VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE PRIMARY CARE MANAGEMENT OF HEADACHE

Department of Veterans Affairs
Department of Defense

QUALIFYING STATEMENTS

The Department of Veterans Affairs and the Department of Defense guidelines are based upon the best information available at the time of publication. They 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 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 clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every healthcare professional making use of these guidelines is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation.

These guidelines are not intended to represent Department of Veterans Affairs or TRICARE policy. Further, inclusion of recommendations for specific testing and/or therapeutic interventions within these guidelines does not guarantee coverage of civilian sector care. Additional information on current TRICARE benefits may be found at www.tricare.mil or by contacting your regional TRICARE Managed Care Support Contractor.

Version 1.0 – 2020

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The Primary Care Management of Headache Work Group

With support from:

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&
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Table of Contents

I. Introduction

The Department of Veterans Affairs (VA) and Department of Defense (DoD) Evidence-Based Practice Work Group (EBPWG) was established and first chartered in 2004, with a mission to advise the Health Executive Committee (HEC) "…on the use of clinical and epidemiological evidence to improve the health of the population…" across the Veterans Health Administration (VHA) and Military Health System (MHS), by facilitating the development of clinical practice guidelines (CPGs) for the VA and DoD populations.[1] This CPG is intended to provide primary care providers (PCPs) with a framework by which to evaluate, treat, and manage the individual needs and preferences of patients with headache, thereby leading to improved clinical outcomes.

Consequently, a recommendation to create the VA/DoD Clinical Practice Guideline for the Primary Care Management of Headache (VA/DoD Headache CPG) was initiated in 2018. The CPG includes objective, evidence-based information on the management of headache. It is intended to assist PCPs in all aspects of patient care, including assessment, treatment, and follow-up. The system-wide goal of evidence-based guidelines is to standardize management pathways for providers to improve the health and well-being of patients with headache. The expected outcome of successful implementation of this guideline is to:

- Assess the patient's condition and determine, in collaboration with the patient, the best treatment modality or modalities
- Optimize each individual's health outcomes and improve quality of life (QoL)
- Minimize preventable complications and morbidity
- Emphasize the use of patient- (and family-) centered care (PCC)

II. Background

A. Classification of Headaches

The current diagnostic criteria for headaches[a] are found in the International Classification of Headache Disorders, or ICHD-3, accessible for free online (see Appendix A).[b] In broad terms, headaches 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 headaches can be attributed to an identifiable underlying cause that may be structural, pharmacologic, vascular, or related to a systemic illness or disorder of homeostasis.

a. Primary Headache Disorders

The most common primary headache disorders include tension-type headache (TTH), migraine, and cluster type headaches which are included 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. Diagnosis of migraine requires patients to meet two out of four major criteria and one out of two minor criteria; patients meeting fewer than these requirements may be considered as having probable migraine.

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

Migraine is further characterized by the presence or absence of aura and whether or not it is chronic (i.e., ≥15-days/month for >3-months), while episodic refers to headaches occurring less frequently.

Diagnosis of TTH requires patients to meet two out of four major criteria and both minor criteria; patients meeting fewer than these requirements may be considered as having probable TTH. Tension-type headache is further characterized as being infrequent (i.e., at least 10 headache episodes occurring <1 day/month), frequent (i.e., 10 headache episodes occurring on 1 to 14 days/month for >3-months), or chronic (i.e., ≥15-days/month on average for >3-months) and whether or not it is associated with pericranial tenderness.

Cluster headache is the most common of the trigeminal autonomic cephalalgias (TACs) and is considered to be one of the most painful conditions known to man. The diagnosis of cluster headache requires at least five severe to very severe headache attacks of unilateral orbital, supraorbital, and/or temporal pain occurring once every other day to eight times a day and lasting 15 – 180 minutes. Cluster headache is associated with such autonomic features as nasal congestion and/or rhinorrhea, miosis and/or ptosis, conjunctival injection and/or lacrimation, and swelling of the forehead and/or face as well as a feeling of restlessness and/or agitation.

Across these three primary headache disorders, the term "chronic" is used differently based on the primary headache diagnosis. For migraine and TTH, chronic refers to having headache attacks ≥15-days/month for >3-months, whereas chronic – when applied to cluster headache attacks – occur for one year or longer without remission or with remission periods lasting less than three months. For cluster, the definition of chronic depends on the type of headache disorder. Primary headaches are, by their nature, recurrent, so a single/first-time headache should prompt appropriate evaluation for secondary causes. As with all criteria-based diagnoses, these criteria only apply if a diagnosis is not better accounted for by another ICHD-3 diagnosis.

Table 1. Primary Headache Disorders*

		Tension-type headache[a]	Migraine headache[b]	Cluster headache[c]
Attack duration and frequency	Duration	30-minutes – 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, and/or temporal
	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 may improve symptoms
Associated features	Photophobia and phonophobia	Can have one but not both	Both	Variably present
	Nausea and/or vomiting	Neither	Either or both	May be present
Other features	Autonomic features	None	May occur, but are often subtle and not noticed by the patient	Prominent autonomic features ipsilateral to the pain (see Appendix A)

[a] A diagnosis of TTH requires at least 10 headache attacks 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.

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

[c] A diagnosis of cluster headache requires at least five attacks of severe to very severe unilateral orbital, supraorbital, and/or temporal 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/agitation are required.

* There are definitions for probable TTH, probable migraine, or probable cluster headache where patients may 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).[2] Providers should continually reassess patients during therapy.

b. Secondary Headache Disorders

The initial evaluation of headache should focus on determining whether there is a secondary cause for the headache or if a primary headache diagnosis is appropriate. Emergent evaluation should be considered based on 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 that is known to cause headache, or when a pre-existing headache disorder significantly worsens in close temporal relation to a causative disorder. In these instances, both primary and secondary headache diagnoses should be given (e.g., migraine and medication overuse headache [MOH]). Secondary

headaches include headache attributed to trauma to the head and/or neck; 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.

This CPG addresses the management of three secondary headache types including cervicogenic headache (CGH), post-traumatic headache (PTH) (headache attributed to traumatic injury to the head), and MOH. These were the only three headache types for which specific evidence was found during our literature review.

Cervicogenic headache refers to a headache that is caused by disorders in the bony, disc, or muscular/soft tissue elements of the neck and is usually associated with neck pain. This diagnosis requires clinical or imaging evidence of a disorder in the cervical region that is 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 improvement or resolution of the cervical disorder, cervical range of motion is reduced and the headache is worsened by provocative maneuvers, and/or the headache is abolished following diagnostic blockade of the cervical structure or its nerve supply.

Headaches attributed to traumatic injury of the head, also known as PTH, could occur after mild, moderate, or severe traumatic brain injury (TBI) and is divided into an acute form and a persistent form. The acute form requires a headache of fewer than three months duration that can be attributed to a TBI. In either case, the reported headache must have developed within seven days of the injury or within seven days of discontinuation of medications that could impair the ability to sense or report a headache following head injury. It should be noted that the ICHD-3 reports that, "the stipulation that headache must be reported to have developed within 7 days is somewhat arbitrary."[2] As such, ICHD-3 also recognizes "delayed onset" acute and persistent headache attributed to either mild or moderate to severe injury to the head which begins after seven days and within three months of the index head injury. Headaches occurring after traumatic injury to the head may have clinical features consistent with several primary headache types including TTH, migraine, and TACs such as cluster headache.

In addition, after a traumatic head injury, it is important to rule out other possible secondary causes of headaches, such as cerebrospinal fluid leak, or the presence of a more significant head injury (e.g., an intracranial hematoma). Headaches attributed to traumatic injury to the head are typically accompanied by other features of post-concussion symptoms including nausea, vomiting, visual disturbances, dizziness, gait or postural imbalance, memory and concentration impairment, sleep disorders, and/or affective disorders. The most frequent headache pattern post-TBI resembles TTH or migraine (see Table 1). However, these headaches may be exacerbated with very mild physical or mental exertion, which would be unusual for a non-traumatic TTH. For more information regarding the treatment of non-headache symptoms following a mild TBI (mTBI), see the VA/DoD CPG for the Management of Concussion-mild Traumatic Brain Injury (VA/DoD mTBI CPG).[c]

[c] See the VA/DoD Clinical Practice Guideline for the Management of Concussion-mild Traumatic Brain Injury. Available at: https://www.healthquality.va.gov/guidelines/Rehab/mtbi/

Medication overuse headache, which has 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 and inappropriate use of non-prescription or prescription abortive headache medications (see Appendix A).[3] In the United States (U.S.), nearly a quarter of people with chronic headaches take abortive medications daily.[3] Headache attributed to MOH occurs ≥15-days/month among patients with a prior history of a different type of headache (e.g., migraine) who have overused an abortive medication for symptomatic treatment of discrete headache attacks for more than 3-months.

The ICHD-3 separates the type of MOH based on which abortive medications are used, such that the use of non-prescription medications (e.g., acetaminophen) occurs ≥15-days/month, whereas use of prescription medications (e.g., triptans, opioids) occurs ≥10-days/month (see Appendix A, Sidebar 5). When MOH is not recognized, treatment of the underlying headache disorder which prompted overuse of as-needed medications becomes more difficult. Medication overuse headache is a condition that can be treated once diagnosed and could be prevented with judicious use of abortive pain medications and close communication and collaboration between patients and healthcare providers regarding the degree of headache control and accurate assessment of use of as-needed pain medication.[3]

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

Headache is exceedingly prevalent and imposes a high burden on people living with it.[2,4-9] Worldwide, TTH, migraine, and MOH are the most common headache disorders. The lifetime prevalence of any headache disorder is 66%; half of the people with a history of headache actively experience headache attacks.[9,10] Headache is the second leading cause of years lived with disability (YLDs) across all age groups, trailing only low back pain.[9] Moreover, more disability-adjusted life years (DALYs) are attributable to headache than all other neurological disorders combined.[11]

Within the U.S., the prevalence of self-reported migraine and/or severe headache ranges between 15 – 18% in women and 6 – 10% in men; nearly half of women and men experience TTH.[12-14] Fluctuation in hormone levels can trigger migraine attacks and TTH in women.[15] Several studies note that migraine prevalence in women increases after menarche and peaks before menopause, with the burden of disease highest in women of childbearing age, affecting up to 25% women of reproductive age.[5,16,17] Studies have found a significant relation between migraine, abruption placenta, preeclampsia, and stroke during pregnancy.[18] Given the high prevalence and increased risk of adverse outcomes related to migraine in women 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 group.[16] Ten percent of people living with headache report having multiple different types of headache attacks per week, and 3% report having some type of headache daily.[19]

Disability related to headache has a pronounced impact on individuals, their family members, and healthcare systems. The prevalence of headache, and specific headache conditions, is preferential towards women and people ages 25 – 55.[2,4-9] Headache disability is linked to headache attack characteristics (e.g., throbbing, stabbing), frequency (e.g., hundreds of times a day, annually), associated features (e.g., nausea, photophobia, unilateral weakness), and conditions that are 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, may decrease during a headache attack and in periods between attacks.[20,21] While TTH is the most common type of headache, migraine contributes more to the total amount of disability seen in headache. Health-related QoL scores are consistently lower among patients with migraine compared to healthy, age-matched comparators.[21,22] Headaches have a negative effect on family life, group activities, relationships, and financial stability.[23]

Headache also imposes societal costs that are direct (i.e., attributable to diagnosis and treatment) and indirect (i.e., the impact on productivity).[24,25] The estimated annual direct medical cost of caring for people with migraine attacks in the U.S. is approximately $1 billion, with 60% of costs accounted for by physician office visits. The indirect annual cost is approximately $13 billion, largely attributed to missed days of work (i.e., absenteeism) and impaired work function when people come to work while impaired by their headache attack (i.e., presenteeism).[24]

C. Headache within the VA Population

The management of headache in the Veteran population is complex and literature suggests that the diagnosis has increased over the past decade. In fiscal year 2017, approximately 380,000 Veterans sought care in the VA system for a headache disorder; over 75% of headache management occurred within primary care.[26] The diagnosis of migraine is increasing in Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) combat Veterans less than 60-years old compared to older Veterans (approximately 13% versus 2%).[27,28] Traumatic brain injury is a strong predictor of headache as a complaint in the first year of care for a Veteran within the VA; psychiatric comorbidities increase the likelihood of headache among those with TBI diagnosis.[29] Treatment decisions for PCPs are more complex, further necessitating the need for a clear algorithm for the diagnosis and management of headache disorders.[30] 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 military Service Members, although prevalence data is limited. In a longitudinal study including a large cohort of 77,000 participants (active duty, Reservist, and National Guard), the self-reported prevalence of provider-diagnosed migraine was 6.9% in males and 20.9% in females.[31] This prevalence is similar to the civilian population.[31,32] In contrast, the diagnosis of headache is steadily increasing with the increased prevalence of mTBI, analogous to what is seen in the Veteran population. Over 300,000 individuals in the military have reported an mTBI over an 18-year period.[33] Mild traumatic brain injury results in a complex sequelae of physical, mental, and cognitive comorbidities. The incidence of mTBI and concurrent headache in this population is four to five times higher than that in the general U.S. population.[34] Headaches, combined with the complex sequelae of the comorbidities seen in the military population with mTBI, make clinical management a priority.[35]

E. Post-traumatic Headache among Service Members

With the increased prevalence and awareness of mTBI over the past decade, one headache type that is of particular interest to VA/DoD providers is a persistent headache attributed to a traumatic injury to the

[d] See the VA/DoD Clinical Practice Guideline for the Management of Concussion-mild Traumatic Brain Injury. Available at: https://www.healthquality.va.gov/guidelines/Rehab/mtbi/

head, also known as a PTH. According to ICHD-3, to be defined as a PTH, the onset of the headache must be within seven days of injury, upon regaining consciousness from injury, or upon discontinuation of medications impairing the ability to sense headache (for full ICHD-3 criteria, see Appendix A). To fulfill the definition of PTH, the provider derivation of secondary cause through patient-reported history could often be difficult to link to the trauma. Providers are also faced with the challenge of considering the impact of the higher incidence of comorbidities that contribute to headache, such as post-traumatic stress disorder (PTSD), sleep disorders, and residual neurocognitive deficits.[36]

The treatment of mTBI and headache is one of the most highlighted, mission-related goals for the VA and DoD. In a cross-sectional study of 5,270 soldiers returning from deployment, 35% of those who sustained an mTBI reported a persistent headache.[36] Another study found that soldiers who experienced an mTBI with a PTH complained of "more severe, frequent, and migrainous" type headaches than those experiencing headache without an mTBI.[37] The incidence of musculoskeletal pain and headache within the active duty population has also been investigated.[35] Post-traumatic headache was present in 92% of active duty personnel who reported an mTBI and it is linked to chronic daily headache.[35] Given the frequency of combat deployments and mTBI in VA/DoD populations, PTH was considered during the development of this CPG.

Although identifying a causal relationship between a traumatic event and headache can be difficult, research instructs providers to direct treatment based on the patient's current complaints and symptomatology.[36] The VA/DoD mTBI CPG states, "the treatment of headaches should be individualized and tailored to the clinical features and patient preferences."[e] Despite the challenge of directly linking the cause to the headache, this CPG's recommendations will guide treatment based on symptom presentation and the most efficacious interventions.

III. About this Clinical Practice Guideline

This guideline represents a significant step toward improving the diagnosis and management of headache in the VA and DoD. As with other CPGs, however, challenges remain, including evidence gaps, the need to develop effective strategies for guideline implementation, and the need to evaluate the effect of guideline adherence on clinical outcomes.

As elaborated in the qualifying statement on page one, this CPG is not intended to serve as a standard of care. Standards of care are determined based on all clinical data available for an individual patient and are subject to change as scientific knowledge and technology advance and patterns evolve. This CPG is based on information available by March 6, 2019, and is intended to guide best practices. The guideline can assist providers, but the use of a CPG must always be considered as a recommendation for the care of an individual patient, within the context of a provider's clinical judgment and patient values and preferences.

A. Methods

The methodology used in developing the 2020 CPG follows the *Guideline for Guidelines*, an internal document of the VA and DoD EBPWG, updated in January 2019.[38] The *Guideline for Guidelines* can be

[e] See the VA/DoD Clinical Practice Guideline for the Management of Concussion-mild Traumatic Brain Injury. Available at: https://www.healthquality.va.gov/guidelines/Rehab/mtbi/

downloaded from http://www.healthquality.va.gov/policy/index.asp. This document provides information regarding the process of developing guidelines, including the identification and assembly of the Guideline Champions (Champions) and other subject matter experts from within the VA and DoD, known as the Work Group and, ultimately, the development and submission of a new CPG.

The Champions and Work Group for this CPG were charged with developing evidence-based clinical practice recommendations and writing and publishing a guideline document to be used by providers within the VA/DoD healthcare systems as well as those within the community who treat individuals within the VA and DoD. Specifically, the Champions and Work Group members for this guideline were responsible for identifying the key questions (KQs) with the most clinical relevance, importance, and interest for the primary care management of headache. The Champions and the Work Group also provided direction on inclusion and exclusion criteria for the evidence review and assessed the level and quality of the evidence. The amount of scientific evidence that was available was taken into consideration in the identification of the KQs. In addition, the Champions assisted in:

- Identifying appropriate disciplines of individuals to be included as part of the Work Group
- Directing and coordinating the Work Group
- Participating throughout the guideline development and review processes

The VA Office of Quality and Patient Safety, in collaboration with the Office of Evidence Based Practice, U.S. Army Medical Command, the proponent for CPGs for the DoD, identified four clinical leaders: Franz Macedo, DO and Jason Sico, MD, MHS, FAHA, FACP, FAAN, FANA, FAHS from the VA, and Col Jeffrey D. Lewis, MD, PhD and Christopher Spevak, MD, MPH, JD from the DoD, as Champions for the 2020 CPG.

The Lewin Team, including The Lewin Group, Duty First Consulting, ECRI, Sigma Health Consulting, and Anjali Jain Research & Consulting, was contracted by the VA and DoD to support the development of this CPG and conduct the evidence review. The first conference call was held in September 2018, with participation from the contracting officer's representative (COR), leaders from the VA Office of Quality and Patient Safety and the DoD Office of Evidence Based Practice, and the Champions. During this call, the group discussed the scope of the guideline initiative, the roles and responsibilities of the Champions, the project timeline, and the approach for developing and prioritizing specific research questions on which to base a systematic review (SR) about the assessment and management of patients at risk for headache. Participants also identified a list of clinical specialties and areas of expertise that are important and relevant to the management of headache, from which Work Group members were recruited. The specialties and clinical areas of interest included: addiction medicine, brain injury, dentistry, integrative health and wellness, neurology, nursing, occupational therapy, pain medicine, pharmacology, primary care, physical therapy, psychiatry, psychology, and social work.

The guideline development process for the 2020 CPG consisted of these steps:

1. Formulating and prioritizing KQs and defining critical outcomes
2. Convening patient focus group
3. Conducting the systematic evidence review

4. Convening a face-to-face meeting with the CPG Champions and Work Group members
5. Drafting and submitting a final CPG on the management of headache to the VA/DoD EBPWG

Appendix B provides a detailed description of each of these tasks.

a. Grading Recommendations

The Champions and Work Group used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to assess the quality of the evidence base and assign a strength for each recommendation. The GRADE system uses these four domains to assess the strength of each recommendation:[39]

- Balance of desirable and undesirable outcomes
- Confidence in the quality of the evidence
- Patient or provider values and preferences
- Other implications, as appropriate:
    - Resource use
    - Equity
    - Acceptability
    - Feasibility
    - Subgroup considerations

Using these four domains, the Work Group determined the relative strength of each recommendation as "Strong" or "Weak." A "Strong" recommendation generally indicates a high confidence in the quality of the available scientific evidence, a clear difference in magnitude between the benefits and harms of an intervention, similar patient or provider values and preferences, and understood influence of other implications (e.g., resource use, feasibility). If the Work Group has less confidence after the assessment across these domains and believes that additional evidence may change the recommendation, it generally assigns a "Weak" recommendation. It is important to note that the GRADE terminology used to indicate the assessment across the four domains (i.e., "Strong" versus "Weak") should not be confused with the recommendation's clinical importance. A "Weak" recommendation may still be important to the clinical care of a patient with headache.

Occasionally, instances may occur when the Work Group feels there is insufficient evidence to make a recommendation for or against a particular therapy or preventive measure. This can occur when there is an absence of studies on a specific topic that meet evidence review inclusion criteria, studies included in the evidence review report conflicting results, or studies included in the evidence review report inconclusive results regarding the desirable and undesirable outcomes.

Using these elements, the grade of each recommendation is presented as part of a continuum:

- Strong for (or "We recommend this option …")
- Weak for (or "We suggest this option …")

- No recommendation for or against (or "There is insufficient evidence …")
- Weak against (or "We suggest against this option …")
- Strong against (or "We recommend against this option …")

The grade of each recommendation made in the 2020 CPG can be found in the section on Recommendations. Additional information regarding the use of GRADE can be found in Appendix B.

b. Peer Review Process

The CPG was developed through an iterative process in which the Work Group produced multiple drafts of the CPG. The process for developing the initial draft is described in more detail in Drafting and Submitting the Final Clinical Practice Guideline.

Once a near-final draft of the guideline was agreed upon by the Champions and Work Group, the draft was sent out for peer review and comment. The draft was posted on a wiki website for 14 business days. The peer reviewers comprised individuals working within the VA and DoD healthcare systems and experts from relevant outside organizations designated by the Work Group members. Organizations designated by the Work Group to participate in the peer review and who provided feedback include:

- The American Occupational Therapy Association

The VA and DoD Leadership contacted both the internal and external peer reviewers to solicit their feedback on the CPG. Reviewers were provided a hyperlink to the wiki website where the draft CPG was posted. All feedback from the peer reviewers was discussed and considered by the Work Group. Modifications made during the CPG development process were made in accordance with the evidence.

B. Summary of Patient Focus Group Methods and Findings

When forming guideline recommendations, consideration should be given to the values and preferences of those most affected by the recommendations: patients and their caregivers. Patients bring perspectives, values, and preferences into their healthcare experience that can vary from those of providers. These differences can affect decision making in various situations, and should thus be highlighted and made explicit given their potential to influence a recommendation's implementation.[40,41] Focus groups can be used as an efficient method to explore ideas and perspectives of a group of individuals and collect qualitative data on a thoughtfully predetermined set of questions.

Therefore, as part of the effort to develop this CPG, VA and DoD Leadership, along with the Headache CPG Work Group, held a patient focus group on January 16, 2019, at the Audie L. Murphy Memorial VA Hospital in San Antonio, TX. The aim of the focus group was to further understand the perspectives of patients who are receiving treatment for headache within the VA and/or DoD healthcare systems, as they are most affected by the recommendations put forth in the new Headache CPG. The focus group explored patients' perspectives on a set of topics related to management of headache in the VA and DoD healthcare systems, including the impact of headache on a patient's life, the management of headache, patient education, and their experiences with treatments.

There were five focus group participants. One participant was an active duty Service Member and the rest were Veterans. One participant was female and the remaining were male. Participants ranged in age from

40 – 60 years and each patient had experienced headaches for over 10-years at the time of the focus group. The Work Group recognizes the lack of generalizability and other limitations inherent in the small sample size. Less than 10 people in total were included in the focus group to be consistent with the requirements of the federal Paperwork Reduction Act, 1980. The Work Group acknowledges that the sample included in the focus group is not representative of all patients within the VA and DoD healthcare systems. Further, time limitations for the focus group prevented exhaustive exploration of all topics related to headache management in VA and DoD and the patients' broader experiences with their care. Thus, the Work Group made decisions regarding the priority of topics to discuss at the focus group. These limitations, as well as others, were considered during guideline development as the information collected from the discussion was being used. Recruitment for participation in the focus group was managed by the Champions and VA and DoD Leadership, with assistance from coordinators at the focus group location.

The following concepts are ideas and suggestions about aspects of care that are important to patients who are living with headache and emerged as recurring themes during the discussions (Table 2). These concepts were important parts of the participants' care and added to the Work Group's understanding of patient values and perspectives. Additional details regarding the patient focus group methods and findings can be found in Appendix C.

Table 2. Headache CPG Patient Focus Group Concepts

Headache CPG Patient Focus Group Concepts	
A.	Provide comprehensive information to patients regarding available treatment options, pain management strategies, and self-management interventions, including expanding available information on complementary and integrative therapies.
B.	Offer education to patients and providers regarding headaches, including the cause, diagnostic criteria, self-management, and treatment options.
C.	Use a team approach to improve care coordination and information sharing between providers to ensure patients receive a comprehensive, individualized care plan that is responsive to the patients' goals, values, and preferences.
D.	Headaches can be an "invisible disease," but should still be treated as important medical conditions that can have a significant impact on patients' quality of life and function.

C. Conflicts of Interest

At the start of this guideline development process and at other key points throughout, the project team was required to submit disclosure statements to reveal any areas of potential conflict of interest (COI) in the past 24-months. Verbal affirmations of no COI were used as necessary during meetings throughout the guideline development process. The project team was also subject to random web-based surveillance (e.g., Centers for Medicare & Medicaid Services open payments, ProPublica).

No conflicts of interest were identified for the Headache CPG Work Group members or Champions. If a project team member reported a COI (actual or potential), then it was reported to the Office of Evidence Based Practice. It was also discussed with the Headache CPG Champions in tandem with their review of the evidence and development of recommendations. The Office of Evidence Based Practice and the Headache CPG Champions determined whether or not action, such as restricting participation and/or voting on sections related to the conflict or removal from the Work Group, was necessary. If it was deemed necessary, action to mitigate the COI was taken by the Champions and Office of Evidence Based

Practice, based on the level and extent of involvement. Disclosure forms are on file with the VA Evidence Based Practice Program office and available upon request.

D. Scope of this Clinical Practice Guideline

This guideline is designed to assist PCPs (including case managers, dentists, general internal medicine and family medicine physicians, headache educators, ophthalmologists, optometrists, physician assistants, pharmacists, nurse practitioners, nurses, physical therapists, mental health providers, social workers, and others) in managing or co-managing patients with headache. Moreover, the patient population of interest for this CPG consists of patients who are living with headache and are eligible for care in the VA and DoD healthcare delivery systems who are being treated in an ambulatory care setting. It includes Veterans and deployed and non-deployed active duty Service, Guard, and Reserve Members and their dependents. This CPG does not comprehensively address emergency management or inpatient care for patients with headache. Other comprehensive reviews of emergency management of headache can be found elsewhere. However, the CPG does review intravenous therapies which can be delivered in such care settings as the emergency room and infusion suites for which primary care and other ambulatory care for which providers may deem their patients with headache eligible.

Regardless of the setting, any patient in the healthcare system should ideally have access to the interventions that are recommended in this guideline after taking into consideration the patient's specific circumstances. Guideline recommendations are intended to be patient centered. Thus, treatment and care should take into account a patient's needs and preferences. Good communication between healthcare professionals and the patient is essential and should be supported by evidence-based information tailored to the patient's needs. Use of an empathetic and non-judgmental approach facilitates discussions sensitive to gender, culture, ethnic, and other differences. The information that patients and caregivers are given about treatment and care should be culturally appropriate and available to people with limited literacy skills. It should also be accessible to people with additional needs such as physical, sensory, or learning disabilities. Family involvement should be considered, if appropriate.

E. Highlighted Features of this Clinical Practice Guideline

The VA/DoD Headache CPG provides practice recommendations for headache. A particular strength of this CPG is the multidisciplinary stakeholder involvement from its inception, ensuring representation from the broad spectrum of clinicians engaged in the treatment and management of headache with and without co-occurring conditions.

The framework for recommendations in this CPG considered factors beyond the strength of the evidence, including balancing desired outcomes with potential harms of the intervention, equity of resource availability, the potential for variation in patient values and preferences, and other considerations (e.g., resource use, subgroup considerations) as appropriate. Applicability of the evidence to VA/DoD populations was also taken into consideration. An algorithm accompanies the guideline to provide an overview of the recommendations in the context of the flow of patient care and to assist with training providers (see Algorithm). The algorithm may help facilitate the translation of guideline recommendations into effective practice.

F. Patient-centered Care

VA/DoD CPGs encourage clinicians to use a patient- (and family-) centered care approach that is individualized based on patient needs, characteristics, and preferences. Regardless of the setting, all patients in the healthcare system should be able to access evidence-based care appropriate to that patient. When properly executed, PCC may decrease patient anxiety, increase trust in clinicians, and improve treatment adherence.[42-44] Improved patient-clinician communication and a PCC approach conveys openness and supports disclosure of current and future concerns.

As part of the PCC approach, clinicians should engage patients in shared decision making (SDM) to review the outcomes of previous healthcare experiences with the patients who are living with headache. They should ask each patient about any concerns s/he has or barriers to high quality care s/he might experience. Lastly, they should educate the patient on the actions that need to be taken and any decisions that need to be made and should involve the individual in decision making regarding management of headache.

When a patient or provider identifies a psychosocial barrier, a referral to a social worker should be considered. A social worker's primary focus is to assist patients, their families, and caregivers in resolving psychosocial, emotional, and economic barriers to health and well-being by using a "person in environment" perspective. Social workers address the social determinants of health and assess the patient's psychological and emotional adjustment to illness within the context of medical diagnosis, prognosis, and treatment options. An assessment of environmental factors includes a review of the dynamics of the Veteran's support system, functional status, vocational, economic, housing, spiritual, cultural, and legal factors that influence their ability to accomplish their healthcare goals.

G. Shared Decision Making

This CPG encourages providers to practice SDM. Shared decision making was emphasized in *Crossing the Quality Chasm,* an Institute of Medicine (IOM) (now called the National Academy of Medicine [NAM]) report, in 2001.[45] Providers must be adept at presenting information to patients regarding individual treatments, expected risks, expected outcomes, and levels and/or locations of care, especially as differences between risks and benefits become less clear. Providers are encouraged to use SDM strategies to individualize treatment goals and plans based on patient capabilities, needs, and preferences.

H. Co-occurring Conditions

Co-occurring medical and mental health conditions are important to recognize because they can modify the management of headache, patient or provider treatment priorities, and clinical decisions. Furthermore, the appropriate providers need to be involved in headache management and ongoing healthcare based on the co-occurring medical and mental health conditions of each patient. Providers should expect that many Veterans, Service Members, and their families will have one or more co-occurring health conditions. Because of the nature of the management of headache, which sometimes takes place in parallel with ongoing care for co-occurring conditions, it is generally best to manage headache in collaboration with the care for other health conditions that are being treated in primary or specialty care.

I. Implementation

This CPG and algorithm are designed to be adapted by individual healthcare providers with consideration of local needs and resources. The algorithm serves as a tool to prompt providers to consider key decision points in the course of an episode of care.

Although this CPG represents the recommended practice on the date of its publication, medical practice is evolving and this evolution requires continuous updating based on published information. New technology and more research will improve patient care in the future. The CPG can assist in identifying priority areas for research and informing the optimal allocation of resources. Future studies examining the results of CPG implementation may lead to the development of new evidence particularly relevant to clinical practice.

IV. Guideline Work Group

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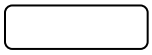
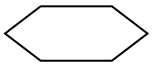
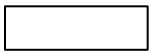
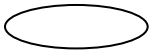
V. Algorithm

The CPG algorithm is designed to facilitate understanding of the clinical pathway and decision making process used in the management of 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:

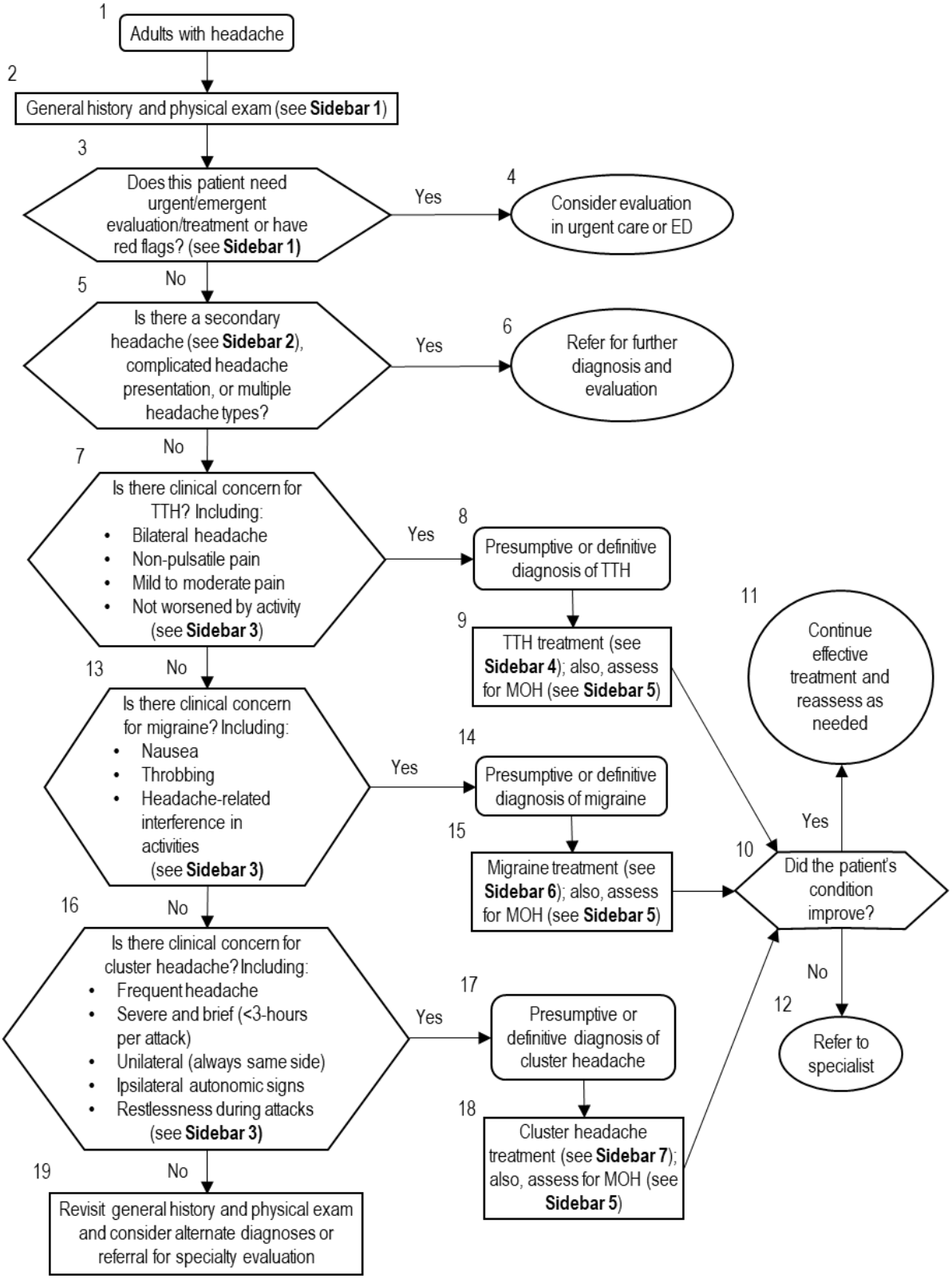
- An ordered sequence of steps of care
- Recommended observations and examinations
- Decisions to be considered
- Actions to be taken

The algorithm is a step-by-step decision tree. Standardized symbols are used to display each step, and arrows connect the numbered boxes indicating the order in which the steps should be followed.[46] Sidebars 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 guideline, 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 guideline

Appendix E contains alternative text descriptions of Module A.

