Management of chronic migraine

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Abstract

Chronic migraine is a neurologic disorder associated with considerable disability, lost productivity, and a profound economic burden worldwide. The past five years have seen a dramatic expansion in new treatments for this often challenging condition, among them calcitonin gene related peptide antagonists and neuromodulatory devices. This review outlines the epidemiology of and diagnostic criteria and risk factors for chronic migraine. It discusses evidence based drug and non-drug treatments, their advantages and disadvantages, and the principles of patient centered care for adults with chronic migraine, with attention to differential diagnosis and comorbidities, clinical reasoning, initiation and monitoring, cost, and availability. It discusses the international guidelines on drug treatment for chronic migraine and evaluates non-drug treatments including behavioral and complementary therapies and lifestyle modifications. Finally, it discusses the management of chronic migraine in special populations, including pediatrics, pregnancy, and older people, and considers future questions and emerging research in the field.

Introduction

Chronic migraine, once called transformed migraine, is a neurologic disorder that causes pain and impaired functioning. Migraine alone is the leading cause of disability worldwide in patients under the age of 50.[1] Chronic migraine is associated with a major global economic burden due to lost productivity from work and healthcare costs. The direct costs of chronic migraine have been found to be at least 4.8 times higher than those of episodic migraine.[2] The actual financial impact of chronic migraine has been difficult to establish, but studies have found that the direct and indirect all cause healthcare costs for patients with chronic migraine range from $8243 to $9380.[2] In Europe, the total cost is estimated to be as high as €95bn ($95bn; £82bn) anually.[3]

The pathophysiology of migraine is complex, with clinical and laboratory evidence suggesting that vulnerability to migraine can be genetic or acquired. Individual migraine attacks may be triggered by a disruption of homeostatic function resulting in a cascade of effects including activation of a neuronal phenomenon known as cortical spreading depression, central and peripheral sensitization, and triggering of the trigeminovascular pathway. This pathway results in release of vasodilatory, pro-inflammatory, or pain producing neuropeptides such as calcitonin gene related peptide (CGRP), a recent target for pharmacotherapy.[4] Chronic migraine is associated with a change in nociception threshold, sensitization, and structural brain changes such as cortical thinning.[5]

Over the past five years, new treatments for patients with this painful condition have emerged. Clinicians therefore need to be aware of the therapeutics for chronic migraine and skilled in counseling patients about them. Equally, clinicians should be able to tackle risk factors that contribute to the development and protraction of chronic migraine. Understanding these variables helps to reduce the morbidity of this treatable condition.

The aims of this review are to discuss the diagnosis and epidemiology of chronic migraine and international guidelines for available preventive treatments, with special focus on recently developed CGRP antagonists and neuromodulatory devices. We will outline principles of personalized management, including tackling comorbidities and lifestyle factors and non-pharmacologic treatments. Management in special populations including pediatrics, pregnancy, and older people will be explored.

A more detailed discussion of the pathophysiology of migraine, treatment of acute migraine attacks in emergency settings, individual rescue medications, treatment of other headache conditions (for example, medication overuse headache), and controversies around patent foramen ovale closure are outside the scope of this review.

Sources and selection criteria

We searched PubMed for English language articles published between 1 January 2012 and 1 March 2022, using the keyword terms in box 1.

We then manually reviewed the results and included only English language published guidelines, randomized controlled trials, systematic reviews, and meta-analyses. We did an additional search of the Cochrane Library in Cochrane Reviews and Trials by using the search term “chronic migraine

Box 1: PubMed search terms

((“chronic”[All Fields] OR “chronical”[All Fields] OR “chronically”[All Fields] OR “chronicities”[All Fields] OR “chronicity”[All Fields] OR “chronicization”[All Fields] OR “chronics”[All Fields]) AND (“migraine”[All Fields] OR “migraine disorders”[MeSH Terms] OR (“migraine”[All Fields] AND “disorders”[All Fields]) OR “migraine disorders”[All Fields] OR “migraine”[All Fields] OR “migraines”[All Fields] OR “migraines”[All Fields] OR “migraineous”[All Fields] OR “migrainers”[All Fields] OR “migrainous”[All Fields]) AND (“therapeutics”[MeSH Terms] OR “therapeutics”[All Fields] OR “treatments”[All Fields] OR “therapy”[MeSH Subheading] OR “therapy”[All Fields] OR “treatment”[All Fields] OR “treatment s”[All Fields])) AND ((clinicaltrial OR guideline OR meta-analysis OR randomized controlled trial OR review OR systematic review) AND (humans)) AND (2012/1/1:2022/3/1[pdat]) AND (english)

treatment” with the following limits: human studies, English, and publication date from January 2012 to March 2022. Finally, we included additional pertinent manuscripts not previously identified through PubMed or Cochrane Reviews on the basis of a review of current guidelines and landmark journal articles, to supplement the initial findings, or where we noted a paucity of data.

We excluded all studies not specifically examining treatment for chronic migraine, small case series, case reports, pilot studies, observational studies, narrative reviews, animal studies, non-randomized or proof of concept studies, duplicative studies or follow-ups of previous studies, and primary studies in which findings were already accounted for in a larger systematic review.

The PubMed search retrieved 1027 papers, but after applying the exclusion criteria through the manual review we reviewed 154 articles. The Cochrane search retrieved 20 articles, but after manual review for relevance we included four articles.

For the pharmacotherapy section specifically, the aim of the paper was to review evidence based guidelines on the treatment of chronic migraine, not to extrapolate treatment of chronic migraine from prevention of episodic migraine. On this basis, we included 10 guidelines.

Epidemiology

Migraine has an estimated global prevalence of 14% on the basis of the 2016 Global Burden of Disease study.[6] Of this burden, chronic migraine composes 2-8% of all migraine,[7 8] with a greater prevalence in women. The actual incidence and prevalence are not fully established, as studies attempting to quantify chronic migraine face several challenges. Firstly, the definition of the disorder and its terminology have varied over time (previously referred to as transformed migraine). Secondly, several chronic daily headache disorders bearing resemblance to chronic migraine, including medication overuse headache, chronic tension-type headache, new daily persistent headache, and hemicrania continua, can be captured in self-reporting, creating a barrier to accurate quantification.[6 7]

Patients might self-report “chronic migraine,” but clinicians need to recognize that chronic migraine has a specific definition that differentiates it from episodic migraine by frequency of headache over time. The International Classification of Headache Disorders, third edition (ICHD-3) sets out the most widely used diagnostic criteria for chronic migraine. It defines chronic migraine as a “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.”[9] Chronic migraine must be distinguished from other headache conditions, including medication overuse headache (fig 1).[9] Between 2.5% and 3% of patients with episodic migraine will progress to chronic migraine in the following year,[7 10] adding to the complexity in capturing an accurate incidence and prevalence. Box 2 includes reversible/treatable risk factors for the conversion from episodic to chronic migraine.[8 11 12]

Other risk factors include female sex, cutaneous allodynia, and social determinants of health such as lower socioeconomic status, lower education levels, and, in societies without universal healthcare, lack of insurance.[13] Notably, up to 70% of patients may revert from chronic to episodic migraine with effective treatment if risk factors for chronic migraine, particularly overuse of analgesics, are corrected.[14]

Diagnosis

Chronic migraine is a clinical diagnosis based on a patient’s history and examination, excluding other causes of headache and identifying comorbid disorders, as treatment success is reliant on an accurate diagnosis.[15] To diagnose migraine, clinicians must elicit the location, quality, and associated symptoms of the headache including nausea, emesis, photophobia, phonophobia, and osmophobia. Additionally, clinicians should ask whether the headache worsens with exertion or, conversely, improves with rest. Migraine might have specific triggers and exacerbating and alleviating factors. All patients should be screened for associated neurologic symptoms including aura, features of increased and decreased intracranial pressure, cervicogenic headache,[16] and thunderclap headache.[17] As migraine semiology and severity may be the most memorable to patients, those days with milder headaches may be underreported by patients. Asking about all headache days is important to ascertain whether patients meet the frequency criteria for chronic migraine.

For most patients, chronic migraine will occur as an evolution from episodic migraine.[7 10] Clinicians should identify the onset, duration, and frequency of the headache, clarifying whether this is an evolution of a previous headache pattern or a new semiology. Medication overuse can also trigger conversion from episodic to chronic migraine,[18] a comorbidity that must be carefully evaluated. Patients should also be screened for lifestyle factors and mood symptoms that contribute to the frequency and severity of migraine, listed in box 3.

Patients should be screened for secondary headache syndromes both on history (assessing for

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characteristics, risk factors, and comorbidities[19]) and physical examination (with attention to associated key findings), as outlined in figure 2. If the patient has concerning features for a secondary headache process on history and/or examination, additional investigations should be pursued, including imaging

	DESCRIPTION	DIAGNOSTIC CRITERIA
Chronic migraine diagnostic criteria	Headache occurring on ≥15 days/month for >3 months, which, on ≥8 days/month, has the features of migraine headache.	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 Migraine without aura and/or criteria B and C for Migraine with aura C. On ≥8 days/months for >3 months, fulfilling any of the following: ■ Criteria C and D for Migraine without aura ■ Criteria B and C for Migraine with aura ■ 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
Migraine without aura diagnostic criteria	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.	A. At least five attacks fulfilling criteria B-D B. Headache attacks lasting 4-72 h (untreated or unsuccessfully treated) C. Headache has at least two of the following four characteristics: ■ Unilateral location ■ Pulsating quality ■ Moderate or severe pain intensity ■ Aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs) D. During headache, at least one of the following: ■ Nausea and/or vomiting ■ Photophobia and phonophobia E. Not better accounted for by another ICHD-3 diagnosis
Migraine with aura diagnostic criteria	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.	A. At least two attacks fulfilling criteria B and C B. One or more of the following fully reversible aura symptoms: ■ Visual ■ Sensory ■ Speech and/or language ■ Motor ■ Brainstem ■ Retinal C. At least three of the following six characteristics: ■ At least one aura symptom spreads gradually over ≥5 minutes ■ Two or more aura symptoms occur in succession ■ Each individual aura symptom lasts 5-60 minutes ■ At least one aura symptom is unilateral ■ At least one aura symptom is positive ■ The aura is accompanied, or followed within 60 minutes, by headache D. Not better accounted for by another ICHD-3 diagnosis
Medication overuse headache diagnostic criteria	Headache occurring on ≥15 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 ≥15 days/month, depending on the medication) for >3 months. It usually, but not invariably, resolves after the overuse is stopped.	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

Fig 1 | International Classification of Headache Disorders, 3rd edition (ICHD-3)[9]

Box 2: Treatable risk factors for chronic migraine[11 12]

- Caffeine intake
- Obesity
- Depression
- Sleep disorders: insomnia, snoring, sleep apnea
- Chronic pain conditions: low back pain, neck pain, arthritis
- Analgesic overuse
- Stressors
- Ineffective acute migraine treatment

as needed,[19] even if a primary headache disorder is also being considered.

The detailed history and examination allow clinicians to differentiate chronic migraine from other primary and secondary headache syndromes and those that may occur simultaneously. Headache due to intracranial hypertension or hypotension must also be considered.[20] Misdiagnosis of migraine, especially as sinus disease,[21] is not uncommon.

