic reviews, meta-analyses, and randomized controlled trials		See end of table

KQ #	Set #	Description	EMBASE Search String
KQ 7	#1	Cluster headache, migraine, tension-type headache	"cluster headache"/exp OR "migraine"/exp OR "tension headache"/exp OR (((cluster OR tension) NEXT/2 headache*) OR migrain* OR ((essential OR idiopathic OR "muscle contraction" OR neurological OR psychogenic OR stress) NEXT/1 headache*)):ti,ab,kw
	#2	General headache	"headache and facial pain"/mj/exp OR headache*:ti
	#3	Primary headache (other than cluster, migraine, tension)	"chronic daily headache"/exp OR "chronic headache"/de OR "cough headache"/de OR "episodic headache"/de OR "exertional headache"/de OR "hemicrania continua"/exp OR "hypnic headache"/de OR "nummular headache"/de OR "primary headache"/exp OR "recurrent headache"/de OR "stabbing headache"/de OR "thunderclap headache"/de OR "trigeminal autonomic cephalalgia"/exp OR (((chronic OR compression OR cough OR daily OR episodic OR exercise OR exertional OR hypnic OR neuralgiform OR nummular OR persistent) NEXT/2 headache*) OR "hemicrania continua" OR "paroxysmal hemicrania" OR (primary NEAR/2 headache*) OR SUNA OR SUNCT OR "trigeminal autonomic cephalalgia*"):ti,ab,kw
	#4	Secondary headache (other than post-traumatic or medication overuse)	"secondary headache"/exp OR "vascular headache"/de OR (((cervicogenic OR musculoskeletal OR secondary OR vascular) NEAR/2 headache*) OR "occipital neuralgia*"):ti,ab,kw
	#5	Combine population sets	#1 OR #2 OR #3 OR #4
	#6	Complementary integrative health interventions - controlled terms	"acupressure device"/de OR "acupuncture"/de OR "acupuncture point"/exp OR "alternative medicine"/exp OR "biofeedback"/de OR "breathing exercise"/exp OR "diaphragmatic breathing"/de OR "green light"/de OR "green light exposure"/de OR "guided imagery"/de OR "light exposure"/de OR "massage"/exp OR "meditation"/exp OR "mindfulness"/exp OR "phototherapy"/exp OR "qigong"/de OR "relaxation training"/de OR "stress management"/de OR "tai chi"/de OR "white light"/de OR "yoga"/exp
	#7	Complementary integrative health interventions – text words	("acu point*" OR acupoint* OR acupressure OR acupuncture OR biofeedback OR "breathing exercise*" OR "breathing technique*" OR ((deep OR diaphragmatic) NEXT/1 breathing) OR "green light" OR "guided imagery" OR "light exposure" OR "light therapy" OR massag* OR meditat* OR "mind-body" OR mindful* OR "myofascial release" OR "non pharmacologic*" OR "nonpharmacologic*" OR photodynamic OR phototherapy OR "progressive muscle relaxation" OR "qi gong" OR qigong OR "relaxation therap*" OR "relaxation training" OR (stress NEAR/2 manag*) OR "tai chi" OR taichi OR "tai ji" OR taiji* OR "thermal therapy" OR thermazone* OR "tinted glasses" OR yoga OR yogic):ab,ti,kw OR ((alternative OR complementary OR integrative) NEXT/3 (approach* OR intervention* OR manag* OR medical OR medicine* OR technique* OR therap* OR treat*)):ti
	#8	Combine intervention sets	#5 AND #6