A. 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

Headache history

- Frequency
- Character
- Onset
- Location
- Duration
- Exacerbating factors
- Relieving factors
- Prodrome/aura
- Associated symptoms
- Jaw symptoms
- Neck symptoms
- Visual deficits/changes
- Dizziness/imbalance
- Current medications, abortive dose and frequency per month, prophylactic dose
- Prior medication trials
- Hydration
- Meals
- Caffeine
- Sleep
- Exercise
- Nicotine/stimulant use
- Other comorbid conditions that may contribute to or exacerbate headaches
- Risk factors for MOH
- History of trauma to the head and/or neck

Red flags SNOOP(4)E [47]

- Systemic 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)
- Neurologic 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)
- Onset (e.g., abrupt or "thunderclap" where pain reaches maximal intensity immediately or within minutes after onset; first ever, severe, or "worst headache of life")
- Older onset (age ≥50-years)
- Progression or change pattern (e.g., in attack frequency, severity, or clinical features)
- Precipitated by Valsalva (e.g., coughing or bearing down)
- Postural aggravation
- Papilledema
- Exertion

Examination

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

Standardized headache assessments:

- MIDAS [48]
- HIT-6 [49]
- MSQL [50]

Abbreviations: 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; ROM: range of motion; SNOOP(4)E: Systemic, Neurologic, Onset sudden, Onset after 50, Pattern change, Precipitated, Postural, Papilledema, Exertion; UMN: upper motor neuron

Sidebar 2: Criteria for Determining Primary Versus Secondary Headache Disorders

Initial evaluation of headache should be targeted at determining if there is a secondary cause for the headache or if 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 that is known to cause headache. It can also be diagnosed when a pre-existing 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.[2]

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

The secondary headaches include: headache attributed to trauma or injury to the head and/or neck, cranial or cervical vascular disorder, non-vascular intracranial disorder, a 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: Primary Headache Disorders Criteria*				
		Tension-type headache[a]	**Migraine headache[b]**	**Cluster headache[c]**
Attack duration and frequency	Duration	30-minutes – 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, and/or temporal
	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 may improve symptoms
Associated features	Photophobia and phonophobia	Can have one but not both	Both	Variably present
	Nausea and/or vomiting	Neither	Either or both	May be present
Other features	Autonomic features	None	May occur, but are often subtle and not noticed by the patient	Prominent autonomic features ipsilateral to the pain (see Appendix A)

[a] A diagnosis of TTH requires at least 10 headache attacks 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.

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

[c] A diagnosis of cluster headache requires at least five attacks of severe to very severe unilateral orbital, supraorbital, and/or temporal 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/agitation are required.

* There are definitions for probable TTH, probable migraine, or probable cluster headache where patients may 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).[2] Providers should continually reassess patients during therapy (see Box 19 in Module A).

Sidebar 4: Treatment Options for Tension-type Headache[a, b]		
Type	**Treatment**	**Notes**
Non-pharmacologic Therapy – Preventive	Physical therapy↑	• "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
Pharmacotherapy – Preventive	Amitriptyline↑	• Accessible for general practitioners to prescribe, inexpensive, and may help with patients who suffer from insomnia. Side effects include dry mouth, dry eyes, weight gain, sedation, dizziness, blurred vision, GI distress, and nausea
	Botulinum toxin/ neurotoxin↓	• Evidence suggests intervention is ineffective for preventing chronic TTH
Pharmacotherapy – Abortive	Ibuprofen 400 mg or acetaminophen 1,000 mg↑	• Evidence suggests a statistically significant between-group difference for acetaminophen 1,000 mg versus placebo, favoring acetaminophen

[a] For the full recommendation language, see Recommendations

[b] Sidebar 8 presents additional treatment options for general headache

Abbreviations: GI: gastrointestinal; mg: milligram; TTH: tension-type headache

↑ Indicates a "Weak for" recommendation strength; ↓ indicates a "Weak against" recommendation strength

Sidebar 5: Common Medications and their Association with MOH	
MOH Type	**Medication Overuse Frequency**
Acetaminophen overuse	≥15-days/month for >3-months
NSAID overuse	
Other non-opioid analgesic overuse	
Triptan overuse	≥10-days/month for >3-months
Ergotamine overuse	
Opioid overuse	≥10-days/month for >3-months
Combination-analgesic overuse	

Abbreviations: MOH: medication overuse headache; NSAID: nonsteroidal anti-inflammatory drug

Sidebar 6: Treatment Options for Migraine Headache[a, b]		
Type	**Treatment**	**Notes**
Pharmacotherapy – Preventive	AbobotulinumtoxinA and onabotulinumtoxinA↓	• Not FDA approved or effective for prevention of episodic migraine
	Candesartan or telmisartan↑↑	• Applies to episodic and chronic migraine
	Combination pharmacotherapy↔	• Evidence was very low quality for the use of combinations of more than one pharmacotherapeutic agent for prevention of migraine
	Erenumab, fremanezumab, or galcanezumab↑	• Applies to episodic and chronic migraine • FDA approved and effective for prevention of migraine
	Gabapentin↔	• Applies to episodic migraine • Not FDA approved or effective for prevention of migraine
	Lisinopril↑	• Applies to episodic migraine only
	Magnesium, oral↑	• Oral magnesium formulations varied in the evidence, including magnesium sulfate, magnesium 2-propyl valerate, and magnesium oxide
	Nimodipine or nifedipine↔	• Applies to episodic migraine only
	Nutraceuticals: CoQ10, feverfew, melatonin, omega-3, vitamin B2, vitamin B6↔	• Evidence suggests small but somewhat inconsistent benefits in reducing migraine frequency, which slightly outweighed potential harms, such as dose variability in supplements, and some specific harms, such as post-feverfew syndrome or vitamin B6 neurotoxicity in high, sustained doses
	OnabotulinumtoxinA↑	• Applies to chronic migraine only • FDA approved and effective for prevention of chronic migraine
	Propranolol↑	• FDA approved for prevention of migraine
	Topiramate↑	• Applies to episodic migraine only • FDA approved and effective for prevention of migraine
	Valproate↔	• Applies to episodic and chronic migraine • FDA approved and effective for prevention of migraine
Pharmacotherapy – Abortive	Frovatriptan or rizatriptan↑	• FDA approved and effective for treatment of migraine
	GON block↑	• Evidence suggests improvement of pain intensity
	Ibuprofen, naproxen, aspirin, or acetaminophen↑	• FDA approved and effective for treatment of migraine
	IV magnesium↑	• Evidence suggests pain reduction with minimal risks
	Sumatriptan, sumatriptan/naproxen, or zolmitriptan↑↑	• Sumatriptan alone and in combination with naproxen are FDA approved and effective for prevention of migraine • Zolmitriptan is FDA approved and effective for treatment of migraine
	Triptans↑	• Triptans alone and in combination with naproxen are FDA approved and effective for treatment of migraine

[a] For the full recommendation language, see Recommendations

[b] Sidebar 8 presents additional treatment options for general headache

Abbreviations: CoQ10: coenzyme Q10; FDA: U.S. Food and Drug Administration; GON: greater occipital nerve block; IV: intravenous

↑↑ Indicates a "Strong for" recommendation strength; ↑ indicates a "Weak for" recommendation strength; ↓ indicates a "Weak against" recommendation strength; ↔ indicates a "Neither for nor against" recommendation strength

Sidebar 7: Treatment Options for Cluster Headache[a, b]		
Type	**Treatment**	**Notes**
Non-pharmacologic Therapy – Abortive	Non-invasive vagus nerve stimulation↑	• For episodic cluster headache only
Pharmacotherapy – Prevention	Galcanezumab↑	• FDA approved and effective for episodic cluster headache only
	Lovastatin#	• For episodic and chronic cluster headache
	Pravastatin#	• For episodic and chronic cluster headache
Pharmacotherapy – Abortive	Oxygen therapy↔	• For episodic cluster headache only
	Pharmacotherapy for acute treatment↔	• Evidence is limited for specific pharmacotherapy for acute treatment of cluster headache
	Sumatriptan SQ (not oral)#	• For episodic and chronic cluster headache
	Zolmitriptan nasal spray#	• FDA approved and effective for episodic and chronic cluster headache

[a] For the full recommendation language, see Recommendations

[b] Sidebar 8 presents additional treatment options for general headache

Abbreviations: FDA: U.S. Food and Drug Administration; SQ: subcutaneous

↑ Indicates a "Weak for" recommendation strength; ↔ indicates a "Neither for nor against" recommendation strength; # indicates the treatment was "Not reviewed" in the evidence review

Sidebar 8: Treatment Options for Headache in General[a]		
Type	**Treatment**	**Notes**
Non-pharmacologic Therapy	Acupuncture↔	• Evidence suggests small or inconsistent benefits for migraine and TTH in comparison to sham acupuncture • No statistically significant differences when compared to beta-blockers, valproic acid, or CCBs, which are also reviewed in this CPG
	Aerobic exercise/ progressive strength training↑	• Evidence suggests aerobic exercise and progressive strength training decreases headache frequency
	CBT or biofeedback↔	• Although CBT and biofeedback are commonly used, there was insufficient evidence in this CPG's systematic evidence review to support a recommendation
	Dietary trigger education↑	• While the evidence regarding dietary trigger avoidance is limited, it is reasonable to offer patient education regarding diet modification to decrease the frequency and/or severity of their migraine headache
	Dry needling↔	• Evidence of dry needling compared to no treatment was limited
	Elimination-based diet testing↔	• There was insufficient evidence in this CPG's systematic evidence review to support a recommendation
	Mindfulness-based therapy↑	• Improved outcomes of headache frequency and other potential benefits outweigh the harms with this relatively low-risk activity
	Neuromodulation↔	• There was insufficient evidence in this CPG's systematic evidence review to support a recommendation • Some patients experienced headache following treatment
	Pulsed radiofrequency or SPG↔	• There was insufficient evidence in this CPG's systematic evidence review to support a recommendation • Feasibility and acceptability limit these interventions
Pharmacotherapy – Preventive	Fluoxetine or venlafaxine↔	• There was insufficient evidence in this CPG's systematic evidence review to support a recommendation
Pharmacotherapy – Abortive	IV ketamine↓	• Further research should be conducted before administering to patients with headache
	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 F for pharmacotherapy tables for Headache

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

↑ Indicates a "Weak for" recommendation strength; ↓ indicates a "Weak against" recommendation strength; ↔ indicates a "Neither for nor against" recommendation strength

VI. Recommendations*

Topic	Sub-topic	#	Recommendation[a]	Strength[b]
Screening and Healthcare Settings		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
		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
Non-pharmacologic Therapy		3.	We suggest physical therapy for the management of tension-type headache.	Weak for
		4.	We suggest aerobic exercise or progressive strength training for the management of headache.	Weak for
		5.	We suggest mindfulness-based therapies for the treatment of headache.	Weak for
		6.	We suggest education regarding dietary trigger avoidance for the prevention of migraine.	Weak for
		7.	We suggest non-invasive vagus nerve stimulation for the acute treatment of episodic cluster headache.	Weak for
		8.	There is insufficient evidence to recommend for or against acupuncture for the treatment of headache.	Neither for nor against
		9.	There is insufficient evidence to recommend for or against dry needling for the treatment of headache.	Neither for nor against
		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
		11.	There is insufficient evidence to recommend for or against cognitive behavioral therapy or biofeedback for the treatment of headache.	Neither for nor against
		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
		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

Topic	Sub-topic	#	Recommendation[a]	Strength[b]
Pharmacotherapy	*a. Migraine – Preventive*	14.	We recommend candesartan or telmisartan for the prevention of episodic or chronic migraine.	Strong for
		15.	We suggest erenumab, fremanezumab, or galcanezumab for the prevention of episodic or chronic migraine.	Weak for
		16.	We suggest lisinopril for the prevention of episodic migraine.	Weak for
		17.	We suggest oral magnesium for the prevention of migraine.	Weak for
		18.	We suggest topiramate for the prevention of episodic migraine.	Weak for
		19.	We suggest propranolol for the prevention of migraine.	Weak for
		20.	We suggest onabotulinumtoxinA injection for the prevention of chronic migraine.	Weak for
		21.	We suggest against abobotulinumtoxinA or onabotulinumtoxinA injection for the prevention of episodic migraine.	Weak against
		22.	There is insufficient evidence to recommend for or against gabapentin for the prevention of episodic migraine.	Neither for nor against
		23.	There is insufficient evidence to recommend for or against nimodipine or nifedipine for the prevention of episodic migraine.	Neither for nor against
		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
		25.	There is insufficient evidence to recommend for or against combination pharmacotherapy for the prevention of migraine.	Neither for nor against
	b. Migraine – Abortive	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
		27.	We suggest frovatriptan or rizatriptan for the acute treatment of migraine.	Weak for
		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
		29.	We suggest ibuprofen, naproxen, aspirin, or acetaminophen for the acute treatment of migraine.	Weak for
		30.	We suggest greater occipital nerve block for the acute treatment of migraine.	Weak for
		31.	We suggest intravenous magnesium for the acute treatment of migraine.	Weak for
	c. Tension-type Headache – Preventive	32.	We suggest amitriptyline for the prevention of chronic tension-type headache.	Weak for
		33.	We suggest against botulinum/neurotoxin injection for the prevention of chronic tension-type headache.	Weak against
	d. Tension-type Headache – Abortive	34.	We suggest ibuprofen (400 mg) or acetaminophen (1,000 mg) for the acute treatment of tension-type headache.	Weak for

Topic	Sub-topic	#	Recommendation[a]	Strength[b]
Pharmacotherapy (cont.)	*e. Cluster Headache – Preventive*	35.	We suggest galcanezumab for the prevention of episodic cluster headache.	Weak for
	f. Cluster Headache – Abortive	36.	There is insufficient evidence to recommend for or against any particular medication for the acute treatment of cluster headache.	Neither for nor against
	g. Headache – Preventive	37.	There is insufficient evidence to recommend for or against oxygen therapy for the acute treatment of primary headache.	Neither for nor against
		38.	There is insufficient evidence to recommend for or against valproate for the prevention of headache.	Neither for nor against
		39.	There is insufficient evidence to recommend for or against fluoxetine or venlafaxine for the prevention of headache.	Neither for nor against
	h. Headache – Abortive	40.	We suggest against intravenous ketamine for the acute treatment of headache.	Weak against
		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
	i. Secondary Headache – Abortive	42.	There is insufficient evidence to recommend for or against prescription or non-prescription pharmacologic agents for the treatment of secondary headache.	Neither for nor against

[a] For more information regarding the scope of the CPG, please refer to Scope of this Clinical Practice Guideline

[b] For additional information, please refer to Grading Recommendations

* The category for all recommendations is *Reviewed*, *New-added*. For additional information on recommendation categories, please refer to Recommendation Categorization and Appendix B

A. Screening and Healthcare Settings

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)

Discussion

An 11-year prospective cohort study by Hagen et al. (2012) (n=25,596), mean age 43 – 47 years with the percent of male subjects ranging from 28 – 44, found the risk factors that were associated with an increased risk of MOH incidence among patients with headache were use of anxiolytics, use of analgesics, and use of sleep-inducing medications.[51]

Hagen et al. (2012) found that headache frequency of 7 – 14 days/month at baseline was the most potent risk factor when compared to any headache (odds ratio [OR]: 5.9), migraine (OR: 8.1), or non-migrainous headache (OR: 4.9).[51] Hagen et al. (2012) utilized the Hospital Anxiety and Depression Scale (HADS) scores to identify psychological risk factors associated with a higher incidence of MOH: a high anxiety score with HADS A score $\geq$11 (OR: 2.0) and a high depression score with HADS D score $\geq$11 (OR: 2.6), or a specific syndrome including both a HADS score $\geq$11, with musculoskeletal complaints, and gastrointestinal (GI) complaints (OR: 4.7). Other risk factors associated with a higher incidence of MOH included physical inactivity, sick leave of more than two weeks in the last year, self-reported whiplash, and smoking.[51]

Other studies reviewed had evidence consistent with the above findings.[52-54] Medication overuse headache risk factors included combination medicines, high-frequency use of acute headache medications from 13 – 23 days/month, lack of headache prevention, allodynia, headache frequency before drug withdrawal, and higher Headache Impact Test-6 (HIT-6) scores. It may be difficult to discuss the various associated risk factors during time-limited visits. However, specialty referral is advised for subgroup populations with multiple psychological risk factors or extensive medication use. Patient preferences somewhat vary (and impact treatment decisions) because of a reluctance to discuss smoking or exercise habits with providers or to implement recommended behavior changes.

The Work Group's confidence in the quality of the evidence was moderate.[51] The body of evidence had limitations including no reported exclusion criteria for the study. Other considerations regarding this recommendation are that the benefits of preventing MOH outweigh the harms of a prolonged office visit to assess multiple risk factors. However, patient values and preferences were somewhat varied because some patients do not want to discuss smoking or exercise. Feasibility was also considered as resources for assessments are widely available because most providers ask about these risk factors. Thus, the Work Group decided upon a "Weak for" recommendation.

Future research should focus on developing a model to analyze multiple risk factors contributing to MOH.

Recommendation

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)**

Discussion

An SR by de Goffau et al. (2017) evaluated the treatment of MOH using multiple methods and healthcare settings and found no differences in any of the treatments.[55] This SR evaluated the use of prednisone or celecoxib in the treatment of MOH.[55] The SR evaluated the method of medication withdrawal to include abrupt withdrawal, inpatient or outpatient treatment, or follow-up with a general practitioner or neurologist. There were no statistically significant differences in any of these methods. There were no statistically significant differences between abrupt withdrawal versus 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 did not produce any statistically significant results with regard to reduction in headache days, number of headache days per month, headache frequency, or pain-related QoL.

A randomized controlled trial (RCT) by Karadas et al. (2017) evaluated the use of medication withdrawal alone and medication withdrawal with greater occipital nerve (GON) block.[56] There was very low quality evidence that favored three stage GON block for the reduction in the number of headache days and the number of triptans used for MOH. The benefit's effect size was insufficient to recommend for the use of GON block for MOH.

The Work Group's confidence in the quality of the evidence was very low.[55,56] The benefits and harms were balanced as there are numerous methods for the treatment of MOH with varying levels of risk. Some medications are dangerous when stopped abruptly (e.g., barbiturates and benzodiazepines) and each patient's comorbidities should be considered when determining the withdrawal timing and method. There is large variation in patient preferences based on a reluctance to stop using their medication. Resource use may vary significantly since some patients may prefer to use a medication to help with withdrawal while others may prefer a procedure. A PCP and/or specialist can treat MOH, rendering inpatient treatment unnecessary, which may improve access to care and reduce the burden to the healthcare system. Thus, the Work Group decided upon a "Neither for nor against" recommendation.

B. Non-pharmacologic Therapy

Recommendation

3. We suggest physical therapy for the management of tension-type headache. **(Weak for | Reviewed, New-added)**

Discussion

The term "physical therapy" refers to numerous interventions carried out by licensed physical therapists, including manual therapy, therapeutic exercise, strength and endurance training, self-management training, patient education, and adjunctive modalities. Evidence suggests these interventions decrease

headache frequency in patients with TTH. Physical therapists are licensed healthcare providers who specialize in movement and provide multimodal care including patient education, hands-on treatment, and exercise prescription with a focus on QoL and function across the lifespan. An SR by Mesa-Jimenez et al. (2015) found that manual therapy combined with therapeutic exercise was associated with a reduction in headache frequency, intensity, and duration immediately following the intervention period when compared to a pharmacologic intervention of the same duration; however, this difference was not maintained at 24-weeks.[57]

The Work Group reviewed three RCTs focusing on manual therapy administered by physical therapists for patients with TTH.[58-60] Ferragut-Garcias et al. (2017) found a statistically significant decrease in headache frequency, intensity, and disability (HIT-6) with large effect sizes favoring all active manual interventions compared to placebo, with combined techniques yielding the greatest impact.[60] It is important to note that the control group had more subjects who used abortive medication repeatedly compared to subjects in any of the manual therapy intervention groups.

The remaining two RCTs examined various manual techniques compared to control.[58,59] Both found a statistically significant improvement in disability at four weeks (Headache Disability Inventory [HDI]) favoring a combination of manual techniques directed at the suboccipital and upper cervical spine.[58,59] A statistically significant difference was not found on the HDI frequency subscale in Espi-Lopez et al. (2014a) between manual treatment and control; however, this instrument asks for a range – as opposed to the number of days – and, thus, may impact sensitivity to change.[58] Espi-Lopez et al. (2014b) found a statistically significant decrease in headache frequency (self-reported number of days) at four and eight weeks when compared to baseline for the combined manual techniques with a large effect size.[59] Espi-Lopez (2014b) did not find statistically significant HIT-6 differences between groups at any time period.[59]

An SR by Luedtke et al. (2015) evaluated the data from three RCTs analyzing the components of physical therapy interventions on TTH, CGH, and migraine headache.[61] The data found a statistically significant decrease in TTH intensity with physical therapy interventions and no statistically significant improvement in TTH frequency, despite one RCT showing a statistically significant decrease in TTH frequency for the manual therapy component.[61] Luedtke et al. (2015) found that physical therapy interventions decreased CGH frequency and intensity at up to 52-weeks.[61] However, since this data was limited to only one RCT, the Work Group determined it was insufficient to warrant inclusion in this recommendation.

As the studies evaluated for this recommendation focus on manual therapy provided by physical therapists, it is important to note that this phrase is used to describe a set of techniques applied by a healthcare provider to musculoskeletal tissues to modulate pain and/or create movement. Although 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.[57,61] The ability to employ various manual techniques in conjunction with active approaches contributes to the generalizability of these findings to typical physical therapy management and mitigates the potential pitfalls of monotherapy with a constrained approach.

Our systematic evidence review found studies on specific manual approaches for headache management including osteopathic manipulation, spinal manipulation, craniosacral, and myofascial trigger point

massage.[58,62-64] Given the low quality of the evidence and lack of generalizability in these studies, there was insufficient evidence to make a recommendation specific to any of these approaches.

The Work Group's confidence in the quality of the evidence was low.[57-64] There were limitations in methodological quality and imprecision in the evidence. The benefits of physical therapy outweigh the likelihood of adverse events (AEs), which were not explicitly reported in the studies reviewed since physical therapy is considered safe. The improved outcomes of decreased headache frequency, intensity, and patient preference for non-pharmacologic interventions create high perceived value for this treatment option. There may be variation in patient values and preferences related to willingness to engage in active interventions (e.g., asking someone to exercise at home). A patient may be more willing to engage in active interventions if supplemented with passive interventions (e.g., manual therapy, dry needling, modalities). Physical therapy is a non-pharmacologic treatment option, which aligns with patient focus group participant preferences. Physical therapy, as part of a team approach, would meet the patient focus group participant preferences related to care coordination. While the risk of AEs of physical therapy is extremely low, the variable decrease in headache frequency reported may not be worth the opportunity cost to some patients of attending appointments. This could be mitigated by fewer visits to the physical therapist, more time spent on independent home practice, or by including telemedicine visits for care. Alternatively, a patient may be more willing to engage in combined interventions reviewed (e.g., manual therapy, dry needling, modalities, and therapeutic exercise). Initial training and services must be provided by a licensed professional, which may present barriers related to time for appointments and access to physical therapists. Embedding physical therapists within primary care teams may mitigate some barriers. Thus, the Work Group decided upon a "Weak for" recommendation.

More research is needed on the impact of physical therapy, other rehabilitation therapies, and the multiple modalities under that umbrella on TTH, migraines, and CGH because these treatments present an opportunity for non-pharmacologic intervention.

Recommendation

4. We suggest aerobic exercise or progressive strength training for the management of headache. **(Weak for | Reviewed, New-added)**

Discussion

Evidence suggests aerobic exercise decreases headache frequency. An SR by Lemmens et al. (2019) evaluated the effectiveness of aerobic exercise in patients with the diagnosis of migraine headache across five RCTs and one non-randomized controlled trial.[65] Pooled data from four of the studies (n=176) with similar design demonstrated that aerobic exercise significantly improved the number of headache days at 10 – 12 weeks in comparison to the controls. The mean improvement in headache days was 0.6 headache days per month. Of note, the mean baseline frequency of headaches ranged from 3.8 – 7.6 days per month. This minimal effect size likely stems from the variability of interventions assessed in this SR. The dosage or amount of prescribed aerobic exercise varied across each study design; in three studies patients exercised at least three times per week versus twice per week in the other study. Exercise interventions included jogging, high-intensity interval training, moderate continuous training, combination exercise (i.e., cycling, cross-training, brisk walking, and running), and indoor cycling. Comparators across the studies

included no intervention, medication management with topiramate, education, and relaxation therapy. The variability of comparators also likely decreased the effect size.

Sertel et al. (2017) compared 60-minutes sessions, three times per week for six weeks of aerobic exercise, body awareness therapy, and control (n=20 in each group) in patients with TTH.[66] In this study, the aerobic exercise intervention was a step-dance board exercise with a progressive increase in the length of exercise over time. Body awareness therapy consisted of relaxation, motion, and massage applied by a physical therapist. Headache impact (measured by HIT-6) decreased an average of 10 points for both active interventions; no change was noted in the scores for the control. The number of days of "moderate pain" was 2.2 for the body awareness group, 1.6 for the aerobic exercise group, and 4 in the control group. Both outcomes were found to be statistically significant. When investigating analgesic use, aerobic exercise significantly reduced medication use compared to body awareness therapy and control.

Evidence suggests progressive strength training decreases headache frequency, with one study addressing TTH and one that did not specify headache type.[67,68] Madsen et al. (2018) utilized a progressive strength training regimen using resistance bands, compared with instruction on ergonomic and postural correction (n=30 per group).[67] In an intention-to-treat analysis, both interventions demonstrated a similar reduction in TTH frequency, with an 11% reduction in headache frequency and duration in the strength-training group after 19 – 22 weeks. The authors noted the reduction did not meet their a priori threshold of 30% for clinical significance, but the Work Group determined that the change in outcomes is an important consideration for exercise prescription in this population.

Gram et al. (2014) evaluated a strength-training regimen of dumbbell exercises to strengthen neck, shoulder, and wrist muscles to reduce neck pain, shoulder pain, and headache.[68] The headache type was not specified. Participants were divided into regular supervision, minimal supervision, and control groups. The interventions were applied three times weekly for 20-weeks. Both supervised groups demonstrated a mean reduction of approximately one headache day per month from baseline of approximately 3.5 days per month. Headache severity also decreased by approximately 0.9 on a 0 – 10 scale, from a baseline severity of approximately 3.5.

Regarding exercise training, there is general consistency supporting either aerobic conditioning and/or progressive strength training. In all studies reviewed, no AEs were reported. There is some variability in patient preferences regarding these interventions, and equipment availability may not be equal across DoD and VA facilities. Aerobic and/or progressive strength training addresses the desire for non-pharmacologic therapies expressed by the patient focus group. Also, the mental and physical benefits of exercise, in general, can improve overall health and well-being.

The Work Group's confidence in the quality of the evidence was low.[65-68] The body of evidence had limitations (e.g., small sample size and heterogeneity of headaches studied).[65,67,68] The Work Group determined the benefits (e.g., reduced headache frequency and severity) outweigh the potential harm of AEs, which was small. Patient values and preferences vary somewhat given different patients' willingness to exercise. Equity was considered because patients may be able to exercise at inexpensive gyms or at home. Prior injuries or disabilities may impact the feasibility for some patients. This recommendation may not be appropriate for patients who have experience with exercise worsening headaches. Thus, the Work Group decided upon a "Weak for" recommendation.

Recommendation

5. We suggest mindfulness-based therapies for the treatment of headache.
   (Weak for | Reviewed, New-added)

Discussion

Mindfulness-based therapies facilitate the process of intentional awareness in a non-judgmental manner and often include meditation, relaxation, mindfulness-based stress reduction (MBSR), mindfulness-based cognitive therapy (MBCT), acceptance-based approaches, and yoga among others. Over the past decade, patient interest and consumer awareness of such therapies have grown, and many therapies have demonstrated that a positive impact was successfully applied. An SR by Gu et al. (2018) found that mindfulness meditation demonstrated improvement in pain intensity and headache frequency when compared to control group data.[69] Interventions such as MBSR had a significantly positive influence on pain intensity when compared to other forms of meditation (MBCT, Vipassana, Zen) and interventions (relaxation, education, pharmacotherapy, delayed treatment, or wait-list).

Patient focus group participants expressed an interest in alternative measures for the treatment of headache. The risk of using mindfulness-based techniques is low and there is potential for additional benefits (i.e., self-awareness, self-regulation, relaxation). It is also well-suited for telehealth delivery. The Work Group also considered the potential for outcome variability because some patients may resist the intervention or feel it is incompatible with their personal religious and spiritual beliefs/values. Indeed, outcomes depended on a patient's willingness to learn and work at mindfulness practices.[69]

The Work Group's confidence in the quality of the evidence was low.[69] The body of evidence had limitations including high dropout rates and variability in interventions and providers. Findings favored intervention for the outcome of headache frequency with no statistical significance for QoL outcomes or headache intensity. Improved outcomes of headache frequency and other potential benefits outweigh the harms with this relatively low-risk activity. There is some variation in patient preference because some patients would not be willing to commit to mindfulness practices. Additionally, teaching mindfulness to patients can be resource intensive (e.g., certified staff, time to complete program/learn techniques) and inconsistent (i.e., styles/interventions vary by practitioner). Nonetheless, it provides an opportunity for standardizing approaches. Thus, the Work Group decided upon a "Weak for" recommendation.

Future research should address the variability in modalities offered and the addition of behavioral health interventions, including cognitive behavioral therapy (CBT), and biofeedback. Research should study telehealth delivery of mindfulness therapies, explore the feasibility of standard approach/replication, investigate the "dose" or required length of the intervention, and the sustainability of desired outcomes.

Recommendation

6. We suggest education regarding dietary trigger avoidance for the prevention of migraine.
   (Weak for | Reviewed, New-added)

Discussion

Many publicly available resources include discussion and education on dietary restrictions. One way of identifying the food(s) is by elimination –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 patients who avoided trigger foods or modified diet for the prevention of migraine had fewer migraine attacks per month and the total monthly analgesic consumption rate decreased.[70,71]

Participants (n=50) in Ozon et al. (2018) first identified migraine-triggering foods using a questionnaire, then participated in an elimination based diet for two months.[70] Following this dietary change, the groups were divided: one group of 25 individuals relaxed their diet restrictions, the other arm of 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 four months, compared to the group that could relax their diet (p=0.013).

Zencirci et al. (2010), separated 50 participants into two groups: one group of 25 who used medications as identified in the study (metoprolol 120 milligrams [mg]/day, riboflavin 600 mg three times/day, and naproxen sodium 550 mg at the aura or beginning of an attack) and a second group that used these same medications plus trigger food avoidance (participants were provided a standard list).[71] Both groups were followed every 15-days for 12-months. Those who combined medications with trigger food avoidance experienced 2.45 fewer migraine attacks per month (p=0.007).