Treatment of chronic migraine

The goal of chronic migraine treatment is to reduce the frequency and severity of migraine, improving health related quality of life. Many patients find that abortive medications are more effective as their chronic migraine is treated. Published recommendations suggest starting preventive treatment for migraine on the basis of the total number of headache days and the degree of disability from migraine, criteria by which all patients with chronic migraine qualify.[22]

Migraine treatment should be patient centered, individualized to the patient's specific needs, preferences, and comorbidities. A typical treatment regimen is a balance of non-drug interventions and acute and preventive drug therapy tailored to the patient. When a physician is developing a treatment plan, specific attention should be paid to counseling the patient about expectations of treatment, including duration, expected efficacy, cost, availability of therapies, and potential side effects. Patients of childbearing age should be counseled about reproductive implications (that is, interactions of drugs with contraception and risks of teratogenicity).[23] Some special populations, discussed later, may warrant a balance of treatment more heavily weighted toward non-drug options.

Shared decision making about therapeutic interventions should also cover comorbidities and lifestyle factors that increase the risk of chronic migraine or exacerbate it, outlined below. Clinicians and interdisciplinary care teams may use educational materials to facilitate the discussion and improve adherence.

Box 3: Lifestyle factors and mood symptoms that contribute to migraine frequency/severity

- Sleep patterns: insomnia, obstructive sleep apnea
- Skipping meals and fluids
- Exercise frequency
- Analgesic/medication overuse
- Caffeine use
- Depression screening

Lifestyle counseling and interventions

Lifestyle interventions are a mainstay of migraine counseling. Disruptions of routines can frequently result in migraine attacks. The "SEEDS" mnemonic, which stands for "Sleep, Exercise, Eat, Diary, Stress,"[24] reminds clinicians and patients to pay attention to these key lifestyle triggers. These recommendations are based on observations and evidence that tracking, regulating, and improving dysfunctional sleep, dietary, physical activity, and stress patterns can lessen the burden of migraine. The evidence for lifestyle interventions in chronic migraine is limited, so clinicians extrapolate given that episodic migraine and chronic migraine are likely on a continuum.

A bidirectional association exists between insomnia and migraine, suggesting a possible role for behavioral interventions such as cognitive behavioral therapy to treat both conditions.[25-27] A small systematic review in 2019 (only three studies were retained) examined the use of behavioral sleep interventions to improve headaches (including migraine and tension-type headache).[28] These interventions were found to improve headache frequency and sleep, but conflicting evidence was present regarding influence on severity of headache attacks. Obstructive sleep apnea, a frequent cause of morning headache, has been found to be a trigger rather than a cause of migraine.[25] However, obesity is linked with both obstructive sleep apnea and chronic, severe migraine, so polysomnography is indicated in the investigation of chronic migraine, especially in patients with elevated body mass index.

Identification of specific dietary triggers is popular among patients, but high quality evidence for specific diets for migraine is fairly limited.[29] Alcohol and caffeine have been shown to be the most consistent dietary triggers. Instead of specific elimination diets, clinicians can provide guidance on the importance of adequate hydration and maintaining routine through regular, healthy meals.[24] Obesity is an exacerbating factor for chronic migraine, especially in women. A randomized controlled trial of 110 study participants found behavioral weight loss to be as effective in reducing the burden of migraine as lifestyle education/counseling (although not more so) among overweight female patients with migraine.[30] Participants in the behavioral weight loss group lost more weight after the intervention than did those in the migraine education control group (−3.8 (95% confidence interval −2.5 to −5.0) kg *v* 0.9 (−0.4 to 2.2) kg; P<0.001) and kept the weight off better (−3.2 (−2.0 to -4.5) kg *v* 1.1 (−0.2 to 2.4) kg; P<0.001) at follow-up. No statistically significant differences were seen between the two groups regarding migraine days per month after the intervention (−3.0 (−2.0 to −4.0) *v* −4.0 (−2.9 to −5.0); P=0.19) or at follow-up (−3.8 (−2.7 to −4.8) *v* −4.4 (−3.44 to −5.5); P=0.38).[30] However, a subsequent systematic review

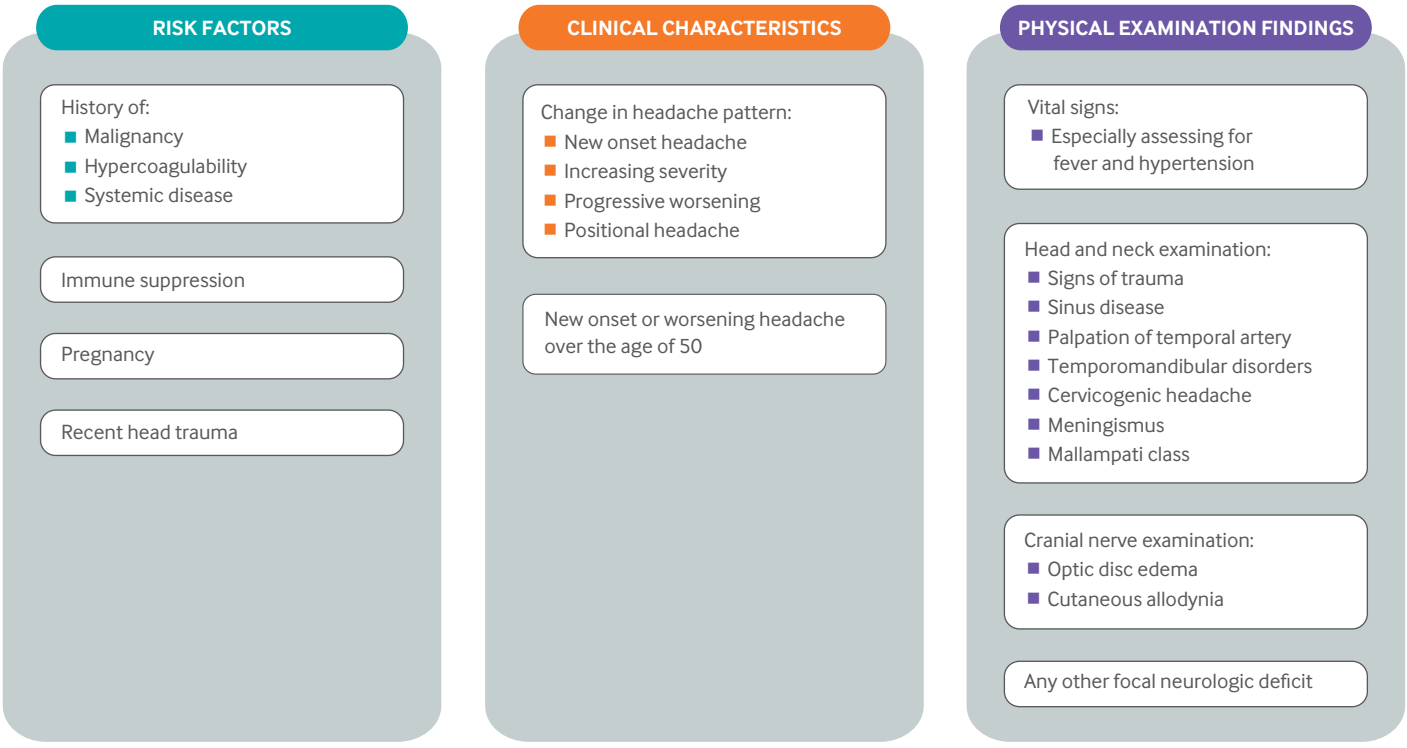

Fig 2 | Secondary headache: risk factors, clinical characteristics, and physical examination findings

with meta-analysis of 10 studies (n=473), which included retrospective, prospective observational, non-randomized, and randomized controlled trials reported in English, with or without a control group, investigating behavioral or surgical interventions for weight loss, showed that intentional weight loss due to either surgical or behavioral interventions could provide a significant improvement in the frequency and severity of migraine attacks, regardless of body mass index.[31 32]

Several small studies including randomized controlled trials in which participants were randomized to treatment as usual versus increasing daily fluid intake by 1.5 L (n=102), and cross sectional, questionnaire based studies (n=256), have shown that improved hydration status was associated with better migraine control (measured by an improvement of 4.5 on the Migraine-Specific Quality of Life questionnaire) and that dehydration can be a provoking factor in migraine severity, frequency and disability ($p<0.001$ for all three measures), as well as a provoking factor for secondary causes of headache.[33-35] Although intravenous fluids have not shown analgesic effects in the treatment of acute migraine in the emergency department, assessment and counseling of volume status may aid in the prevention of migraine.[31]

The relation between exercise and migraine can be complicated; regular exercise has beneficial effects for chronic migraine, but exercise can often trigger migraine attacks.[36] A systematic review with meta-analysis that included 10 articles (randomized controlled trials only; n=508) found beneficial effects of aerobic exercise for reducing the severity (five studies, n=166; standard mean difference (SMD) 1.25, 95% confidence interval 0.47 to 2.04) and frequency (six studies, n=214; SMD 0.76, 0.32 to 1.2) of migraine, as well as potential improvements in health related quality of life (four studies, n=150; SMD 2.7, 1.17 to 4.24), although publication bias was noted in the analysis portion for quality of life measures.[37] Many patients with migraine avoid physical activity for fear that it may provoke a migraine.[38] Clinicians should therefore discuss both exercise and exercise avoidance with patients.

Stress management is a key component to coping with any relapsing medical condition. Because migraine has a strong association with depression and anxiety, clinicians and patients often gravitate toward the incorrect conclusion that one disease "causes" the other.[39] These conditions should be considered comorbidities and treated as such, as treating one condition can often favorably affect the other.[40 41] Patients should be screened for stress and mood disorders and referred appropriately for treatments as needed.

Diagnosing comorbidities of chronic migraine

Migraine is comorbid with several other medical conditions. In addition to the comorbid headache disorders, reviewed in the diagnosis section above, chronic migraine is associated with a higher incidence of depressive disorders, anxiety, post-traumatic stress disorder, back pain, fibromyalgia (and other musculoskeletal pain conditions), hypertension, cardiovascular disease, allergies,

asthma, restless leg syndrome, other sleep disorders, irritable bowel syndrome, epilepsy, skin conditions, and anemia, among others.[42] In some situations, genetic conditions clearly link comorbidities—stroke with migraine, for example, in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Migraine with aura is a risk factor for cardiovascular disease and for stroke, and patients with the condition are advised not to smoke tobacco or use estrogen containing treatments in an effort to mitigate vaso-occlusive risks.[43]

Initiation of drug therapy

Initiation of preventive drug therapy should be evidence based and informed by comorbidities, polypharmacy, cost, availability, and preferences. To facilitate an informed discussion about treatment, the clinician should engage in a risk-benefit discussion with the patient that accounts for drug interactions and teratogenicity. Low doses should be initiated to increase tolerability and adherence.

Cost

The cost and availability of migraine treatment vary considerably across healthcare systems. Drug expenses may be displaced as direct costs to the patient and be quite extensive,[2] depending on health coverage structures. Clinicians should be aware of the financial implications of treatments, including additional expenses incurred by patients such as visits to infusion centers and laboratory tests for monitoring.

Expense and availability have been areas of concern with the advent of the CGRP antagonists, which were the first migraine specific medications developed in several decades. In the US, these drugs were approved starting in 2018 and priced at a similar annual cost to onabotulinumtoxin A, but their use was initially limited by insurance company coverage.[44] Elsewhere in the world, approval and availability were delayed. With time and increasing use, barriers to the use of these drugs are expected to diminish.

When factoring in the cost of treatment, clinicians should carefully weigh the direct cost of the drug and access to its use, as well as the true cost of chronic migraine, including lost productivity, emergency department visits, and disability resulting from the condition.