KQ #	Set #	Description	EMBASE Search String
KQ 7 (cont.)	#9	Combine population and intervention sets	
	Apply standard exclusion and inclusion filters		See end of table
	Limit to systematic reviews, meta-analyses, and randomized controlled trials		See end of table
KQ 8	#1	Cluster headache, migraine, tension-type headache	"cluster headache"/exp OR "migraine"/exp OR "tension headache"/exp OR (((cluster OR tension) NEXT/2 headache*) OR migrain* OR ((essential OR idiopathic OR "muscle contraction" OR neurological OR psychogenic OR stress) NEXT/1 headache*)):ti,ab,kw
	#2	General headache	"headache and facial pain"/mj/exp OR headache*:ti
	#3	Primary headache (other than cluster, migraine, tension)	"chronic daily headache"/exp OR "chronic headache"/de OR "cough headache"/de OR "episodic headache"/de OR "exertional headache"/de OR "hemicrania continua"/exp OR "hypnic headache"/de OR "nummular headache"/de OR "primary headache"/exp OR "recurrent headache"/de OR "stabbing headache"/de OR "thunderclap headache"/de OR "trigeminal autonomic cephalalgia"/exp OR (((chronic OR compression OR cough OR daily OR episodic OR exercise OR exertional OR hypnic OR neuralgiform OR nummular OR persistent) NEXT/2 headache*) OR "hemicrania continua" OR "paroxysmal hemicrania" OR (primary NEAR/2 headache*) OR SUNA OR SUNCT OR "trigeminal autonomic cephalalgia*"):ti,ab,kw
	#4	Secondary headache (other than post-traumatic or medication overuse)	"secondary headache"/exp OR "vascular headache"/de OR (((cervicogenic OR musculoskeletal OR secondary OR vascular) NEAR/2 headache*) OR "occipital neuralgia*"):ti,ab,kw
	#5	Combine population sets	#1 OR #2 OR #3 OR #4
	#6	Behavioral health approaches – controlled terms	"acceptance and commitment therapy"/de OR "behavior therapy"/de OR "breathing exercise"/exp OR "biofeedback"/de OR "cognitive behavioral therapy"/exp OR "compassion focused therapy"/de OR "diaphragmatic breathing"/de OR "guided imagery"/de OR "mindfulness based cognitive therapy"/de OR "mindfulness-based stress reduction"/de OR "psychotherapy"/exp OR "relaxation training"/de

KQ #	Set #	Description	EMBASE Search String
KQ 8 (cont.)	#7	Behavioral health approaches – text words	("acceptance and commitment" OR (behav* NEXT/2 (approach* OR health OR intervention* OR manag* OR technique* OR therap* OR treat*)) OR biofeedback OR "breathing exercise*" OR "breathing technique*" OR "cognitive behav*" OR combin* OR "compassion focused therapy" OR ((deep OR diaphragmatic) NEXT/1 breathing) OR desensiti* OR dialectical OR "educational intervention*" OR "guided imagery" OR (manag* NEAR/3 trigger*) OR "mind body" OR (mindful* NEXT/2 ("cognitive therapy" OR "stress reduction")) OR "progressive muscle relaxation" OR psychotherap*):ti,ab,kw OR (cbt OR intervention* OR manag* OR mbct OR mbsr OR psychological OR trigger*):ti
	#8	Combine population and intervention sets	#5 AND (#6 OR #7)
	Apply standard exclusion and inclusion filters		See end of table
	Limit to systematic reviews, meta-analyses, and randomized controlled trials		See end of table
KQ 11	#1	Any headache	"headache and facial pain"/mj/exp OR (headache* OR hemicrania OR migrain*):ti
	#2	Comorbid/Co-occurring conditions – general terms	"comorbidity"/mj OR "dual diagnosis"/mj OR "secondary headache"/mj OR ("co morbid*" OR comorbid* OR "co-occur*" OR dual OR secondary):ti
	#3	Chronic pain/Chronic overlapping pain conditions (including IBS)/Other chronic pain, including: fibromyalgia, TMD, lower back pain, neck pain, and arthritis)	"arthritis"/mj/exp OR "chronic pain"/mj OR "fibromyalgia"/mj OR "irritable colon"/mj OR "low back pain"/mj OR "neck pain"/mj OR "stress related disorder"/de OR "temporomandibular joint disorder"/mj OR (arthrit* OR fibromyalg* OR IBS OR (irritable NEXT/1 (bowel OR colon)) OR osteoarthrit* OR (pain NEAR/2 (back OR cervical OR chronic OR joint* OR lumbar OR neck)) OR "stress-related disorder*" OR temporomandibular OR TMJ OR TMD):ti
	#4	Mental health conditions (depression/anxiety/stress-related disorders or PTSD/mood disorders)	"anxiety disorder"/exp/mj OR "mood disorder"/exp/mj OR (anxiety OR bipolar OR depressive OR depression OR dysthym* OR mental* OR "mood disorder*" OR (("post traumatic" OR posttraumatic) NEXT/1 stress) OR psychiatr* OR PTSD OR "stress-related disorder*"):ti
	#5	Military exposures (TBI, military sexual trauma)	"battle injury"/mj OR "blast injury"/mj OR "head and neck injury"/mj/exp OR "posttraumatic headache"/mj/exp OR (((blast OR brain OR facial OR head OR "maxillo facial" OR maxillofacial OR "oro facial" OR orofacial OR neck) NEAR/3 (injur* OR trauma)) OR combat OR concuss* OR craniotom* OR military OR postconcuss* OR "post trauma*" OR posttrauma* OR (sexual NEXT/1 (abuse OR assault* OR trauma*)) OR whiplash):ti
	#6	Sleep disorders	"sleep disorder"/exp/mj OR (apnea* OR apnoea* OR dyssomnia* OR hypersomnia* OR hyposomnia* OR insomia* OR narcoleps* OR night* OR parasomnia* OR "restless legs" OR sleep*):ti