While the evidence regarding dietary trigger avoidance is limited, it is reasonable to offer education to patients regarding diet modification as an option to decrease the frequency and/or severity of their migraine headaches. There is a minimal risk associated with diet change education or the potential elimination of trigger foods and education may be very beneficial for certain patients. Telehealth could be utilized to provide nutritional counseling and access to dietitians if not physically available. Furthermore, patient focus group participants expressed an interest in education and specific information regarding their condition. Providing education does not automatically translate into a patient's behavior change, and providers should use caution with offering an elimination diet in patients with underlying eating disorders. Strict elimination diets could lead to disordered eating, social isolation, and insufficient nutritional intake.

The Work Group's confidence in the quality of the evidence was low.[70,71] The body of evidence had limitations including self-reporting of trigger foods and a small number of participants.[70] The benefits (a reduction in headache days and medication usage) outweighed the minimal risk of providing education to a properly selected patient. Patient preferences likely vary because some may not want to adhere to new diets. Resource use was considered minimal, requiring someone to offer education (i.e., a PCP or dietitian) and a dietitian to provide it. Thus, the Work Group decided upon a "Weak for" recommendation.

More research is needed in the safety and effectiveness of any self-directed lifestyle modification.

Recommendation

7. We suggest non-invasive vagus nerve stimulation for the acute treatment of episodic cluster headache.
   (Weak for | Reviewed, New-added)

Discussion

Non-invasive vagus nerve stimulation (n-VNS) devices have been recently cited as a non-pharmacologic treatment modality to provide relief for migraines and cluster headaches. Non-invasive vagus nerve

stimulation is applied transcutaneously through a handheld device, with two metallic transmitters. Thedevice uses an alternating current of five 5,000 hertz (Hz) pulses at a rate of 25 Hz delivered through surface electrodes to the cervical branch of the vagus nerve. In 2018, the Food and Drug Administration (FDA) approved its use in the treatment of episodic cluster headache and migraine headache.

The Work Group evaluated the use of n-VNS in episodic and chronic cluster headaches and migraines, but the research reviewed supports its use in individuals experiencing episodic cluster headache only. The literature does not support n-VNS treatment of chronic cluster headache due to low quality evidence.[72,73] The studies investigated acute pain relief (two RCTs) without the use of abortive medication in individuals with episodic cluster headache (one RCT). The evidence reviewed also compared the use of n-VNS to sham treatment in episodic and chronic migraine (two RCTs).[73,74]

There is low to moderate quality evidence supporting n-VNS for individuals experiencing episodic cluster headaches.[72,73] Goadsby (2018) found in a small group (n=102) receiving n-VNS (n=50) versus sham (n=52) treatment a statistically significant improvement in pain at 15- and 30-minutes for episodic cluster headaches.[63] In a similar group (n=150), Silberstein (2016) found a 50% response rate at 15- and 60-minutes in pain reduction (defined as 0-1 on a 5 point scale) favoring n-VNS over sham.[73] Responders were also defined as reporting less pain, and without the use of abortive medication during 15-, 30-, and 60-minute study periods. The primary AEs were site irritation, pain, and erythema and some musculoskeletal disorders such as lip or facial drooping, or twitching.[72,73] The evidence consistently demonstrated that the use of n-VNS was less effective for individuals with chronic cluster headaches.[72-74] Thus, n-VNS should not be offered to patients experiencing chronic cluster headache.

Non-invasive vagus nerve stimulation was evaluated for the treatment of episodic and chronic migraine and similar intervention parameters were utilized as in previous studies.[72-74] A multicenter RCT by Tassorelli (2018) studied the primary outcomes of efficacy, reductions in pain (at 30-, 120-minutes), and headache days, which were found to be not clinically significant in the n-VNS group (n=122) compared to sham (n=126) treatment.[75]

The Work Group identified episodic and chronic cluster headaches as one of the most debilitating and painful headaches described in this CPG. As such, the Work Group determined that any treatment that may provide relief should be offered to patients.

The Work Group's confidence in the quality of evidence was low given the outcomes and the potential for bias as the device manufacturer or parent company funded some studies.[72,75] Nonetheless, the benefits of acute pain reduction, reduction in abortive medication, and reduction in the number of headache days in this population far outweigh the harm/burden.

Despite general consistency in the evidence supporting n-VNS in the treatment of acute episodic cluster headache, provider and patient preferences somewhat vary. The patient focus group was interested in alternative treatments to medication, which an n-VNS device can offer. However, due to the device cost and distribution limitations, this treatment may not be accessible. The primary AEs reported indicated that stimulation can be uncomfortable and intolerable, resulting in pain or irritation at the application site.

The Work Group's confidence in the quality of the evidence was low.[72-75] The body of evidence had limitations (e.g., small sample size and confounders in the analysis). The Work Group determined the

benefits of relief from episodic cluster headaches outweigh the potential harm of AEs. Patient values and preferences were somewhat varied because all patients may not want to try this intervention. The Work Group also considered resource use (e.g., the device and refill cost) and equity (i.e., the device cost may make it less available in primary care or urgent care setting). Thus, the Work Group decided upon a "Weak for" recommendation.

More research is needed in the use and application of n-VNS in cluster headaches, both episodic and chronic, as these are quite debilitating and impair QoL across various domains of patient values. Future research directives should determine if early intervention modifies the frequency or prevalence of episodic and/or chronic cluster headaches.

Recommendation

8. There is insufficient evidence to recommend for or against acupuncture for the treatment of headache.
   (Neither for nor against | Reviewed, New-added)

Discussion

Two SRs assessing the efficacy of acupuncture versus sham were reviewed for the treatment of migraine and demonstrated mixed outcomes.[76,77] An SR by Linde et al. (2016a) demonstrated no statistically significant change to the number of headache days per month or medication use over the course of a month but did demonstrate improvement in headache frequency.[76] The large number of patients (n=1,534) evaluated for this outcome and lack of bias resulted in moderate confidence in these findings.

An SR by Xu et al. (2018) favored acupuncture but the quality of the evidence was low given concerns for bias and the challenge of blinding the studies reviewed.[77] Of note, this SR had the shortest follow-up (i.e., 4 – 12 weeks) in comparison to a six month follow-up in the other reviews and in Zhao et al. (2018).[76,78]

The single RCT reviewed, Zhao et al. (2018), favored acupuncture for three outcomes when compared to sham, but demonstrated no significant difference for QoL and had a small number of patients (n=74 in the acupuncture group) in comparison to Linde et al. (2016a).[78] Given the inconsistency with statistical significance of outcomes in comparison to sham and small study size relative to Linde et al. (2016a), Zhao et al. (2018) was considered a low quality study.

Linde et al. (2016b) assessed the efficacy of acupuncture versus sham for TTH.[79] This SR was a low quality study since improving headache frequency by 1.5 headache days per month was determined not to be clinically relevant given the burden required of repetitive acupuncture treatments (6 – 15 treatments) and lack of significance for improving medication use over a month.

Linde et al. (2016b) evaluated the efficacy of acupuncture in comparison to pharmacotherapy for episodic migraine.[79] The comparators were beta-blockers, calcium channel blockers (CCBs), and valproic acid and the evidence suggested no statistically significant difference between acupuncture and these medication classes. When evaluating this finding, the Work Group considered the strength of recommendation for these specific medication classes within this CPG. This CPG suggests beta-blockers for migraine prophylaxis

(see Recommendation 19), but there was insufficient evidence to recommend for or against the use of valproic acid (see Recommendation 38) and CCBs for migraine headache (see Recommendation 23).

Of note, the sham comparators and acupuncture interventions were highly variable across the included studies. The use of sham as a comparator for acupuncture studies complicates the overall evidence review and determination of the efficacy of acupuncture. Sham acupuncture and sham interventions can demonstrate a large non-specific effect in many pain conditions. While a comparison to other active treatments would have more clearly outlined the efficacy of acupuncture, such studies were not found in this CPG's systematic evidence review. 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. Since multiple outcomes demonstrated that acupuncture did not have a statistically significant difference compared with the sham comparators, the Work Group determined that the evidence did not clearly define whether acupuncture itself is beneficial, or if non-specific needling resulting in a diffuse noxious inhibitory effect improved headache in the included studies.

Acupuncture interventions in the SRs required at least one session per week over six weeks, with some studies requiring more treatments. In the studies reviewed, the harms of acupuncture were not assessed as outcomes, either versus sham or pharmacotherapy. Acupuncture is generally considered to be safe.

Provider and patient preferences regarding this treatment are likely somewhat varied. The patient focus group expressed interest in complementary and integrative health (CIH) therapies while simultaneously minimizing medication options. The need for ongoing treatments, often on a weekly basis or more frequently, may be burdensome for some patients. At this time within the DoD, only medical acupuncturists can provide this treatment, which limits the availability for active duty Service Members or those receiving treatment at smaller military treatment facilities. Within the VA, there has been an increase in acupuncture provider availability, and Veterans may be able to access acupuncture more easily. However, Veterans in rural locations may have less access to acupuncturists than those in large urban areas or closer to larger VA medical centers. Veterans and Service Members may incur an out of pocket cost acupuncture visits, and the need for multiple visits could pose a financial burden that exceeds other treatments. Acupuncture could be a relative contraindication for patients who are pregnant.

The Work Group's confidence in the quality of the evidence was low.[76-79] The body of evidence had limitations, including small sample size and confounders in the analysis, and the effect size was very small for the most robust outcome.[76-79] The Work Group determined the harms and benefits of acupuncture were balanced. 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 the burdens imposed on patients and the medical system. Patient values and preferences were somewhat varied because some patients will not try acupuncture or do not tolerate needles. Thus, the Work Group decided upon a "Neither for nor against" recommendation.

Future research should compare acupuncture for headaches against active controls (i.e., not with sham). The Work Group concluded studies should evaluate acupuncture versus medications with a strong evidence base (e.g., triptans or calcitonin gene-related peptide [CGRP] receptor antibodies/antagonists).

Evaluating the role of acupuncture in combination treatment (e.g., along with exercise or behavioral treatments versus medications) would also help determine its place in headache management.

Recommendation

9. There is insufficient evidence to recommend for or against dry needling for the treatment of headache.
   (Neither for nor against | Reviewed, New-added)

Discussion

Invasive treatment of trigger points is often divided into two broad categories, dry needling and wet needling. Dry needling is the insertion of a thin solid filiform needle, similar to those used in acupuncture, into muscles, fascia, scar tissue, ligaments, and tendons without injection of any solution or medications. This differs from wet needling, which uses hollow-bore needles to deliver solutions or medications into the same tissues listed above.

The RCT by De Venancio et al. (2009) evaluated the outcomes of trigger point dry needling versus injection of lidocaine or botulinum toxin (specific subtype was not noted) for patients with myofascial pain and headaches.[80] In this small study (n=44, divided among the three groups), there were no statistically significant differences in headache frequency, headache duration, or use of abortive medication. No other studies met inclusion criteria for this CPG's systematic evidence review.

When assessing the balance of harms and benefits, the Work Group determined that the use of botulinum toxin was a higher risk than an injection of low volumes of local anesthetic or dry needling alone. 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 in comparison to 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 in comparison to the injection of local anesthetic or botulinum toxin.

Despite the lack of evidence for dry needling over trigger point injection with lidocaine or botulinum toxin, patient and provider preferences likely somewhat vary. Some patients prefer passive injection-based treatments over the potential need for medication adherence or self-management, while others would avoid needle-based treatment altogether. The availability of providers trained and willing to provide trigger point injections and/or dry needling varies, especially in rural areas or locations far from larger medical centers, which may limit the accessibility of these treatment modalities. Unlike the comparator injection options, dry needling exists beyond the purview of physicians or licensed independent providers (e.g., advanced practice registered nurses or physician assistants). In fact, it could be more accessible because physical therapists can provide this treatment in settings where it is allowed within their scope of practice. Lastly, the Work Group determined if wet needling is chosen as a preferred modality, lidocaine may be preferred as a first-line option over botulinum toxin given its lower cost and equivalent efficacy.

The Work Group's confidence in the quality of the evidence was low.[80] The single study reviewed had limitations (e.g., small sample size and lack of statistical significance between interventions).[80] Benefits slightly outweighed harms because dry needling is less destructive to tissue than an injection of toxin.

Patient values and preferences vary somewhat. Additionally, the Work Group considered resource use (e.g., some providers may not be trained or willing to use dry needling) and feasibility (e.g., variable patient acceptability of needles). The Work Group also considered subgroups (e.g., patients where medication may restrict job ability, women who are pregnant). Thus, the Work Group decided upon a "Neither for nor against" recommendation.

More research is needed regarding the safety and effectiveness of trigger point dry needling compared to no treatment since there is a paucity of evidence to this effect. Should the evidence show benefit, the availability of dry needling, provided by physicians, licensed independent practitioners, or physical therapists would make it the most accessible of the reviewed interventions outlined above.

Recommendation

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)

Discussion

A small RCT by Yang et al. (2015) found pulsed radiofrequency (pRF) of the posterior medial branches of cervical nerves two and three decreased migraine disability (Migraine Disability Assessment [MIDAS]), the number of headache days, and the mean aspirin dosage in chronic migraine patients who had a prior positive response to a GON block with local anesthetic.[81] No serious AEs were reported. In a small RCT (n=38) by Cady et al. (2015a), repetitive sphenopalatine ganglion (SPG) blockade using nasal catheter delivered bupivacaine for chronic migraine and found no statistically significant benefit compared to saline for the number of headache days, disability (HIT-6), average pain, or acute medication usage.[82] No AEs were reported.

Although evidence demonstrates that pRF may be beneficial, the feasibility and acceptability of this intervention limits its use. This intervention is not widely available and requires special training and equipment that confines its use to interventional pain specialists, although there are multiple blockade technique options 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 evidence review utilized the patented Tx-360® device.[82]

The Work Group's confidence in the quality of the evidence was low. The body of evidence had limitations including small sample size.[81,82] The benefits and harms are balanced for both interventions, as there were no reported side effects for either intervention. Patient preferences may vary because this is a needle-based intervention 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 decided upon a "Neither for nor against" recommendation.

Future research using larger sample sizes would help establish the effectiveness of these interventions, as both would provide viable non-pharmacologic treatment options for chronic migraine patients, if effective.

Recommendation

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)

Discussion

There is insufficient evidence to recommend for or against for the use of CBT and biofeedback in the treatment of headache when considering the outcomes of change in monthly headache days from baseline, disability/QoL (e.g., MIDAS-A [days], HIT-6, Migraine-Specific Quality of Life Questionnaire [MSQ], Migraine Physical Function Impact Diary [MPFID]), change in acute headache treatment days/abortive medication use, and change in number of moderate/severe headache days.

An SR by Lee et al. (2019) demonstrated that CBT and biofeedback significantly reduced the number of headache days each month compared to controls.[83] However, in another SR, Probyn et al. (2017), and two small RCTs, Martin et al. (2015) and Fritsche et al. (2010), the authors did not find statistically significant differences to support a recommendation for CBT in the treatment of headache.[84-86]

Although CBT interventions did not demonstrate any AEs, there was insufficient evidence to support a direct recommendation for or against the use of psychological interventions for any headache type.

The effects of CBT on headache outcomes when compared to routine primary care, including pharmacotherapy and other therapies. A small RCT, Martin et al. (2015), found a significant reduction in headache intensity compared to routine care at 14-weeks follow-up. Individuals with comorbid mood disorder concerns derived additional benefit from the psychological focus of these interventions.[85] This suggests CBT combined with other interventions may result in more prolonged headache relief, and empowering individuals for long-term self-management. The overarching importance of this should not be underestimated given the high numbers of veterans and service members with mTBI and chronic comorbidities such as pain, and comorbidities that contribute to headache, such as post-traumatic stress disorder (PTSD), sleep disorders, and residual neurocognitive deficits.

When interpreting the Work Group's recommendations, considerations that the typical goals of biofeedback and CBT study designs were not specifically targeting reduction in headache days, intensity, or quality of life as defined specifically by the screening methods defined in this search. Rather, the intent of CBT and biofeedback interventions is to improve ones' ability to manage biopsychosocial functioning, thereby improving QoL, self-help, and self-management skills and to mitigate exacerbations of other comorbidities that may arise with an individual with chronic, debilitating headache.

There is likely some variation in patient and provider preferences. Though some time commitment is needed to achieve typical treatment dosage in behavioral health interventions, patient focus group participants expressed an interest in non-pharmacologic approaches. For subgroups not interested or able to seek typical primary care treatment modalities (e.g., pregnant or nursing, special military duty status limitations), this non-invasive alternative may be worthwhile. As with many behavioral health interventions, self-management strategies are generalizable to QoL improvement over time. Some concern exists regarding the limited availability of these treatment approaches, as there are few providers with specific training in the treatment of headache through psychological and behavioral modalities.[85]

Psychological interventions such as CBT for headache may be delivered via telehealth technologies for improved access and widespread dissemination. When telebehavioral health is offered, the availability of these interventions dramatically improves in rural settings. Because internet-based services demonstrate effectiveness, such modes of healthcare delivery should be considered.[87]

The Work Group's confidence in the quality of the evidence was very low.[83-87] The body of evidence collected during the 10-year window for this CPG had significant limitations (i.e., small sample size and confounders). Patient values and preferences were somewhat varied given the time investment in these treatment approaches. Resource use was considered because this intervention requires a significant time investment, which may burden providers and patients. The Work Group also considered subgroup considerations. Access to this type of care may present an equity issue. Feasibility was discussed; since the intervention can vary based on the provider, it would be difficult to standardize. Thus, the Work Group decided upon a "Neither for nor against" recommendation.

While the current CPG systematic evidence review failed to capture the evidence published prior to the search window, the Work Group acknowledges the standard accepted practice of adjunctive treatment of headache through both biofeedback and CBT. Biofeedback and CBT have historically been accepted as standard practice in the treatment of headache and additional research is less likely to be published due to the known effectiveness in addressing headache.[88-91] Future RCTs should consider specifically targeting the above outcomes when reviewing the effectiveness of CBT, biofeedback training used as a stand-alone intervention, or in combination with other therapists in the treatment of headache.

Recommendation

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)

Discussion

Some foods may precipitate migraines in certain patients, though the reasons for this are poorly understood. The usefulness of an elimination-based diet is discussed in Recommendation 6. Elimination diets can be cumbersome and time-consuming.

Some studies show a relationship between immunoglobulin G (IgG) and food sensitivity.[92,93] Two studies evaluated whether conducting an enzyme-linked immunosorbent assay (ELISA) to identify food hyper-sensitivities via IgG would be more effective and/or timely than the traditional elimination diet method. Both studies used IgG antibody testing to identify potential dietary triggers and then implemented an elimination diet to prevent headache based on those results. The primary outcome measure in both studies was a decrease in total number of headache days.[92,93]

Alpay et al. (2010) found a significant difference favoring the elimination diet for decreasing the total number of headache days, but the study had a small sample size (n=30) and patients were followed for two six week diet-modification periods only.[93] Mitchell et al. (2011) studied 167 participants and found no significant difference in the number of headache days between the group following a diet developed based on ELISA findings and the group that was given a standardized sham diet.[92] This study also had a short follow-up period.

The Work Group's confidence in the quality of the evidence was low.[92,93] There were few studies that adequately evaluated the potential impact of this treatment approach. The body of evidence had limitations including small sample size and short follow-up.[93] The benefits did not outweigh the burdens because of the requisite laboratory testing (i.e., IgG antibody evaluation) for an elimination diet. Patient values and preferences were somewhat varied because some patients may not want to follow a new diet. Immunoglobulin G antibody identification may be unavailable in some areas, with increased cost but little identified gain. Thus, the Work Group decided upon a "Neither for nor against" recommendation.

Given the limited data, more research is needed on the safety and effectiveness of utilizing IgG antibodies to develop and implement an elimination diet to reduce the total number of headache days. Alpay et al. (2010) is promising but was the first of its kind and warrants reproduction on a larger scale.[93] Further study, combined with studies on an elimination diet's utility, would better identify whether the ELISA test is worth the time and expense to more quickly and/or accurately identify trigger foods.

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)

Discussion

The Work Group reviewed the effect of transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), external trigeminal nerve stimulation (eTNS), and supraorbital electrical stimulation (SOES) compared to sham intervention in the treatment of episodic and chronic migraine and post-traumatic type secondary headache (i.e., mTBI).[94-98] Overall, there was insufficient evidence to support the use of these modalities in the treatment of the above-mentioned headaches. Adverse events were reported only via the use of tDCS and included headache and sleepiness.

The evidence for the outcome of reducing the number of pain-free days for TMS was low quality in patients with migraine and/or PTH. An SR by Lan et al. (2017) evaluated five RCTs (OR: 2.93 for chronic migraine; OR: 2.28 for migraine with aura) with the odds of having more pain-free days compared to sham treatment over a treatment period of 12 – 23 sessions.[94] They noted great heterogeneity in the application of TMS, which complicates the assessment of its effectiveness. Four studies investigated applied repetitive TMS in chronic migraine and one applied single pulse TMS in acute migraine with aura. Transcranial magnetic stimulation was also investigated and identified as pain-free days from "debilitating headache."[94] In the mTBI population with persistent PTH, there was a statistically significant difference in headache intensity at one week post interventions, but this did not extend to the four week period.

In Leung et al. (2017), TMS was directed over the left prefrontal cortex and reported in terms of relief with headache and depressive symptoms.[95] Transcranial magnetic stimulation is an FDA approved modality in the treatment of depression. The efficacy in its use for anxiety and trauma-related disorders are being investigated with promising results, although more stringent research designs are needed before this

modality becomes standard clinical practice. When considering the benefit of using TMS to manage chronic migraine, participant bias in reporting reduction in headache may be confounded by a reduction in depression and/or anxiety influenced by a reduction in other mental health symptoms.

Transcranial direct current stimulation was found through the analysis of three RCTs (episodic migraine) and one RCT (chronic migraine) to reduce the pain intensity in episodic migraine.[98] The outcomes of frequency of migraine and use of pain medications were statistically significant. The use of tDCS was found to have minimal unwanted side effects of sleepiness (OR: 1.32) and headache (OR: 0.48) as compared to sham across the four studies.[98]

External trigeminal nerve stimulation and/or SOES were examined in both acute and chronic migraine sufferers and TTH.[96,97] In Chou et al. (2018), there was low quality evidence to support the use of eTNS in the reduction of pain intensity at 60-minutes and use of abortive medication in episodic migraines alone.[96] Patients with chronic migraine found little effect.[96]

To investigate the use of SOES in TTH, an RCT by Harmed et al. (2018) compared three groups: SOES plus physical therapy, physical therapy alone, and medication alone.[97] When SOES was combined with physical therapy, participants reported a reduction in HIT-6 and pain intensity; there were no differences in outcomes in the medication-only group. Given the study design and the known positive impacts of physical therapy on TTH, the addition of SOES cannot be isolated as the causative factor in positive outcomes.

The Work Group's confidence in the quality of the evidence was low.[94-98] The body of evidence had limitations including small sample size and imprecision given the heterogeneity of interventions. Benefits in the application of neurostimulation to reduce migraine and TTH may be preferential for some patients. The harms and benefits are balanced because of the high cost of these devices (some costing $5,000). Adverse events reported included some participants developing a headache from the neurostimulation and the possibility of seizures, although little is known about the latter. The resources needed (e.g., staff training, product availability, and cost) tend to impact treatment choice. In individuals who have exhausted all resources, this alternative to medication may be valuable. Thus, the Work Group decided upon a "Neither for nor against" recommendation.

More robust research is needed to support the use of these modalities in the treatment or prevention of headache.

C. Pharmacotherapy

a. Migraine – Preventive

Recommendation

14. We recommend candesartan or telmisartan for the prevention of episodic or chronic migraine. **(Strong for | Reviewed, New-added)**

Discussion

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

telmisartan.[99-102] These studies found a significant reduction in headache frequency per month favoring ARBs over placebo.

A parallel design RCT randomized 60 patients with migraine with or without aura who experienced two to six migraine attacks per month to two separate treatment periods.[101] One group of patients received a 16 mg candesartan tablet daily during the first 12-week treatment period followed by one placebo tablet daily during the second 12-week treatment period. In the second arm, patients received placebo during the first 12-week treatment period followed by a 16 mg of candesartan tablet in the second 12-week treatment period. 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). Days with migraine, 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 that seen in the placebo arm.

A crossover RCT randomized adults (n=72) with episodic or chronic migraine in three 12-week treatment periods: candesartan (16 mg), slow-release propranolol (160 mg), or placebo.[100] For improving migraine days per month, candesartan (2.95%, 95% confidence interval [CI]: 2.35 – 3.55%) and propranolol (2.91%, 95% CI: 2.36 – 3.45%) were both superior to placebo (3.53, 95% CI: 2.98 – 4.08%, p=0.02 for candesartan and propranolol, compared to placebo). Candesartan and propranolol were comparable to each other. Fifty percent responder rates were significantly improved in the candesartan (43%, p=0.025) and propranolol (40%) groups compared to placebo (23%, p<0.05). Adverse events were highest among those receiving candesartan and lowest in the placebo group.

A Phase 2 trial, a similarly designed RCT, examined the efficacy and safety of telmisartan in the prevention of migraine attacks among patients with episodic migraine.[99] Patients experiencing between three to seven migraine attacks during a three month period were randomized to receive 80 mg of telmisartan or placebo. The primary endpoint was the reduction of the number of migraine days between the four week baseline period compared to the last four weeks of the 12-week treatment period. Patients receiving telmisartan had a significant improvement in migraine days compared to placebo (1.65 versus 1.14, p=0.03) without a significant improvement in ≥50% responder rate between groups (40% versus 25%, p=0.07). The AEs were similar between groups.

The Work Group's confidence in the quality of the evidence was moderate.[102] There was a statistically significant reduction in the number of headache and/or migraine days. The benefits of improved headache control outweighed the burden of taking a daily medication with a favorable side effect profile. As ARBs are associated with hyperkalemia, renal failure, and hypotension, providers should monitor electrolytes, renal function, and blood pressure. Providers considering these ARBs should be aware that this class is contraindicated in pregnant patients and that appropriate counseling among women of childbearing age regarding ARB-associated fetal toxicity should be provided.[103] Unlike angiotensin-converting enzyme (ACE) inhibitors, ARBs are not associated with cough secondary to ACE-inhibition or angioneurotic edema. Patient and provider values and preferences would be similar to ARBs as they are with ACE inhibitors since ARBs are accessible and well tolerated and could be prescribed by primary and specialty care providers alike. Thus, the Work Group decided upon a "Strong for" recommendation.

Future research should focus on determining whether there is a role for ARBs in the management of other headache disorders.

Recommendation

15. We suggest erenumab, fremanezumab, or galcanezumab for the prevention of episodic or chronic migraine.
    (Weak for | Reviewed, New-added)

Discussion

Calcitonin gene-related peptide is a proinflammatory vasodilatory neuropeptide that has a central role in migraine pathogenesis.[104] Calcitonin gene-related peptide levels have been found to be elevated during a migraine attack, whereas its blockade has been associated with reduction in migraine symptoms. Erenumab, fremanezumab, and galcanezumab are CGRP inhibitors which were FDA approved for episodic and chronic migraine in 2018.[105,106]

Erenumab

Erenumab is FDA approved for the prevention of migraine in adults based on the results of three trials (two conducted among patients with episodic migraine and one conducted among patients with chronic migraine).[107-109] Subsequent trials determined the efficacy of erenumab in patients with episodic migraine who had been unsuccessfully treated with two to four preventive treatments. Outcomes included reducing headache days and improving ≥50% responder rate as well as its impact on migraine-related disability and health-related QoL.[110,111]

Dodick et al. (2018) reported a significant reduction in monthly migraine days ($p<0.001$) and improvement in ≥50% responder rate over a three month period among patients receiving erenumab 70 mg ($p=0.010$) compared to placebo.[107] Goadsby et al. (2019) reported significant reduction in monthly migraine days, improvement in ≥50% responder rate, reduction in abortive medication use, and improvement in MPFID scores over a six month period for patients receiving erenumab 70 mg and 140 mg.[107,108] In a Phase 2 trial conducted among patients with chronic migraine, Tepper et al. (2017) reported that erenumab at doses of 70 mg and 140 mg significantly improved the number of monthly migraine days, ≥50% responder rate, and use of abortive medication compared to placebo without a significant increase in AEs.[109] Reuter et al. (2018) reported a significant improvement in ≥50% responder rate among patients receiving erenumab 140 mg compared to placebo at 12-weeks.[110] The authors noted erenumab, "might be an option for patients with difficult-to-treat migraine who have high unmet needs and few treatment options."[110] Buse et al. (2018) reported that erenumab at doses of 70 mg and 140 mg significantly improved QoL and reduced migraine-related disability over a six month period compared to placebo.[111] Further, improvements in these outcomes began soon after treatment and were seen among patients with severe and very severe migraine-related disability.

Across all studies, safety and tolerability profiles were similar to placebo with significant improvements seen in migraine frequency, severity, impairment in QoL, and disability. These improvements were seen in patients who did not respond to several other preventive migraine medications and those with the most pronounced migraine-related disability.

Fremanezumab

Fremanezumab, as a fully monoclonal antibody that binds CGRP ligands (both alpha and beta peptides), is currently the only monoclonal antibody targeting CGRP that is available in both monthly (225 mg) and quarterly (675 mg) regimens.[106] Patients administer this medication via subcutaneous injection.

Dodick et al. (2018) reported the efficacy and safety of fremanezumab in the treatment of episodic migraine.[112] Adult patients with episodic migraine (i.e., having 6 – 14 headache days during a 28-day pretreatment period, at least four of these days being migraine days) were randomized either to monthly or quarterly fremanezumab treatment regimens or to placebo. Fremanezumab administered monthly and quarterly resulted in a significant reduction in mean migraine days per month compared to placebo ($p<0.001$ for both) over a 12-week treatment period. The rate of AEs leading to discontinuation of treatment was ≤2% in each treatment group and consisted of injection-site reactions, including erythema and induration; diarrhea; anxiety; and depression.

In considering the efficacy and safety of fremanezumab in the treatment of chronic migraine, Silberstein et al. (2017) reported that both monthly and quarterly treatment regimens significantly improved monthly migraine headache days, monthly headache days, ≥50% responder rate, and HIT-6 scores while reducing the use of abortive medication compared to placebo over a 12-week treatment period.[113] AEs were significantly more common among patients receiving monthly fremanezumab injections ($p=0.03$ compared to placebo) but not quarterly fremanezumab injections ($p=0.03$ compared to placebo). Injection-site reaction was the most commonly reported AE.

Galcanezumab

Galcanezumab is available in a monthly subcutaneous injection (120 mg self-administered). The efficacy and safety of galcanezumab were demonstrated in two Phase 3 clinical trials in patients with episodic migraine, and one Phase 3 clinical trial in patients with chronic migraine.[114-116]

In the Evaluation of Galcanezumab in the Prevention of Episodic Migraine 1 (EVOLVE-1) trial, Stauffer et al. (2018) examined the efficacy and safety of galcanezumab at doses of 120 mg and 240 mg administered monthly, compared to placebo, over a six month treatment period.[114] The study was conducted exclusively in North America, and predominantly within the U.S. The authors reported a statistically significant improvement in the primary outcome of a reduction in monthly migraine headache days for both galcanezumab at 120 mg (4.7 days) and 240 mg (4.6 days) compared with placebo (2.8 days, $p<0.001$). Efficacy was similar for both doses of galcanezumab. All key secondary outcomes were significant, including a reduction in monthly migraine headache days (by at least 50%, 75%, and 100%), reduction in acute medication use, and improved scores on the MSQ, MIDAS, and the Patient Global Impression of Severity scores. The overall AE rate was <5% among patients receiving galcanezumab. Injection site pruritus and reactions were statistically more common among patients receiving either dose of galcanezumab compared with placebo ($p<0.05$). Generalized pruritus was more common (2.7%) only among patients receiving galcanezumab 240 mg compared to placebo (0.2%, $p<0.05$).

In the Evaluation of Galcanezumab in the Prevention of Episodic Migraine 2 (EVOLVE-2) trial, Skljarevski et al. (2018) similarly examined the efficacy and safety of galcanezumab at doses of 120 mg and 240 mg administered monthly, compared to placebo, over a six month treatment period.[115] The study

demonstrated statistically significant improvement in their primary outcome of improvement of mean monthly migraine headache days for galcanezumab at 120 mg (4.3 days) and 240 mg (4.2 days) compared with placebo (2.3 days, p<0.001). All key secondary outcomes were significant, including responder rates of ≥50, 75, and 100%, reduction in monthly migraine headache days with acute medication use, and improvement in MSQ, Patient Global Impression of Severity rating, and Role Function-Restrictive scores. Treatment-emergent AE rates leading to discontinuation in trial participation were low and similar between galcanezumab groups. Both dosing groups had significantly higher rates of injection site reactions and injection site pruritus, whereas patients receiving galcanezumab at 240 mg experienced higher rates of injection site erythema when compared to placebo.

Detke et al. (2018) examined the efficacy and safety of galcanezumab at doses of 120 mg and 240 mg administered monthly, compared to placebo, over a three month treatment period among patients with chronic migraine.[116] The study found statistically significant improvement in the primary outcome of a reduction in monthly migraine headache days starting at month one during the treatment period, compared to placebo. The authors reported a reduction in the use of abortive medications and in MIDAS. There were no statistically significant differences in safety outcomes between the two doses of galcanezumab and placebo, with the exception of AEs related to injection and sinusitis more common in the galcanezumab 240 mg dose, compared to placebo.