Clinical monitoring of response to treatment

To establish the efficacy of chronic migraine treatment, patients and clinicians may benefit from the use of objective measures and validated rating scales of migraine frequency, severity, and disability.[45] These may include:

- Headache diary or calendar to assess headache frequency and cyclical patterns; many examples are available online, as well as apps for patients
- Measures of the effect of migraine on functioning:
  - Headache Impact Test (HIT-6)—measures the effect of headache on a patient's ability to function at work/school, home, or socially[11]
  - Migraine Physical Function Impact Diary (MPFID)—measures the effect of symptoms on physical functioning over 24 hours[46]
  - Migraine Disability Assessment (MIDAS)—measures symptoms over three months
- Migraine Treatment Optimization Questionnaire (M-TOQ)—measures the efficacy and tolerability of migraine drug therapies[11 47 48]

Efficacy of treatment should be evaluated on the basis of a reduction in the frequency and severity of headache and the impact on functioning. Use of a headache diary and the addition of one or more of the metrics above can therefore be useful in clinical practice for both patients and clinicians to reduce recall bias.

Evaluation of efficacy and adjustment of treatment

Most migraine prophylaxis drugs require patients to be treated for a minimum of eight weeks before response to treatment can be assessed. Onabotulinumtoxin A, however, can take up to three treatment cycles before patients experience significant reduction in migraine. CGRP antagonist treatments can also take more than one cycle before patients see an improvement in symptoms.[49]

Patients should therefore be re-evaluated every 12 weeks for response to treatment, adverse events, goals of treatment, potential confounding new medications and comorbidities, and cost.[50] Efficacy of treatment should be evaluated on the basis of a reduction in the frequency and severity of headache and the impact on functioning (as noted by lost days at work, school, or other meaningful activities and response to abortive treatments; see Clinical monitoring of response to treatment section above). Drug doses should be titrated as needed and tolerated to the goal dose range. Additionally, some drugs require regular serum monitoring. Clinicians should consider a patient's response to one drug class, as this may predict future response/side effects to other drugs in the same category.[51]

Although avoiding polypharmacy should be a goal of chronic migraine treatment, some patients benefit from combination prophylactic drugs. This can be especially true for patients who have been refractory to monotherapy, and research on the utility of newer combination therapies for refractory migraine is ongoing. Limited data are available on older combination treatments, but class II evidence (moderate quality randomized controlled trials) shows that the addition of long acting propranolol to topiramate is ineffective for patients with chronic migraine.[52] Some polypharmacy will prevent the use of drugs owing to the risks of interactions. Many preventive migraine drugs were designed for other purposes (treatment of anxiety, depression, hypertension, or epilepsy), although dosages effective for migraine tend to be lower than for these conditions.

Discontinuation of treatment

Treatment should be discontinued at any point if a patient has an adverse reaction or if a change in

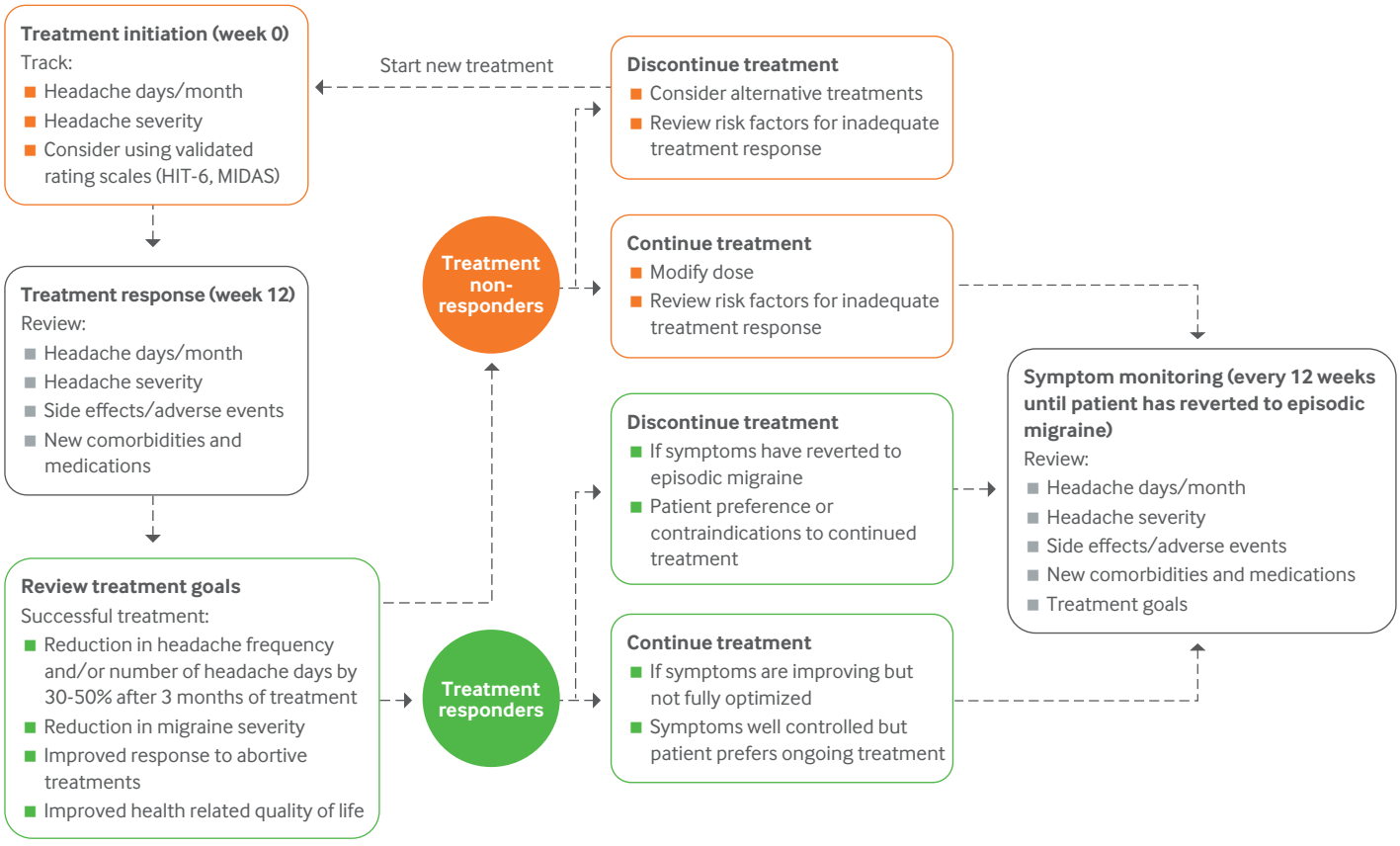

Fig 3 | Treatment initiation and reassessment for chronic migraine. HIT-6=Headache Impact Test; MIDAS=Migraine Disability Assessment

health status occurs that requires treatment goals to be revised (for example, pregnancy, new comorbid condition, or drug with potential interactions). Treatment should also be discontinued, and new options considered, if a patient does not have an adequate response to the current regimen (fig 3). Common reasons for an inadequate response include insufficient drug dosing, inadequate duration of treatment, and untreated comorbidities known to exacerbate migraine.

Successful treatment is generally considered to comprise a reduction in the frequency of headache and/or the number of headache days by 30-50% after three months of treatment. Reduction in migraine severity, improved response to abortive treatments, and improved health related quality of life are other metrics of successful outcomes.[53]

Once a patient has reverted from chronic migraine to episodic migraine for six to 12 months, the prophylactic treatment should be tapered slowly.[23 54] Some drugs require a gradual taper to avoid adverse effects—for example, β blockers can cause tachycardia, hypertension, and even ischemia in patients at risk if discontinued abruptly. Patients should be counseled that episodic migraine can relapse into chronic migraine after discontinuation of treatment and to avoid triggers/risk factors. Monitoring should continue in the following months to assess for recurrence.

Prophylactic treatments

Historically, very few drugs have been specifically studied for the treatment of chronic migraine. Most studies on preventive treatments for migraine were designed for episodic migraine rather than chronic migraine. Those studies specifically for prevention of chronic migraine have significant heterogeneity in study design and clinical endpoints, and many have methodologic limitations resulting in low quality data. This makes interpretation of the efficacy of treatment challenging.[53 55] A discussion of evidence based treatment, reviewing current chronic migraine guidelines, is included in the Guidelines section and summarized in table 1.

Preventive drugs for episodic migraine

Much of the guidance on treatment of chronic migraine is extrapolated from data for prevention of episodic migraine. Many healthcare settings require patients to try treatments for prevention of episodic migraine in a tiered approach before trying a CGRP antagonist or onabotulinumtoxin A. Episodic migraine prevention treatments are often tiered into first, second, and third line therapies and include three main drug categories: antihypertensives, antidepressants, and antiseizure drugs.[53] Reviews of the evidence and guidelines for preventive treatments for episodic migraine have been published widely and inform many of the international guidelines on chronic

Table 1 | Drug treatments for prevention of chronic migraine, based on international guideline recommendations

Drug; category	Dosing, delivery, and frequency	Benefits	Adverse reactions and clinical considerations	Guidelines/consensus statements	Guideline/ consensus recommendation*
Antidepressants					
Amitriptyline; tricyclic antidepressant	10-100 mg PO QHS (initial dosing 10 mg increased by 10 mg weekly to goal dose). Pediatric dosing: 1 mg/kg/d	May help with insomnia and depression	Side effects: may cause QT prolongation, weight gain, constipation, dry mouth, sedation/fatigue. Contraindications: glaucoma, prostatic adenoma; use with caution in patients aged >65 owing to increased risk of adverse side effects	Revised guidelines of the French Headache Society for the diagnosis and management of migraine in adults. Part 2: Pharmacological treatment 2021[53]	Fair
				Practice guideline update summary: Pharmacologic treatment for pediatric migraine prevention: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society 2019[56]	High
				Latin American consensus on guidelines for chronic migraine treatment 2013[57]	Included but noted not to be specifically studied for chronic migraine
Antiseizure drugs					
Topiramate	50-200 mg (initial dosing 25 mg QHS, increased weekly by 25 mg; typical dose range is 50-100 mg; can be administered Qday or BID). Pediatric dosing: 100 mg/d or 2-3 mg/kg/d	May help with weight loss	Side effects: cognitive side effects, paresthesias, may make OCPs less effective, nephrolithiasis, glaucoma, visual changes. Contraindications: should be avoided in patients with nephrolithiasis, glaucoma, depression	Revised guidelines of the French Headache Society for the diagnosis and management of migraine in adults. Part 2: Pharmacological treatment 2021[53]	High
				Practice guideline update summary: Pharmacologic treatment for pediatric migraine prevention: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society 2019[56]	Moderate
				Latin American consensus on guidelines for chronic migraine treatment 2013[57]	Class 1, level A
				VA/DoD Clinical Practice Guideline for the Primary Care Management of Headache 2020[55]	Recommended for episodic migraine only: weak
Valproic acid	500-2000 mg (initial dose 300-500 mg; typical dosing range is 600-1000 mg)	May help with mood stabilization and seizure control	Side effects: weight gain, hair loss, nausea, acne, transaminitis, tremor. Contraindications: pregnancy; known to be teratogenic, should only be used with extreme caution and appropriate counseling and contraception in patients of childbearing age; avoid in patients with hepatic disease	Revised guidelines of the French Headache Society for the diagnosis and management of migraine in adults. Part 2: Pharmacological treatment 2021[53]	Medium
				Latin American consensus on guidelines for chronic migraine treatment 2013[57]	Class 1, level B
Antihypertensives					
Propranolol; β blocker	40-240 mg total daily divided into 2-3 times/ day for short acting formulation or 1-2 times/ day for extended release formulation. Pediatric dosing: 20-40 mg, 3 times/day (short acting formulation)	May help with hypertension, anxiety or tremor	Side effects: bradycardia, fatigue; may worsen depression in susceptible patients. Contraindications: should be avoided in patients with bronchospastic disease, heart failure, bradycardia, or atrioventricular block	Revised guidelines of the French Headache Society for the diagnosis and management of migraine in adults. Part 2: Pharmacological treatment 2021[53]	Fair
				Practice guideline update summary: Pharmacologic treatment for pediatric migraine prevention: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society 2019[56]	Low
				VA/DoD Clinical Practice Guideline for the Primary Care Management of Headache[55]	Weak: migraine prevention, not chronic migraine specifically
Atenolol; β blocker	50-200 mg (100 mg) QAM	May help with tachycardia, hypertension, and some arrhythmias	Side effects: bradycardia hypotension; use with caution in patients with diabetes mellitus and heart failure. Contraindications: should be avoided in patients with bronchospastic disease, bradycardia, hypotension, orpheochromocytoma	Revised guidelines of the French Headache Society for the diagnosis and management of migraine in adults. Part 2: Pharmacological treatment 2021[53]	Fair