KQ #	Set #	Description	EMBASE Search String
KQ 11 (cont.)	#7	Vascular disease: Cerebrovascular and cardiovascular disease	"cardiovascular disease"/mj/exp OR "cerebrovascular disease"/mj/exp OR "cerebrovascular accident"/mj/exp OR "ischemic heart disease"/mj/exp OR "patent foramen ovale"/mj OR "vascular disease"/mj/exp OR (angina OR arterio* OR athero* OR atrial OR cardiac OR cardiovascular OR cerebral OR cerebrovascular OR coronary OR heart OR infarct* OR ischaem* OR ischem* OR myocardial OR "patent foramen ovale" OR stroke OR vascular):ti
	#8	Vascular risk factors (metabolic syndrome / obesity / diabetes/ hypertension)	diabetes/mj/exp OR "hypertension"/mj/exp OR "metabolic syndrome x"/mj OR "obesity"/mj/exp OR ("blood pressure" OR diabet* OR hypertens* OR "insulin resistance" OR metabolic OR obes* OR "over weight" OR overweight):ti
	#9	Combine comorbid/co-occurring sets	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
	#10	Combine population sets	#1 AND #9
	Apply standard exclusion and inclusion filters		See end of table
	Limit to systematic reviews, meta-analyses, randomized controlled trials		See end of table
KQ 12	#1	Suspected / confirmed medication overuse headache	"drug induced headache"/exp OR (("drug induced" OR "medication overuse" OR rebound*) NEAR/2 (headache* OR migrain*)):ti,ab,kw OR (overus* AND (headache* OR migrain*)):ti
	#2	Medication withdrawal - main search	"detoxification"/exp OR "treatment withdrawal"/exp OR (detox* OR discontinu* OR reduc* OR taper* OR withdraw*):ab,ti,kw
	#3	Medication withdrawal - additional search to identify studies with alternative wording	(overus* AND (approach* OR intervention* OR manag* OR therap* OR treat*)):ti
	#4	Combine population and intervention sets	#1 AND (#2 OR #3)
	Apply standard exclusion and inclusion filters		See end of table
	Limit to systematic reviews, meta-analyses, and randomized controlled trials, and observational comparative studies		See end of table

KQ #	Description	EMBASE Search String
Standard Exclusions	***Animals***	([animals]/lim NOT [humans]/lim) OR ((animal OR animals OR canine* OR dog OR dogs OR feline OR hamster* OR lamb OR lambs OR mice OR monkey OR monkeys OR mouse OR murine OR pig OR piglet* OR pigs OR porcine OR primate* OR rabbit* OR rat OR rats OR rodent* OR sheep* OR swine OR veterinar* OR (vitro NOT vivo)) NOT (human* OR patient*)):ti