Summary of CGRP Inhibitors

Currently, there are no head to head studies comparing CGRP inhibitors to one another nor have there been comparative effectiveness studies for this new family of medications. As such, the Work Group cannot recommend one CGRP inhibitor over another. However, based on the current body of evidence, the Work Group can comment on practical consideration for these different agents. For example, given that fremanezumab is the only CGRP inhibitor that can be administered quarterly (rather than a monthly formulation), it may be preferable for some patients. Erenumab, fremanezumab, and galcanezumab all come in monthly formulations, which may be better options for patients than pharmacotherapies taken daily. For galcanezumab, 120 mg dosage may be preferred given the higher rates of AEs seen with galcanezumab 240 mg. Galcanezumab may also be preferred when patients have both migraine and episodic cluster headache (see Recommendation 35). These medications are found on the VA formulary.[117]

While there is much potential benefit of CGRP inhibitors, as a newer class of medications and one which represents a new molecular entity (as defined by the FDA), the Work Group recognizes that long-term follow-up data from the aforementioned RCTs and additional reports of real-world experience with CGRP inhibitors will be necessary to determine the role of these medications in treating episodic and chronic migraine. While additional data evaluating the use of these drugs for a longer time period is needed, some emerging data is worth highlighting. For example, patients with episodic migraine treated with erenumab experienced safety and tolerability profiles three years into treatment which were similar to the shorter term studies.[118] In considering real world experience with erenumab, fremanezumab, and galcanezumab, a retrospective analysis of the first 6-months post-FDA approval showed that reporting rates of AEs per 1,000 people were common for all three agents, including “headache” (3.32 for erenumab, 1.27 for fremanezumab, and 3.07 for galcanezumab), “drug being ineffective” (3.68 for

erenumab, 1.14 for fremanezumab, and 1.69 for galcanezumab), and "injection site pain" (2.94 for erenumab, 0.81 for fremanezumab, and 4.90 for galcanezumab).[119]

The Work Group's confidence in the quality of the evidence was moderate.[107-116] For fremanezumab, the body of evidence's major limitation was the lack of longer term follow-up regarding efficacy and safety; however, ongoing research and studies that began after our exclusionary period seek to understand the potential benefits and risks of long-term treatment. There was serious imprecision for galcanezumab and lack of longer term follow-up regarding efficacy and safety. The Work Group determined that the benefits of erenumab, fremanezumab, and galcanezumab outweighed harms/burden as the AEs were not statistically significant or significantly harmful. Patients would likely have similar values regarding taking a once per month medication shown to be efficacious, safe, and tolerable, and may prefer a once per month option compared to treatments that may be thrice daily and have AE rates higher than placebo. Even though some may not want to experience a needle, patients are generally tolerant of injections given via an autoinjector. Moreover, providers are generally comfortable with prescribing auto-injectable therapies. Providers will likely become more comfortable with CGRP inhibitors as this class of medications becomes more available and additional studies examining longer term efficacy, safety, and tolerability are published. In considering the recommendation for CGRP inhibitors and their role in the prevention of episodic and chronic migraine, apart from considering that data regarding the efficacy, effectiveness, safety, and tolerability beyond the relatively short timeframe is needed, the Work Group also recognized that drug withdrawals in the U.S. occur in a bimodal distribution (within 1 – 5 years of being on the market and later at 15 – 20 years, or near the time of patent expiration). Furthermore, in the U.S. it is estimated that less than 1% of AEs are reported; hence, by the time safety signal becomes apparent, more than just those for whom AEs were reported may have been affected.[120-124] Thus, the Work Group decided upon a "Weak for" recommendation.

Apart from continued research regarding long-term efficacy, safety, and tolerability of erenumab, fremanezumab, and galcanezumab, future research should focus on understanding the role of CGRP inhibition in other headache conditions, especially those that have migrainous features, including PTH. An ongoing critical appraisal of the literature regarding long-term benefits and risks associated with long-term use is also warranted. Furthermore, comparative effectiveness studies of CGRP inhibitors to one another and to other treatment strategies found to be efficacious, safe, and well tolerated should be considered.

Recommendation

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

Discussion

As an ACE inhibitor, lisinopril is commonly used within primary and specialty care settings and has FDA indications for hypertension, for patients with chronic kidney disease, after myocardial infarction, and among patients with cardiomyopathy.[125] Lisinopril is also used off-label for patients with proteinuric kidney disease, left ventricular hypertrophy, mitral valve regurgitation, diabetic retinopathy and neuropathy, peripheral arterial disease, and the prevention of diabetes.[126] As such, this class of medications is widely prescribed in primary care settings. While ACE inhibitors are often used for patients with cardiovascular disease (CVD) and vascular risk factors, they may help manage headache.

An SR by Jackson et al. (2015) reported the results of one RCT examining the efficacy of lisinopril as a preventive therapy for migraine.[102] Sixty patients aged 18 – 60 years with a history consistent with episodic migraine headache received either lisinopril (10 mg once daily for one week followed by 20 mg once daily for 11-weeks) or placebo. After a 12-week intervention period, among the 47 patients who completed the study, several endpoints were significantly improved among patients taking lisinopril, including number of headache days (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 to placebo. The authors concluded that lisinopril, "has a clinically important prophylactic effect in migraine."[102]

The Work Group's confidence in the quality of the evidence was low.[102] The benefits slightly outweighed the harms, especially since most patients who develop migraine headaches are between the ages of 18 – 55 years and, therefore, are generally in a separate demographic from those who develop vascular disease. Since 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 be largely similar since lisinopril is widely prescribed within primary and specialty care settings. Thus, the Work Group decided upon a "Weak for" recommendation.

Recommendation

17. We suggest oral magnesium for the prevention of migraine.
    (Weak for | Reviewed, New-replaced)

Discussion

Evidence suggests magnesium reduces migraine frequency.[127-129] 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.[127] 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 attack days, which was statistically significant.[128] This SR also found a statistically significant reduction in migraine intensity. Oral magnesium formulations varied in this SR, including magnesium sulfate, magnesium 2-propyl valerate, and magnesium oxide.

An additional randomized crossover study compared 500 mg magnesium oxide to 400 mg valproate sodium twice daily (n=70; 63 completed the study).[129] 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 benefits outweigh 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/day, with side effects of hypotension, ileus, muscle weakness, and lethargy that can progress to cardiac arrest. The risk of these AEs is increased with reduced renal function.[130]

The Work Group's confidence in the quality of the evidence was moderate.[127-129] 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 outweighed the limited harms of this intervention, particularly relative

to other pharmacotherapy. There is some variability in patient preferences because some may prefer not to experience its potential for GI side effects (e.g., it may be poorly tolerated in patients with irritable bowel syndrome). Thus, the Work Group decided upon a "Weak for" recommendation.

Recommendation

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

Discussion

Initially developed as an oral hypoglycemic agent, topiramate is an anticonvulsant medication that is FDA approved for migraine prevention and epilepsy and used off-label in the treatment of bipolar disorder, alcohol use disorder, obesity, and borderline personality disorder.[131,132] The combination of phentermine/topiramate is FDA approved for weight loss.[133] The exact means by which topiramate has its therapeutic effects are not known.[131]

An SR by Mulleners et al. (2015) examined the efficacy of topiramate as a treatment option for adults with episodic migraine.[134] This SR included 17 unique studies comparing various doses of topiramate (50 – 200 mg/day across studies) and examined the effect of topiramate on MSQ and ≥50% responder rate. Of note, a topiramate dose of 25 mg/day was not included in any study. Seven clinical trials compared various doses of topiramate against another pharmacologic agent (e.g., amitriptyline, propranolol) or a non-pharmacologic intervention (i.e., relaxation therapy). The mean duration of therapy was 19-weeks (SD: 4 – 52-weeks). Compared to placebo, topiramate significantly reduced the frequency of headaches and improved the ≥50% responder rate. Topiramate at doses of 100 – 200 mg/day was "significantly superior" to a dose of 50 mg/day in improving headache frequency and ≥50% responder rate and were equivalent to one another in improving outcomes. Rates of AEs increased with escalating topiramate doses. The most common AEs included dizziness/vertigo, flu-like syndrome, somnolence, and cognitive complaints.

Providers are encouraged to embrace the adage, "start low and go slow" with topiramate. Consideration of comorbidity profiles is important when discussing potential benefits and harms. For instance, topiramate may be effective for patients with comorbid obesity or epilepsy. On the other hand, it may be less appropriate for patients with kidney stones, low weight, eating disorders, and baseline cognitive difficulties. Further, patients of reproductive potential should be counseled about the association between topiramate use during pregnancy (and especially during the first trimester) and the increased risk of teratogenicity and low birth weight. Providers should engage in discussions with patients regarding effective contraception, especially with women who are dosed at >200 mg/day.[135,136] Patients with alcohol use disorder should be counseled that topiramate may also reduce alcohol use and alcohol craving.[137] Among patients with alcohol use disorder and comorbid PTSD, alcohol use, alcohol craving, and PTSD symptomatology may decrease with the use of topiramate.[138]

In considering optimal dosing of topiramate, providers should recognize that:

1. There is no evidence for the prevention of episodic migraine at 25 mg/day
2. 50 mg/day is less efficacious than 100 – 200 mg/day dosing
3. 100 – 200 mg/day dosing is of comparable efficacy
4. >200 mg/day is associated with increased rates of AEs

Should a provider consider active alcohol use disorder when deciding whether to offer topiramate as a treatment for both migraine and alcohol use disorder, the Work Group finds guidance offered by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the Substance Abuse and Mental Health Services Administration (SAMHSA) regarding pharmacotherapy for alcohol use disorder helpful. Specifically, "consideration should be given to the factors motivating a patient toward treatment, [and] the patient's stage of change."[139] Providers may also be more comfortable with prescribing topiramate than valproic acid (another anticonvulsant used for headache treatment) but less comfortable with topiramate than they are with gabapentin, which is used widely to treat peripheral neuropathy, another common neurological condition seen within primary care settings.

The Work Group's confidence in the quality of the evidence was low.[133,134] An important limitation for the Mulleners et al. (2015) SR was the fact that only studies involving patients with episodic migraine were identified. The Work Group determined that the benefits (improved outcomes) slightly outweighed the harms/burden (AEs that may impair QoL or lead to medication discontinuation) of treating episodic migraine with topiramate. There may be some variation across patient values and preferences. Patients may prefer a twice-daily medication over a medication taken more frequently (e.g., gabapentin, as a thrice-daily medication), especially if the agent improved important headache outcomes. Treating providers should discuss the potential of cognitive side effects with topiramate, noting that cognitive concerns are more common among patients taking topiramate at 200 mg/day than at 100 mg/day. Thus, the Work Group decided upon a "Weak for" recommendation.

Future research should focus on the utility of using topiramate for other types of headache disorders.

Recommendation

19. We suggest propranolol for the prevention of migraine.
    (Weak for | Reviewed, New-added)

Discussion

An SR of three studies, He et al. (2017), found propranolol decreased monthly migraine headache days when compared with placebo in patients with migraine headaches.[140] This moderate quality evidence supports clinical practice and guideline recommendations from other organizations.[141] He et al. (2017) found the ≥50% responder rate was not statistically significant and all AEs favored placebo.[140]

The evidence supporting propranolol for the prevention of migraine headaches is generally favorable. In clinical practice, it has been shown to have fewer serious AEs than many of the other older medications used for headache prevention, especially when compared to anti-epileptic drugs. However, while not serious, many of the common AEs are bothersome (e.g., fatigue, dizziness, lightheadedness, exercise intolerance, and sexual dysfunction). The evidence reviewed 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 may be needed for monitoring. Propranolol is used to treat hypertension and certain types of tremors and may be effective for patients with these conditions. However, multiple times a day dosing, possible monitoring concerns, and AEs can be burdensome and cause discontinuation.

The Work Group's confidence in the quality of the evidence was moderate.[140] The body of evidence had limitations including small sample size, limited duration of follow-up (12 – 16 weeks), and imprecision. The benefits (i.e., fewer monthly migraine headache days) outweighed the small potential harm of AEs. Patient values and preferences were similar because of the lower serious side effect profile than other antiepileptic drugs. The Work Group also considered this recommendation's impact on patients with severe anxiety, tremors, or hypertension. Thus, the Work Group decided upon a "Weak for" recommendation.

More research is needed on the comparable efficacy and tolerability of propranolol for migraine prevention when compared to other agents, especially newer agents, such as the CGRP inhibitors.

Recommendation

20. We suggest onabotulinumtoxinA injection for the prevention of chronic migraine.
    (Weak for | Reviewed, New-added)

Discussion

An SR of four RCTs, Herd et al. (2018), showed that onabotulinumtoxinA injections provide a statistically significant decrease in monthly migraine headache days and monthly headache days in patients with chronic migraine.[142] Based on a review of two RCTs, treatment with onabotulinumtoxinA was not effective at reducing the use of abortive medications and treatment-related AEs favored placebo.[142] There was insufficient data to recommend for or against the use of other neurotoxins (e.g., incobotulinumtoxinA, abobotulinumtoxinA, or rimabotulinumtoxinB) for the prevention of migraines and headaches in patients with chronic migraine.

Despite the need for repeat injections every 12-weeks, some patients may prefer periodic injections over taking daily oral medications. OnabotulinumtoxinA's side effects are usually mild, though some are severe, including ptosis, neck pain or weakness, trouble swallowing, speaking or breathing, and very rarely, spread of toxin to distant sites causing weakness in muscles far from the injection site. Patients with a fear of needles may decline this treatment. Access to this treatment is limited because it requires administration by a provider with specialized training. While not as expensive as the newer CGRP antagonists, it is more expensive than some of the older oral preventive treatment agents.

The Work Group's confidence in the quality of the evidence was low.[142] The body of evidence had limitations including the risk of bias given the small sample size in most included studies. Also, the Herd et al. (2018) SR showed there was not a statistically significant change in the amount of abortive medication used when compared to placebo. The benefits slightly outweighed the risks. Given onabotulinumtoxinA's efficacy and few side effects, patients generally favor the use of this agent. There is variable patient acceptability of needles. This intervention is expensive and takes time to be effective, often three to six months prior to adequate response. Thus, the Work Group decided upon a "Weak for" recommendation.

It would be helpful for future research on botulinum toxin to focus on the effect of the other neurotoxins on the prevention of migraine and headaches and the effectiveness of neurotoxins compared to the newer CGRP antagonists in patients with chronic migraine.

Recommendation

21. We suggest against abobotulinumtoxinA or onabotulinumtoxinA injection for the prevention of episodic migraine.
    (Weak against | Reviewed, New-added)

Discussion

Treatment with onabotulinumtoxinA and abobotulinumtoxinA is not effective for the prevention of headaches or migraines in patients with episodic migraine when compared to placebo. The evidence reviewed includes an SR of 28 trials by Herd et al. (2018).[142] One RCT showed that treatment with onabotulinumtoxinA failed to reduce monthly migraine days and monthly headache days in patients with episodic migraine.[142] In addition, four RCTs showed AEs frequency favored treatment with placebo.[142] One RCT regarding abobotulinumtoxinA failed to show evidence for any relevant outcomes.[142]

The Work Group's confidence in the quality of the evidence was low.[142] The body of evidence had limitations including small sample size and imprecision in the analysis. Given the lack of demonstrated outcomes in patients with episodic migraine and the clear possibility of harm, the harms outweighed the potential benefits. While some patients may request this treatment by name and prefer intermittent injections to daily oral medications, the lack of benefit helped support this recommendation. There is variable patient acceptability of needles. Treatment with onabotulinumtoxinA and abobotulinumtoxinA is also expensive and resource intensive. Thus, the Work Group decided upon a "Weak against" recommendation.

Future research on botulinum toxin should focus on the effect of neurotoxins other than onabotulinumtoxinA on the prevention of migraine and headaches and the effectiveness of neurotoxins compared to the newer CGRP antagonists in patients with chronic and episodic migraine.

Recommendation

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

Discussion

Gabapentin is FDA approved for use in epilepsy and post-herpetic neuralgia and is frequently used off-label to treat headache.[143,144] The Mulleners et al. (2015) SR examined the efficacy of gabapentin as a treatment option for adults with episodic migraine.[134] This SR included six studies comparing gabapentin at doses ranging between 900 – 2,400 mg with placebo and their effect on headache frequency and responder rate. There was a median 12-week treatment phase (range 12 – 20 weeks) across studies. The trial using gabapentin at a dose of 1,800 – 2,400 mg/day found a "small but significant" improvement in the ≥50% responder rate, but not at doses below 1,800 mg/day. However, across doses, gabapentin was not found to be efficacious for the treatment of episodic migraine.

Rates of AEs were higher among those taking gabapentin compared to placebo (68% versus 57%).[134] Rates of AEs did not differ between patients receiving more than 1,800 mg of gabapentin daily compared

with patients receiving a lower dose. Adverse events leading to medication discontinuation included dizziness/vertigo, somnolence, abnormal thinking, and flu-like syndrome. This recommendation is limited to the prophylaxis of episodic migraine, as the Work Group found no evidence regarding the use of gabapentin in the treatment of chronic migraine.

Given the breadth of uses for gabapentin, many PCPs feel comfortable prescribing it, especially compared to other anticonvulsant medications. Gabapentin may be a viable treatment option for patients with comorbidities for which there are FDA approved label (e.g., seizures) and off-label uses (e.g., painful peripheral neuropathy, musculoskeletal pain, alcohol abuse disorder). Prescribers should counsel patients against abruptly stopping gabapentin, as this is associated with both withdrawal seizures and a withdrawal syndrome resembling that of abruptly discontinued benzodiazepines or alcohol (i.e., agitation, anxiety, irritability, diaphoresis, and tachycardia).[145]

The Work Group's confidence in the quality of the evidence was low.[134] Data on the outcomes of ≥50% responder rate and incidence of AEs were both rated as low. The body of evidence had limitations, including the evaluation of episodic migraine only, short follow-up time, and little information regarding the up-titration schedule of gabapentin. The potential harms/burden slightly outweighed the benefits given the higher rates of AEs among patients taking gabapentin, compared to those receiving placebo, and the high pill burden (thrice daily). While patients would be agreeable to pursue migraine prophylaxis, most patients with episodic migraine would prefer options that had lower to no daily pill burden and agents with more robust efficacy data and lower side effect profiles. Thus, the Work Group decided upon a "Neither for nor against" recommendation.

More research is needed on whether gabapentin impacts headache outcomes when patients with episodic migraine are followed for longer periods of time. Also, more research is needed to assess a greater breadth of headache outcomes and the potential role for gabapentin use among patients with other headache types (e.g., chronic migraine, other primary headache disorders [chronic TTH], and PTH).

Recommendation

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)

Discussion

Jackson et al. (2015), through an SR of 11 RCTs (n=878), compared the effect of CCBs versus placebo in headache frequency per month among patients with episodic migraines.[102] The study population averaged 35-years in age (range 15 – 65 years) with 78% women. The study found no significant difference between the groups after a range of follow up from 4 – 20 weeks (mean of 11-weeks). Nifedipine and nimodipine were represented in 10 RCTs, with the remaining CCBs represented by one study, none of which showed a significant between-group difference. A subset of the overall SR included eight RCTs that compared CCBs to placebo in patients with episodic migraines to determine >50% improvement in migraine frequency (measured by <15 migraines/month); risk ratio (RR) ranged from 0.45 – 4.5 across the eight trials; seven trials found no significant between-group difference.

The Work Group's confidence in the quality of the evidence was very low.[102] A major limitation was that the SR only analyzed studies for nimodipine and nifedipine at specific time points for measuring headache frequency; other limitations included brief study duration for a chronic condition and unclear risk of bias. The benefits and general acceptability of CCBs in usual practice slightly outweighed the harms of potential expense or side effects. Calcium channel blockers are commonly prescribed by PCPs, are on the VA and DoD formulary, and are widely available. There is some variability in patient preferences. Patients with headache already on medication for hypertension would prefer if the medication would also treat migraines, although the patient focus group did express a preference for non-prescription treatment. Further, the Work Group noted that nimodipine is expensive and CCBs have side effects of edema and constipation. Thus, the Work Group decided upon a "Neither for nor against" recommendation.

Given the limited body of evidence identified, more research is needed on the use of common CCBs for prevention of episodic migraine, specifically to measure whether treatment benefit changes over time.

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)

Discussion

The evidence for coenzyme Q10 (CoQ10) in reducing the frequency of migraine attacks/month is inconsistent.[127,146,147] An SR by Parohan et al. (2019) considered four RCTs (n=221) and found a weighted mean reduction of 1.87 headache days per month, which was statistically significant compared to placebo.[146] An SR by Okoli et al. (2019) included two RCTs (n=97) and showed no difference compared to placebo in reduction of headache days/month.[127] Zeng et al. (2019) reviewed three RCTs and one observational study (n=266 patients) and demonstrated no significant difference between CoQ10 and placebo.[147]

The evidence for feverfew was limited to an SR of four placebo-controlled RCTs by Wider et al. (2015), which reported a change in migraine frequency per month (n=433).[148] Results were mixed. Two studies showed a statistically significant reduction and two studies showed no difference compared to placebo.

The evidence for melatonin was limited to an SR by Long et al. (2019).[149] Three of the four RCTs (n=285) were included in a meta-analysis that demonstrated a reduction in headache frequency favoring melatonin. Because of differences in outcome measures used, a mean change in headache frequency could not be calculated.

The evidence for omega-3 supplementation was an SR by Maghsoumi-Norouzabad et al. (2018), which included five RCTs.[150] The weighted mean difference in headache frequency was not statistically significantly different than placebo.

The evidence for vitamin B-2 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.[127] This study demonstrated a mean reduction of two headaches per month, which was statistically significantly lower than placebo.

The evidence for vitamin B-6 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.[151]

There is limited and sometimes conflicting evidence supporting a number of nutraceuticals for migraine prevention, including these options. The patient focus group expressed an interest in non-pharmacologic treatment and whether these treatments are considered such may vary by patient and provider.

The Work Group's confidence in the quality of the evidence was very low.[127,146-151] The body of evidence had limitations including small sample sizes, limited numbers of studies, and significant variability in results. The Work Group determined the small but somewhat inconsistent benefits in reducing migraine frequency slightly outweighed potential harms (e.g., dose variability in supplements) and specific harms (e.g., post-feverfew syndrome or vitamin B6 neurotoxicity in high, sustained doses). Patient values and preferences were somewhat varied because of the lack of regulation of nutraceuticals. There may be reduced access to these treatments since some are not listed on DoD or VA formularies and patients would likely need to pay for them out of pocket. Finally, the number of active ingredients in nutraceuticals can vary. Thus, the Work Group decided upon a "Neither for nor against" recommendation.

More research is needed on the safety and effectiveness of peppermint oil or extracts for patients with migraine, as well as the use of vitamin B2 in pregnant women with migraine. More research is needed on the effectiveness and tolerability of nutraceuticals for the prevention and treatment of headache.

Recommendation

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

Discussion

Pharmacologic therapies are mainstay options for the prevention of both episodic and chronic migraine headache. When headache attacks are not controlled adequately enough with one preventive agent, a second medication may be offered to patients. Combining pharmacotherapies is common in clinical practice and, although it is recognized that different medication classes may target their therapeutic effects via different mechanisms, few studies have examined the efficacy of combination pharmacotherapy for the prevention of headache. Pharmacotherapy may also be combined with another treatment modality (e.g., behavioral interventions or CIH options).

An RCT by Dominigues et al. (2009) examined the efficacy of a combination of nortriptyline and propranolol to monotherapy with either nortriptyline or propranolol over a two month treatment period with a primary endpoint of ≥50% responder rate among patients with either episodic or chronic migraine who had not received preventive pharmacotherapy for migraine.[152] Twenty-five patients were randomized to receive nortriptyline (20 mg/day) alone, 24 patients received propranolol (40 mg/day) alone, and 27 patients received combination pharmacotherapy. While combination therapy was as safe as either monotherapy in a trial with treatment naïve patients, it neither significantly improved the ≥50% responder rate for the entire study population nor for the subgroup of chronic migraine patients.

Krymchantowski et al. (2012) examined the efficacy of a combination of topiramate and nortriptyline to monotherapy with either topiramate or nortriptyline over a six week treatment period among patients with episodic migraine who already had experienced less than a 50% reduction in headache frequency after eight weeks of monotherapy with either topiramate (100 mg/day) or nortriptyline (30 mg/day).[153] In this RCT (n=68), 30 patients were randomized to the placebo arm (and, hence, continued on monotherapy) and 38 patients were randomized to receive a second pharmacotherapy. Patients in the combination pharmacotherapy group experienced a significant improvement in primary (4.6 versus 3.5 headache days, $p<0.05$) and secondary (≥50% responder rate of 78.3% versus 37.0%, $p<0.04$) endpoints.

An RCT by Silberstein et al. (2012) examined a combination of topiramate and propranolol to topiramate alone over a six month period among 250 patients with chronic migraine with poorly controlled headaches (i.e., ≥10 headaches/month) while on topiramate (50 – 100 mg/day).[154] Patients received either long-acting propranolol (240 mg/day) or placebo. Although this combination therapy was deemed safe, the trial was terminated early after a pre-planned interim analysis concluded that adding propranolol to topiramate among patients with chronic migraine was, "highly unlikely for the combination to result in a significant reduction in 28-day headache rate compared to topiramate alone."[154]

Dominigues et al. (2009) started a combination of nortriptyline and propranolol concurrently among patients with both episodic and chronic migraine who were naïve to preventive pharmacotherapy.[152] Krymchantowski et al. (2012) and Silberstein et al. (2012) started with one agent (topiramate in each study) and added a second agent (nortriptyline or propranolol, respectively) to the treatment regimen of patients with episodic migraine [153] or chronic migraine.[154] In both studies, a second agent was introduced to patients who had unsatisfactory headache control while on topiramate monotherapy.[153,154] Results of the studies differed, as the addition of nortriptyline to topiramate improved headache control among patients with episodic migraine whereas the addition of propranolol to topiramate did not result in improved headache control among patients with chronic migraine.

Across these three studies, combination pharmacotherapy among patients with:

1. Episodic or chronic migraine naïve to preventive pharmacotherapy combination pharmacotherapy as a first treatment did not experience improvement in the ≥50% responder rate compared to monotherapy, suggesting that providers should not consider starting combination pharmacotherapy on patients who have not been trialed on monotherapy; [152]
2. Chronic migraine patients with inadequate headache control who received combination pharmacotherapy did not experience an improvement in 28 headache day rate compared to patients taking monotherapy, and; [154]
3. Episodic migraine with inadequate headache control on monotherapy, combination pharmacotherapy with nortriptyline and topiramate significantly reduced headache days and improved the ≥50% responder rate compared to monotherapy.[153]

The Work Group's confidence in the quality of the evidence was very low.[152-154] The harms/burden slightly outweighed the benefits since only one study had significant findings in favor of combination preventive pharmacotherapy for migraine prevention (and only among patients with episodic migraine). The potential for patients to experience AEs could be substantial if patients take combination therapy longer than the trial periods noted above. Of note, pharmacotherapy for migraine prevention is typically

given for time periods longer than those observed in the three trials. The pill burden and its associated financial and non-financial costs should be considered and discussed with patients. Thus, the Work Group decided upon a "Neither for nor against" recommendation.

Future studies should evaluate whether certain combinations of medication work better than others to improve headache outcomes. For example, determining if a certain combination of pharmacologic agents using different mechanisms of action may be effective and whether offering pharmacologic agents that use different mechanisms are better than regimens with similar mechanisms of action.

b. Migraine – Abortive

Recommendation

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-replaced)

Discussion

Comparison of Triptans

Although triptans share a common mechanism of action, they differ in available routes of administration, onset of action, and duration of action. Routes of administration include oral, intranasal, subcutaneous, transdermal, and intramuscular. Sumatriptan can be given as a subcutaneous injection (usually administered by autoinjector in the thigh), as a nasal spray, as a nasal powder, as a transdermal patch, or orally. Zolmitriptan is available for nasal or oral use. Sumatriptan combined with naproxen 500 mg is available as an oral tablet. The FDA approved a low-dose intranasal sumatriptan powder for migraine in January 2016. The product consists of 22 mg of sumatriptan powder and is the first breath-powered intranasal medication delivery system to treat migraines.

Subcutaneous sumatriptan (6 mg) is associated with more AEs than oral sumatriptan. Subcutaneous sumatriptan has the fastest onset of action. For acute migraine, the usual initial dose of subcutaneous sumatriptan is 6 mg. The dose may be repeated once after one hour if needed. For patients who are intolerant of the 6 mg dose but need a parenteral formulation (e.g., due to protracted vomiting with migraine), a lower initial/repeat dose (e.g., 3 or 4 mg) may be appropriate. Sumatriptan for injection is commercially available in 3, 4, and 6 mg. The recommended maximum is 6 mg per dose and 12 mg per 24-hours. In one trial of subcutaneous sumatriptan (n=639), administration of a second dose 60-minutes after the first, in those who did not respond well initially, provided little additional benefit.[155]

Sumatriptan (Oral)

A Cochrane Review by Derry et al. (2012a) included 61 studies (n=37,250) that compared oral sumatriptan with placebo or an active comparator.[156] 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 number needed to treat (NNT) was 6.1, 7.5, and 4.0 for pain-free at two hours and headache relief at one and two hours, respectively. The NNT for sustained pain-free and sustained headache relief during the 24-hours post-dose were 9.5 and 6.0, respectively. For sumatriptan 100 mg versus placebo, the NNT 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 50 mg dose, while sumatriptan 100 mg was significantly better than 50 mg for pain-free and headache relief at two hours, and for sustained pain-free during 24-hours. Treating early (i.e., during the mild pain phase) gave significantly better NNTs for pain-free at two hours and sustained pain-free for 24-hours compared to treating established attacks 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, 80 mg) demonstrated an NNT of 9.7 in favor of eletriptan. Increasing the dose of sumatriptan to 100 mg resulted in an NNT 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. Individual AEs were reported inconsistently between studies. Most studies reported only the most commonly occurring AEs; for example, those occurring in >3% of participants in any of the treatment arms, while others used different terms to describe the same or similar events. Reported AEs included malaise/fatigue/asthenia, and dizziness/vertigo which showed increased risk with higher doses of sumatriptan (25 – 100 mg). Higher doses of sumatriptan (100 – 300 mg) were associated with an increased rate of disturbance in taste/metallic taste in the mouth, of nausea/vomiting, and of 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.[155] Most of the data represented the sumatriptan 6 mg dose. Sumatriptan surpassed placebo for all efficacy outcomes; pain-free at one and two hours, headache relief at one and two hours, and sustained pain-free at 24-hours. The 4 mg and 8 mg dose results were similar to the 6 mg dose. Sumatriptan was compared directly with several other active treatments but there was insufficient data for any pooled analyses. In a comparison to naratriptan (doses 0.5, 1, 2.5, 5, 10 mg), 55% of sumatriptan-treated patients were pain-free at two hours, compared to 30%, 44%, 60%, 79%, and 88% (respectively) of participants treated with subcutaneous naratriptan.

Common side effects of subcutaneous sumatriptan include an injection site reaction, chest pressure or heaviness, flushing, weakness, drowsiness, dizziness, malaise, a 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 placebo was 24%.

Sumatriptan/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 attacks of mild, moderate, or severe pain intensity.[157] Twelve studies contributed data for analyses: 3,663 participants received combination treatment, 3,682 received placebo, 964 received sumatriptan, and 982 received naproxen. The combination of sumatriptan plus naproxen was better than placebo for relieving acute migraine attacks 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-free at two hours, the combination formulation was better than placebo for mild, moderate, and severe pain at baseline. The NNT was 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. There were more AEs reported with the combination product; however, the incidence of any single AE was quite low (<4%). The development of AEs did not appear to increase withdrawal rates in treated patients.[157]

Zolmitriptan

Zolmitriptan can be offered to treat acute migraine attacks. There are several methods of dose delivery; oral tablet, oral disintegrating tablet (ODT), and nasal spray. A Cochrane Review by Bird et al. (2014) included 25 studies that involved over 20,000 participants reporting the effects of zolmitriptan on migraine attacks.[158] For zolmitriptan 1 mg (oral or intranasal) versus placebo, the NNT for pain-free at two hours was 7.0. Increasing the dose to 2.5 mg, the NNT became 5.0. Zolmitriptan 5 mg versus placebo had an NNT of 4.8 for the oral formulation compared to 3.0 for the intranasal product. The dose-related improvement continued when zolmitriptan 10 mg was compared to placebo with an NNT of 3.0.[158] 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 two hours, comparable to oral sumatriptan 50 mg, with no difference in AEs.[158]

The proportion of AEs with zolmitriptan 2.5 mg (oral and nasal), 5 mg (oral and nasal), and 10 mg demonstrated in 12 studies compared to placebo resulted in a dose-dependent increase in AEs. 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.

Subcutaneous sumatriptan (6 mg) resulted in pain reduction from moderate or severe to no pain by two hours in 59% participants compared to 15% taking placebo, and was reduced from moderate or severe to no worse than mild pain by two hours in 79% taking sumatriptan compared with 31% taking placebo.[155] Subcutaneous sumatriptan can be used in patients who need rapid administration and/or have vomiting. High quality evidence supports that oral zolmitriptan 2.5 mg and 5 mg provided headache relief at two hours to the same proportion of people as oral sumatriptan 50 mg (66%, 67%, and 68%, respectively), although these patient populations were not equal in all baseline measures.