(*Continued*)

Table 1 | Continued

Drug; category	Dosing, delivery, and frequency	Benefits	Adverse reactions and clinical considerations	Guidelines/consensus statements	Guideline/ consensus recommendation*
Antidepressants					
Candesartan; angiotensin II receptor blocker	8-16 mg QAM or BID	May help with hypertension or for patients who warrant treatment with angiotensin-converting enzyme inhibitor but cannot tolerate this class	Side effects: hypotension, renal impairment. Contraindications: should be avoided in patients with pregnancy, heart failure, renal artery stenosis, or angioedema	Revised guidelines of the French Headache Society for the diagnosis and management of migraine in adults. Part 2: Pharmacological treatment 2021[53]	Fair
				VA/DoD Clinical Practice Guideline for the Primary Care Management of Headache 2020[55]	Strong
Telmisartan; angiotensin II receptor blocker	80 mg Qday (initial dosing 20-40 mg Qday)	May help with hypertension or for patients who warrant treatment with angiotensin-converting enzyme inhibitor but cannot tolerate this class	Side effects: chest pain, claudication. Contraindications: should be avoided in patients with pregnancy, renal artery stenosis, or angioedema	VA/DoD Clinical Practice Guideline for the Primary Care Management of Headache 2020[55]	Strong
Flunarizine; calcium channel blocker (not available in US)	5-10 mg QHS (initial 5 mg; stop after 6 months owing to risk of central nervous system side effects)	-	Side effects: somnolence, weight gain, depression, parkinsonism; use with caution in patients with depression or obesity. Contraindications: Parkinson's disease, parkinsonism, pregnancy	Revised guidelines of the French Headache Society for the diagnosis and management of migraine in adults. Part 2: Pharmacological treatment 2021[53]	Fair
Injectable therapies					
Onabotulinumtoxin A	31 injections (155 units total); every 12 weeks; may be increased to 39 injections and 195 units)	No systemic drug interactions or side effects	Side effects: injection site reactions, facial weakness, most commonly ptosis, increased neck pain, worsening headache. Contraindications: pregnancy, myasthenia gravis, amyotrophic lateral sclerosis	Revised guidelines of the French Headache Society for the diagnosis and management of migraine in adults. Part 2: Pharmacological treatment 2021[53]	High
				The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice 2021[22]	Probably effective
				Latin American consensus on guidelines for chronic migraine treatment 2013[57]	Class 1, level A
				Guideline on the use of onabotulinumtoxin A in chronic migraine: a consensus statement from the European Headache Federation 2018[58]	Expert panel
				VA/DoD Clinical Practice Guideline for the Primary Care Management of Headache 2020[55]	Weak
Calcitonin gene related peptide antagonists					
Erenumab	70 mg or 140 mg, subcutaneous, monthly	-	Side effects: injection site reaction, constipation, immunologic antibody development, hypertension; use with caution in patients with hypertension. Contraindications: pregnancy and lactation, uncontrolled CVD	Revised guidelines of the French Headache Society for the diagnosis and management of migraine in adults. Part 2: Pharmacological treatment 2021[53]	High
				European headache federation guideline on the use of monoclonal antibodies acting on the calcitonin gene related peptide or its receptor for migraine prevention 2019[59]	Medium
				VA/DoD Clinical Practice Guideline for the Primary Care Management of Headache 2020[55]	Weak
Fremanezumab	225 mg monthly or 675 mg quarterly, subcutaneous	-	Side effects: injection site reaction; immunologic antibody development. Not studied in patients with CVD. Contraindications: pregnancy and lactation, uncontrolled CVD	Revised guidelines of the French Headache Society for the diagnosis and management of migraine in adults. Part 2: Pharmacological treatment 2021[53]	High
				European headache federation guideline on the use of monoclonal antibodies acting on the calcitonin gene related peptide or its receptor for migraine prevention 2019[59]	Medium; increased to high when dose was raised to 675 mg loading dose + 225 mg monthly
				VA/DoD Clinical Practice Guideline for the Primary Care Management of Headache 2020[55]	Weak

(*Continued*)

Table 1 | Continued

Drug; category	Dosing, delivery, and frequency	Benefits	Adverse reactions and clinical considerations	Guidelines/consensus statements	Guideline/consensus recommendation*
Antidepressants					
Galcanezumab	Subcutaneous, 120 mg (240 loading dose), monthly	-	Side effects: injection site reaction, immunologic antibody development. Not studied in patients with recent or active CVD, PVD, or stroke. Contraindications: pregnancy and lactation	Revised guidelines of the French Headache Society for the diagnosis and management of migraine in adults. Part 2: Pharmacological treatment 2021[53]	High
				European headache federation guideline on the use of monoclonal antibodies acting on the calcitonin gene related peptide or its receptor for migraine prevention 2019[59]	Medium
				VA/DoD Clinical Practice Guideline for the Primary Care Management of Headache 2020[55]	Weak
Eptinezumab	Intravenous, 100 mg or 300 mg, quarterly	-	Side effects: nausea, immunologic antibody development; hypersensitivity reactions including anaphylaxis and angioedema are rare. Contraindications: pregnancy and lactation	Revised guidelines of the French Headache Society for the diagnosis and management of migraine in adults. Part 2: Pharmacological treatment 2021[53]	High

BID=twice daily; CVD=cardiovascular disease; PO=oral; PVD=peripheral vascular disease; OCP=oral contraceptive pill; QAM=once daily in the morning; Qday=once daily; QHS=once daily at bedtime; VA/DoD=Department of Veterans Affairs/Department of Defense.
*Guideline/consensus recommendation included in table are directly shared from international guidelines on chronic migraine specifically and do not reflect authors' interpretation. Heterogeneity of terms reflects variation between international guidelines in use of criteria and language.

migraine included below.[51 53 55 60-62] Antidepressants are often used for migraine prophylaxis, despite scant evidence for their efficacy in chronic migraine. A Cochrane review from 2015 reviewed the evidence for selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors compared with placebo or amitriptyline in chronic migraine.[63] This review noted that the studies were of poor quality, with incomplete data and design flaws, and found low or very low quality evidence for the efficacy or safety of these drugs.

Onabotulinumtoxin A

Chemodenervation with onabotulinumtoxin A has been shown to be effective for the treatment of chronic migraine.[60] A 2018 Cochrane review of botulinum toxins for the prevention of migraine included patients with chronic migraine.[61] This review found that, in the chronic migraine population, botulinum toxin reduced the number of headache days per month by 1.9 (95% confidence interval −2.7 to −1.0) days (two trials; 1384 participants; high quality evidence).[61]

This treatment requires injection in 31 standardized sites across the head and neck (155 units total) every 12 weeks, with an optional additional 40 units of injections in other pain sites in the "follow the pain" protocol. Patients should be assessed for efficacy after the third injection cycle, as some patients do not respond to the first or second cycle. Allodynia is considered predictive of a good response to treatment.[51] If patients experience a benefit, injections should be continued every 12 weeks until the patient reverts to episodic migraine.

Calcitonin gene related peptide antagonists

The neuropeptide CGRP is thought to be instrumental in the pathophysiology of migraine.[64] In recent years, several anti-CGRP monoclonal antibodies and CGRP receptor antagonists have been developed for prophylaxis of chronic migraine. Key differences between anti-CGRP monoclonal antibodies and CGRP receptor antagonists include the target, molecule size, half life, and drug delivery.

Anti-CGRP monoclonal antibodies are large molecules, delivered subcutaneously or intravenously, that target either the CGRP ligand (fremanezumab, galcanezumab, eptinezumab) or receptor (erenumab).[48] They have a prolonged half life of weeks and are not believed to cross the blood-brain barrier. By contrast, CGRP receptor antagonists are small molecules with short half lives in the order of minutes to hours, administered orally. At the time of writing, only one CGRP receptor antagonist, rimegepant, has been approved for prevention of migraine,[65] although two others are approved for episodic migraine. Further study is needed to assess the efficacy of CGRP receptor antagonists for chronic migraine.

When choosing which treatment to start, clinicians should note that both galcanezumab and erenumab have been shown to have a rapid onset of efficacy in some patients.[66 67] The CONQUER trial of

galcanezumab (120 mg/month, 240 mg loading dose) was a randomized, double blind, placebo controlled, phase 3b study involving 232 patients with episodic or chronic migraine who had not responded to two to four categories of preventive drugs in the previous decade. For patients with chronic migraine, this study showed a reduction in monthly migraine headache days compared with placebo (−3.7, −5.2 to −2.2; P<0.001); 54% of patients with chronic migraine who were treated with galcanezumab had a 30% reduction in monthly migraine headache days compared with placebo (odds ratio 3.8, 2.2 to 6.3; P<0.001). Notably, patients who had previously not responded to migraine prophylaxis treatments still had a reduction in monthly migraine days when treated with galcanezumab: two previous treatment failures −2.0 (−2.9 to −1.0; P<0.001); three previous treatment failures −4.1 (−5.8 to −2.4; P<0.001); and four previous treatment failures −6.1 (−9.5 to −2.8; P<0.001).[66] A randomized, double blind, placebo controlled trial of erenumab in adult patients with chronic migraine (n=667) showed that the adjusted odds ratio of achieving a ≥50% reduction from baseline in migraine days per week compared with placebo at week 1 was 1.8 (1.1 to 2.8; P=0.011) for the 70 mg dose and 1.9 (1.2 to 2.9; P=0.009) for the 140 mg dose. By week 4, the odds ratios were 2.2 (1.5 to 3.3; P<0.001) for 70 mg and 2.4 (1.6 to 3.5; P<0.001) for 140 mg.[67]

CGRP antagonists may also improve treatment outcomes when used in combination with onabotulinumtoxin A. A small case series of 17 patients with chronic migraine who had all been previously treated with onabotulinumtoxin A without full response were treated with dual therapy with fremanezumab (n=9), erenumab (n=4), or galcanezumab (n=4). All groups experienced an improvement in the number of headache-free days (P=0.007), with the greatest improvement seen in the fremanezumab group (mean improvement of 12.6 headache-free days). The erenumab group experienced a mean improvement in headache-free days of 6.4, and the smallest improvement was seen in the galcanezumab group (3.8 headache-free days).[68 69] Most CGRP antagonists have not been studied in patients with cardiovascular disease and should therefore be used with caution in patients with these comorbidities. They should not be used in pregnant or lactating patients. Cost and access remain barriers to use.