KQ #	Description	EMBASE Search String
Standard Exclusions (cont.)	***Undesired publications***	"book"/de OR "case report"/de OR "conference paper"/exp OR "editorial"/de OR "letter"/de OR (book OR chapter OR conference OR editorial OR letter):it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR (abstract OR annual OR conference OR congress OR meeting OR proceedings OR sessions OR symposium):nc OR ((book NOT series) OR "conference proceeding"):pt OR ("case report" OR comment* OR editorial OR letter OR news):ti OR ((protocol AND (study OR trial)) NOT ("therapy protocol*" OR "treatment protocol*")):ti
	Children and adolescents	((adolescen* OR babies OR baby OR boy* OR child* OR girl* OR infancy OR infant* OR juvenile* OR neonat* OR newborn* OR nurser* OR paediatric* OR pediatric* OR preschool* OR "school age*" OR schoolchildren* OR teen* OR toddler* OR youth*):ti NOT (adult*:ti,ab OR father*:ti OR matern*:ti,ab OR men:ti,ab OR mother*:ti OR parent*:ti OR patern*:ti,ab OR women:ti,ab))
Standard Inclusions	***English language***	[english]/lim
	Publication year	[2018-2023]/py
	Entry date	([06-03-2019]/sd NOT [16-08-2022]/sd)
Study Designs	***Systematic reviews and meta-analyses***	(("meta analysis"/exp OR "systematic review"/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR (cochrane* OR metaanaly* OR "meta analy*" OR (search* AND (cinahl* OR databases OR ebsco* OR embase* OR psychinfo* OR psycinfo* OR "science direct*" OR sciencedirect* OR scopus* OR systematic* OR "web of knowledge*" OR "web of science")) OR (systematic* NEAR/3 review*)):ti,ab) NOT ((protocol NEXT/3 review) OR "review protocol" OR "scoping review"):ti)
	Randomized controlled trials	("random sample"/de OR "randomization"/de OR "randomized controlled trial"/exp OR "phase 3":ti,ab OR "phase iii":ti,ab OR random*:ti,ab OR RCT:ti,ab)
	Observational comparative studies	"case control study"/exp OR "cohort analysis"/de OR "comparative study"/exp OR "controlled clinical trial"/de OR "controlled study"/de OR "crossover procedure"/de OR "observational study"/de OR "prospective study"/de OR ("2 arm*" OR "3 arm*" OR "between groups" OR "case control" OR cohort* OR compar* OR "control group*" OR ((controlled OR experimental OR "non random*" OR nonrandom* OR observational OR prospective) NEXT/3 (design OR study OR trial)) OR "cross over" OR crossover OR "double arm*" OR "double blind*" OR "matched controls" OR "multiple arm*" OR "non inferiority" OR noninferiority OR placebo* OR "quasi experiment*" OR quasiexperiment* OR registries OR registry OR sham OR "three arm*" OR "triple arm*" OR "triple blind*" OR "two arm*"):ti,ab OR (versus OR vs):ti

EMBASE.com Syntax: *truncation character (wildcard)

NEAR/n = search terms within a specified number (n) of words from each other in any order

NEXT/n = search terms within a specified number (n) of words from each other in the order specified

/ = search as a subject heading

exp = “explodes” controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary’s hierarchy)

mj = denotes a term that has been searched as a major subject heading

de = non-major subject heading

:lnk = floating subheading

Appendix K: Alternative Text Descriptions of Algorithm

The following outline narratively describes the Management of Headache Algorithm. An explanation of the purpose of the algorithm and description of the various shapes used within the algorithm can be found in the Algorithm section. The sidebars referenced within this outline can also be found in the Algorithm section.