Sixteen studies (11,599 participants/attacks) provided data on sumatriptan of any dose versus active comparators. Comparing sumatriptan to other triptan agents, zolmitriptan (all doses) demonstrated an AE incidence of 0.23% in comparison to sumatriptan (25, 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).

Triptans are first-line treatment for severe migraines as they are generally highly effective, with a low risk of side effects. Failure of one triptan does not indicate the failure of the entire medication class. Providers should consider trying a second triptan medication if the first one does not improve symptoms. The use of a combination triptan and nonsteroidal anti-inflammatory drugs (NSAIDs) (sumatriptan and naproxen) may be more effective than either medication alone.

The Work Group's confidence in the quality of the evidence was moderate.[155-158] The benefits (improved outcomes of pain-free at two hours, headache relief at two hours, sustained pain-free during the 24-hours post-dose, and sustained headache relief during the 24-hours post-dose), outweighed the potential harm of AEs because reducing the pain was deemed worth experiencing mild and infrequent side effects. There is some variation in patient preferences because not all patients tolerate needles. Small

subgroups of patients are intolerant of triptans and/or experience hemiplegic migraine and cannot use these medications. Subcutaneous medications are also more expensive than oral medications, though they are less expensive than a stay in the emergency room (ER). Thus, the Work Group decided upon a "Strong for" recommendation.

Further research will be needed in this area as new therapeutic agents are approved for the acute treatment of migraine which will determine the place in therapy for all abortive agents.

Recommendation

27. We suggest frovatriptan or rizatriptan for the acute treatment of migraine.
    (Weak for | Reviewed, New-added)

Discussion

Triptans are recommended as first-line abortive therapy for the treatment of acute migraine attacks. They can be used as monotherapy or in combination with an NSAID or paracetamol (acetaminophen). Triptans, as well as NSAIDs and acetaminophen, can result in MOH if used >10-days a month. It is important to evaluate patients requiring frequent use of these agents for prophylaxis therapy.

Rizatriptan is available as an oral tablet and an ODT formulation. Doses of 5 mg or 10 mg are used with a maximum dose of 30 mg. The dose of rizatriptan must be reduced to 5 mg in patients taking propranolol. Frovatriptan is available as a 2.5 mg tablet, with a daily maximum dose of 7.5 mg. Rizatriptan and frovatriptan have both been shown to improve headache relief at two hours and sustained pain freedom at 24-hours.

In an RCT by Moon et al. (2010), 122 Korean patients received frovatriptan to treat an acute migraine attack.[159] Extrapolating this study to a non-Asian population could be complicated by the fact that Asians exhibit different results for mitochondrial polymorphism (A11084G), different pharmacokinetic and pharmacodynamic profiles, greater placebo effects, and higher incidences of AEs than Caucasian patients. This study demonstrated that frovatriptan significantly increased the two hour headache response rate compared with placebo (52.9% versus 34.0%, p=0.004). Also, headache response rates at 4-, 6-, and 12-hours were significantly higher in the frovatriptan group than in the placebo group, as was the pain-free rate at two hours (19.0% versus 5.7%, p=0.004), four hours (40.7% versus 23.0%, p=0.006), and six 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). Abortive medication use was more common in the placebo group (p=0.005).

An RCT by Cady et al. (2009) evaluated the effects of rizatriptan.[160] There were 207 patients enrolled in the trial with 91% experiencing an acute migraine attack which was treated. Outcomes favored rizatriptan compared to placebo by report of pain freedom at two hours (66.3% versus 28.1%, p<0.001), and 24-hour sustained pain freedom (52.2% versus 17.7%, p<0.001). A greater proportion of patients in the rizatriptan plus education group reported pain freedom at two hours compared with those in the rizatriptan plus no education group (71.7% versus 60.9%, p=0.430).

Triptans, as a class, are most effective when taken early during a migraine and all may be repeated in two hours as needed, with a maximum of two doses daily. While different formulations of a specific triptan

may be used in the same 24-hour period, only one triptan may be used during this time frame. 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.

The safety of triptans is well established, and the risk of de novo coronary vasospasm from triptan use is exceedingly rare. However, triptans should not be taken by patients with known or suspected coronary artery disease, as they may increase the risk of myocardial ischemia, infarction, or other cardiac or cerebrovascular events. They should not be prescribed for patients who are taking ergot or in patients with hemiplegic or basilar migraine.

The Work Group's confidence in the quality of the evidence was low.[159,160] Frovatriptan and rizatriptan demonstrated a significant improvement in migraine symptoms compared to placebo. However, the Work Group advises caution in extrapolating the results to a large population.[159] The benefit of rizatriptan or frovatriptan slightly outweighed the harms/burdens. Patients likely have similar values because most have utilized triptans before. Triptans may present cardiovascular risks for patients with a history of coronary artery disease. Thus, the Work Group decided upon a "Weak for" recommendation.

The Work Group recommends further trials that include a broader population base. Additionally, comparative trials between the triptan agents should be conducted.

Recommendation

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)

Discussion

An SR of 29 observational studies (n=3,092), Thorlund et al. (2016), compared the effect of triptans versus analgesics, opioids, and ergots in patients with MOH.[161] The SR found triptans were associated with a significantly lower proportion of patients with MOH compared to analgesics or opioids. A subset of the SR, including 14 observational studies, found no significant difference in MOH prevalence between patients receiving ergots or patients receiving triptans, but these findings were inconclusive. Within the same SR, 12 observational studies found that ergots were associated with a significantly lower proportion of patients with MOH than analgesics. Although the SR found no significant difference in MOH prevalence between patients receiving ergots compared to opioids or between patients receiving analgesics compared to opioids, these findings were inconclusive.[161] These findings are consistent with a large prospective cohort study by Hagen et al. (2012), which found a significantly higher MOH incidence among patients taking analgesics and tranquilizers.[51]

Despite general consistency in the evidence supporting migraine-specific abortive treatments of triptans and ergots compared to opioids and non-opioid analgesics, there is some variability in patient preferences. The Work Group noted that provider practice favors triptans over ergots in usual care settings. Patient focus group participants indicated that some patients dislike taking prescription medication, which favors the occasional use of non-opioid analgesics. However, some patients prefer triptans since it is migraine specific. In general, opioids are not recommended for the management of migraine.

The Work Group's confidence in the quality of the evidence was very low.[51,161] Limitations included no assessment of the risk of bias, lack of information on patient characteristics, and focus on observational studies only. The benefits outweighed the harms of increased opioid or analgesic use for migraines that could precipitate MOH. Triptans are preferred for migraine-specific use by patients, are widely available in the U.S., and are on the VA and DoD formularies. Despite early concerns regarding the combination of triptans and serotonin and norepinephrine reuptake inhibitors (SNRIs) or selective serotonin reuptake inhibitors (SSRIs), there remains no evidence, clinical or mechanistic, to suggest that an interaction exists; therefore, triptans would be preferred in patients with other medications. Thus, the Work Group decided upon a "Weak for" recommendation.

Given the limited evidence identified, more research is needed on the incidence of MOH for over-the-counter (OTC) medications. Future research should clearly delineate between individual categories of medication, monotherapy, and combination within analgesics and opioids to further clarify variations in the incidence of MOH.

Recommendation

29. We suggest ibuprofen, naproxen, aspirin, or acetaminophen for the acute treatment of migraine. **(Weak for | Reviewed, New-added)**

Discussion

Pharmacotherapy for acute management of migraine headaches should be based on the rapidity of onset, headache severity, associated symptoms (e.g., nausea/vomiting), and patient preference. Therapy selection for abortive management may include OTC agents such as ibuprofen, naproxen, acetaminophen, or aspirin. Abortive treatments are usually more effective if they are given early in the course of the headache; a large single dose tends to work better than repetitive small doses. Many oral agents are ineffective because of poor absorption, secondary to migraine-induced gastric stasis.

Ibuprofen

An SR by Rabbie et al. (2013) examined the use of ibuprofen as an acute management therapy for migraine.[162] The analysis included nine studies and a large study population (4,373 patients with 5,223 acute migraine attacks). Outcomes assessed were two hour pain-free, two hour headache relief, and 24-hour sustained headache relief with an analysis of NNT for each outcome. All assessments were conducted after a single dose of medication per attack. For ibuprofen 400 mg versus placebo, NNT for two hour pain-free, two hour headache relief, and 24-hour sustained headache relief was 7.2, 3.2, and 4.0, respectively. For ibuprofen 200 mg versus placebo, NNT for two hour pain-free and two hour headache relief were 9.7 and 6.3, respectively. The higher dose was significantly better than the lower dose for two hour headache relief. Adverse events from this analysis include dizziness, paresthesia, somnolence, nausea, dyspepsia, dry mouth, and abdominal discomfort.[162]

An RCT conducted by Yadav et al. (2016) in 150 patients with episodic migraine reported a 28.2% pain-free response at two hours for the ibuprofen 400 mg and placebo groups.[163] However, these findings were inconclusive because of 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.[164] The SR included six RCTs comparing naproxen 275, 500, or 825 mg, with or without an antiemetic, to placebo and/or active comparator in patients with acute migraine with or without aura. The percentage of female patients in the included studies ranged from 81 – 91%. Follow-up was 24-hours post-treatment. For percent pain-free response at two 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.[164] Given the increased incidence of AEs with doses of naproxen >500 mg and relatively equal efficacy, naproxen 500 mg is advised over higher doses.

Several of these studies are limited by varying outcome measures and definitions of migraine, but all NSAIDs may be beneficial in patients who have migraine with or without aura. It should be noted that there are no studies comparing the relative efficacy of different NSAIDs. If one NSAID is ineffective, a different drug may be tried. In comparing ibuprofen to naproxen, ibuprofen demonstrates evidence of benefit with an NNT of 7 (for all efficacy outcomes), naproxen has an NNT of 11 for these same measures. The maximum daily dose for ibuprofen is 3,200 mg and 1,000 – 1,500 mg for naproxen. 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 need to be included in the daily total.

Acetaminophen

An SR by Derry et al. (2013) included 11 RCTs comparing paracetamol (acetaminophen), with or without an antiemetic, to placebo and/or active comparator in patients with acute migraine with or without aura.[165] For percent pain-free response at two hours, results suggest a statistically significant between-group difference 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, with NNTs of 12, 5.0, and 5.2 for two hour pain-free and two and one hour headache relief, respectively, when the medication was taken for moderate to severe pain. 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 two hours is inferior to other commonly used analgesics.[165] The maximum dose of acetaminophen is 4,000 mg and patients should be cautioned that this dose would 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, to placebo and/or active comparator in patients with acute migraine with or without aura.[166] 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, with NNTs of 8.1, 4.9, and 6.6 for two hour pain-free, two hour headache relief, and 24-hour headache relief with aspirin alone versus placebo, and 8.8, 3.3, and 6.2 with aspirin plus metoclopramide versus placebo.[166] 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 review, aspirin 1,000 mg demonstrated similar outcomes as sumatriptan 50 mg or 100 mg. However, AEs were higher in the sumatriptan treated patients.

The Work Group's confidence in the quality of the evidence was low.[162-166] The trials employed poor methods and some trials were very small. Since MOH can be associated with chronic use of OTC analgesics, the harms slightly outweighed the benefits. Patient values and preferences are likely similar because of the accessibility and affordability of OTC medications. Thus, the Work Group decided upon a "Weak for" recommendation.

Further research is needed in regard to direct comparisons that are adequately powered.

Recommendation

30. We suggest greater occipital nerve block for the acute treatment of migraine.
    (Weak for | Reviewed, New-added)

Discussion

Evidence suggests GON blocks improve pain intensity and decrease analgesic medication consumption when used in the acute treatment of migraine.[167-169] An SR and meta-analysis by Zhang et al. (2018) found GON blocks significantly reduced migraine pain intensity compared to placebo.[169] Two additional RCTs conducted in an ER setting demonstrated the comparable effectiveness of GON blocks to the standard ER pharmacologic treatments of metoclopramide or intravenous (IV) dexketoprofen plus metoclopramide.[167,168] Evidence indicates GON blocks do not cause more AEs than placebo, although needle site discomfort may be viewed negatively by some patients.[169]

Despite general consistency in the evidence supporting the use of GON blocks, provider and patient factors may affect this treatment. Provider-related factors involve injection technique preference, as there are two injection techniques reported in the literature.[169] One technique targets the nerve at the occipital ridge without image guidance using anatomic landmarks, while the other uses ultrasound guidance to target the nerve in the suboccipital region. Both techniques appear to be equally effective for improving acute migraine intensity.[169]

A second provider-related factor involves the choice of medicaments between local anesthetic alone (bupivacaine or lidocaine) or local anesthetic plus corticosteroid, both commonly reported in the literature. The SR by Zhang et al. (2018) included studies from both groups, which provided a significant decrease in acute migraine pain intensity.[169] Small studies have reported that injecting certain corticosteroids may cause focal cutaneous alopecia and atrophy, which should be considered before use.[170] Additionally, it does not appear that adding a corticosteroid provides an additional benefit to the duration or strength of benefit over a local anesthetic only, which should be considered before use.[171]

The Work Group's confidence in the quality of the evidence was low.[167-169] The body of evidence had limitations including small sample size and variability in injection technique and medicament. The benefits of improved pain intensity and decreased analgesic medication consumption outweighed the potential harm of AEs, which was minimal. Patient preferences were somewhat varied based on preference for a needle-based intervention. The Work Group also considered the increased staffing and provider training required by this intervention. Providers preferring to perform ultrasound-guided injections may be limited by equipment availability. Thus, the Work Group decided upon a "Weak for" recommendation.

Future research studying this technique for chronic migraine reduction is needed.

Recommendation

31. We suggest intravenous magnesium for the acute treatment of migraine.
    (Weak for | Reviewed, New-added)

Discussion

Evidence suggests a benefit from IV magnesium for the treatment of acute migraine. In an SR by Chiu et al. (2016), 11 RCTs (n=948) found IV magnesium reduced pain at 15 – 45 minutes, 120-minutes, and 24-hours when compared to controls (reported OR: 0.23, 0.20, and 0.25, respectively).[128] A smaller SR, Choi et al. (2014), included five RCTs (n=295) and failed to show statistical significance.[172] The Work Group considered evidence of AEs, but no relevant studies met the systematic evidence review inclusion criteria.

There is a possibility of AEs for magnesium to include flushing, hypotension, or vasodilation.[173] While oral administration causes GI upset, including loose stool, for many patients, this is not expected with IV administration.[173,174] There is the potential for hypermagnesemia if dosed incorrectly; muscle paralysis or cardiac conduction abnormalities could cause significant harm and alternative treatments should be considered in patients with renal disease or myasthenia gravis.[175,176] Proper dosing and review of a patient's medical history are essential for the safe administration of IV magnesium.

The Work Group's confidence in the quality of the evidence was low.[128,172] The benefits slightly outweighed the harms/burdens because most harms are evident in very high doses only. Patient values may vary somewhat because there is a slight burn when administered, although it is not unbearable and is a quick procedure. It is also widely available, inexpensive, and providers are familiar with it. Thus, the Work Group decided upon a "Weak for" recommendation.

c. Tension-type Headache – Preventive

Recommendation

32. We suggest amitriptyline for the prevention of chronic tension-type headache.
    (Weak for | Reviewed, New-added)

Discussion

Jackson et al. (2012), an SR of three RCTs, examined amitriptyline versus placebo in patients with chronic TTH. Amitriptyline at doses of 50 mg and 100 mg (n=63) versus placebo (n=54) was effective at reducing monthly headache days after four weeks.[177] At four weeks, the amitriptyline group experienced 6.2 fewer headaches per month (95% CI: -8.1 – -4.2) than placebo. There were similar findings for eight weeks, 12-weeks, and 24-weeks of preventive treatment with amitriptyline.[177] Patients receiving a preventive regimen of amitriptyline 100 mg versus placebo used significantly fewer monthly abortive medication pills at 12-weeks than those receiving placebo (95% CI: -26.7, – 6.3). The treatment effect was similar at 24-weeks (95% CI: -28.2 – -7.8). The treatment benefit for amitriptyline 75 – 100 mg measured at four weeks was not significant (95% CI: -24.6 – 6.1) in reducing monthly abortive medications, suggesting that longer treatment duration may be needed to reduce analgesic abortive medication in patients with chronic TTH.

Caution should be used when prescribing tricyclic antidepressants to individuals with CVD or a family history of sudden death. Electrocardiogram monitoring at baseline is advised in patients aged >40-years

and in those with cardiac disease. The anticholinergic burden should also be considered when used in patients aged >65-years.[177] There is also a risk of serotonin syndrome, particularly when combining with other medications (e.g., antidepressants). All antidepressants carry the black box warning of increased risk of suicidality in children, adolescents, and young adults.[177]

The Work Group's confidence in the quality of the evidence was low.[177] There were limitations in the methodological quality of the RCT and imprecision in the effect estimates. The benefits slightly outweighed the harms. While patients can experience AEs from amitriptyline, including dry mouth, dry eyes, weight gain, sedation, dizziness, blurred vision, GI distress, and nausea, amitriptyline is inexpensive, accessible for PCPs to prescribe, and may help patients who suffer from insomnia. The Work Group recognized the literature review only included the prior 10-years, limiting the evidence for amitriptyline. Thus, the Work Group decided upon a "Weak for" recommendation.

Recommendation

33. We suggest against botulinum/neurotoxin injection for the prevention of chronic tension-type headache.
    (Weak against | Reviewed, New-added)

Discussion

Evidence suggests botulinum/neurotoxin injection is ineffective for the prevention of chronic TTH. One SR of seven RCTs, Jackson et al. (2012), showed no statistically significant difference in the incidence of monthly headaches when the intervention was compared to placebo in patients experiencing chronic TTH.[177] Three RCTs in the same SR found no statistically significant change in the ≥50% responder rate.[177] These studies had serious limitations, including a small sample size across all eight studies (n=703) and imprecision.

The Work Group's confidence in the quality of the evidence was low.[177] The body of evidence had limitations. In addition to evidence showing no statistically significant benefit, there is clear potential for harm from these medications. Thus, the harms outweighed the benefits. Some patients may request this treatment by name and prefer intermittent injections to daily oral medications. There is variable patient acceptability of needles. Treatments with botulinum/neurotoxin are more expensive than oral preventive medications and are resource-intensive. Thus, the Work Group decided upon a "Weak against" recommendation.

d. Tension-type Headache – Abortive

Recommendation

34. We suggest ibuprofen (400 mg) or acetaminophen (1,000 mg) for the acute treatment of tension-type headache.
    (Weak for | Reviewed, New-added)

Discussion

Three SRs and one RCT evaluated pharmacologic interventions for acute treatment of TTH.[178-181] For TTH percent pain-free response at two hours, Derry et al. (2015) reported a statistically significant between-group difference for ibuprofen 400 mg versus placebo, favoring ibuprofen, but no statistically

significant between-group difference for ibuprofen sodium 400 mg versus placebo.[180] Neither Derry et al. (2015) nor Packman et al. (2015) reported statistically significant between-group differences for AEs of ibuprofen 400 mg versus placebo.[180,181]

An SR by Stephens et al. (2016) included 23 RCTs comparing paracetamol to placebo and/or an active comparator and addressed percent TTH pain-free response at two hours.[179] It suggested a statistically significant between-group difference for paracetamol 1,000 mg versus placebo, favoring paracetamol. Reported AEs showed no statistically significant between-group differences for paracetamol 500 – 650 mg (combined data) versus placebo or paracetamol 1,000 mg versus placebo.[179]

The Work Group included nine drug classes in this systematic evidence review (i.e., antiemetic agents, antiepileptic agents, CGRP inhibitors, combination agents, serotonin 5-HT receptor agonists, serotonin 5-HT1F receptor agonists, NSAIDs, acetaminophen), but relevant studies were identified for only NSAIDs and acetaminophen in the treatment of TTH. When asked, patient focus group participants described headaches (all types) as an "invisible disease" that significantly impacts their QoL and function. Participants expressed a desire to approach headaches with a multi-modal response and minimal use of pharmacologic agents, particularly those with significant potential for side effects; thus, participants may support the use of NSAIDs and acetaminophen as an early option for TTH.

The Work Group's confidence in the quality of the evidence was very low.[178-181] The benefits, including improved outcomes of TTH pain-free response at two hours, outweighed the potential harm of AEs from either intervention, which was not statistically significant versus placebo.[179-181] Patient values and preferences are likely similar, as these are easily obtained OTC medications that most adults are familiar with. Resource use was thought to be low because these medications are widely available. Thus, the Work Group decided upon a "Weak for" recommendation.

Although these classes of medications have been available for decades, ongoing research in their utility for headache management, alone and in combination with new pharmaceutical agents and other interventions, is encouraged.

e. Cluster Headache – Preventive

Recommendation

35. We suggest galcanezumab for the prevention of episodic cluster headache.
    (Weak for | Reviewed, New-added)

Discussion

As a primary headache disorder, cluster headache is one of the TACs.[2,108,182] The pain associated with cluster headache attacks is known as one of the "worst pains known to man" and referred to as "suicide headache," given the significantly higher odds of experiencing active suicidal ideation during a cluster headache attack.[183,184] Many pharmacotherapies have been used in the treatment of cluster headache within routine clinical care (e.g., verapamil, lithium). However, the FDA approved the first medication for the treatment of episodic cluster headache in adults, galcanezumab as a once monthly 300 mg subcutaneous injection, based on Goadsby et al. (2019).[108]

Goadsby et al. (2019) sought to determine the efficacy and safety of galcanezumab for the prevention of episodic cluster headache.[108] The study reported a significant reduction in the frequency of weekly cluster headache attacks among patients randomized to receive 300 mg once monthly of galcanezumab compared to those receiving placebo (-3.5 cluster headache attacks/week, p=0.04). A greater percentage of patients randomized to galcanezumab had at least a 50% reduction in weekly cluster headache attack frequency at week three, compared to patients receiving placebo (71% versus 53%, p=0.046). No serious AEs, deaths, or suicidal ideation/behavior were reported in either group. Adverse event rates were more common in the treatment group, with 8% of patients who received galcanezumab experiencing pain at the injection site. Of note, the study was stopped before reaching the planned sample size of 162 since not enough patients met eligibility criteria.

The Work Group's confidence in the quality of the evidence was low.[108] The benefits of galcanezumab outweighed the harms/burden. Patients likely have similar values regarding this medication that has been shown to be efficacious, safe, and tolerable, especially given the difficulty in treating cluster headache attacks and since galcanezumab is the only FDA approved pharmacotherapy. While there is variable patient acceptability of needles, patients generally tolerate subcutaneous injections and may be more apt to do so given the paucity of efficacious treatments for episodic cluster headache attacks. Providers are generally comfortable with this type of therapy and with prescribing subcutaneous injections. Providers managing headache disorders likely will become more comfortable using immunologic therapies as healthcare 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 decided upon a "Weak for" recommendation.

Apart from continued research regarding the long-term use of galcanezumab, future research should focus on understanding the role of galcanezumab in other headache conditions (e.g., paroxysmal hemicrania, other TACs) and those phenotypically similar to cluster headache (e.g., chronic PTH with cluster features).

f. Cluster Headache – Abortive

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)

Discussion

Law et al. (2013) conducted an SR of two crossover RCTs to assess the efficacy and tolerability of triptan medications compared to placebo and other interventions in the acute treatment of episodic and chronic cluster headache in adults.[185] This SR included six studies comparing sumatriptan (n=3) or zolmitriptan (n=3) to placebo using sumatriptan (subcutaneous, 6 mg) versus placebo, zolmitriptan (intranasal, 5 mg) versus placebo and zolmitriptan (intranasal, 10 mg) versus placebo. Triptans were more effective versus placebo for headache relief and pain-free responses at 15-minutes. Based on limited data, subcutaneous sumatriptan 6 mg was superior to intranasal zolmitriptan 5 mg or 10 mg at 15-minutes. Secondary outcomes reported included AEs of local reaction paresthesia (the most common), pain or tightness, sweating, feeling of heaviness, dizziness, somnolence, nausea and vomiting, injection site reaction (i.e., pain, swelling, burning, erythema, tingling) or neurologic symptoms (i.e., dizziness, tiredness,

numbness of hands, tingling, paranesthesia, feeling of paralysis of face, cold and hot sensations), bad taste or discomfort of nasal cavity, pain or tightness in the throat or chest or neck, or bitter taste. Adverse events were more common with a triptan versus placebo but were generally mild/moderate in severity. Since this was the only relevant study included in the systematic evidence review, there is insufficient evidence to recommend for or against any particular medication for the treatment of cluster headaches.

The systematic evidence review included one published SR, Law et al. (2013), that evaluated pharmacologic interventions (triptans or serotonin 5-HT receptor agonists) in patients with cluster headache.[185] There were no relevant studies identified regarding antiemetic agents, antiepileptic agents, CGRP inhibitors, combination agents, NSAIDs, other agents, OTC agents, or serotonin 5-HT1F receptor agonists.

Law et al. (2013) had serious limitations, including concerns about the method of allocation concealment for four of the six included studies.[185] Additionally, two included studies were considered high risk of bias due to small numbers of treated cluster headache attacks. Law et al. (2013) revealed moderate quality evidence only on AEs and not on efficacy data.[185] This study suggests a statistically significant difference in AEs between the zolmitriptan group and the placebo group (RR: 1.79, 95% CI: 1.15 – 2.77, p=0.0093). The primary outcome for Law et al. (2013) was pain-free at 30-minutes. However, the identified outcome in the systematic evidence review was percent pain-free at two hours, which was not addressed. The only relevant outcome in the Law et al. (2013) SR was AEs, which revealed nothing of clinical concern.

Other implications include resource use, as the noted medications are readily available and frequently used in treatment recommendations currently. The Work Group expected the lack of supporting literature and data regarding the treatment of cluster headaches as they are generally uncommon and treatment can be complex. Data was reviewed on other medications (i.e., antiemetic agents, antiepileptic agents, CGRP inhibitors, combination agents, NSAIDs, other agents, OTC agents, or serotonin 5-HT1F receptor agonists) and was absent. Law et al. (2013) was the only study yielded from the search and focused exclusively on serotonin 5-HT receptor agonists (triptans).[185]

The Work Group's confidence in the quality of the evidence was moderate.[185] The body of evidence had serious limitations. The benefits and harms/burden were balanced as there was no efficacy data for the outcome of percent pain-free at two hours and the noted AEs were of little concern clinically. Patient values and preferences are likely similar because there are no major issues associated with these medications and they are commonly used among patients. These medications are also readily available. Thus, the Work Group decided upon a "Neither for nor against" recommendation.

More research is needed on the efficacy of acute prescription and non-prescription pharmacologic treatment of cluster headache, including outcomes of percent pain-free at two hours as the extant literature offers evidence regarding AEs and percent pain-free at 15- and 30-minutes, which is not adequate to determine acute outcomes with a treatment intervention.

g. Headache – Preventive

Recommendation

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-replaced)

Discussion

The Work Group identified very little evidence for the use of oxygen therapy in acute cluster and migraine headaches. One SR by Bennett et al. (2015) and two crossover RCTs compared normobaric oxygen therapy (NBOT) to sham in patients with cluster headache or migraine.[185-187] There is inconsistent evidence for being pain-free after treatment.

The first-line treatment of cluster headaches includes triptans and oxygen therapy. Although there is limited evidence for the use of NBOT in acute cluster headache, it is established as safe and often found to be effective in aborting cluster headaches in the clinical setting. For ICHD-3 diagnostic criteria for cluster headaches, see Appendix A.

The Work Group's confidence in the quality of the evidence was very low.[185-188] The Work Group determined the benefits and harms were balanced given limited evidence proving either. Patient values and preferences were somewhat varied because some patients may not want to try this intervention. Also, supplemental oxygen is not always available in the clinical setting. Thus, the Work Group decided upon a "Neither for nor against" recommendation.

Recommendation

38. There is insufficient evidence to recommend for or against valproate for the prevention of headache.
    (Neither for nor against | Reviewed, New-added)

Discussion

Valproate products have been used by providers for over 50-years in formulations that include valproate sodium, valproic acid, and divalproex sodium.[189,190] Valproate products are FDA approved for migraine prevention, seizures, and bipolar disorder, and are used off-label as adjunctive therapy for schizophrenia, agitation, aggression, impulsivity, and alcohol use disorder.[189,191]

The Mulleners et al. (2015) SR examined the efficacy of valproate as a treatment for adults with episodic migraine.[134] This SR included 10 trials (six with sodium valproate, four with divalproex sodium) and examined the effect of valproate on headache frequency and ≥50% responder rate. Across studies, the mean duration of therapy was 11-weeks (SD: 8 – 12 weeks). Doses of valproate products ranged from 400 – 1,500 mg/day. Sodium valproate reduced headache days over a 28-day period compared to placebo whereas divalproex sodium was associated with a higher ≥50% responder rate, both compared to placebo.

The most common AEs included nausea, tremor, and dizziness/vertigo. Weight gain was not significantly associated with valproate product use. However, weight gain has been reported in 57% of adults on valproate products. Weight gain in the first year of valproate therapy has ranged from 6 – 14 pounds, with

women typically gaining more weight than men.[134,192-194] Other AEs associated with valproate use include alopecia, congenital anomalies, thrombocytopenia, and hepatotoxicity.[195]

Consideration of comorbidities and patient values and preferences is imperative to maximizing treatment success and mitigating negative consequences. When considering comorbidities, valproate products may be a reasonable choice for patients with seizures, those who would benefit from mood stabilization, or patients seeking treatment for alcohol abuse disorder. They are less appropriate for patients with a history of liver disease or thrombocytopenia. Providers should be aware of the FDA black box warning that valproate products should not be used in pregnancy, women planning to become pregnant, or in women of childbearing age not taking effective contraception.[196] Providers should be aware of drug-drug interactions.[197]

The Work Group's confidence in the quality of the evidence was low.[134] The harms/burden slightly outweighed the benefits since the AEs associated with these medications could impair QoL or lead to medication discontinuation. Patient values and preferences likely vary. Some patients would be willing to use valproate products for the prophylaxis of episodic migraine regardless of the side effect profile, whereas others would strongly prefer another agent given the possible side effects. Thus, the Work Group decided upon a "Neither for nor against" recommendation.

Future research should focus on whether valproate is an effective treatment for secondary headache disorders.

Recommendation

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)

Discussion

An SR by Jackson et al. (2015) included two RCTs that evaluated the effectiveness and side effects of fluoxetine or venlafaxine for the prevention of headache.[102] One RCT (n=53) found a significant reduction in frequency of episodic headache favoring fluoxetine over placebo at 4- and 12-weeks (95% CI: -1.44 – -0.03), but the difference was small and not significant at eight weeks (95% CI: -0.98 – 0.35). The other RCT (n=60) found a significant reduction in frequency, favoring venlafaxine over placebo at eight weeks (95% CI: -4.0 – -0.05).[102] An SR by Banzi et al. (2015) with five RCTs (n=221) found no significant between-group difference in withdrawal due to AEs or occurrence of minor AEs (n=84).[198] However, improvement in migraine scores was not significant at eight weeks (95% CI: -.057 – 0.30) or 12-weeks (95% CI: -0.88 – 0.25).

The Work Group's confidence in the quality of the evidence was very low.[102,198] The evidence of only two RCTs that studied fluoxetine and venlafaxine in the SR presented very serious risk of bias and serious imprecision for the outcomes of interest. The potential benefits slightly outweighed the harms/burdens. Fluoxetine is an SSRI and venlafaxine is an SNRI (though it requires a dose of at least 150 mg daily to affect the norepinephrine receptors). While SSRIs and SNRIs are widely used medications that treat multiple conditions, they have AEs such as nausea, weight gain, dry mouth, sexual dysfunction, and constipation. Venlafaxine has been associated with increased blood pressure. There is a possibility of the development

of serotonin syndrome, particularly when combined with other serotonergic medication, recognizing that this has not been seen clinically in patients using triptans (5-HT_{1b} and 5-HT_{1d} agonists). These agents may be preferable in patients with comorbid depression or anxiety. There may be some variation in patient values and preferences due to the perceived stigma associated with using this class of medications. Thus, the Work Group decided upon a "Neither for nor against" recommendation.

Further research evaluating the effectiveness of SNRIs is warranted as these are commonly used in the treatment of headache.

h. Headache – Abortive

Recommendation

40. We suggest against intravenous ketamine for the acute treatment of headache.
    (Weak against | Reviewed, New-added)

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)

Discussion

The Work Group reviewed evidence from multiple studies evaluating treatment protocols for ER or inpatient-based headache treatment (presumably for medically refractory pain such as that of status migrainosus). There was insufficient evidence to recommend any particular agents in these settings – other than for IV magnesium (see Recommendation 31) – but the Work Group wanted to comment on IV ketamine, IV metoclopramide (Reglan®), IV prochlorperazine (Compazine®), and intranasal lidocaine given their frequent and/or increasing use.

Intravenous ketamine is a dissociative anesthetic with analgesic properties at sub-anesthetic doses. It has grown increasingly popular as an alternative treatment for refractory headaches in the emergency setting since the recent discovery of its significant analgesic effects for acute pain in general.[199,200] Despite its growing popularity, the Work Group identified only a single small RCT comparing IV ketamine to placebo.

Etchinson et al. (2018) enrolled 30 patients and found no significant difference in pain scores at 30-minutes after administration.[201] Intravenous ketamine has potential side effects of significant cognitive changes (e.g., hallucinations, confusion, behavioral changes) and requires closer observation for cardiac compromise in some patients.[202] Intravenous ketamine carries additional risks of abuse and diversion relative to other medications used for headache treatment. For this reason, it is a scheduled medication. Of note, 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.