Long term monitoring of the safety and efficacy of CGRP treatment for chronic migraine, duration of treatment, and use in special populations are critical. Additional studies will need to assess whether any predictors or biomarkers exist that allow clinicians to identify which patients may benefit or be so-called super-responders and should therefore be referred for early intervention.

Interventions

Occipital nerve blocks are sometimes used as additional treatment for chronic migraine. They were previously reserved for the treatment of occipital neuralgia, identified by exquisite tenderness to palpation over the occipital nerve, but some data suggest a benefit in chronic migraine even when this finding is not present. Several open label, non-randomized studies have shown efficacy of occipital nerve block in reducing the frequency and severity of migraine, but only four small randomized controlled trials of the procedure have been conducted in chronic migraine, with mixed techniques, data, and outcome measures.[70-73] Local injections with either lidocaine or bupivacaine (different amounts in each study) have shown improvements in outcomes in chronic migraine, as measured between one week and three months on a visual analog scale, without serious adverse events.[70 71 74-76] The efficacy of occipital nerve blocks with standardized techniques or the addition of corticosteroid requires further study. Some patients might also benefit from supra-orbital, auriculotemporal, and maxillary nerve blocks, but data are insufficient to inform recommendations for treatment of chronic migraine.[70 77 78]

Non-drug treatments

Behavioral interventions

Biobehavioral treatment strategies are commonly recommended for migraine in spite of several recent systematic reviews showing low level or insufficient evidence and small sample or effect sizes.[79-82] Challenges with study design and control groups also make interpretation more difficult. Several primary studies as well as systematic reviews have examined behavioral interventions for more general chronic pain, including migraine. An earlier systematic review (2016), including 25 randomized controlled trials in a total of 1285 patients with chronic pain, with subsequent meta-analysis, found moderate improvements in pain and depressive symptoms associated with behavioral interventions such as acceptance and commitment therapy, mindfulness based cognitive therapy, and mindfulness based stress reduction. These interventions were compared with wait list, treatment as usual, education, and support group controls and were found to have a small but statistically significant (P<0.05) effect on pooled standardized mean difference for pain intensity (SMD 0.24, 0.06 to 0.42), depression (0.43, 0.01 to 0.79), and disability (0.40, −0.05 to 0.93); a moderate but statistically significant (P<0.05) effect was found for anxiety (SMD 0.51, 0.10 to 0.92) and pain interference (0.62, 0.21 to 1.03).[83] Additionally, a Cochrane review (systematic review) of 75 randomized controlled trials (9401 participants) examining chronic pain excluding headache found low to moderate evidence for efficacy for cognitive behavioral therapy in the treatment of chronic pain, with low quality evidence for other behavioral therapy and acceptance and commitment therapy resulting in inconclusive recommendations.[84] As mindfulness based interventions gain traction, a growing body of evidence exists for the treatment of chronic migraine since these systematic reviews were

published, including at least one additional positive phase 2b randomized controlled trial of mindfulness based cognitive therapy for episodic and chronic migraine at the time of publication of this review.[85]

Biofeedback was previously shown to be beneficial in the treatment of migraine. It was therefore recommended in 2000 by the US Headache Consortium, although recent evidence about biofeedback modalities is quite limited.[86 87]

Acupuncture has undergone scrutiny over the years owing in part to the challenges inherent to designing an appropriate control or "sham treatment" arm. Many people have criticized the practice as having a placebo effect, despite its use in symptom management for centuries. Recently, a Cochrane review from two decades ago was updated to account for recent robust studies evaluating the therapeutic benefits of acupuncture in the prevention of chronic migraine.[84] Reviewers compared acupuncture in chronic migraine with preventive drug therapies, no therapies, and sham acupuncture. Among the 22 trials identified (>4000 participants), the results showed favorable treatment of migraine with fewer side effects than drug interventions. However, no clear difference in outcome between acupuncture and "sham" acupuncture was apparent, perhaps related to the selection of therapeutic targets.

Over the years, small studies have attempted to characterize the role of noninvasive, physical interventions such as yoga, relaxation, and mindfulness in the treatment of several health conditions, including migraine.[88 89] A systematic review (12 randomized controlled trials and 681 patients) of craniosacral therapy for chronic pain (including migraine) found strong and statistically significant evidence for efficacy, both immediately post-treatment and at six months after treatment, compared with manual and non-manual sham treatment, with reduction in pain intensity post-treatment (SMD −0.63, −0.90 to −0.37) and disability (−0.54, −0.81 to −0.28); findings held up at six months after treatment (pain intensity SMD −0.59, −0.99 to −0.19; disability SMD −0.53, −0.87 to −0.19) compared with sham treatment. Safety data were underreported in the randomized controlled trials, although no serious adverse events occurred.[90]

Although a previous systematic review found that many such physical treatments, including physical therapy, were not harmful in the treatment of chronic headache conditions including migraine, the strength of evidence was very low for all interventions, and the review itself needs to be updated.[91] Further study is needed to inform and update guidelines. However, potential benefits of some noninvasive interventions may outweigh risks in chronic migraine.

Neuromodulatory (neurostimulation) devices

Neuromodulation, or neurostimulation, with either electrical or magnetic stimulation, has gained in popularity in the treatment of migraine over the past decade. Most devices are noninvasive; invasive methods such as the surgically implanted occipital nerve stimulator have mixed data and elevated risks of complications.[92-94] Noninvasive neuromodulation devices include transcutaneous supraorbital nerve stimulation (also known as external trigeminal nerve stimulation, or eTNS), noninvasive vagal nerve stimulation (nVNS), single pulse transcranial magnetic stimulation (sTMS), and distal transcutaneous electrical stimulation (distal TENS).

These handheld neuromodulation devices are approved for home use and can be used acutely or preventively for migraine treatment, although they seem to be more effective when used acutely.[95] The mechanism of action of these devices varies and is often theoretical: stimulation of a peripheral or cranial nerve is meant to provide feedback to the central nervous system, which modulates the brain's response to pain. One exception is sTMS, which stimulates the brain directly. Accurate evaluation of devices is limited in clinical trials owing to study participants' ability to feel the electrical or magnetic impulses in treatment arms. Consequently, caution is needed when drawing conclusions about neuromodulation devices, which might show seemingly large effect sizes or benefits in acute use that do not always translate to prevention of chronic migraine. For example, an open label study testing eTNS yielded a mean reduction of four days a month with moderate to severe headaches among 43 study participants (P=0.016), and an open label study of nVNS among 50 participants with chronic migraine or high frequency episodic migraine yielded a reduction in pain of at least 50% on a visual analog scale (56.3% at one hour and 64.6% at two hours). In fact, at two hours, 22.9% of participants were pain-free. However, when compared against sham treatment in a multicenter, double blinded, sham controlled study of 59 participants, nVNS, although well tolerated, conferred no reduction in the number of headache days versus sham.[96 97]

Two recent systematic reviews have shown eTNS to have a favorable although modest treatment effect in prevention of chronic migraine—a difference of one to three fewer headache days per month, as well as mild reduction in pain severity on a visual analog scale when used acutely.[95 98] Whereas one review included randomized controlled trials, prospective case controlled trials and single arm interventional trials,[98] the other included only randomized controlled trials in which eTNS was compared against sham stimulation.[95] Four studies were included, with 161 migraine patients in the treatment group and 115 in the sham group. A statistically significant reduction of headache days (SMD −0.48 (−0.73 to −0.23); P<0.001) was noted, as well as a reduction in the need for analgesic drugs (SMD −0.78 (-1.14 to −0.42); P<0.001) in the eTNS group versus sham.

A systematic review including 983 patients from six clinical trials found that nVNS showed efficacy versus sham treatment in acute migraine attacks (pain relief status at 60 minutes: odds ratio 1.93, 1.2 to 3.1; P=0.006) and cluster headache but not in

the prevention of migraine, no significant difference was seen in headache days between nVNS and sham stimulation (SMD −0.16, −0.36 to 0.04; P=0.117).[99] A small systematic review of five randomized controlled trials, including 313 patients, showed efficacy of sTMS for acute migraine attacks, although just one study contributed the observation that patients with migraine with aura may be pain-free at two hours (odds ratio 2.28, 1.15 to 4.52; P=0.02) after sTMS; no statistically significant benefit for prevention of chronic migraine was seen (odds ratio 2.93, 0.71 to 12.15; P=0.14), and heterogeneity among treatment regimens was noted.[100] The distal TENS device—worn on the upper arm at the onset of a migraine attack—is the newest device, approved in October 2020 for use in the treatment of acute migraine attacks in episodic but not chronic migraine.[101] Neuromodulation is gaining traction, but the cost and availability of these devices are barriers to widespread use, and data are so far limited in chronic migraine management.

Other complementary therapies

Patients commonly ask clinicians about other complementary therapies in the treatment of chronic migraine. Daith is an ear piercing at the crux of the helix of the ear, its popularity bolstered by advocacy groups and case reports postulating a vagally mediated treatment mechanism. However, no evidence exists that daith piercing improves migraine frequency or severity.[102 103]

Magnesium, riboflavin, CoEnzyme Q10, and feverfew have shown efficacy in prevention of migraine in clinical trials and in small systematic reviews, but up-to-date guidelines are still pending.[104-106] Recent small studies have examined the role of non-traditional nutraceuticals, such as probiotics, in reducing the burden of migraine, perhaps through anti-inflammatory effects.[107] Butterbur,[108] another herbal supplement, is no longer recommended for prevention of chronic migraine owing to reported cases of liver toxicity. Several narrative literature reviews have outlined current use of nutraceuticals in chronic migraine.[22 108]

Emerging treatments

Anti-CGRP monoclonal antibodies, CGRP receptor antagonists, and neurostimulation devices are all areas of ongoing active research for chronic migraine (https://clinicaltrials.gov/). Atogepant is being studied for the prevention of chronic migraine (NCT04437433) and for its potential synergistic effects in combination onabotulinumtoxin A for chronic migraine in adults (NCT05216263). Several ongoing active studies are examining the use of CGRP antagonism in children and adolescents. Galcanezumab (NCT04616326), fremanezumab (NCT04464707), erenumab (NCT03832998), and eptinezumab (NCT04965675) are being studied for efficacy, safety, and tolerability in chronic migraine in adolescents aged 12-17 years. Similarly, erenumab (NCT03832998), fremanezumab (NCT04464707), and eptinezumab (NCT05164172) are all being studied for efficacy, safety, and tolerability in chronic migraine in children aged 6-12. Biomarkers and genetic predictors for response to treatment for CGRP antagonism are also an area of active research (NCT04503083). For treatment of refractory chronic migraine, sphenopalatine ganglion nerve block techniques (NCT03337620) are being researched. These studies are actively enrolling and are expected to come to completion in the next two to four years.

Special populations

Pediatric, pregnant, and older populations can all develop chronic migraine. Very little is known about the management of this disorder in these cohorts. Drug therapies may be contraindicated, as outlined below. Behavioral and physical therapies may therefore be preferable, but access, transportation, and cost can pose barriers to care.