Module A: Evaluation and Treatment of Headache

1. The algorithm begins with Box 1, in the shape of a rounded rectangle: “Adults with headache”
2. Box 1 connects to Box 2, in the shape of a rectangle: “General history and physical exam (see **Sidebar 1**)”
3. Box 2 connects to Box 3, in the shape of a hexagon, which asks, “Does this patient need urgent/emergent evaluation/treatment or have red flags? (see **Sidebar 1**)”
    a. If the answer is “Yes” to Box 3, then Box 4, in the shape of an oval: “Consider evaluation in urgent care or ED”
    b. If the answer is “No” to Box 3, then Box 5, in the shape of a hexagon, which asks, “Is there a secondary headache (see **Sidebar 2**), complicated headache presentation, or multiple headache types requiring specialist referral?”
        i. If the answer is “Yes” to Box 5, then Box 6, in the shape of an oval: “Refer to specialist for further diagnosis and evaluation”
        ii. If the answer is “No” to Box 5, then Box 7, in the shape of a hexagon, which asks, “Is there clinical concern for TTH? Including: Bilateral headache; Non-pulsatile pain; Mild to moderate pain; Not worsened by activity (see **Sidebar 3**)”
            1. If the answer is “Yes” to Box 7, then Box 8, in the shape of a rounded rectangle: “Definitive or probable diagnosis of TTH”
                a. Box 8 connects to Box 9 in the shape of a rectangle: “TTH treatment (see **Sidebar 4**); also, assess for MOH (see **Sidebar 5**)”
                b. Box 9 connects to Box 10, in the shape of a hexagon, which asks, “Did the patient’s condition improve? (See **Sidebar 1**)”
                    i. If the answer is “Yes” to Box 10, then Box 11, in the shape of an oval: “Continue effective treatment and reassess as needed”
                    ii. If the answer is “No” to Box 10, then Box 12 in the shape of an oval: “Refer to specialist”

2. If the answer is “No” to Box 7, then Box 13, in the shape of a hexagon, which asks, “Is there clinical concern for migraine? Including: Nausea; Throbbing; Headache-related interference in activities (see **Sidebar 3**)”
    a. If the answer is “Yes” to Box 13, then Box 14, in the shape of a rounded rectangle: “Definitive or probable diagnosis of migraine”
        i. Box 14 connects to Box 15, in the shape of a rectangle: “Migraine treatment (see **Sidebars 6a and 6b**); also, assess for MOH (see **Sidebar 5**)”
        ii. Box 15 connects to Box 10, in the shape of a hexagon, which asks, “Did the patient’s condition improve? (See **Sidebar 1**)”
            1. If the answer is “Yes” to Box 10, then Box 11, in the shape of an oval: “Continue effective treatment and reassess as needed”
            2. If the answer is “No” to Box 10, then Box 12, in the shape of an oval: “Refer to specialist”
    b. If the answer is “No” to Box 13, then Box 16, in the shape of a hexagon, which asks, “Is there clinical concern for cluster headache? Including: Bouts of severe and brief headaches (lasting <3 hours); Unilateral (always same side); Autonomic signs ipsilateral to headache; Restlessness during attacks (see **Sidebar 3**)”
        i. If the answer is “Yes” to Box 16, then Box 17, in the shape of a rounded rectangle: Definitive or probable diagnosis of cluster headache”
            1. Box 17 connects to Box 18, in the shape of a rectangle: “Cluster headache treatment (see **Sidebar 7**); also, assess for MOH (see **Sidebar 5**)”
            2. Box 18 connects to Box 10, in the shape of a hexagon, which asks, “Did the patient’s condition improve? (See **Sidebar 1**)”
                a. If the answer is “Yes” to Box 10, then Box 11, in the shape of an oval: “Continue effective treatment and reassess as needed”
                b. If the answer is “No” to Box 10, then Box 12 in the shape of an oval: “Refer to specialist”
        ii. If the answer is “No” to Box 16, then Box 19, in the shape of a rectangle: “Revisit general history and physical exam and consider alternate diagnoses or referral for specialty evaluation”