Intravenous metoclopramide (Reglan®) and IV prochlorperazine (Compazine®) are anti-emetic medications frequently used off-label for the treatment of severe migraine. Due to possible dystonic reactions, both are usually given after pre-treatment with diphenhydramine. The Work Group identified several RCTs of these medications – alone or in combination with diphenhydramine – compared to various other agents. Regarding IV metoclopramide, only one study directly compared IV metoclopramide alone with placebo.

Dogan et al. (2019) enrolled 148 patients and evaluated pain scores at 15-minutes, 30-minutes, and after discharge at 24 – 72 hours.[203] The only significant difference identified was the percentage of patients reaching a 50% reduction in pain at 30-minutes (66% with IV metoclopramide versus 45% with placebo). Friedman et al. (2016) compared IV metoclopramide with diphenhydramine to placebo in a total of 205 patients.[204] Pain responses at one hour or 48-hours and total length of stay were not significantly different between the groups. Khazaei et al. (2019) compared IV metoclopramide to dexamethasone, ketorolac, and chlorpromazine in a small study with 32 patients in each group.[205] There were no significant differences in headache intensities at one hour or 24-hours. Recurrence of headache in those who initially responded occurred in 25% of patients receiving metoclopramide. Friedman et al. (2017) compared IV metoclopramide with IV ketorolac and IV valproate in 330 patients.[206] The pain was compared at one, two, and 24-hours with no significant differences between IV metoclopramide and IV ketorolac; both were determined to be superior to IV valproate. Faridaalaee et al. (2015) compared IV metoclopramide to IV acetaminophen in a small study of 100 patients.[207] Intravenous acetaminophen was superior at all studied time points (15-, 30-, and 60-minutes).

Regarding IV prochlorperazine, Freidman et al. (2017) compared IV hydromorphone with IV prochlorperazine plus diphenhydramine in 127 patients and found the latter was significantly favored for headache relief at 48-hours and total length of stay.[208] Kostic et al. (2010) compared IV prochlorperazine to sumatriptan in 66 patients and found prochlorperazine reduced mean pain intensity on a 100 point visual analog scale at 80-minutes by 73 points versus 50 points with sumatriptan.[209] Thus, with limited evidence comparing either IV metoclopramide or IV prochlorperazine directly to placebo and concern for dystonic side effects, the Work Group cannot recommend for or against the use of these agents for headache in ER or inpatient-based settings.

The RCT by Mohammadkarimi et al. (2014) evaluated a total of 90 patients with pain scores at one minute, five minutes, 15-minutes, and 30-minutes and found lidocaine were superior at all time points versus placebo.[210] This study was conducted in Iran and enrolled multiple patients with secondary causes of headache (e.g., sinusitis, brain tumor, glaucoma), which makes extrapolation to VA/DoD populations with acute headache difficult. Thus, the Work Group concluded there is insufficient evidence to recommend for or against the use of intranasal lidocaine for headache in the emergency or inpatient-based settings.

The Work Group's confidence in the quality of the evidence was very low.[201,203-210] There were small sample sizes and consistently poor study designs in the studies captured by the guideline review criteria. There are some risks to using IV medications for headache; mostly with ketamine, but also with IV metoclopramide and IV prochlorperazine. Because of this, the Work Group determined the harms outweighed the potential benefit of headache relief with the available evidence. Patients would likely prefer not to be treated with ketamine given its stigma as a potential drug of abuse. Intravenous ketamine requires intensive monitoring of patients resulting in an increased time commitment for providers. Thus, the Work Group decided upon a "Weak against" recommendation for Recommendation 40 and a "Neither for nor against" recommendation for Recommendation 41.

Research on headache treatment in the emergency or inpatient-based settings has been limited by poor study design. We 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.

i. Secondary Headache – Abortive

Recommendation

42. There is insufficient evidence to recommend for or against prescription or non-prescription pharmacologic agents for the treatment of secondary headache.
(Neither for nor against | Reviewed, New-added)

Discussion

The Work Group began by reviewing the definition and classification of secondary headache, which includes PTH, headaches of musculoskeletal origin, CGH, and MOH.[2] An SR of one RCT by Basurto Ona et al. (2015) met the criteria for inclusion for acute treatment of secondary headache.[211] The Work Group analyzed one RCT by Vahabi et al. (2014) that met inclusion criteria for the preventive treatment of secondary headache.[212]

The Work Group's confidence in the quality of the evidence was very low.[211,212] There was study limitations, indirectness, and imprecision. The Work Group determined that the benefits and harms were balanced given the incredible variety in the potential mechanisms and lack of evidence. The values and preferences of patients are likely similar since most would prefer treating their pain/headache. Also, some treatments may not be accessible everywhere. Thus, the Work Group decided upon a "Neither for nor against" recommendation.

Additional research determining prescription or non-prescription pharmacologic agent utility in the treatment of secondary headache is needed. For additional guidance on the management of PTH, refer to the VA/DoD mTBI CPG.[f]

[f] See the VA/DoD Clinical Practice Guideline for the Management of Concussion-mild Traumatic Brain Injury. Available at: https://www.healthquality.va.gov/guidelines/Rehab/mtbi/

VII. Research Priorities

Through the development of this CPG, the Work Group discovered there were many aspects of headache care that were not addressed sufficiently in the evidence to confidently provide recommendations. Apart from the large, placebo-controlled clinical trials supporting the CGRP inhibitors, many of the intervention studies were small and lacked proper control groups. There are many research opportunities to advance headache care within the VA and DoD.

The Work Group identified several research priorities during the evidence review such as the lack of recent, high quality clinical trials evaluating historically used pharmacotherapy including topiramate, propranolol, gabapentin, and others. Our initial intent was to be able to offer recommendations on the comparative effectiveness of these medications, but there was insufficient data for evaluation. Given the current cost of newer medications such as the CGRP inhibitors, research comparing the relative effectiveness versus other classes is needed.

The data regarding the treatment of PTH was more limited than expected. Additional research is needed, including RCTs on reducing the frequency, severity, and disability associated with PTH. Furthermore, researchers should consider enrolling patients who meet the ICHD-3 definitions of PTH and delayed-onset PTH. Ideally, this research would be conducted in VA and DoD patients given the prevalence of this specific type of secondary headache disorder.

The data was limited on MOH, cluster headaches, postdural puncture headache, and post cerebral sinus thrombosis pain.

Generally, data for non-pharmacologic and supplement interventions for the prevention of headache were limited to small studies that often lacked a suitable comparator. One surprise was the limited data for acupuncture given the number of anecdotal success stories Work Group members shared regarding this modality. Other interventions with insufficient or limited evidence include mindfulness, psychotherapeutic interventions, and supplements such as vitamins and herbal products. Limited evidence was available for various components of physical therapy and non-invasive neurostimulation. Non-pharmacologic treatment options were identified as an area of interest by the patient focus group participants, so clinical trials in these areas are of significant interest to both patients and providers. The need for more education was also identified by the focus group participants. Expanding research on headache education content and delivery models to mirror that for chronic pain could aide in the development of educational offerings. Another research priority that should be considered is more information on oxygen therapy for chronic and episodic cluster headache.

To aid in the practical application of the myriad options for treatment, research should consider the comparative effectiveness of individual treatment modalities and explore the combination of various options. Information on dosing and patient stratification is important to inform a plan of care for an individual patient as well as planning for resources across VA and DoD.

Given the various headache types affecting patients within the VA and DoD the wide range of potential treatment options, and the currently limited clinical trial data, there are many opportunities for research that improves this ubiquitous, debilitating medical condition.

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

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 fulfilling criteria B-D

B. Headache attacks lasting 4-72 hr (untreated or unsuccessfully treated)

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.

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
    4. At least one aura symptom is unilateral
    5. At least one aura symptom is positive
    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.

Diagnostic criteria:

A. Headache (migraine-like or tension-type-like) 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:
    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.

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.

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.

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

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.

2.3 Chronic tension-type headache

Coded elsewhere

4.10 New daily persistent headache.

Description:

A disorder evolving from frequent episodic tension-type headache, with daily or very frequent episodes of headache, typically bilateral, pressing or tightening in quality and of mild to moderate intensity, lasting hours to days, or unremitting. The pain does not worsen with routine physical activity, but may be associated with mild nausea, photophobia or phonophobia.

Diagnostic criteria:

A. Headache occurring on ≥15-days/month on average for >3-months (≥180-days/year), fulfilling criteria B-D
B. Lasting hours to days, or unremitting
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 more than one of photophobia, phonophobia or mild nausea
    2. Neither moderate or severe nausea nor vomiting
E. Not better accounted for by another ICHD-3 diagnosis.

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)

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
      - 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

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

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-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 of a disorder or lesion within the cervical spine or soft tissues of the neck, known to be able to cause headache

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.

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 (GCS) score <13
   - Post-traumatic amnesia lasting >24-hours
   - 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.

Note:

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

Comment:

The diagnostic criteria for mild and those for moderate or severe traumatic injury to the head allow for substantial variability in the severity of the injury classified into each category. This has led some experts to suggest inclusion of additional categories: *headache attributed to very mild traumatic injury to the head* and *headache attributed to very severe traumatic injury to the head*. There is insufficient evidence for adding these categories at present, but future studies should investigate the utility of doing so.

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 (GCS) score <13
    - Post-traumatic amnesia lasting >24-hours
    - 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.

Note:

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

8.2 Evaluating and Treating Medication Overuse Headache

Description:

Medication overuse headache (MOH) is defined by the ICHD-3 as: "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.

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

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

Management:

A. Diagnosing MOH.

B. Gaining an accurate understanding of the dose, frequency, and types of medications which patients are taking as well as whether as needed pain medication(s) are being used to treat other comorbid disease (e.g., neck pain, lower back pain). Headache diaries, both paper and electronic, can allow for a more accurate understanding of these items than an initial history, which is subject to recall bias.

C. Determining whether patients may also have "Headache attributed to substance withdrawal" (e.g., caffeine-withdrawal headache), which differs from medication overuse headache.

D. Understanding the extent to which patients may also be psychologically dependent on abortive medication. This can be done via such standardized questionnaires as the Medication Dependence Questionnaire for Headache sufferers (MDQ-H) and the Severity of Dependence Scale.

    1. Given that MOH is comorbid with and its treatment complicated by the presence of depression, anxiety, impulsiveness, and catastrophizing, such standardized questionnaires as the Beck Depression Inventory (BDI-13), the State Trait Anxiety Inventory (STAI-state), Barratt Impulsiveness Scale (BIS- 11), and Pain Catastrophizing Scale could be used to understand whether these conditions exist.

    2. Educating the patient regarding MOH, the need to safely and comfortably discontinuation medication or medications which have resulted in the development of MOH, and potential treatment approaches which can occur in either outpatient or inpatient settings.

    3. Outpatient approaches include abrupt medication withdrawal or a slow taper of medication with and without transitional therapy.

E. Inpatient approaches may be advisable dependent on patient comorbidities, the degree to which headaches are interfering with activities of daily living, and the medication or medications which are resulting in MOH. Inpatient approaches may be favored among patients on higher doses of benzodiazepines, barbiturates, and/or opioids, psychiatry or medical comorbidities, those who have failed outpatient management, those with poorer social support, those with little motivation to engage in an outpatient approach, or with debilitating headaches affecting their activities of daily living.

F. Transitional therapy should be considered in patient with overuse of benzodiazepines, barbiturates, butalbital containing analgesics, and/or opioid analgesics.

G. Determine the pattern of headache(s) after withdrawal of the offending medication or medications.

H. Reevaluate prior headache diagnosis or diagnoses and consult ICDH-3/Headache CPG regarding diagnosis of underlying primary (e.g., migraine, tension type headache) and/or secondary (e.g., post-traumatic headache) disorders.

I. Monitor for relapse. Of note, patient with MOH secondary to overusing opioids have the highest rate of relapse after medication withdrawal.

J. In concert with the patient and taking into account patient preferences and comorbidities, develop an acute and preventive care plan to treat the underlying primary headache disorder. Behavioral interventions and/or pharmacological treatment of depression, anxiety, impulsiveness, and catastrophizing may be necessary to promote short and long term successful MOH management.

Related Headache Disorders

8.3 Headache attributed to substance withdrawal:

Headache following and caused by interruption in use of or exposure to a medication or other substance that has lasted for weeks or months.

Diagnostic criteria for select substance withdrawal headaches

8.3.1 Caffeine-withdrawal Headache

Description:

Headache developing within 24-hours after regular consumption of caffeine in excess of 200 mg/day for more than 2-weeks, which has been interrupted. It resolves spontaneously within 7-days in the absence of further consumption.

Diagnostic Criteria:

A. Headache fulfilling criterion C

B. Caffeine consumption of >200 mg/day for >2-weeks, which has been interrupted or delayed

C. Evidence of causation demonstrated by both of the following:

    1. Headache has developed within 24-hours after last caffeine intake

2. Either or both of the following:
    - Headache is relieved within 1-hour by intake of caffeine 100 mg
    - Headache has resolved within 7-days after total caffeine withdrawal

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

8.3.2 Opioid-withdrawal Headache

Description:

Headache developing within 24-hours after daily consumption of opioid(s) for more than 3-months, which has been interrupted. It resolves spontaneously within 7-days in the absence of further consumption.

Diagnostic Criteria:

A. Headache fulfilling criterion C

B. Opioid intake daily for >3-months, which has been interrupted

C. Evidence of causation demonstrated by both of the following:

1. Headache has developed within 24-hours after last opioid intake
2. Headache has resolved within 7-days after total opioid withdrawal

Not better accounted for by another ICHD-3 diagnosis.

Appendix B: Evidence Review Methodology

A. Developing the Key Questions

The CPG Champions, along with the Work Group, were tasked with identifying KQs to guide the systematic evidence review on the management of headache. These questions, which were developed in consultation with the Lewin Team, addressed clinical topics of the highest priority for the VA and DoD populations. The KQs follow the population, intervention, comparison, outcome, timing, and setting (PICOTS) framework for evidence questions, as established by the Agency for Healthcare Research and Quality (AHRQ). Table B-1 provides a brief overview of the PICOTS typology.

Table B-1. PICOTS [213]

PICOTS Elements	Description
Patients, Population, or Problem	Describes the patients of interest. It includes the condition(s), populations or sub-populations, disease severity or stage, co-occurring conditions, and other patient characteristics or demographics.
Intervention or Exposure	Refers to the specific treatments or approaches used with the patient or population. It includes doses, frequency, methods of administering treatments, etc.
Comparison	Describes the interventions or care that is being compared with the intervention(s) of interest described above. It includes alternatives such as placebo, drugs, surgery, lifestyle changes, standard of care, etc.
Outcome	Describes the specific results of interest. Outcomes can include short, intermediate, and long-term outcomes, or specific results such as quality of life, complications, mortality, morbidity, etc.
Timing, if applicable	Describes the duration of time that is of interest for the particular patient intervention and outcome, benefit, or harm to occur (or not occur).
Setting, if applicable	Describes the setting or context of interest. Setting can be a location (such as primary, specialty, or inpatient care).

The Champions, Work Group, and evidence review team carried out several iterations of this process, each time narrowing the scope of the CPG and the literature review by prioritizing the topics of interest. Due to resource constraints, all developed KQs were not able to be included in the systematic evidence review. Thus, the Champions and Work Group determined which questions were of the highest priority, and those were included in the review. Table B-2 contains the final set of KQs used to guide the systematic evidence review for this CPG.

Once the KQs were finalized, the Work Group prioritized the outcomes they had defined for each KQ based on how important the Work Group judged each outcome to be. Ranking outcomes by their relative importance can help focus attention on those outcomes that are considered most important for clinical decision making when making judgments regarding the overall quality of the evidence to support a recommendation.[214]

Using GRADE methodology, 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 outcomes judged to be critical were used to determine the overall quality of evidence (see Grading Recommendations).

a. Population(s)

- Adults 18-years or older who are experiencing primary or secondary headache

b. Interventions

- Key Questions 1, 2 – Prophylactic/preventive pharmacotherapy
    - Antiepileptic agents
        - Gabapentin
        - Topiramate
        - Divalproex sodium
        - Sodium valproate
    - 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
    - Beta-blockers
        - Propranolol
        - Metoprolol
        - Timolol

        - Atenolol
        - Nadolol
    - Antidepressants
        - Amitriptyline
        - Nortriptyline
        - Venlafaxine
        - Fluoxetine
    - CGRP inhibitors
        - Erenumab
        - Fremanezumab
        - Galcanezumab
        - Eptinezumab
        - Atogepant
    - Botulinum toxin
        - Onabotulinum
        - Abobotulinum
        - Incobotulinum
        - Rimabotulinum
    - Long-acting dihydropyridine (DHP) calcium channel blockers (CCBs)
        - Amlodipine
        - Felodipine
        - Nicardipine SR
        - Nifedipine SR (XL, CC)
        - Nisoldipine ER
- Key Question 3
    - History/physical
    - Diagnostic tests (cranio-cervical rotation test, elevated sedimentation rate [ESR], lumbar puncture, fundoscopic exam, presence or absence of low-amplitude nystagmus)
    - Diagnostic imaging (MRI/MRA/MRV/CT)
- Key Question 4 – Exposure
    - Overuse of medication (by type) intended for acute headache treatment
    - Healthcare provider type

- Key Questions 5, 6 – Acute/abortive pharmacotherapy
  - Nonsteroidal anti-inflammatory drugs (NSAIDs)
    - Ibuprofen
    - Naproxen
    - Ketorolac injection
    - Other NSAIDs
  - Serotonin (5-HT) receptor agonist
    - Sumatriptan
    - Sumatriptan/naproxen sodium
    - Rizatriptan
    - Naratriptan
    - Zolmitriptan
    - Almotriptan
    - Eletriptan
    - Frovatriptan
    - Lasmidatan
  - Combination agents
    - Butalbital/acetaminophen/caffeine
    - Butalbital/aspirin/caffeine
    - Acetaminophen/isometheptene/dichloralphenazone
    - Acetaminophen/caffeine
    - Acetaminophen/aspirin/caffeine
  - Over-the-counter agents
    - Acetaminophen
    - Aspirin
    - NSAIDs
  - CGRP inhibitors
    - Ubrogepant
    - Atogepant
    - Rimegepant
  - Antiemetic agents
    - Prochlorperazine
    - Promethazine

        - Chlorpromazine
        - Reglan®
    - Antiepileptic agent
        - Depacon – sodium valproate/valproic acid/divalproex sodium
    - Other
        - Ergotamine
        - Dihydroergotamine
        - Ketamine
        - Caffeine
        - Intranasal lidocaine
        - IV magnesium
        - Butorphanol (stadol)
        - Opioids (including tramadol)
- Key Question 7 – Interventional procedures
    - Cervical medial branch radiofrequency
    - Cervical medial branch neurotomy
    - Pulsed radiofrequency
    - Occipital nerve blocks
    - Occipital nerve pulsed radiofrequency
    - Sphenopalatine ganglion blocks
    - Supraorbital nerve blocks
    - Trigger point injections
- Key Question 8 – Integrative health interventions
    - Relaxation therapy
    - Stress management
    - Mindfulness
    - Meditation
    - Self-management
    - Acupuncture
    - Massage
    - Yoga
    - Tai chi

- Key Question 9 – Behavioral health approaches
    - Behavioral therapy
    - CBT
    - Biofeedback including diaphragmatic breathing
    - MBSR
- Key Question 10 – Exercise-based approaches
    - Exercise
    - Cardiovascular or aerobic exercise
    - Weight-bearing exercise
    - Physical activity
    - Clinician-directed exercise (e.g., prescription)
    - Use of posture-correcting/training device (Upright, "GO", etc.)
- Key Question 11
    - Oxygen therapy
        - Normobaric oxygen (NBOT)
        - Low flow
        - High flow
- Key Question 12 – Nutraceuticals, dietary supplements, herbal medicines
    - Magnesium
    - Magnesium oxide/glycinate/citrate
    - Vitamin B2
    - Vitamin B6
    - CoQ10
    - Butterbur
    - Feverfew
    - Peppermint
    - Omega-3 fatty acids
    - Alpha-lipoic acid
    - Melatonin
- Key Question 13 – Manual interventions
    - Manual therapy technique
    - Mobilization (e.g., Maitland, Mulligan) to cervical or thoracic
    - Chiropractic care

  - Spinal manipulation
  - High-velocity low amplitude manipulation
  - Osteopathic manipulation
  - Dry needling by a physical therapist
  - Cervical traction
- Key Question 14 – Lifestyle modifications
  - Diet (e.g., gluten-free/histamine-free/glycemic index)
  - Trigger food avoidance (e.g., avoiding aged cheese, red wine, other triggers)
  - Sleep
  - Posture
- Key Question 15
  - Non-invasive neurostimulation
  - Transcranial magnetic stimulation
  - Trigeminal nerve stimulation (Cefaly)
  - Transcranial direct current stimulation
  - Vagus nerve stimulation (e.g., gammaCore)
  - Alpha stimulation
- Key Question 16
  - Multidisciplinary or interdisciplinary treatment
  - Team-based care (or integrative practice unit [e.g., including primary care])
  - Behavioral health (psychiatry, psychology, health psychology, social work)
  - Pharmacist
  - Biofeedback/wellness
  - Neurology (+/- Botox)
  - Pain/anesthesia/physical medicine and rehabilitation
  - Case management
- Key Question 17
  - Any medication listed under KQ 1 in combination with behavioral therapy, biofeedback, CBT/other therapies that use cognitive behavior elements
  - Any combined therapy approach
- Key Question 18 – Emergency room-based and inpatient headache treatment protocols
  - Inpatient treatments
  - Oral medications

    - IV medications (Dihydroergotamine [DHE], IV fluids, IV anti-inflammatories, IV lidocaine)
    - Other invasive procedures
- Key Question 19
    - Medication withdrawal (removal of medication suspected of causing medication overuse headache) without replacement, or withdrawal with medication replacement
- Key Question 20
    - Botulinum toxin
        - Onabotulinum
        - Abobotulinum
        - Incobotulinum
        - Rimabotulinum
    - CGRP inhibitors
        - Erenumab
        - Fremanezumab
        - Galcanezumab
        - Eptinezumab

c. Comparators

- Key Questions 1,2
    - Placebo
    - Usual care
- Key Question 3
    - Diagnosis or treatment without the relevant physical exam or diagnostic imaging
- Key Question 4
    - Headache patients who do not develop medication overuse headache
- Key Question 5
    - Placebo
    - Usual care
- Key Question 6
    - Placebo
    - Usual care
- Key Question 7
    - Placebo
    - Usual care

    - Sham
    - Other types of invasive procedures
    - Other types of pharmacologic interventions
- Key Question 8
    - Pharmacologic therapy
    - Active control
    - Sham or placebo
- Key Question 9
    - Pharmacologic therapy
    - Active control
    - Sham or placebo
- Key Question 10
    - Each other
    - Pharmacologic therapy
    - Active control
    - Sham or placebo
- Key Question 11
    - Sham or placebo
    - Low versus high flow mask types
- Key Question 12
    - Pharmacologic therapy
    - Other nutraceuticals
    - Active control
    - Placebo
- Key Question 13
    - Pharmacologic intervention or medical-based treatment approaches (i.e., trigger point injections, nerve blocks)
    - Exercise only
    - Sham
- Key Question 14
    - No dietary lifestyle changes

- Key Question 15
  - Placebo
  - Sham
  - Other approaches to treatment and prevention
- Key Question 16
  - Treatment as usual (TAU)
  - Single discipline addressing comorbidities
  - Fragmented (i.e., uncoordinated) intervention
- Key Question 17
  - Pharmacotherapy intervention only
  - Behavioral intervention only
- Key Question 18
  - TAU
  - Conservative/outpatient
- Key Question 19
  - No intervention / continue to treat symptomatically
  - Add prophylactic treatment
- Key Question 20
  - Other pharmacotherapies for prevention of headaches

d. Outcomes

- Key Questions 1, 2
  - Critical outcomes
    - Change in monthly headache days
    - Change in acute headache treatment days/abortive medication use
    - Disability/QoL outcomes (e.g., MIDAS-A [days], HIT-6, MSQ, Migraine Physical Function Impact Diary [MPFID])
  - Important outcomes
    - Change in number of moderate/severe headache days
    - Responder rate (percent reduction in monthly headache days) (e.g., 50% or 75% responder rate)
    - Conversion from chronic to episodic headache (15-day threshold)
    - Adverse events

- Key Question 3
  - Critical outcomes
    - Red flags (e.g., for the use of imaging)
    - Indications for imaging (e.g., non-urgent, autonomic features, family history)
  - Important outcomes
    - Comorbidities
    - Psychosocial factors
    - Medical error rates
- Key Question 4
  - Critical outcomes
    - Rates of developing MOH by risk factor
    - Rates of developing MOH by medication type/number
  - Important outcomes
    - Headache severity (e.g., MIDAS)
    - Rates of developing MOH by demographic/comorbidity profiles
    - Migraine symptom severity
    - Pain intensity
    - Cutaneous allodynia
- Key Questions 5, 6
  - Critical outcomes
    - Percent pain-free at 2-hours
    - Disability/QoL outcomes (e.g., MIDAS-A [days], HIT-6, MSQ, MPFID)
    - Adverse events
  - Important outcomes
    - Responder rate (percent reduction in monthly headache days) (e.g., 50% or 75% responder rate)
    - Headache attack intensity, MIDAS-B (Intensity)
    - Change in number of moderate/severe headache days
    - Change in monthly headache days from baseline
- Key Question 7
  - Critical outcomes
    - Change in monthly headache days from baseline
    - Disability/QoL outcomes (e.g., MIDAS-A [days], HIT-6, MSQ, MPFID)

        - Responder rate (percent reduction in monthly headache days) (e.g., 50% or 75% responder rate)
        - Change in acute headache treatment days/abortive medication use
        - Adverse events
        - Change in number of moderate/severe headache days (critical for prevention only)
    - Important outcomes
        - Headache attack intensity, MIDAS-B (Intensity)
        - Change in number of moderate/severe headache days (important for acute treatment only)
- Key Questions 8 – 10, 12 – 16
    - Critical outcomes
        - Change in monthly headache days from baseline
        - Disability/QoL outcomes (e.g., MIDAS-A [days], HIT-6, MSQ, MPFID)
        - Change in acute headache treatment days/abortive medication use
        - Change in number of moderate/severe headache days
    - Important outcomes
        - Responder rate (percent reduction in monthly headache days) (e.g., 50% or 75% responder rate)
        - Headache attack intensity, MIDAS-B (Intensity)
        - Conversion from chronic to episodic headache (15-day threshold)
- Key Question 11
    - Critical outcomes
        - Percent pain-free at 2-hours
        - Disability/QoL outcomes (e.g., MIDAS-A [days], HIT-6, MSQ, MPFID)
        - Adverse events
    - Important outcomes
        - Responder rate (percent reduction in monthly headache days) (e.g., 50% or 75% responder rate)
        - Headache attack intensity, MIDAS-B (Intensity)
        - Change in number of moderate/severe headache days
        - Change in monthly headache days from baseline

- Key Question 17
    - Critical outcomes
        - Change in monthly headache days from baseline
        - Disability/QoL outcomes (e.g., MIDAS-A [days], HIT-6, MSQ, MPFID)
        - Change in acute headache treatment days/abortive medication use
        - Change in number of moderate/severe headache days
        - Responder rate (percent reduction in monthly headache days) (e.g., 50% or 75% responder rate)
    - Important outcomes
        - Headache attack intensity, MIDAS-B (Intensity)
        - Conversion from chronic to episodic headache (15-day threshold)
- Key Question 18
    - Critical outcomes
        - Degree of pain reduction
        - Time to relief from pain
        - Rate of sustained pain relief
        - Time to discharge/length of stay (from treatment start) (inpatient population)
    - Important outcomes
        - Responder rate (percent reduction in monthly headache days) (e.g., 50% or 75% responder rate)
        - Headache attack intensity, MIDAS-B (Intensity)
        - Disability/QoL outcomes (e.g., MIDAS-A [days], HIT-6, MSQ, MPFID)
- Key Question 19
    - Critical outcomes
        - Change in monthly headache days from baseline
        - Relief of pain
        - Time from withdrawal to headache resolution
        - Conversion from chronic to episodic headache (15-day threshold)
        - Responder rate (percent reduction in monthly headache days) (e.g., 50% or 75% responder rate)
        - Change in acute headache treatment days/abortive medication use
        - Disability/QoL outcomes (e.g., MIDAS-A [days], HIT-6, MSQ, MPFID)

- Key Question 20
  - Critical outcomes
    - Change in monthly headache days from baseline
    - Disability/QoL outcomes (e.g., MIDAS-A [days], HIT-6, MSQ, MPFID)
    - Change in acute headache treatment days/abortive medication use
    - Change in number of moderate/severe headache days
    - Responder rate (percent reduction in monthly headache days) (e.g., 50% or 75% responder rate)
  - Important outcomes
    - Discontinuations due to adverse events
    - Conversion from chronic to episodic headache (15-day threshold)

e. Timing

- Key Questions 1, 2, 17
  - Minimum treatment duration of two months
- Key Question 12
  - Minimum follow-up of one month, except for peppermint and magnesium which had no minimum follow-up
- All other Key Questions
  - No minimum follow-up

f. Settings

- Key Question 3
  - Outpatient and specialty care
- Key Questions 6, 7
  - Outpatient and ED
- Key Question 9
  - Outpatient and telehealth
- Key Questions 10, 13
  - Outpatient and inpatient
- Key Question 18
  - Inpatient, ED, or acute/urgent care settings
- Key Question 19
  - Outpatient, inpatient, and ED
- All other Key Questions
  - Primary outpatient care

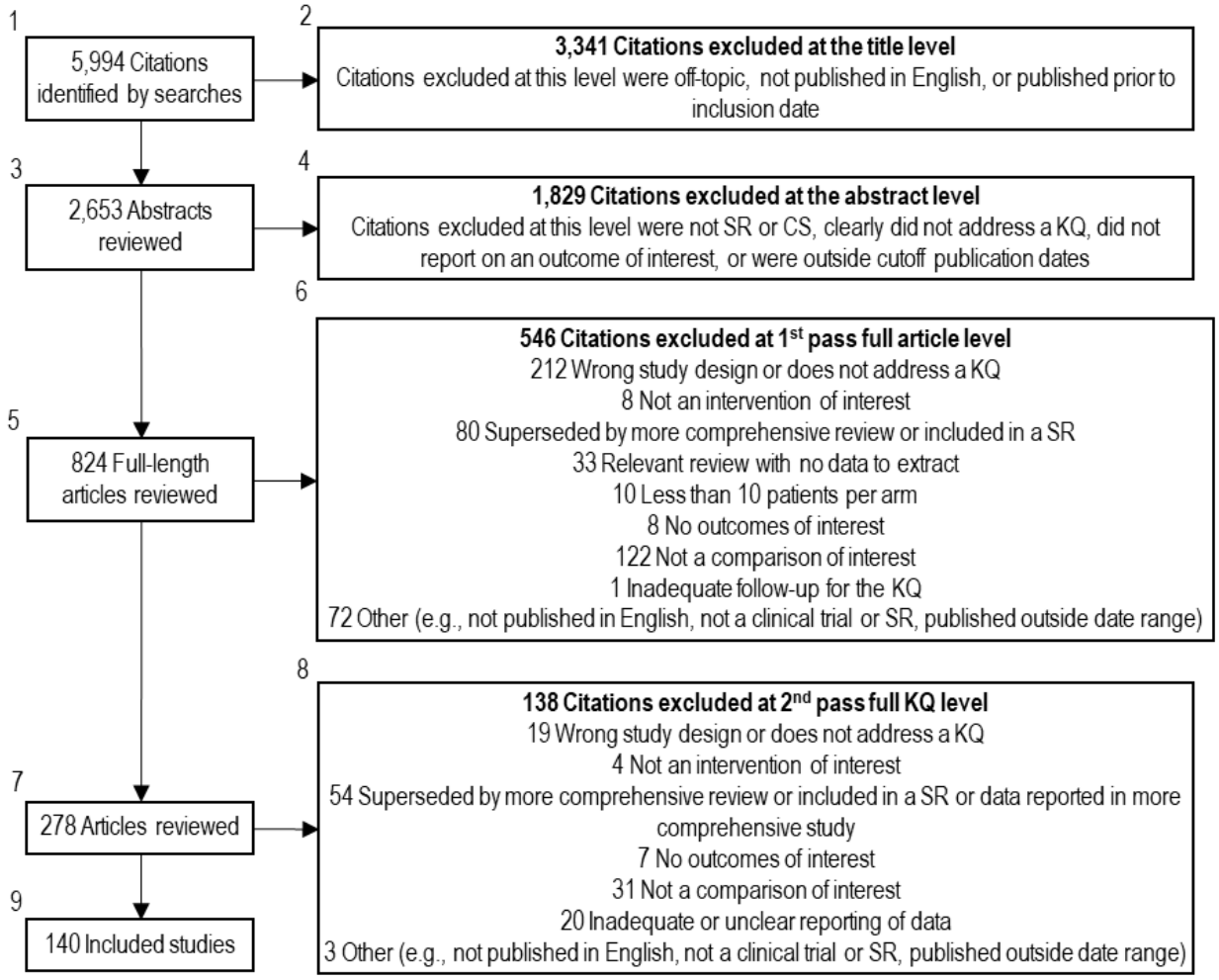
B. Conducting the Systematic Evidence Review

Based on the decisions made by the Champions and Work Group members regarding the scope, the KQs, and the PICOTS statements, the Lewin Team produced a systematic evidence review protocol prior to conducting the review. The protocol was reviewed and approved by the Champions and Work Group members. It described in detail the final set of KQs, the methodology to be used during the systematic evidence review process, and the inclusion/exclusion criteria to be applied to each potential study, including, but not limited to, study type, sample size, and PICOTS criteria.