Chronic migraine in children

Migraine occurs in children and adolescents with a prevalence of 1-3% in younger children aged 3-7 years, 4-11% in those aged 7-11 years, and 8-23% in those aged 11-15 years.[56] The incidence of chronic migraine in these populations is not well characterized. Because drugs may work differently in younger patients, and because not all drugs are approved for use in this population, this cohort warrants special focus.[109]

Guidelines published by the American Academy of Neurology (AAN) in 2019 reviewed drug therapy for preventive treatment of migraine in children and adolescents. To formulate these clinical guidelines, databases were searched from January 2003, extended through August 2017. Fifteen class I-III studies on migraine prevention in children and adolescence met inclusion criteria (participants were aged 0-18 years of age and diagnosed as having migraine; treatment was compared with placebo). Standard classification of evidence was applied, with class 1 evidence defined as high quality randomized controlled clinical trials in which the objective outcome assessments were performed in a representative population, with the following conclusions. Propranolol was found to be possibly effective in reducing migraine frequency by 50% compared with placebo (risk ratio 5.2, 1.59 to 17.00; low confidence but large effect size, based on single class III study). Topiramate and cinnarizine (not available in the US or Canada) were possibly associated with reduced frequency of headache compared with placebo (topiramate reduced headache days by 50% on the basis of on four class I studies (SMD 0.391, 0.127 to 0.655); no definite reduction in migraine associated disability (low confidence based on imprecision in spite of two class I studies; SMD 0.538, −0.097 to 1.174). Amitriptyline alone showed insufficient efficacy versus placebo, but the combination of amitriptyline plus cognitive behavioral therapy was more effective than amitriptyline plus education about headache in reducing the frequency headache in children (high

confidence in evidence, based on one class I study; SMD 0.48, 0.14 to 0.82). All three recommendations represented level B evidence.[56] Insufficient evidence was available to allow determination of whether divalproex, onabotulinumtoxin A, or amitriptyline alone have a benefit to children and adolescents without concurrent behavioral therapy, nimodipine, or flunarizine. Two further studies examining the use of onabotulinumtoxin A, published after the publication of these guidelines, suggested that treatment was well tolerated, with one additional study suggesting efficacy.[110 111]

The guidelines also supported screening for mental health disorders including anxiety and depression, considering contraception and childbearing potential, and lifestyle interventions. The safety and efficacy of newer drugs, as well as neuromodulation and nutraceuticals, in children and adolescents is largely unknown and varies by individual treatment. Table 1 includes data from these guidelines and for treatment of chronic migraine specifically.

Chronic migraine in pregnancy

Pregnant patients are another special population for whom treatment options are limited due to teratogenic effects. Migraine is known to be a strongly hormonally mediated disorder, and about 50-75% of pregnant patients with migraine find that their migraine attacks improve during pregnancy.[112] However, this is not the case for all patients, and migraine, among other primary headache disorders, affects 10-17% of pregnancies. Data are lacking on the management of chronic migraine in pregnancy specifically.

A recent systematic review of management of migraine during pregnancy identified 16 studies of 14 185 patients and 26 systematic reviews providing additional indirect evidence on drug therapy in pregnancy.[113] Results included the following: preventive therapy with calcium channel blockers and with antihistamines may not be associated with adverse fetal or child outcomes; acute therapy with a combination of metoclopramide and diphenhydramine was found to possibly be more effective than codeine; and triptans and low dose aspirin may not be associated with adverse effects in the fetus/child. Adverse child and fetal outcomes were identified among groups of pregnant patients taking antiepileptics, venlafaxine, tricyclic antidepressants, benzodiazepines, β blockers, prednisolone, and oral magnesium, although these findings were identified in systematic reviews in which the drugs were studied for indications other than migraine and often at higher doses.

Promising treatment modalities in pregnancy, such as occipital nerve block[114] and behavioral and physical therapies, did not meet inclusion criteria for systematic review on the basis of study design but are nevertheless worthy of further exploration given their favorable safety profile. Neuromodulation devices are not always specifically tested in pregnancy when approval by regulatory agencies is sought, so clinicians should exercise caution before recommending device use.

Although no cases of harm have been reported, anti-CGRP monoclonal antibodies are generally avoided in pregnancy. These are systemic drugs with very long half lives, so they should be stopped months in advance of a planned pregnancy. Onabotulinumtoxin A is not thought to travel systemically, but its manufacturer recommends against its use in pregnancy, despite some published favorable safety reports.[115] Drug therapy should be evaluated in pregnancy and lactation on a case-by-case basis, with pregnancy and lactation databases serving as guides.

Chronic migraine in older people

Little is known about chronic migraine in older people. Migraine is often considered a disorder of younger people, and any new onset headache in people over the age of 50 warrants further investigation to exclude secondary causes. Many female patients find that migraine improves after menopause. This is not always the case, and chronic migraine in older people seems to be more common in women.[116]

With ageing, special attention should be given to medical comorbidities, changes in absorption, drug-drug interactions, and consequences of polypharmacy on cognition and risk of falls.[117] Evidence for drug and non-drug therapies in elderly patients is scarce, as is that for associations with diseases more prevalent in older populations (for example, cardiovascular disease, stroke, hypertension, and vestibulopathy).

Guidelines

The mainstay of chronic migraine treatment is prevention. Treatment of acute migraine attacks is essential and is the same for chronic migraine and episodic migraine. Many guidelines on abortive treatments for episodic migraine have been published (including the use of non-steroidal anti-inflammatory drugs, triptans, ergotamines, CGRP receptor antagonists, and lasmitidan),[22 118 119] but discussion of this topic exceeds the scope of this review. Patients must be counseled on avoidance of overuse of drugs.

Guidelines on preventive treatment for chronic migraine are challenged by the fact that most prophylactic agents have been studied for episodic migraine and not chronic migraine. Clinicians must therefore extrapolate responses to treatment without evidence. The Canadian Headache Society articulated this challenge well in its 2012 Guideline for Migraine Prophylaxis: "Although it is likely that physicians may extrapolate from the evidence presented here and use it for the care of patients with higher migraine frequencies, the literature reviewed for these guidelines did not include patients with chronic migraine (headache on >14 days a month)."[62] The International Headache Society attempted to correct this deficiency in 2018

by publishing guidelines outlining best practices for study design and outcome measures for controlled trials of preventive treatment of chronic migraine in adults.[120]

Another limitation is that many international chronic migraine guidelines were published before the advent of the first approved CGRP antagonists in 2018. Two examples include the 2012 American Headache Society (AHS)/AAN guidelines for prevention of episodic migraine and the 2012 Canadian Headache Society Guideline for migraine prophylaxis.[56 119]

Table 1 summarizes treatment recommendations from international guidelines and consensus statements on chronic migraine treatment, including current dosing and adverse reactions. Some notable differences among international recommendations exist. Topiramate was included in most guidelines as a recommended treatment of chronic migraine,[57] although the Department of Veterans Affairs/Department of Defense (VA/DoD) Clinical Practice Guideline for the Primary Care Management of Headache did not recommend it for this, recommending it only for episodic migraine with weak evidence.[55] Recommendations on the use of atenolol, telmisartan, and flunarizine also vary, although the latter may be due to differences in availability in different countries. The 2021 AHS consensus statement recommended a minimum of eight weeks of oral treatments before assessing efficacy and that patients with a partial response may have further improvement with continued treatment over the following six to 12 months.[22]

Multiple international guidelines support the use of chemodenervation with onabotulinumtoxin A for the treatment of chronic migraine.[60] Costs vary across healthcare settings and countries and influence recommendations for high value care. For example, the 2013 Latin American consensus guideline for chronic migraine treatment recommended onabotulinumtoxin A as a first line prophylactic treatment, instead of a second tier option for patients resistant to oral drugs.[57] By contrast, the European Headache Federation (EHF) recommended that patients first try two or three other migraine prophylactics before starting onabotulinumtoxin A as a cost effective practice.[58] No consensus exists on the duration of treatment with onabotulinumtoxin A, but the EHF recommends that treatment should be stopped once a patient has achieved a reduction of headaches to less than 10 headache days per month for three months. The patient should be re-evaluated four to five months after onabotulinumtoxin A is discontinued to assess for relapse.[58]

Notably, rimegepant was too new to be included in any of the published recommendations. The AHS published a consensus statement in 2021 with recommendations on how to integrate CGRP antagonists into clinical practice.[22] This statement does not focus specifically on evidence for chronic migraine but does offer a recommendation that injectable CGRP antagonists should be started when a patient has a diagnosis of chronic migraine and has either had an inadequate response to or inability to tolerate an eight week trial of two of topiramate, valproic acid, β blockers (metoprolol, propranolol, timolol, atenolol, nadolol), tricyclic antidepressant (amitriptyline, nortriptyline), serotonin-norepinephrine reuptake inhibitors (venlafaxine, duloxetine), or other level A or B treatments based on the AAN classification of evidence or an inadequate response to or inability to tolerate a minimum of two treatment cycles of onabotulinumtoxin A

These recommendations are very similar to the EHF's 2019 guideline on the use of monoclonal antibodies acting on the calcitonin gene related peptide or its receptor for migraine prevention.[107] This guideline recommends the use of erenumab, fremanezumab, or galcanezumab in patients with chronic migraine who have not responded to at least two medical treatments or who have adverse side effects or comorbidities that prevent their use. The AHS recommendation for the assessment of efficacy of CGRP treatment is evaluation at three months for monthly treatments or at six months for injections at three month intervals.[22]

One challenge, especially in tertiary headache centers, is the treatment of patients with refractory chronic migraine. The EHF consensus statement identified that, in these cases, attention should be given to the reasons for treatment failure, including side effects, lack of adherence, genetic predispositions, timing of therapy, untreated comorbidities, and other contributing factors.[121] For these patients, exploring non-drug therapies in greater depth may also be indicated. Growing evidence suggests that some patients with refractory chronic migraine will have better outcomes with CGRP antagonist treatment. Newer guidelines therefore recommend that CGRP antagonists should be trialed after a patient has had an inadequate response to two prophylaxis treatments for at least eight months.[53]

In spite of an older body of evidence, cognitive behavioral therapy, biofeedback, behavioral therapies, and relaxation treatments are still listed in guidelines as having "grade A" evidence and are therefore recommended through the AHS consensus statement (2021).[22] Complementary and alternative therapies were previously reviewed in 2012 by the AAN, AHS, and Canadian Society, resulting in published guidelines for the management of migraine headaches; however, these guidelines were not designed for chronic migraine specifically and have not been updated recently, and in some cases outdated information has been retracted.[62 122] Most other non-drug therapies have not been outlined in recent international chronic migraine guidelines.

Conclusions

Chronic migraine is a neurologic condition associated with individual, societal, and economic burden. Little evidence exists specifically on treatments for chronic migraine, as studies to date have primarily

focused on prevention of episodic migraine. Historically, methodologic limitations were also a barrier to the interpretation of the few studies on chronic migraine therapies. Clinicians have therefore had to extrapolate treatments on the basis of data for episodic migraine prevention, but this approach is not evidence based.

New treatments for chronic migraine have become available since 2018. Those with the most robust evidence include onabotulinumtoxin A, erenumab, fremanezumab, galcanezumab, and eptinezumab. Moderate evidence for topiramate and recent evidence for rimegepant exist, although the latter is a new drug and guidelines on its use are still in development. Newer noninvasive or non-drug therapies such as neuromodulation warrant more research.