Appendix L: Abbreviations

Abbreviation	Definition
AAC	aspirin/acetaminophen/caffeine
AE	adverse event
ARB	angiotensin II receptor blocker
BMI	body mass index
CAGE	Cutting down on their drinking, whether they are Annoyed by criticism for their drinking, if they ever feel Guilty about their drinking, and if they ever take an Early morning or “eye-opener,” drink
CBT	cognitive behavioral therapy
CCB	calcium channel blockers
CGRP	calcitonin gene-related peptide
CI	confidence interval
CIH	complementary and integrative health
COI	conflicts of interest
CoQ10	coenzyme Q10
CPG	clinical practice guideline
CV	cardiovascular
CYP3A4	cytochrome P450 3A4
DALY	disability-adjusted life years
DEA	Drug Enforcement Agency
DHA	Defense Health Agency
DoD	Department of Defense
EBPWG	Evidence-Based Practice Work Group
ECG	electrocardiogram
ED	emergency department
ELISA	enzyme-linked immunosorbent assay
ER	extended release
FDA	U.S. Food and Drug Administration
GI	gastrointestinal
GON	greater occipital nerve
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale-Anxiety
HADS-D	Hospital Anxiety and Depression Scale-Depression
HBOT	hyperbaric oxygen therapy
HDI	Headache Disability Index
HIT-6	Headache Impact Test, 6th edition
HIV	human immunodeficiency virus
ICHD-3	International Classification of Headache Disorders, 3rd edition

Abbreviation	Definition
IgG	immunoglobulin G
IM	intramuscular
IV	intravenous
KQ	key question
LT	Likert-Type
mAb	monoclonal antibody
MBS	most bothersome symptom
MD	mean difference
mg	milligram
MID	minimally important difference
MIDAS	Migraine Disability Assessment
MOH	medication overuse headache
MPFID	Migraine Physical Function Impact Diary
MRI	magnetic resonance imaging
MSQL	Migraine-Specific Quality of Life Questionnaire
mTBI	mild traumatic brain injury
NAM	National Academy of Medicine
NBOT	normobaric oxygen therapy
NMA	network meta-analysis
NNH	number needed to harm
NNT	number needed to treat
NSAID	nonsteroidal anti-inflammatory drug
n-VNS	non-invasive vagus nerve stimulation
OMT	Osteopathic manipulative treatment
OR	odds ratio
OTC	over the counter
PCP	primary care provider
PFO	patent foramen ovale
PMR	progressive muscle relaxation
pRF	pulsed radiofrequency
PSS	pain scale score
PTH	posttraumatic headache
PTSD	posttraumatic stress disorder
QoL	quality of life
RCT	randomized controlled trial
REN	remote electrical neuromodulation
ROB	risk of bias
RR	relative risk
rTMS	repetitive transcranial magnetic stimulation

Abbreviation	Definition
SD	standard deviation
SMD	standardized mean difference
SNOOP(4)E	Systemic, Neurologic, Onset sudden, Onset after 50, Pattern change, Precipitated, Postural, Papilledema, Exertion
SNRI	Serotonin and norepinephrine reuptake inhibitor
SON	supra orbital nerve
SPG	sphenopalatine ganglion
SR	systematic review
STOP-BANG	Snoring history, Tired during the day, Observed stop breathing while sleep, High blood pressure, BMI more than 35 kg/m2, Age more than 50 years, Neck circumference more than 40 cm, and male Sex
TAC	trigeminal autonomic cephalalgia
TAU	treatment as usual
ta-VNS	transauricular vagus nerve stimulation
TBI	traumatic brain injury
TCA	tricyclic antidepressants
tDCS	transcranial direct current stimulation
TENS	transcutaneous electrical nerve stimulation
TMD	temporomandibular disorder
TTH	tension-type headache
U.S.	United States
UMN	upper motor neuron
USPSTF	U.S. Preventive Services Task Force
VA	Department of Veterans Affairs
VAS	Visual Analog Scale
VHA	Veterans Health Administration
VNS	vagus nerve stimulation
WHO	World Health Organization
WMD	weighted mean difference
XL	extended release

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