Extensive literature searches identified 5,994 citations potentially addressing the key questions of interest to this evidence review. Of those, 3,341 were excluded upon title review for clearly not meeting inclusion criteria (e.g., not pertinent to the topic, not published in English, published prior to study inclusion publication date). Overall, 2,653 abstracts were reviewed with 1,829 of those being excluded for the following reasons: not an SR or clinical study, not addressing a KQ of interest to this review, not reporting on an outcome of interest, or published outside the specified date range (January 1, 2009, to March 6, 2019). A total of 824 full-length articles were reviewed. Of those, 546 were excluded at a first pass full article level review. A total of 278 full-length articles were thought to address one or more KQs and were further reviewed. Of these, 138 were ultimately excluded and reasons for their exclusion are presented in Figure B-1 below.

Overall, 140 studies addressed one or more of the KQs and were considered as evidence in this review. Table B-2 indicates the number of studies that addressed each of the questions.

Figure B-1. Study Flow Diagram



Abbreviations: CS: clinical study; KQ: key question; SR: systematic review

Alternative Text Description of Study Flow Diagram

Figure B-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: 5,994 citations identified by searches
    a. Right to Box 2: 3,341 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: 2,653 abstracts reviewed
    a. Right to Box 4: 1,829 citations excluded at the abstract level
        i. Citations excluded at this level were not SR or CS, clearly did not address a KQ, did not report on an outcome of interest, or were outside cutoff publication dates
    b. Down to Box 5
3. Box 5: 824 full-length articles reviewed
    a. Right to Box 6: 546 citations excluded at 1st pass full article level
        i. 212 wrong study design or does not address a KQ
        ii. 8 not an intervention of interest
        iii. 80 superseded by more comprehensive review or included in a SR
        iv. 33 relevant review with no data to extract
        v. 10 less than 10 patients per arm
        vi. 8 no outcomes of interest
        vii. 122 not a comparison of interest
        viii. 1 inadequate follow-up for the KQ
        ix. 72 other (e.g., not published in English, not a clinical trial or SR, published outside date range)
    b. Down to Box 7
4. Box 7: 278 articles reviewed
    a. Right to Box 8: 138 citations excluded at 2nd pass full KQ level
        i. 19 wrong study design or does not address a KQ
        ii. 4 not an intervention of interest
        iii. 54 superseded by more comprehensive review or included in a SR or data reported in more comprehensive study
        iv. 7 no outcomes of interest
        v. 31 not a comparison of interest
        vi. 20 inadequate or unclear reporting of data
        vii. 3 other (e.g., not published in English, not a clinical trial or SR, published outside date range)
    b. Down to Box 9
5. Box 9: 140 included studies

Table B-2. Evidence Base for KQs

Question Number	Question	Number of Studies & Type of Studies
1(a)	What is the effectiveness of preventive/prophylactic prescription pharmacologic agents in the treatment of migraine?	6 SRs 9 RCTs
1(b)	What is the effectiveness of preventive/prophylactic prescription pharmacologic agents in the treatment of tension-type headache?	2 SRs
1(c)	What is the effectiveness of preventive/prophylactic prescription pharmacologic agents in the treatment of cluster headache?	1 RCT
2	What is the effectiveness of preventive/prophylactic prescription pharmacologic agents in the treatment of secondary headache?	1 RCT
3	What is the clinical utility of history, physical, and diagnostic tests in improving treatment choices and patient outcomes?	No evidence
4	What are the risk factors for medication overuse headache?	1 SR 2 case-control studies 1 prospective cohort study
5(a)	What is the effectiveness of acute prescription and non-prescription pharmacologic agents in the treatment of cluster headache?	1 SR
5(b)	What is the effectiveness of acute prescription and non-prescription pharmacologic agents in the treatment of migraine?	9 SRs 9 RCTs
5(c)	What is the effectiveness of acute prescription and non-prescription pharmacologic agents in the treatment of tension-type headache?	3 SRs 1 RCT
6	What is the effectiveness of acute prescription and non-prescription pharmacologic agents in the treatment of secondary headache?	1 SR
7	What is the effectiveness of interventional procedures (e.g., nerve blocks) for acute treatment or prevention?	2 SRs 4 RCTs in 5 publications
8	What is the effectiveness of integrative health interventions in the treatment/prevention of headache?	4 SRs 3 RCTs
9	What is the effectiveness of behavioral health approaches for the treatment/prevention of headache?	3 SRs 2 RCTs
10	What is the effectiveness of exercise-based approaches in the treatment/prevention of headache?	1 SR 3 RCTs
11	In adults with primary headache, what is the effectiveness of oxygen therapy for the acute treatment of headache?	1 SR 3 randomized crossover studies
12	What is the effectiveness of nutraceuticals and dietary supplements in the treatment/prevention of headache?	7 SRs 2 RCTs 2 randomized crossover studies
13	For adults with headache of musculoskeletal origin, what is the effectiveness of clinician-directed manual interventions	2 SRs 8 RCTs
14	What is the effectiveness of self-directed lifestyle modifications such as trigger management, diet, sleep, posture?	4 RCTs 2 randomized crossover studies
15	What is the effectiveness of non-invasive neurostimulation, compared to placebo, on prevention/treatment of headache?	2 SRs 8 RCTs

Question Number	Question	Number of Studies & Type of Studies
16	What is the effectiveness of multidisciplinary or interdisciplinary treatment? Are there specific comorbidities that are more amenable to the interdisciplinary approach?	3 RCTs
17	What is the effectiveness of combination therapies (e.g., combining pharmacotherapies, enhancing pharmacotherapy with behavioral interventions) for headache prevention?	4 RCTs
18	What is the evidence for emergency room-based and inpatient headache treatment protocols?	2 SRs 17 RCTs
19	Is medication withdrawal an effective strategy to manage suspected medication overuse headache?	1 SR 1 RCT
20	What is the comparative effectiveness of CGRP inhibitors or botulinum toxin preparations versus other pharmacotherapies used for migraine prophylaxis?	1 SR
	Total Evidence Base	**140 studies (some studies addressed more than 1 KQ)**

Abbreviations: CGRP: calcitonin gene-related peptide, RCT: randomized controlled trial; SR: systematic review

a. General Criteria for Inclusion in Systematic Review

- Clinical studies or systematic reviews published on or after January 1, 2009, to March 6, 2019.
- If multiple SRs addressed a key question, we selected the most recent and/or comprehensive review. Systematic reviews were supplemented with clinical studies published subsequent to the SR.
- Studies must be published in English.
- Publication must be a full clinical study or SR; abstracts alone were not included. Similarly, letters, editorials, and other publications that are 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 one used by the Evidence-based Practice Centers of the AHRQ). If an existing review did not assess the overall quality of the evidence, evidence from the review must be 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 not able to assess the overall quality of the evidence in the review.
- Studies assessed a pharmacologic or non-pharmacologic treatment, multidisciplinary/interdisciplinary treatment, emergency room-based and inpatient treatment protocols, clinical exams, diagnostic tests, or risk factors (for MOH). Study designs varied across different key questions (see Key Question Specific Criteria).
- Study must have enrolled at least 20 patients (10 per study group) unless otherwise noted (see Key Question Specific Criteria).

- Study must have enrolled at least 85% of patients who meet the study population criteria: adults aged 18-years or older who are experiencing primary or secondary headaches.
- Study must have reported on at least one outcome of interest.

b. Key Question Specific Criteria

- For KQs 1, 2, 5, 8 – 17, 19, and 20, SRs of RCTs and individual RCTs not included in SRs.
- For KQs 4, 6, 7, and 18, SRs of acceptable study designs and individual RCTs not included in SRs were used. For interventions not represented in these study types, comparative observational studies, such as prospective or retrospective cohort or case-controlled trials were used.
- For KQ 3, systematic reviews of RCTs and/or diagnostic cohort studies, and individual RCTs and diagnostic cohort studies not included in SRs that compare a physical exam or diagnostic test to diagnosis or treatment without the physical exam or diagnostic test.

Table B-3. Bibliographic Database Information

Source	Name	Date Limits	Platform/Provider
Bibliographic Databases	Embase (Excerpta Medica)	January 1, 2009, to March 6, 2019	Elsevier
	Medline	January 1, 2009, to March 6, 2019	Elsevier
	PubMed (In-process and Publisher records)	January 1, 2009, to March 6, 2019	NLM
	PsycINFO (KQ9 only)	January 1, 2009, to March 6, 2019	Ovid
Gray Literature Resources	Agency for Healthcare Research and Quality (AHRQ)	January 1, 2009, to March 6, 2019	AHRQ
	Cochrane Database of Systematic Reviews	January 1, 2009, to March 6, 2019	Wiley

C. Convening the Face-to-face Meeting

In consultation with the COR, the Champions, and the Work Group, the Lewin Team convened a three and one-half day face-to-face meeting of the CPG Champions and Work Group members on September 16 – 19, 2019. These experts gathered to develop and draft the clinical recommendations for the 2020 Primary Care Management of Headache CPG. Lewin presented findings from the evidence review in order to facilitate and inform the process.

Under the direction of the Champions, the Work Group members were charged with interpreting the results of the evidence review and were asked to develop new clinical practice recommendations based on the 2019 evidence review. The subject matter experts were divided into three smaller subgroups at this meeting.

As the Work Group members drafted clinical practice recommendations, they also assigned a grade for each recommendation based on a modified GRADE and USPSTF methodology. Each recommendation was graded by assessing the quality of the overall evidence base, the associated benefits and harms, the variation in values and preferences, and other implications of the recommendation.

D. Grading Recommendations

This CPG uses the GRADE methodology to assess the quality of the evidence base and assign a strength for each recommendation. The GRADE system uses the following four domains to assess the strength of each recommendation:[39]

- Balance of desirable and undesirable outcomes
- Confidence in the quality of the evidence
- Values and preferences
- Other implications, as appropriate, e.g.,:
    - Resource use
    - Equity
    - Acceptability
    - Feasibility
    - Subgroup considerations

The following sections further describe each domain.

Balance of desirable and undesirable outcomes refers to the size of anticipated benefits (e.g., increased longevity, reduction in morbid event, resolution of symptoms, improved QoL, decreased resource use) and harms (e.g., decreased longevity, immediate serious complications, AE, impaired QoL, increased resource use, inconvenience/hassle) relative to each other. This domain is based on the understanding that the majority of clinicians will offer patients therapeutic or preventive measures as long as the advantages of the intervention exceed the risks and adverse effects. The certainty or uncertainty of the clinician about the risk-benefit balance will greatly influence the strength of the recommendation.

Some of the discussion questions that fall under this domain include:

- Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa?
- Are the desirable anticipated effects large?
- Are the undesirable anticipated effects small?
- Are the desirable effects large relative to undesirable effects?

Confidence in the quality of the evidence reflects the quality of the evidence base and the certainty in that evidence. This second domain reflects the methodological quality of the studies for each outcome variable. In general, the strength of recommendation follows the level of evidence, but not always, as other domains may increase or decrease the strength. The evidence review used for the development of recommendations, conducted by ECRI, assessed the confidence in the quality of the evidence base using GRADE methodology and assigned a rating of “High,” “Moderate,” “Low,” or “Very Low.” The outcomes judged to be critical were used to determine the overall quality of evidence. Per GRADE, if the quality of evidence differs across the critical outcomes, the lowest quality of evidence for any of the relevant critical outcomes determines the overall quality of the evidence for a recommendation; the overall confidence

cannot be higher than the lowest confidence in effect estimates for any outcome that is determined to be critical for clinical decision making.[41,214]

The elements that go into the confidence in the quality of the evidence include:

- Is there high or moderate quality evidence that answers this question?
- What is the overall certainty of this evidence?

Values and preferences is an overarching term that includes patients' perspectives, beliefs, expectations, and goals for health and life. More precisely, it refers to the processes that individuals use in considering the potential benefits, harms, costs, limitations, and inconvenience of the therapeutic or preventive measures in relation to one another. For some, the term "values" has the closest connotation to these processes. For others, the connotation of "preferences" best captures the notion of choice. In general, values and preferences increase the strength of the recommendation when there is high concordance and decrease it when there is great variability. In a situation in which the balance of benefits and risks are uncertain, eliciting the values and preferences of patients and empowering them and their surrogates to make decisions consistent with their goals of care becomes even more important. A recommendation can be described as having "similar values," "some variation," or "large variation" in typical values and preferences between patients and the larger populations of interest.

Some of the discussion questions that fall under the purview of values and preferences include:

- Are you confident about the typical values and preferences and are they similar across the target population?
- What are the patient's values and preferences?
- Are the assumed or identified relative values similar across the target population?

Other implications consider the practicality of the recommendation, including resource use, equity, acceptability, feasibility, and subgroup considerations. Resource use is related to the uncertainty around the cost-effectiveness of a therapeutic or preventive measure. For example, statin use in the frail elderly and others with multiple co-occurring conditions may not be effective and, depending on the societal benchmark for willingness to pay, may not be a good use of resources. Equity, acceptability, feasibility, and subgroup considerations require similar judgments around the practicality of the recommendation.

The Work Group used the framework below (Table B-4) to guide discussions on each domain.

Table B-4. GRADE Evidence to Recommendation Framework

Decision Domain	Questions to Consider	Judgment
Balance of desirable and undesirable outcomes	• Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa? • Are the desirable anticipated effects large? • Are the undesirable anticipated effects small? • Are the desirable effects large relative to undesirable effects?	• Benefits outweigh harms/burden • Benefits slightly outweigh harms/ burden • Benefits and harms/burden are balanced • Harms/burden slightly outweigh benefits • Harms/burden outweigh benefits
Confidence in the quality of the evidence	• Is there high or moderate quality evidence that answers this question? • What is the overall certainty of this evidence?	• High • Moderate • Low • Very low
Values and preferences	• Are you confident about the typical values and preferences and are they similar across the target population? • What are the patient's values and preferences? • Are the assumed or identified relative values similar across the target population?	• Similar values • Some variation • Large variation
Other implications (e.g., resource use, equity, acceptability, feasibility, subgroup considerations)	• Are the resources worth the expected net benefit from the recommendation? • What are the costs per resource unit? • Is this intervention generally available? • Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? • Is there lots of variability in resource requirements across settings?	• Various considerations

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 combines the four domains.[215] GRADE methodology does not allow for recommendations to be made based on expert opinion alone. While strong recommendations are usually based on high or moderate confidence in the estimates of effect (quality of the evidence) there may be instances where strong recommendations are warranted even when the quality of evidence is low.[39] In these types of instances where the balance of desirable and undesirable outcomes and values and preferences played large roles in determining the strength of a recommendation, this is explained in the discussion section for the recommendation.

The GRADE of a recommendation is based on the following elements:

- Four decision domains used to determine the strength and direction (described above)
- Relative strength (Strong or Weak)
- Direction (For or Against)

The relative strength of the recommendation is based on a binary scale, "Strong" or "Weak." A strong recommendation indicates that the Work Group is highly confident that desirable outcomes outweigh undesirable outcomes. If the Work Group is less confident in the balance between desirable and undesirable outcomes, they present a weak recommendation.

Similarly, a recommendation for a therapy or preventive measure indicates that the desirable consequences outweigh the undesirable consequences. A recommendation against a therapy or preventive measure indicates that the undesirable consequences outweigh the desirable consequences.

Occasionally, instances may occur when the Work Group feels there is insufficient evidence to make a recommendation for or against a particular therapy or preventive measure. This can occur when there is an absence of studies on a particular topic that met evidence review inclusion criteria, studies included in the evidence review report conflicting results, or studies included in the evidence review report inconclusive results regarding the desirable and undesirable outcomes.

Using these elements, the grade of each recommendation is presented as part of a continuum:

- Strong For (or "We recommend offering this option …")
- Weak For (or "We suggest offering this option …")
- No recommendation for or against (or "There is insufficient evidence …")
- Weak Against (or "We suggest not offering this option …")
- Strong Against (or "We recommend against offering this option …")

Note that weak (For or Against) recommendations may also be termed "Conditional," "Discretionary," or "Qualified." Recommendations may be conditional based upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented. Recommendations may be at the discretion of the patient and clinician or they may be qualified with an explanation about the issues that would lead decisions to vary.

E. Recommendation Categorization

a. Recommendation Categories and Definitions

A set of recommendation categories was adapted from those used by the National Institute for Health and Care Excellence (NICE).[216,217] These categories, along with their corresponding definitions, are used to account for the various ways in which CPG recommendations can be developed or updated from a previous version of a CPG. The categories and definitions can be found in Table B-5.

Table B-5. Recommendation Categories and Definitions

Evidence Reviewed*	Recommendation Category*	Definition*
Reviewed	New-added	New recommendation following review of the evidence
	New-replaced	Recommendation from the previous CPG that has been carried forward to the updated CPG and has been changed following review of the evidence
	Not changed	Recommendation from the previous CPG that has been carried forward to the updated CPG where the evidence has been reviewed but the recommendation is not changed
	Amended	Recommendation from the previous CPG that has been carried forward to the updated CPG where the evidence has been reviewed and a minor amendment has been made
	Deleted	Recommendation from the previous CPG that has been removed based on review of the evidence
Not reviewed	Not changed	Recommendation from the previous CPG that has been carried forward to the updated CPG, but for which the evidence has not been reviewed
	Amended	Recommendation from the previous CPG that has been carried forward to the updated CPG where the evidence has not been reviewed and a minor amendment has been made
	Deleted	Recommendation from the previous CPG that has been removed because it was deemed out of scope for the updated CPG

* Adapted from the NICE guideline manual (2012) [216] and Garcia et al. (2014) [217]

Abbreviation: CPG: clinical practice guideline

b. Categorizing Recommendations with an Updated Review of the Evidence

Because the VA/DoD Headache CPG is a new CPG, all recommendations were categorized as "Reviewed, New-added." "Reviewed, New-added" recommendations are original, new recommendations.

F. Drafting and Submitting the Final Clinical Practice Guideline

Following the face-to-face meeting, the Champions and Work Group members were given writing assignments to craft discussion sections to support each of the new recommendations. During this time, the Champions and Work Group also made additional revisions to the algorithms, as necessary.

After developing the initial draft of the CPG, an iterative review process was used to solicit feedback on and make revisions to the CPG. Once they were developed, the first two drafts of the CPG were posted on a wiki website for a period of 14 – 20 business days for internal review and comment by the Work Group. All feedback submitted during each review period was reviewed and discussed by the Work Group and appropriate revisions were made to the CPG.

Draft 3 of the CPG was made available for peer review and comment. This process is described in the section titled Peer Review Process. After revisions were made based on the feedback received during the peer review and comment period, the Champions presented the CPG to the EBPWG for their approval. Changes were made based on feedback from the EBPWG and the guideline was finalized.

The Work Group also produced a set of guideline toolkit materials which included a provider summary, pocket card, and patient summary. The final 2020 Primary Care Management of Headache CPG was submitted to the EBPWG in June 2020.

Appendix C: Patient Focus Group Methods and Findings

A. Methods

As part of the effort to develop this CPG, the VA and DoD Leadership held a patient focus group on January 16, 2019, at the Audie L. Murphy Memorial VA Hospital – South Texas Veterans Health Care System in San Antonio, TX. The aim of the focus group was to further understand patients' perspectives who are receiving treatment for headache within the VA and/or DoD healthcare systems as they are most affected by the recommendations in the new Headache CPG. The focus group explored patients' perspectives on a set of topics related to the management of headache in the VA and DoD healthcare systems, including their knowledge of treatments for headache, views on the delivery of care, priorities and treatment challenges, and the impact of comorbidities on patients and their treatments for headache.

VA and DoD Leadership and the Headache CPG Champions recruited participants for the focus group. Patient focus group participants were not intended to be a representative sample of VA and DoD patients who have headaches. However, recruitment focused on eliciting a range of perspectives likely to be relevant and informative in the guideline development process. Patients were not incentivized for their participation or reimbursed for travel expenses.

The Headache CPG Champions and Work Group, with support from Lewin, developed a set of questions to help guide the focus group. The focus group facilitator led the discussion using the previously prepared questions as a general guide to elicit the most important information from the patients regarding their experiences and views about their treatment and overall care. Given the limited time and the range of interests of the focus group participants, not all of the listed questions were addressed.

B. Patient Focus Group Findings

a. Provide comprehensive information to patients regarding available treatment options, pain management strategies, and self-management interventions, including expanding available information on complementary and integrative therapies.

- Patients feel it is important to explore all of the appropriate treatment options available with their providers and have a two-way dialogue about the treatment that is right for them.
- Some patients felt that their providers did not discuss the full range of available treatment options with them.
- Providers may prioritize pharmacologic interventions without offering the option of other management strategies including complementary and integrative therapy interventions.
- Many patients had implemented self-management strategies such as changing their environments, managing triggers, and monitoring their responses to various treatments.

b. Offer education to patients and providers regarding headaches, including the cause, diagnostic criteria, self-management, and treatment options.

- Patients emphasized the need for more education to be offered to both patients and providers on various topics surrounding headaches.

- Education may also include communication strategies and a common language to use when interacting with their providers about their headaches.
- Increasing available education resources will allow both providers and patients to make well-informed decisions when developing a treatment plan.

c. *Use a team approach to improve care coordination and information sharing between providers to ensure patients receive a comprehensive, individualized care plan that is responsive to the patients' goals, values, and preferences.*

- Patients emphasized how important it is that a team of providers with relevant expertise engaged throughout their care.
- Patients often have complex co-occurring conditions such as chronic health conditions (e.g., hypertension, CVD), chronic pain, TBI, and other blast injuries, as well as mental health conditions (e.g., depression, suicidal behavior).
- Patients were interested in having technology-based solutions available to communicate with their doctors, including telehealth and mobile applications. These technologies may increase patients' access to their providers, especially at critical times during an episode when it may not be feasible to see their provider in-person.

d. *Headaches can be an "invisible disease," but should still be treated as important medical conditions that can have a significant impact on patients' quality of life and function.*

- Providers should take patients' headaches seriously and work with them to identify treatments that will allow them to achieve their personal goals.
- Because headache diagnosis is based on patient symptoms and pain cannot be objectively measured, they may not be treated with the same seriousness as other health conditions.
- Providers should acknowledge that headaches can have serious effects on functional status and QoL.
- Headache can affect family, occupational, and social functioning. Patients described limiting their family and social activities and restricting their work because of their headaches.
- While pain might not disappear with treatment, patients wished for management strategies and interventions that would allow them to function as normally as possible.

Appendix D: Participant List

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Appendix E: Alternate Text Descriptions of Algorithm

The following outline narratively describes Module A. 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.

A. Module A: Evaluation and Treatment of Headache

1. Module A 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 the question: "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, asks the question: "Is there a secondary headache (see Sidebar 2), complicated headache presentation, or multiple headache types?"
        i. If the answer is "Yes" to Box 5, then Box 6, in the shape of an oval: "Refer for further diagnosis and evaluation"
        ii. If the answer is "No" to Box 5, then Box 7, in the shape of a hexagon, asks the question: "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: "Presumptive or definitive 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 the question: "Did the patient's condition improve?"
                    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, asks the question: "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: "Presumptive or definitive diagnosis of migraine"
                    i) Box 14 connects to Box 15, in the shape of a rectangle: "Migraine treatment (see Sidebar 6); also, assess for MOH (see Sidebar 5)"

ii) Box 15 connects to Box 10, in the shape of a hexagon, which asks the question: "Did the patient's condition improve?"

(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, asks the question: "Is there clinical concern for cluster headache? Including: frequent headache; severe and brief (<3-hours per attack); unilateral (always same side); ipsilateral autonomic signs; 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: "Presumptive or definitive 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)"

ii) Box 18 connects to Box 10, in the shape of a hexagon, which asks the question: "Did the patient's condition improve?"

(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"

c) 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 F: Pharmacotherapy Tables

Table F-1. Pharmacotherapy – Prevention Dosing Information

Type	Drug	Initial Dose	Usual Range	Comments
Beta-adrenergic antagonists	Atenolol (Tenormin®)	50 mg/day	50 – 200 mg/day	• Dose should be titrated and maintained for at least three months before assessment of response
	Metoprolol (Toprol®, Toprol XL®)	100 mg/day in divided doses	100 – 200 mg/day in divided doses	• Dose short-acting four times a day and long-acting two times a day • Available as extended release • Dose should be titrated and maintained for at least three months before assessment of response
	Nadolol (Corgard®)	40 – 80 mg/day	80 – 240 mg/day	• Dose should be titrated and maintained for at least three months before assessment of response
	Propranolol (Inderal®, Inderal® LA)	40 mg/day in divided doses	40 – 160 mg/day in divided doses	• Dose short-acting 2 – 3 times a day and long-acting 1 – 2 times a day • Available as extended release • Dose should be titrated and maintained for at least three months before assessment of response
	Timolol (Blocadren®)	20 mg/day in divided doses	20 – 60 mg/day in divided doses	• Dose should be titrated and maintained for at least three months before assessment of response
Antidepressants	Amitriptyline (Elavil™)	10 mg at bedtime	20 – 50 mg at bedtime	• Use slow titration to reduce sedation
	Venlafaxine (Effexor®, Effexor-XR®)	37.5 mg/day	75 – 150 mg/day	• Available as extended release • Increase dose after one week
Anticonvulsants	Topiramate (Topamax®)	25 mg/day	50 – 200 mg/day in divided doses	• As effective as amitriptyline, propranolol, or valproate • Increase by 25 mg/week
	Valproic acid/ divalproex sodium (Depakene®, Depakote®, Depakote ER®)	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	• Monitor levels if compliance is an issue

Type	Drug	Initial Dose	Usual Range	Comments
Calcitonin Gene-related Peptide Inhibitors	Eptinezumab-jjmr (Vyepti™)	100 mg IV every 3 months	up to 300 mg IV every 3 months	• May contain polysorbate 80 (also known as Tweens), which can cause hypersensitivity reactions
	Erenumab-aooe (Aimovig®)	70 mg SQ monthly	70 – 140 mg SQ monthly	• May cause constipation, packaging may contain latex
	Fremanezumab-vfrm (Ajovy®)	225 mg SQ monthly	225 mg SQ monthly or 675 mg SQ every 3 months	• May contain polysorbate 80 (also known as Tweens), which can cause hypersensitivity reactions
	Galcanezumab-gnlm (Emgality®)	120 mg SQ monthly (migraine), 300 mg SQ (cluster)	Can use 240 mg loading dose for migraine, use in cluster should continue monthly until end of cluster period	• May contain polysorbate 80 (also known as Tweens), which can cause hypersensitivity reactions
Nonsteroidal Anti-inflammatory Drugs	Ibuprofen (Motrin®)	400 – 1,200 mg/ day in divided doses	Same as initial dose	• Use intermittently, such as for menstrual migraine prevention; daily or prolonged use may lead to medication overuse headache and is limited by potential toxicity
	Ketoprofen (Orudis®)	150 mg/day in divided doses	Same as initial dose	• Use intermittently, such as for menstrual migraine prevention; daily or prolonged use may lead to medication overuse headache and is limited by potential toxicity
	Naproxen sodium (Aleve®, Anaprox®)	550 – 1,100 mg/ day in divided doses	Same as initial dose	• Use intermittently, such as for menstrual migraine prevention; daily or prolonged use may lead to medication overuse headache and is limited by potential toxicity
Triptans	Frovatriptan (Frova®)	2.5 mg/day or 5 mg/day in divided doses	Same as initial dose	• Taken in the perimenstrual period to prevent menstrual migraine
	Naratriptan (Amerge®)	2 mg/day in divided doses	Same as initial dose	• Taken in the perimenstrual period to prevent menstrual migraine
	Zolmitriptan (Zomig®)	5 – 7.5 mg/day in divided doses	Same as initial dose	• Taken in the perimenstrual period to prevent menstrual migraine
Miscellaneous	Histamine (Histatrol®)	1 – 10 mg two times/week	Same as initial dose	• May cause transient itching and burning at injection site
	Magnesium	400 mg/day	800 mg/day in divided doses	• May 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 may be associated with increased headaches
	Petasites	100 – 150 mg/ day in divided doses	150 mg/day in divided doses	• Use only commercial preparations, plant is carcinogenic
	Riboflavin	400 mg/day in divided doses	400 mg/day in divided doses	• Benefit only after 3 months

Abbreviations: ER: extended release; LA: long acting; mg: milligrams; SQ: subcutaneously; XL: extended release; XR: extended release

Table F-2. Pharmacotherapy – Abortive Dosing Information

Type	Drug	Dose	Comments
Analgesics	Acetaminophen (Tylenol®)	1,000 mg at onset; repeat every 4 – 6 hours as needed	• Maximum daily dose is 4 g
	Acetaminophen 250 mg/ aspirin 250 mg/caffeine 65 mg (Excedrin® Migraine)	2 tablets at onset and every 6-hours	• Available OTC as Excedrin® Migraine
Nonsteroidal Anti-inflammatory Drugs	Aspirin	500 – 1,000 mg every 4 – 6 hours	• Maximum daily dose is 4 g
	Diclofenac (Cataflam®, Voltaren®)	50 – 100 mg at onset; can repeat 50 mg in 8-hours	• Avoid doses >150 mg/day
	Ibuprofen (Motrin®)	200 – 800 mg every 6-hours	• Avoid doses >2.4 g/day
	Naproxen sodium (Aleve®, Anaprox®)	550 – 825 mg at onset; can repeat 220 mg in 3 – 4 hours	• Avoid doses >1.375 g/day
Ergotamine Tartrate	Oral tablet (1 mg) with caffeine 100 mg (Cafergot®)	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) (Ergomar®)	2 mg SL at the first sign of an attack. Then, 2 mg SL 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 (Cafergot®, Migergot®)	Insert 1/2 to 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
Dihydroergotamine	Injection 1 mg/mL (D.H.E. 45®)	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 (Migranal®)	One spray (0.5 mg) in each nostril at onset; repeat sequence 15-minutes later (total dose is 2 mg or four sprays)	• Maximum dose is 3 mg/day • 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 (Zomig®)	5 – 7.5 mg/day in divided doses Same as initial dose	• Taken in the perimenstrual period to prevent menstrual migraine
	Almotriptan (Axert®)	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 (Relpax®)	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

Type	Drug	Dose	Comments
Triptans (cont.)	Frovatriptan (Frova®)	2.5 or 5 mg at onset; can repeat in 2-hours if needed	• Optimal dose 2.5 – 5 mg • Maximum daily dose is 7.5 mg (three tablets)
	Sumatriptan (Imitrex®) injection	6 mg subcutaneous at onset; can repeat after 1-hour if needed	• Maximum daily dose is 12 mg
	Naratriptan (Amerge®)	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 (one spray) at onset; can repeat after 2-hours if needed	• Maximum daily dose is 10 mg/day
	Sumatriptan nasal spray	5, 10, or 20 mg at onset; can repeat after 2-hours if needed	• Optimal dose is 20 mg • Maximum daily dose is 40 mg • Single-dose device delivering 5 or 20 mg • Administer one spray in one nostril
	Zolmitriptan oral tablets	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
	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 (Maxalt®, Maxalt-MLT®)	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 (Nurtec™)	75 mg orally disintegrating tablet	• 75 mg per day, doses should not be more frequent than ≥48-hours • Avoid strong CYP3A4 inhibitors, strong or moderate CYP3A4 inducers, p-glycoprotein inhibitors
	Ubrogepant (Ubrelvy®)	50 – 100 mg as a single dose, may repeat in ≥2-hours	• Up to 200 mg/24-hours, contraindicated with CYP3A4 inhibitors, dose adjustment in moderate renal impairment and severe (Child Pugh Class C) hepatic impairment
Selective Serotonin 1F Receptor Agonist	Lasmidtan (Reyvow™)	50 mg, maximum of one dose per 24-hours	• 50 – 200 mg per 24-hours as a single dose • Is a Schedule V drug, may not drive for 8-hours after dose

Type	Drug	Dose	Comments
Miscellaneous	Metoclopramide (Reglan®)	10 mg IV at onset	• Useful for acute relief in the office or ED setting
	Prochlorperazine (Compazine®)	10 mg IV or IM at onset	• Useful for acute relief in the office or ED setting

Abbreviations: CYP3A4: cytochrome P450 3A4; DHE: dihydroergotamine; ED: emergency department; IM: intramuscular; IV: intravenous; mg: milligrams; mL: milliliter; OTC: over-the-counter

Appendix G: Evidence Table

Table G-1. Evidence Table[a, b, c]

Recommendation	Evidence	2020 Strength of Recommendation	Recommendation Category
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	[51] **Additional references**: [52-54]	Weak for	Reviewed, New-added
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.	[55,56]	Neither for nor against	Reviewed, New-added
3. We suggest physical therapy for the management of tension-type headache.	[57-64]	Weak for	Reviewed, New-added
4. We suggest aerobic exercise or progressive strength training for the management of headache.	[65-68]	Weak for	Reviewed, New-added
5. We suggest mindfulness-based therapies for the treatment of headache.	[69]	Weak for	Reviewed, New-added
6. We suggest education regarding dietary trigger avoidance for the prevention of migraine.	[70,71]	Weak for	Reviewed, New-added
7. We suggest non-invasive vagus nerve stimulation for the acute treatment of episodic cluster headache.	[72-75]	Weak for	Reviewed, New-added

[a] Evidence column: The first set of references listed in each row in the evidence column constitutes the evidence base for the recommendation. To be included in the evidence base for a recommendation, a reference needed to be identified through the 2019 evidence review. The second set of references in the evidence column (called "Additional References") includes references that provide additional information related to the recommendation, but which were not systematically identified through a literature review. These references were not included in the evidence base for the recommendation and, therefore, did not influence the strength and direction of the recommendation.