Most healthcare systems require that patients are treated using tiered therapies, in accordance with guidelines based on evidence for prevention of episodic migraine despite the lack of data on efficacy in chronic migraine. Future research is needed on tiered approaches specific to chronic migraine, as well as the impact on disability and cost.

Treatment decisions should remain patient centered, focusing on goals, preferences, reduction of disability, and improved quality of life. Treatment expectations should be realistic, and comorbidities, risk factors, and cost should be considered. As new data on CGRP antagonists emerge, including long term safety, efficacy, and use in special populations, the landscape of chronic migraine treatment will continue to evolve. The combination of new treatments including neuromodulation, behavioral approaches, and other interventions such as nerve blocks has created a battery of options for patients. The prognosis for improved health related quality of life for patients with chronic migraine is encouraging as we enter this next treatment era.

RESEARCH QUESTIONS

- What are the new targets for the treatment of refractory chronic migraine?
- What is the effect of covid-19 on the progression and treatment of chronic migraine?
- What are the long term safety and efficacy of calcitonin gene related peptide antagonists?
- What biomarkers predict treatment response to chronic migraine treatments and facilitate personalized medicine?
- Which treatments for prevention of episodic migraine, not yet studied, are effective for chronic migraine?

PATIENT INVOLVEMENT

Two patients with chronic migraine were invited to review the outline and framework of this manuscript. They provided valuable commentary and feedback on lifestyle modifications for chronic migraine and the need for evidence supporting these recommendations. This feedback was incorporated into the final text.

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1 Steiner TJ, Stovner LJ, Vos T. GBD 2015: migraine is the third cause of disability in under 50s. *J Headache Pain* 2016;17:104. doi:10.1186/s10194-016-0699-5
2 Negro A, Sciattella P, Rossi D, Guglielmetti M, Martelletti P, Mennini FS. Cost of chronic and episodic migraine patients in continuous treatment for two years in a tertiary level headache Centre. *J Headache Pain* 2019;20:120. doi:10.1186/s10194-019-1068-y
3 Ferrari MD, Goadsby PJ, Burstein R, et al. Migraine. *Nat Rev Dis Primers* 2022;8:2. doi:10.1038/s41572-021-00328-4
4 Dodick DW. A Phase-by-Phase Review of Migraine Pathophysiology. *Headache* 2018;58(Suppl 1):4-16. doi:10.1111/head.13300
5 Aurora SK, Brin MF. Chronic Migraine: An Update on Physiology, Imaging, and the Mechanism of Action of Two Available Pharmacologic Therapies. *Headache* 2017;57:109-25. doi:10.1111/head.12999
6 Stovner LJ, Nichols E, Steiner TJ, et al, GBD 2016 Headache Collaborators. Global, regional, and national burden of migraine and tension-type headache, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2018;17:954-76. doi:10.1016/S1474-4422(18)30322-3
7 Burch RC, Buse DC, Lipton RB. Migraine: Epidemiology, Burden, and Comorbidity. *Neurol Clin* 2019;37:631-49. doi:10.1016/j.ncl.2019.06.001
8 Buse DC, Manack AN, Fanning KM, et al. Chronic migraine prevalence, disability, and sociodemographic factors: results from the American Migraine Prevalence and Prevention Study. *Headache* 2012;52:1456-70. doi:10.1111/j.1526-4610.2012.02223.x
9 Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia* 2013;33:629-808. doi:10.1177/0333102413485658
10 May A, Schulte LH. Chronic migraine: risk factors, mechanisms and treatment. *Nat Rev Neurol* 2016;12:455-64. doi:10.1038/nrneurol.2016.93
11 Demarquay G, Moisset X, Lantéri-Minet M, et al. Revised guidelines of the French Headache Society for the diagnosis and management of migraine in adults. Part 1: Diagnosis and assessment. *Rev Neurol (Paris)* 2021;177:725-33. doi:10.1016/j.neurol.2021.07.001
12 Buse DC, Fanning KM, Reed ML, et al. Life With Migraine: Effects on Relationships, Career, and Finances From the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study. *Headache* 2019;59:1286-99. doi:10.1111/head.13613
13 Burch R, Rizzoli P, Loder E. The prevalence and impact of migraine and severe headache in the United States: Updated age, sex, and socioeconomic-specific estimates from government health surveys. *Headache* 2021;61:60-8. doi:10.1111/head.14024
14 Seok JI, Cho HI, Chung CS. From transformed migraine to episodic migraine: reversion factors. *Headache* 2006;46:1186-90. doi:10.1111/j.1526-4610.2006.00509.x
15 Katsarava Z, Buse DC, Manack AN, Lipton RB. Defining the differences between episodic migraine and chronic migraine. *Curr Pain Headache Rep* 2012;16:86-92. doi:10.1007/s11916-011-0233-z
16 Vincent MB. Cervicogenic headache: a review comparison with migraine, tension-type headache, and whiplash. *Curr Pain Headache Rep* 2010;14:238-43. doi:10.1007/s11916-010-0114-x
17 Silberstein SD, Lipton RB, Dodick DW. Operational diagnostic criteria for chronic migraine: expert opinion. *Headache* 2014;54:1258-66. doi:10.1111/head.12407
18 Wakerley BR. Medication-overuse headache. *Pract Neurol* 2019;19:399-403. doi:10.1136/practneurol-2018-002048
19 Whitehead MT, Cardenas AM, Corey AS, et al, Expert Panel on Neurologic Imaging. ACR Appropriateness Criteria® Headache. *J Am Coll Radiol* 2019;16(11S):S364-77. doi:10.1016/j.jacr.2019.05.030
20 Graff-Radford SB, Schievink WI. High-pressure headaches, low-pressure syndromes, and CSF leaks: diagnosis and management. *Headache* 2014;54:394-401. doi:10.1111/head.12283
21 Al-Hashel JY, Ahmed SF, Alroughani R, Goadsby PJ. Migraine misdiagnosis as a sinusitis, a delay that can last for many years. *J Headache Pain* 2013;14:97. doi:10.1186/1129-2377-14-97
22 Ailani J, Burch RC, Robbins MS, Board of Directors of the American Headache Society. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. *Headache* 2021;61:1021-39. doi:10.1111/head.14153