[b] 2020 Strength of Recommendation column: Refer to the Grading Recommendations section for more information on how the strength of the recommendation was determined using GRADE methodology.

[c] Recommendation Category column: Refer to the Recommendation Categorization section for more information on the description of the categorization process and the definition of each category.

Recommendation	Evidence	2020 Strength of Recommendation	Recommendation Category
8. There is insufficient evidence to recommend for or against acupuncture for the treatment of headache.	[76-79]	Neither for nor against	Reviewed, New-added
9. There is insufficient evidence to recommend for or against dry needling for the treatment of headache.	[80]	Neither for nor against	Reviewed, New-added
10. There is insufficient evidence to recommend for or against pulsed radiofrequency or sphenopalatine ganglion block for the treatment of headache.	[81,82]	Neither for nor against	Reviewed, New-added
11. There is insufficient evidence to recommend for or against cognitive behavioral therapy or biofeedback for the treatment of headache.	[83-87] **Additional references**: [88-91]	Neither for nor against	Reviewed, New-added
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.	[92,93]	Neither for nor against	Reviewed, New-added
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	[94-98]	Neither for nor against	Reviewed, New-added
14. We recommend candesartan or telmisartan for the prevention of episodic or chronic migraine.	[102] **Additional references**: [99-101,103]	Strong for	Reviewed, New-added
15. We suggest erenumab, fremanezumab, or galcanezumab for the prevention of episodic or chronic migraine.	[107-116] **Additional references**: [104-106,117-124]	Weak for	Reviewed, New-added
16. We suggest lisinopril for the prevention of episodic migraine.	[102] **Additional references**: [125,126]	Weak for	Reviewed, New-added
17. We suggest oral magnesium for the prevention of migraine.	[127-129] **Additional references**: [130]	Weak for	Reviewed, New-added
18. We suggest topiramate for the prevention of episodic migraine.	[133,134] **Additional references**: [131,132,135-139]	Weak for	Reviewed, New-added

Recommendation	Evidence	2020 Strength of Recommendation	Recommendation Category
19. We suggest propranolol for the prevention of migraine.	[140] **Additional references**: [141]	Weak for	Reviewed, New-added
20. We suggest onabotulinumtoxinA injection for the prevention of chronic migraine.	[142]	Weak for	Reviewed, New-added
21. We suggest against abobotulinumtoxinA or onabotulinumtoxinA injection for the prevention of episodic migraine.	[142]	Weak against	Reviewed, New-added
22. There is insufficient evidence to recommend for or against gabapentin for the prevention of episodic migraine.	[134] **Additional references**: [143-145]	Neither for nor against	Reviewed, New-added
23. There is insufficient evidence to recommend for or against nimodipine or nifedipine for the prevention of episodic migraine.	[102]	Neither for nor against	Reviewed, New-added
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.	[127,146-151]	Neither for nor against	Reviewed, New-added
25. There is insufficient evidence to recommend for or against combination pharmacotherapy for the prevention of migraine.	[152-154]	Neither for nor against	Reviewed, New-added
26. We recommend sumatriptan (oral or subcutaneous), the combination of sumatriptan/naproxen, or zolmitriptan (oral or intranasal) for the acute treatment of migraine.	[155-158]	Strong for	Reviewed, New-added
27. We suggest frovatriptan or rizatriptan for the acute treatment of migraine.	[159,160]	Weak for	Reviewed, New-added
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.	[51,161]	Weak for	Reviewed, New-added
29. We suggest ibuprofen, naproxen, aspirin, or acetaminophen for the acute treatment of migraine.	[162-166]	Weak for	Reviewed, New-added
30. We suggest greater occipital nerve block for the acute treatment of migraine.	[167-169] **Additional references**: [170,171]	Weak for	Reviewed, New-added
31. We suggest intravenous magnesium for the acute treatment of migraine.	[128,172] **Additional references**: [173-176]	Weak for	Reviewed, New-added
32. We suggest amitriptyline for the prevention of chronic tension-type headache.	[177]	Weak for	Reviewed, New-added
33. We suggest against botulinum/neurotoxin injection for the prevention of chronic tension-type headache.	[177]	Weak against	Reviewed, New-added

Recommendation	Evidence	2020 Strength of Recommendation	Recommendation Category
34. We suggest ibuprofen (400 mg) or acetaminophen (1,000 mg) for the acute treatment of tension-type headache.	[178-181]	Weak for	Reviewed, New-added
35. We suggest galcanezumab for the prevention of episodic cluster headache.	[108] **Additional references**: [2,182-184]	Weak for	Reviewed, New-added
36. There is insufficient evidence to recommend for or against any particular medication for the acute treatment of cluster headache.	[185]	Neither for nor against	Reviewed, New-added
37. There is insufficient evidence to recommend for or against oxygen therapy for the acute treatment of primary headache.	[185-188]	Neither for nor against	Reviewed, New-added
38. There is insufficient evidence to recommend for or against valproate for the prevention of headache.	[134] **Additional references**: [189-197]	Neither for nor against	Reviewed, New-added
39. There is insufficient evidence to recommend for or against fluoxetine or venlafaxine for the prevention of headache.	[102,198]	Neither for nor against	Reviewed, New-added
40. We suggest against intravenous ketamine for the acute treatment of headache.	[201,203-210] **Additional references:** [199,200,202]	Weak against	Reviewed, New-added
41. There is insufficient evidence to recommend for or against intravenous metoclopramide, intravenous prochlorperazine, or intranasal lidocaine for the acute treatment of headache.	[201,203-210] **Additional references:** [199,200,202]	Neither for nor against	Reviewed, New-added
42. There is insufficient evidence to recommend for or against prescription or non-prescription pharmacologic agents for the treatment of secondary headache.	[211,212] **Additional references**: [2]	Neither for nor against	Reviewed, New-added

Appendix H: Literature Search Strategy

Table H-1. EMBASE and Medline in EMBASE.com syntax (all questions)

Set #	Concept	Strategy
#1	Headache as major focus	'headache and facial pain'/exp/mj AND headache*:ti
#2	Cluster headache	'cluster headache'/exp/mj OR ((cluster NEAR/2 headache*):ab,kw,ti)
#3	Hemicranias continua	'hemicrania continua'/exp/mj OR 'hemicrania* continua':ab,kw,ti
#4	Migraine	'migraine'/exp/mj OR migraine*:ab,kw,ti OR migrainosus:ab,kw,ti
#5	Primary headache	'primary headache'/exp/mj OR ((primary NEAR/2 headache*):ab,kw,ti)
#6	Tension	'tension headache'/exp/mj OR 'essential headache*':ab,kw,ti OR 'idiopathic headache*':ab,kw,ti OR (('muscle contraction' NEAR/2 headache*):ab,kw,ti) OR ((psychogenic NEAR/2 headache*):ab,kw,ti) OR 'stress headache*':ab,kw,ti OR ((tension NEAR/2 headache*):ab,kw,ti)
#7	Primary headache combined	#2 OR #3 OR #4 OR #5 OR #6
#8	Secondary headache	'secondary headache'/exp/mj OR ((secondary NEAR/2 headache*):ab,kw,ti)
#9	Post-traumatic headache	'post-traumatic headache'/exp/mj OR (('post traumatic' NEAR/2 headache*):ab,kw,ti) OR ((post-traumatic NEAR/2 headache*):ab,kw,ti)
#10	Musculoskeletal origin/cervicogenic headache	((cervicogenic NEAR/2 headache*):ab,kw,ti) OR ((musculoskeletal NEAR/2 headache*):ab,kw,ti)
#11	Medication overuse headache	'drug induced headache'/exp/mj OR (('drug induced' NEAR/2 headache*):ab,kw,ti) OR (('medication overuse' NEAR/2 headache*):ab,kw,ti) OR ((rebound NEAR/2 headache*):ab,kw,ti)
#12	Occipital neuralgia	'occipital neuralgia':ab,kw,ti
#13	Secondary headache combined	#9 OR #10 OR #11 OR #12
#14	Headache combined	#1 OR #7 OR #13
#15	Anticonvulsants	'anticonvulsive agent'/exp/mj OR 'gabapentin'/exp OR 'topiramate'/exp OR 'valproate semisodium'/exp OR 'valproic acid'/exp OR 'anti-convuls*':ab,kw,ti OR anticonvuls*:ab,kw,ti OR 'anti-epileptic*':ab,kw,ti OR antiepileptic*:ab,kw,ti OR depacon*:ab,kw,ti OR divalproex*:ab,kw,ti OR divalproic*:ab,kw,ti OR gabapentin*:ab,kw,ti OR topiramate*:ab,kw,ti OR valproate*:ab,kw,ti OR valproic*:ab,kw,ti
#16	Antidepressants	'amitriptyline'/exp/mj OR 'antidepressant agent'/exp/mj OR 'nortriptyline'/exp/mj OR 'venlafaxine'/exp/mj OR amitriptyline*:ab,kw,ti OR 'anti-depressant*':ab,kw,ti OR antidepressant*:ab,kw,ti OR nortriptyline*:ab,kw,ti OR venlafaxine*:ab,kw,ti
#17	Antiemetics	'antiemetic agent'/exp/mj OR 'anti emetic*':ab,kw,ti OR antiemetic*:ab,kw,ti OR chlorpromazine*:ab,kw,ti OR prochlorperazine*:ab,kw,ti OR promethazine*:ab,kw,ti OR reglan*:ab,kw,ti
#18	Beta-blockers	'atenolol'/exp OR 'beta adrenergic receptor blocking agent'/exp/mj OR 'metoprolol'/exp OR 'nadolol'/exp OR 'propranolol'/exp OR 'timolol'/exp OR atenolol*:ab,kw,ti OR 'beta blocker*':ab,kw,ti OR betablocker*:ab,kw,ti OR metoprolol*:ab,kw,ti OR nadolol*:ab,kw,ti OR propranolol*:ab,kw,ti OR timolol*:ab,kw,ti

Set #	Concept	Strategy
#19	Botox	'botulinum toxin A'/exp/mj OR abobotulinum*:ab,kw,ti OR botox*:ab,kw,ti OR botulinum*:ab,kw,ti OR incobotulinum*:ab,kw,ti OR myobloc*:ab,kw,ti OR onabotulinum*:ab,kw,ti OR rimabotulinum*:ab,kw,ti
#20	CGRP Inhibitors	'calcitonin gene related peptide receptor antagonist'/exp/mj OR 'erenumab'/mj OR 'fremanezumab'/mj OR 'galcanezumab'/exp/mj OR atogepant:ab,kw,ti OR "calcitonin gene related peptide" OR CGRP OR erenumab* OR fremanezumab* OR galcanezumab* OR olcegepant*:ab,kw,ti OR rimegepant*:ab,kw,ti OR ubrogepant*:ab,kw,ti
#21	Combination agents	(butalbital* NEAR/3 acetaminophen* NEAR/3 caffeine*) OR (Butalbital* NEAR/3 aspirin* NEAR/3 caffeine*) OR (Acetaminophene* NEAR/3 isometheptene* NEAR/3 dichloalphenazone*)
#22	Nerve blocks	'nerve block'/exp/mj OR (nerve* NEAR/2 block*)
#23	NSAIDs	'nonsteroid antiinflammatory agent'/exp/mj OR ibuprofen*:ab,kw,ti OR ketorolac*:ab,kw,ti OR naproxen*:ab,kw,ti OR 'nonsteroidal antiinflammatory':ab,kw,ti OR 'non-steroidal anti-inflammatory':ab,kw,ti OR NSAID*:ab,kw,ti
#24	OTCs	'acetylsalicylic acid'/exp/mj OR 'caffeine'/exp/mj OR 'paracetamol'/exp/mj OR acetaminophen*:ab,kw,ti OR 'acetylsalicylic acid':ab,kw,ti OR aspirin*:ab,kw,ti OR caffeine*:ab,kw,ti OR paracetamol*:ab,kw,ti
#25	Other	'butorphanol tartrate'/exp/mj OR 'dihydroergotamine'/exp/mj OR 'eptinezumab'/exp/mj OR 'ergotamine'/exp/mj OR 'lasmiditan'/exp/mj OR 'narcotic analgesic agent'/exp/mj OR opiate'/exp/mj OR tramadol'/exp/mj OR butorphanol*:ab,kw,ti OR dihydroergotamine*:ab,kw,ti OR eptinezumab*:ab,kw,ti OR ergotamine*:ab,kw,ti OR 'ketamine'/exp/mj OR lasmiditan*:ab,kw,ti OR 'lidocaine'/exp/mj OR 'magnesium'/exp/mj OR ketamine*:ab,kw,ti OR lidocaine*:ab,kw,ti OR magnesium*:ab,kw,ti OR opiate*:ab,kw,ti OR opioid*:ab,kw,ti OR stadol*:ab,kw,ti OR tramadol*:ab,kw,ti
#26	Serotonin 5-HT receptor agonists	'serotonin agonist'/exp/mj OR almotriptan*:ab,kw,ti OR eletriptan*:ab,kw,ti OR frovatriptan*:ab,kw,ti OR naratriptan*:ab,kw,ti OR rizatriptan*:ab,kw,ti OR sumatriptan*:ab,kw,ti OR zolmitriptan*:ab,kw,ti
#27	Pharmacological interventions combined	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26
#28	Oxygen therapy	'oxygen'/exp/mj OR 'oxygen therapy'/exp/mj OR 'Normobaric oxygen':ab,kw,ti OR NBOT:ab,kw,ti OR (O2 NEAR/2 therap*):ab,kw,ti OR (O2 NEAR/2 treatment*):ab,kw,ti OR (oxygen NEAR/2 therap*):ab,kw,ti OR (oxygen NEAR/2 treatment*):ab,kw,ti
#29	Combination care	'case management'/exp/mj OR 'interdisciplinary care'/exp/mj OR 'multidisciplinary team'/exp/mj OR 'team based care'/exp/mj OR ((coordinate* OR integrated OR interdisciplinary OR multidisciplinary OR multimodal OR team) NEAR/3 (approach* OR care OR manage* OR practice OR therap* OR treatment*)) OR 'case management':ab,kw,ti OR 'organization of care':ab,kw,ti OR 'combination therapy':ab,kw,ti
#30	Emergency & inpatient care	'emergency treatment'/exp/mj OR 'emergency ward'/exp/mj OR 'hospital patient'/exp/mj OR 'intravenous drug administration'/exp/mj OR 'acute care':ab,kw,ti OR 'emergency department':ab,kw,ti OR 'emergency room':ab,kw,ti OR er:ab,kw,ti OR inpatient:ab,kw,ti OR intravenous:ab,kw,ti OR iv:ab,kw,ti OR 'urgent care':ab,kw,ti

Set #	Concept	Strategy
#31	Diagnosis	'diagnostic imaging'/exp/mj OR 'diagnostic test'/exp/mj OR 'family history'/exp/mj OR 'medical history'/exp/mj OR 'physical examination'/exp/mj OR ((family OR medical OR patient) NEAR/3 history) OR (physical NEAR/3 exam*) OR 'red flag' OR 'red flags'
#32	Specific diagnostic tests	'computer assisted tomography'/exp/mj OR 'lumbar puncture'/exp/mj OR 'magnetic resonance angiography'/exp/mj OR 'nystagmus'/exp/mj OR fundoscopic OR 'magnetic resonance venography'/exp/mj OR 'nuclear magnetic resonance imaging'/exp/mj OR 'Cervical Flexion-Rotation' OR 'Cranio-cervical rotation' OR CT OR 'elevated sedimentation rate' OR 'lumbar puncture' OR MRA OR MRI OR MRV
#33	Risk factors	risk factor'/exp/mj OR risk:ab,kw,ti OR risks:ab,kw,ti
#34	Medication withdrawal	'detoxification'/exp/mj OR 'treatment withdrawal'/exp/mj OR detox*:ab,kw,ti OR remov*:ab,kw,ti OR replac*:ab,kw,ti OR stop*:ab,kw,ti OR taper*:ab,kw,ti OR withdraw*:ab,kw,ti
#35	Integrative interventions	'acupuncture'/exp/mj OR 'alternative medicine'/exp/mj OR 'massage'/exp/mj OR 'meditation'/mj OR 'mindfulness'/mj OR 'relaxation training'/mj OR 'self care'/mj OR 'stress management'/mj OR 'Tai Chi'/mj OR 'yoga'/mj OR acupressure:ab,kw,ti OR acupuncture:ab,kw,ti OR alternative:ab,kw,ti OR complementary:ab,kw,ti OR integrative:ab,kw,ti OR massage*:ab,kw,ti OR meditat*:ab,kw,ti OR 'mind-body':ab,kw,ti OR mindful*:ab,kw,ti OR 'nonpharmacologic': ab,kw,ti OR relaxation:ab,kw,ti OR 'self care':ab,kw,ti OR 'self management':ab,kw,ti OR (stress NEAR/2 manage*) OR 'Tai Chi':ab,kw,ti OR 'Tai Ji':ab,kw,ti OR Taiji:ab,kw,ti OR Taijiquan:ab,kw,ti OR yoga:ab,kw,ti OR yogic:ab,kw,ti
#36	Behavioral health interventions	behavior therapy'/exp/mj OR 'behavioral health'/mj OR 'biofeedback'/exp/mj OR 'cognitive behavioral therapy'/exp/mj OR 'diaphragmatic breathing'/mj OR 'mindfulness based stress reduction'/mj OR (behavior* NEAR/2 health):ab,kw,ti OR (behavior* NEAR/2 therap*):ab,kw,ti OR (behaviour* NEAR/2 health):ab,kw,ti OR (behaviour* NEAR/2 therap*):ab,kw,ti OR biofeedback:ab,kw,ti OR 'bio feed back':ab,kw,ti OR 'biofeedback':ab,kw,ti OR CBT:ab,kw,ti OR 'diaphragmatic breath*':ab,kw,ti OR 'mindfulness based stress reduction':ab,kw,ti
#37	Exercise based interventions	'exercise'/exp/mj OR 'physical activity'/exp/mj OR aerobic*:ab,kw,ti OR 'clinician-directed exercise*':ab,kw,ti OR exercise*:ab,kw,ti OR 'physical activity':ab,kw,ti OR (posture NEAR/2 correct*):ab,kw,ti OR (posture NEAR/2 train*):ab,kw,ti OR 'strength train*':ab,kw,ti OR 'upright go':ab,kw,ti OR 'weight bearing exercise*':ab,kw,ti OR ((aerobic* OR endurance OR physical OR plyometric OR resistance) NEAR/2 (exercise* OR therap* OR train*)):ab,ti,kw OR (physical* NEAR/2 activ*):ab,ti,kw
#38	Nutraceuticals	'butterbur'/mj OR 'chinese medicine'/exp/mj OR 'dietary supplement'/mj OR 'herbal medicine'/mj OR 'magnesium'/mj OR 'magnesium citrate'/mj OR 'magnesium glycinate'/mj OR 'magnesium oxide'/mj OR 'melatonin'/mj OR 'nutraceutical'/mj OR 'omega 3 fatty acid'/mj OR 'peppermint'/mj OR 'peppermint oil'/mj OR 'petasites'/exp OR 'petasites hybridus'/exp OR 'petasites hybridus extract'/exp OR 'pyridoxine'/mj OR 'riboflavin'/exp/mj OR 'Tanacetum parthenium'/mj OR 'thioctic acid'/mj OR 'alpha-lipoic acid':ab,kw,ti OR b2:ab,kw,ti OR b6:ab,kw,ti OR butterbur:ab,kw,ti OR 'coenzyme q10':ab,kw,ti OR coq10:ab,kw,ti OR 'dietary supplement*':ab,kw,ti OR feverfew:ab,kw,ti OR 'herbal medicine*':ab,kw,ti OR magnesium:ab,kw,ti OR melatonin:ab,kw,ti OR 'mig 99':ab,kw,ti OR mig99:ab,kw,ti OR nutraceutical*:ab,kw,ti OR 'omega 3':ab,kw,ti OR omega3:ab,kw,ti OR peppermint:ab,kw,ti OR petasites:ab,kw,ti OR petadolex pyridoxine:ab,kw,ti OR riboflavin:ab,kw,ti OR (supplement* NEAR/2 (diet* OR herbal*)):ab,kw,ti

Set #	Concept	Strategy
#39	Manual interventions	'cervical traction device'/exp/mj OR 'cervical traction kit'/mj OR 'dry needling'/mj OR 'manipulative medicine'/exp/mj OR 'mobilization'/mj OR 'spine manipulation'/mj OR 'traction therapy'/exp/mj OR chiropract*:ab,kw,ti OR 'dry needling':ab,kw,ti OR 'high velocity low amplitude manipulation':ab,kw,ti OR maitland:ab,kw,ti OR manual:ab,kw,ti OR manipula*:ab,kw,ti OR mobilization:ab,kw,ti OR mulligan:ab,kw,ti OR 'spin* manipulation*':ab,kw,ti
#40	Lifestyle modifications	'behavior change'/exp/mj OR 'body position'/exp/mj OR 'diet restiction'/exp/mj OR 'diet therapy'/exp/mj OR 'healthy lifestyle'/exp/mj OR lifestyle/exp/mj OR 'lifestyle modification'/mj OR cheese*:ab,kw,ti OR (diet* NEAR/2 change*):ab,kw,ti OR (diet NEAR/2 eliminat*):ab,kw,ti OR (diet* NEAR/2 modif*):ab,kw,ti OR (diet* NEAR/2 restrict*):ab,kw,ti OR (diet* NEAR/2 therap*):ab,kw,ti OR (food* NEAR/2 eliminat*):ab,kw,ti OR (food* NEAR/2 restrict*):ab,kw,ti OR ‘gluten free’:ab,kw,ti OR ‘glycemic index’:ab,kw,ti OR ‘histamine free’:ab,kw,ti OR (lifestyle* NEAR/2 change*):ab,kw,ti OR (lifestyle* NEAR/2 modif*):ab,kw,ti OR posture:ab,kw,ti OR “red wine*”:ab,kw,ti OR trigger*:ab,kw,ti OR ((behavior* OR behaviour* OR habit* OR lifestyle*) NEAR/2 (adjust* OR alter* OR change* OR modif*)):ab,kw,ti
#41	Non-invasive neurostimulation	'transcranial direct current stimulation'/mj OR 'transcranial magnetic stimulation'/exp/mj OR 'trigeminal nerve stimulation'/mj OR 'vagus nerve stimulation'/mj OR 'alphastim*':ab,kw,ti OR cefaly*:ab,kw,ti OR gammacore*:ab,kw,ti OR (‘non-invasive’ NEAR/2 neurostimulat*):ab,kw,ti OR tms:ab,kw,ti OR 'transcranial direct current stimulat*':ab,kw,ti OR 'transcranial magnetic stimulat*':ab,kw,ti OR 'trigeminal nerve stimulat*':ab,kw,ti OR 'vagal nerve stimulat*':ab,kw,ti OR 'vagus nerve stimulat*':ab,kw,ti OR vns:ab,kw,ti
#42	Other interventions	'cervical plexus block'/exp/mj OR 'nerve block'/exp/mj OR 'neurotomy'/exp/mj OR 'pulsed radiofrequency treatment'/exp/mj OR 'radiofrequency therapy'/exp/mj OR 'sphenopalatine ganglion block'/exp/mj OR 'supraorbital nerve block'/exp/mj OR 'trigger point injection'/exp/mj OR “cervical block*”:ab,kw,ti OR “Cervical Facet Radiofrequency Neurotomy”:ab,kw,ti OR “cervical medial branch neurotomy”:ab,kw,ti OR “Cervical medial branch radiofrequency”:ab,kw,ti OR (nerve NEAR/2 block*) OR “Radio Frequency”:ab,kw,ti OR radiofrequency:ab,kw,ti OR 'sphenopalatine ganglion block*':ab,kw,ti OR ‘supraorbital nerve block*’:ab,kw,ti OR (‘trigger point*’ NEAR/2 injection*)
#43	Meta-analyses and systematic reviews	'meta analysis'/de OR 'systematic review'/de OR 'meta analysis'/exp OR 'meta analysis':ti,ab OR 'meta analytic':ti,ab OR metaanaly*:ti,ab OR 'research synthesis':ti,ab OR 'systematic review':ti,ab OR pooled:ti,ab OR pooling:ti,ab OR search*:ti,ab OR 'critical review':ti OR 'evidence based':ti OR systematic*:ti OR cochrane:jt OR [cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim OR ((systematic* NEAR/2 review*):ab,ti) OR metaanaly*:ab,ti OR 'meta analysis':ab,ti OR 'meta analyses':ab,ti
#44	Randomized controlled trials	'random sample'/de OR ‘randomized controlled trial’/exp OR randomization/de OR random*:ab,ti,kw
#45	Observational studies	(‘case control study’/exp OR 'cohort analysis'/de OR ‘controlled study’/exp OR ‘cross-sectional study’/de OR epidemiology/exp/mj OR ‘follow up’/de OR 'longitudinal study'/de OR ‘observational study’/de OR 'prospective study'/de OR ‘retrospective study’/de OR (‘case control’ OR ‘case series’ OR cohort OR compar* OR ‘controlled study’ OR ‘controlled trial’ OR ‘cross sectional’ OR ‘follow-up’ OR followup OR longitudinal OR ‘matched controls’ OR placebo OR prospective OR retrospective):ti,ab OR (epidemiolog* OR versus OR vs):ti)

Set #	Concept	Strategy
#46	Diagnostic studies	('diagnostic test accuracy study'/de OR 'diagnostic test accuracy'/de OR 'differential diagnosis'/exp OR 'sensitivity and specificity':de OR ('sensitivity AND specficity'):ti OR 'accuracy':de OR 'precision'/exp OR 'prediction and forecasting'/exp OR likelihood:ti OR 'predictive value'/exp OR 'predictive value':ti OR diagnos*:ti OR 'diagnostic accuracy')
#47	Excluded publication types	abstract:nc OR annual:nc OR 'book'/exp OR 'case study'/exp OR conference:nc OR 'conference abstract':it OR 'conference paper'/exp OR 'conference paper':it OR 'conference proceeding':pt OR 'conference review':it OR congress:nc OR 'editorial'/exp OR editorial:it OR 'erratum'/exp OR letter:it OR 'note'/exp OR note:it OR meeting:nc OR sessions:nc OR 'short survey'/exp OR symposium:nc OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR [note]/lim OR [short survey]/lim OR comment:ti OR book:pt
#48	Excluded animal studies	mice:ti OR mouse:ti OR rat:ti OR swine:ti OR pig:ti OR porcine:ti OR dog:ti OR dogs:ti
#49	Excluded age groups	adolescen*:ti OR child:ti OR childhood:ti OR children*:ti OR pediatric*:ti OR paediatric*:ti OR teen*:ti
#50	KQs 1-2, 5-6, 17, 20	#14 AND #27 AND (#43 OR #44)
#51	KQ3	(#14 AND (#31 OR #32)) AND (#43 OR #44 OR #46)
#50	KQs 4, 19	(#11 AND (#33 OR #34)) AND (#43 OR #44 OR #45)
#51	KQ 7	(#14 AND #42) AND (#43 OR #44 OR #45)
#52	KQs 8-10, 12-15, 17	(#14 AND (#35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41)) AND (#43 OR #44 OR #45)
#53	KQ 11	(#2 AND #28) AND (#43 OR #44)
#54	KQ 16	(#14 AND #29) AND (#43 OR #44)
#55	KQ 18	(#14 AND #30) AND (#43 OR #44 OR #45)
#56	All KQs combined with excluded publication types removed	(#50 OR #51 OR #52 OR #53 OR #54 OR #55) NOT (#47 OR #48 OR #49)
#57	Date limit	#56 AND [1-1-2009]/sd NOT [7-3-2019]/sd

Table H-2. PsycINFO in OVID Syntax (for KQ 9 only)

Set #	Concept	Strategy
#1	Headache as major focus	exp *headache/ AND headache*.ti.
#2	Primary headache	(primary adj2 headache*).mp.
#3	Cluster	(cluster adj2 headache*).mp.
#4	Hemicranias continua	(hemicrania* adj2 continua).mp.
#5	Migraine	exp *migraine headache/ OR migraine*.mp. OR migrainosus.mp.
#6	Tension	("essential headache*" or "idiopathic headache*" or ("muscle contraction" adj2 headache*) or (psychogenic adj2 headache*) or "stress headache" or (tension adj2 headache*)).mp.
#7	Secondary headache	(secondary adj2 headache*).mp.
#8	Post-traumatic headache	(("post traumatic" adj2 headache*) or (post-traumatic adj2 headache*)).mp.
#9	Musculoskeletal origin/ cervicogenic headache	((cervicogenic adj2 headache*) OR (musculoskeletal adj2 headache*)).mp.
#10	Medication overuse headache	(("drug induced" adj2 headache*) or ("medication overuse" adj2 headache*) or (rebound adj2 headache*)).mp.
#11	Occipital neuralgia	"occipital neuralgia".mp.
#12	Headache combined	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
#13	Behavioral health interventions	exp *Behavior Therapy/ OR exp *biofeedback/ OR exp *Cognitive Behavior Therapy/ OR exp *mindfulness/ OR (behavior* ADJ2 health).mp. OR (behavior* ADJ2 therap*).mp. OR (behaviour* ADJ2 health).mp. OR (behaviour* ADJ2 therap*).mp. OR biofeedback.mp. OR “bio feed back”.mp. OR "bio-feedback".mp. OR CBT.mp. OR "diaphragmatic breathing".mp. OR MBSR.mp. OR "mindfulness based stress reduction".mp.
#14	Combine headache & interventions	12 and 13
#15	Limit to meta-analyses and systematic reviews	14 and (research synthesis or pooled or systematic review/ or meta analysis/ or meta-analysis/ or ((evidence base$ or methodol$ or systematic or quantitative$ or studies or search$).mp. and (review/ or review.pt. or literature review/)))
#16	Limit to randomized controlled trials	14 and ((Randomized controlled trials or random allocation).de. or random$.ti,ab.)
#17	Systematic reviews & RCTs	15 OR 16
#18	Date limit	limit 17 to yr="2009 - 2019"
#19	Deduplication	remove duplicates from 18

Appendix I: Abbreviation List

Abbreviation	Definition
ACEs	angiotensin-converting enzyme
AEs	adverse events
AHRQ	Agency for Healthcare Research and Quality
ARBs	angiotensin II receptor blockers
CBT	cognitive behavioral therapy
CCBs	calcium channel blockers
CDH	chronic daily headache
CGH	cervicogenic headache
CGRP	calcitonin gene-related peptide
CI	confidence interval
CoQ10	coenzyme Q10
CPGs	clinical practice guidelines
DALYs	disability-adjusted life years
DoD	Department of Defense
EBPWG	Evidence-Based Practice Work Group
ELISA	enzyme-linked immunosorbent assay
ER	emergency room
eTNS	external trigeminal nerve stimulation
FDA	Food and Drug Administration
GI	gastrointestinal
GON	greater occipital nerve
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HIT-6	Headache Impact Test-6
ICHD-3	International Classification of Headache Disorders, 3rd edition
IgG	immunoglobulin G
IV	intravenous
KQ	key question
mg	milligram
MHS	Military Health System
MIDAS	Migraine Disability Assessment
MOH	medication overuse headache
MPFID	Migraine Physical Function Impact Diary
MSQ	Migraine-Specific Quality of Life Questionnaire
mTBI	mild traumatic brain injury
NNH	number needed to harm
NNT	number needed to treat
n-VNS	non-invasive vagus nerve stimulation
OR	odds ratio

Abbreviation	Definition
OTC	over-the-counter
PCC	patient-centered care
PCPs	primary care providers
PICOTS	the population, intervention, comparison, outcome, timing and setting
pRF	pulsed radiofrequency
PTH	post-traumatic headache
QoL	quality of life
RCT	randomized controlled trial
RR	risk ratio
SD	standard deviation
SNOOP(4)E	Systemic, Neurologic, Onset sudden, Onset after 50, Pattern change, precipitated, postural, papilledema, Exertion
SNRI	serotonin-norepinephrine reuptake inhibitor
SOES	supraorbital electrical stimulation
SPG	sphenopalatine ganglion
SQ	subcutaneous
SR	systematic review
SSRI	selective serotonin reuptake inhibitors
TBI	traumatic brain injury
tDCS	transcranial direct current stimulation
TMS	transcranial magnetic stimulation
TTH	tension-type headache
U.S.	United States
UMN	upper motor neuron
USPSTF	U.S. Preventive Services Task Force
VA	Department of Veterans Affairs
YLDs	years lived with disability

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