23 Aguilar-Shea AL, Membrilla Md JA, Diaz-de-Teran J. Migraine review for general practice. *Aten Primaria* 2022;54:102208. doi:10.1016/j.aprim.2021.102208
24 Robblee J, Starling AJ. SEEDS for success: Lifestyle management in migraine. *Cleve Clin J Med* 2019;86:741-9. doi:10.3949/ccjm.86a.19009
25 Tiseo C, Vacca A, Felbush A, et al, European Headache Federation School of Advanced Studies (EHF-SAS). Migraine and sleep disorders: a systematic review. *J Headache Pain* 2020;21:126. doi:10.1186/s10194-020-01192-5
26 Smitherman TA, Walters AB, Davis RE, et al. Randomized Controlled Pilot Trial of Behavioral Insomnia Treatment for Chronic Migraine With Comorbid Insomnia. *Headache* 2016;56:276-91. doi:10.1111/head.12760
27 Odegård SS, Sand T, Engstrøm M, Stovner LJ, Zwart JA, Hagen K. The long-term effect of insomnia on primary headaches: a prospective population-based cohort study (HUNT-2 and HUNT-3). *Headache* 2011;51:570-80. doi:10.1111/j.1526-4610.2011.01859.x
28 Sullivan DP, Martin PR, Boschen MJ. Psychological Sleep Interventions for Migraine and Tension-Type Headache: A Systematic Review and Meta-Analysis. *Sci Rep* 2019;9:6411. doi:10.1038/s41598-019-42785-8
29 Hindiyeh NA, Zhang N, Farrar M, Banerjee P, Lombard L, Aurora SK. The Role of Diet and Nutrition in Migraine Triggers and Treatment: A Systematic Literature Review. *Headache* 2020;60:1300-16. doi:10.1111/head.13836
30 Bond DS, Thomas JG, Lipton RB, et al. Behavioral Weight Loss Intervention for Migraine: A Randomized Controlled Trial. *Obesity (Silver Spring)* 2018;26:81-7. doi:10.1002/oby.22069
31 Khorsha F, Mirzababaei A, Togha M, Mirzaei K. Association of drinking water and migraine headache severity. *J Clin Neurosci* 2020;77:81-4. doi:10.1016/j.jocn.2020.05.034
32 Di Vincenzo A, Beghetto M, Vettor R, et al. Effects of Surgical and Non-surgical Weight Loss on Migraine Headache: a Systematic Review and Meta-Analysis. *Obes Surg* 2020;30:2173-85. doi:10.1007/s11695-020-04429-z
33 Arca KN, Halker Singh RB. Dehydration and Headache. *Curr Pain Headache Rep* 2021;25:56. doi:10.1007/s11916-021-00966-z
34 Khorsha F, Mirzababaei A, Togha M, Mirzaei K. Association of drinking water and migraine headache severity. *J Clin Neurosci* 2020;77:81-4. doi:10.1016/j.jocn.2020.05.034
35 Spigt M, Weerkamp N, Troost J, van Schayck CP, Knottnerus JA. A randomized trial on the effects of regular water intake in patients with recurrent headaches. *Fam Pract* 2012;29:370-5. doi:10.1093/fampra/cmr112
36 Amin FM, Aristeidou S, Baraldi C, et al, European Headache Federation School of Advanced Studies (EHF-SAS). The association between migraine and physical exercise. *J Headache Pain* 2018;19:83. doi:10.1186/s10194-018-0902-y
37 La Touche R, Fernández Pérez JJ, Proy Acosta A, et al. Is aerobic exercise helpful in patients with migraine? A systematic review and meta-analysis. *Scand J Med Sci Sports* 2020;30:965-82. doi:10.1111/sms.13625
38 Farris SG, Thomas JG, Abrantes AM, et al. Intentional avoidance of physical activity in women with migraine. *Cephalalgia Rep* 2018;1:25158163187882810.1177/2515816318788284 .
39 Chu HT, Liang CS, Lee JT, et al. Associations Between Depression/Anxiety and Headache Frequency in Migraineurs: A Cross-Sectional Study. *Headache* 2018;58:407-15. doi:10.1111/head.13215
40 Farris SG, Burr EK, Abrantes AM, et al. Anxiety Sensitivity as a Risk Indicator for Anxiety, Depression, and Headache Severity in Women With Migraine. *Headache* 2019;59:1212-20. doi:10.1111/head.13568
41 Lipton RB, Cohen JM, Galic M, et al. Effects of fremanezumab in patients with chronic migraine and comorbid depression: Subgroup analysis of the randomized HALO CM study. *Headache* 2021;61:662-72. doi:10.1111/head.14097
42 Caponnetto V, Deodato M, Robotti M, et al, European Headache Federation School of Advanced Studies (EHF-SAS). Comorbidities of primary headache disorders: a literature review with meta-analysis. *J Headache Pain* 2021;22:71. doi:10.1186/s10194-021-01281-z
43 Curtis KM, Tepper NK, Jatlaoui TC, et al. U.S. Medical Eligibility Criteria for Contraceptive Use, 2016. *MMWR Recomm Rep* 2016;65:1-103. doi:10.15585/mmwr.rr6503a1
44 Siddiqui M, Shah PV, Balani P, Lopez AR, Nobleza CMN, Khan S. Comparing the Efficacy, Safety, and Superiority of Calcitonin Gene-Related Peptide Monoclonal Antibodies and Botox in Preventing and Treating Migraines. *Cureus* 2021;13:e13002.
45 Peng KP, Wang SJ. Migraine diagnosis: screening items, instruments, and scales. *Acta Anaesthesiol Taiwan* 2012;50:69-73. doi:10.1016/j.aat.2012.05.002
46 Hareendran A, Mannix S, Skalicky A, et al. Development and exploration of the content validity of a patient-reported outcome measure to evaluate the impact of migraine- the migraine physical function impact diary (MPFID). *Health Qual Life Outcomes* 2017;15:224. doi:10.1186/s12955-017-0799-1
47 Stewart WF, Lipton RB, Dowson AJ, Sawyer J. Development and testing of the Migraine Disability Assessment (MIDAS) Questionnaire to assess headache-related disability. *Neurology* 2001;56(Suppl 1):S20-8. doi:10.1212/WNL.56.suppl_1.S20
48 Lipton RB, Kolodner K, Bigal ME, et al. Validity and reliability of the Migraine-Treatment Optimization Questionnaire. *Cephalalgia* 2009;29:751-9. doi:10.1111/j.1468-2982.2008.01786.x
49 Caronna E, Starling AJ. Update on Calcitonin Gene-Related Peptide Antagonism in the Treatment of Migraine. *Neurol Clin* 2021;39:1-19. doi:10.1016/j.ncl.2020.09.001
50 Mahon R, Huels J, Hacking V, et al. Economic evaluations in migraine: systematic literature review and a novel approach. *J Med Econ* 2020;23:864-76. doi:10.1080/13696998.2020.1754840
51 Giacomozzi ARE, Vindas AP, Silva AAJr, et al. Latin American consensus on guidelines for chronic migraine treatment. *Arq Neuropsiquiatr* 2013;71:478-86. doi:10.1590/0004-282X20130066
52 Silberstein SD, Dodick DW, Lindblad AS, et al, Chronic Migraine Treatment Trial Research Group. Randomized, placebo-controlled trial of propranolol added to topiramate in chronic migraine. *Neurology* 2012;78:976-84. doi:10.1212/WNL.0b013e31824d5846
53 Ducros A, de Gaalon S, Roos C, et al. Revised guidelines of the French headache society for the diagnosis and management of migraine in adults. Part 2: Pharmacological treatment. *Rev Neurol (Paris)* 2021;177:734-52. doi:10.1016/j.neurol.2021.07.006
54 Silberstein SD. Preventive Migraine Treatment. *Continuum (Minneap Minn)* 2015;21(4 Headache):973-89. doi:10.1212/CON.0000000000000199
55 The Primary Care Management of Headache Work Group. VA/DoD Clinical Practice Guideline for the Primary Care Management of Headache. 2020. https://www.healthquality.va.gov/guidelines/pain/headache/VADoDHeadacheCPGFinal508.pdf.
56 Oskoui M, Pringsheim T, Billinghurst L, et al. Practice guideline update summary: Pharmacologic treatment for pediatric migraine prevention: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology* 2019;93:500-9. doi:10.1212/WNL.0000000000008105
57 Giacomozzi ARE, Vindas AP, Silva AA da JJr, et al. Latin American consensus on guidelines for chronic migraine treatment. *Arq Neuropsiquiatr* 2013;71:478-86. doi:10.1590/0004-282X20130066
58 Bendtsen L, Sacco S, Ashina M, et al. Guideline on the use of onabotulinumtoxinA in chronic migraine: a consensus statement from the European Headache Federation. *J Headache Pain* 2018;19:91. doi:10.1186/s10194-018-0921-8
59 Sacco S, Bendtsen L, Ashina M, et al. European headache federation guideline on the use of monoclonal antibodies acting on the calcitonin gene related peptide or its receptor for migraine prevention. *J Headache Pain* 2019;20:6. doi:10.1186/s10194-018-0955-y
60 Escher CM, Paracka L, Dressler D, Kollewe K. Botulinum toxin in the management of chronic migraine: clinical evidence and experience. *Ther Adv Neurol Disord* 2017;10:127-35. doi:10.1177/1756285616677005
61 Herd CP, Tomlinson CL, Rick C, et al. Botulinum toxins for the prevention of migraine in adults. *Cochrane Database Syst Rev* 2018;6:CD011616. doi:10.1002/14651858.CD011616.pub2
62 Pringsheim T, Davenport W, Mackie G, et al, Canadian Headache Society Prophylactic Guidelines Development Group. Canadian Headache Society guideline for migraine prophylaxis. *Can J Neurol Sci* 2012;39(Suppl 2):S1-59.
63 Banzi R, Cusi C, Randazzo C, Sterzi R, Tedesco D, Moja L. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) for the prevention of migraine in adults. *Cochrane Database Syst Rev* 2015;4:CD002919. doi:10.1002/14651858.CD002919.pub3
64 Urits I, Jones MR, Gress K, et al. CGRP Antagonists for the Treatment of Chronic Migraines: a Comprehensive Review. *Curr Pain Headache Rep* 2019;23:29. doi:10.1007/s11916-019-0768-y
65 Croop R, Lipton RB, Kudrow D, et al. Oral rimegepant for preventive treatment of migraine: a phase 2/3, randomised, double-blind, placebo-controlled trial. *Lancet* 2021;397:51-60. doi:10.1016/S0140-6736(20)32544-7
66 Schwedt TJ, Kuruppu DK, Dong Y, Standley K, Yunes-Medina L, Pearlman E. Early onset of effect following galcanezumab treatment in patients with previous preventive medication failures. *J Headache Pain* 2021;22:15. doi:10.1186/s10194-021-01230-w
67 Schwedt T, Reuter U, Tepper S, et al. Early onset of efficacy with erenumab in patients with episodic and chronic migraine. *J Headache Pain* 2018;19:92. doi:10.1186/s10194-018-0923-6

68 Toni T, Tamanaha R, Newman B, et al. Effectiveness of dual migraine therapy with CGRP inhibitors and onabotulinumtoxinA injections: case series. *Neurol Sci* 2021;42:5373-6. doi:10.1007/s10072-021-05547-x
69 Pellesi L, Do TP, Ashina H, Ashina M, Burstein R. Dual Therapy With Anti-CGRP Monoclonal Antibodies and Botulinum Toxin for Migraine Prevention: Is There a Rationale?*Headache* 2020;60:1056-65. doi:10.1111/head.13843
70 Cuadrado ML, Aledo-Serrano Á, et al, Navarro P. Short-term effects of greater occipital nerve blocks in chronic migraine: A double-blind, randomised, placebo-controlled clinical trial. *Cephalalgia* 2017;37:864-72. doi:10.1177/0333102416655159
71 Gul HL, Ozon AO, Karadas O, Koc G, Inan LE. The efficacy of greater occipital nerve blockade in chronic migraine: A placebo-controlled study. *Acta Neurol Scand* 2017;136:138-44. doi:10.1111/ane.12716
72 Shauly O, Gould DJ, Sahai-Srivastava S, Patel KM. Greater Occipital Nerve Block for the Treatment of Chronic Migraine Headaches: A Systematic Review and Meta-Analysis. *Plast Reconstr Surg* 2019;144:943-52. doi:10.1097/PRS.0000000000006059
73 Dilli E, Halker R, Vargas B, et al. Occipital nerve block for the short-term preventive treatment of migraine: A randomized, double-blinded, placebo-controlled study. *Cephalalgia* 2015;35:959-68. doi:10.1177/0333102414561872
74 Özer D, Bölük C, Türk Börü Ü, Altun D, Taşdemir M, Köseoğlu Toksoy C. Greater occipital and supraorbital nerve blockade for the preventive treatment of migraine: a single-blind, randomized, placebo-controlled study. *Curr Med Res Opin* 2019;35:909-15. doi:10.1080/03007995.2018.1532403
75 Inan LE, Inan N, Karadaş Ö, et al. Greater occipital nerve blockade for the treatment of chronic migraine: a randomized, multicenter, double-blind, and placebo-controlled study. *Acta Neurol Scand* 2015;132:270-7. doi:10.1111/ane.12393
76 Palamar D, Uluduz D, Saip S, Erden G, Unalan H, Akarirmak U. Ultrasound-guided greater occipital nerve block: an efficient technique in chronic refractory migraine without aura?*Pain Physician* 2015;18:153-62. doi:10.36076/ppj/2015.18.153
77 Santos Lasaosa S, Cuadrado Pérez ML, Guerrero Peral AL, et al. Consensus recommendations for anaesthetic peripheral nerve block. *Neurologia* 2017;32:316-30. doi:10.1016/j.nrl.2016.04.017
78 Spindler BL, Ryan M. Medications Approved for Preventing Migraine Headaches. *Am J Med* 2020;133:664-7. doi:10.1016/j.amjmed.2020.01.031
79 Sharpe L, Dudeney J, Williams ACC, et al. Psychological therapies for the prevention of migraine in adults. *Cochrane Database Syst Rev* 2019;7:CD012295. doi:10.1002/14651858.CD012295.pub2
80 Anheyer D, Leach MJ, Klose P, Dobos G, Cramer H. Mindfulness-based stress reduction for treating chronic headache: A systematic review and meta-analysis. *Cephalalgia* 2019;39:544-55. doi:10.1177/0333102418781795
81 Pei JH, Ma T, Nan RL, et al. Mindfulness-Based Cognitive Therapy for Treating Chronic Pain A Systematic Review and Meta-analysis. *Psychol Health Med* 2021;26:333-46. doi:10.1080/13548506.2020.1849746
82 Bae JY, Sung HK, Kwon NY, et al. Cognitive Behavioral Therapy for Migraine Headache: A Systematic Review and Meta-Analysis. *Medicina (Kaunas)* 2021;58:44. doi:10.3390/medicina58010044
83 Veehof MM, Trompetter HR, Bohlmeijer ET, Schreurs KMG. Acceptance- and mindfulness-based interventions for the treatment of chronic pain: a meta-analytic review. *Cogn Behav Ther* 2016;45:5-31. doi:10.1080/16506073.2015.1098724
84 Williams ACC, Fisher E, Hearn L, Eccleston C. Psychological therapies for the management of chronic pain (excluding headache) in adults. *Cochrane Database Syst Rev* 2020;8:CD007407.
85 Seng EK, Singer AB, Metts C, et al. Does Mindfulness-Based Cognitive Therapy for Migraine Reduce Migraine-Related Disability in People with Episodic and Chronic Migraine? A Phase 2b Pilot Randomized Clinical Trial. *Headache* 2019;59:1448-67. doi:10.1111/head.13657
86 Nestoriuc Y, Martin A, Rief W, Andrasik F. Biofeedback treatment for headache disorders: a comprehensive efficacy review. *Appl Psychophysiol Biofeedback* 2008;33:125-40. doi:10.1007/s10484-008-9060-3
87 Andrasik F. Biofeedback in headache: an overview of approaches and evidence. *Cleve Clin J Med* 2010;77(Suppl 3):S72-6. doi:10.3949/ccjm.77.s3.13
88 Dutta A, Aruchunan M, Mukherjee A, Metri KG, Ghosh K, Basu-Ray I. A Comprehensive Review of Yoga Research in 2020. *J Integr Complement Med* 2022;28:114-23. doi:10.1089/jicm.2021.0420
89 Anheyer D, Klose P, Lauche R, Saha FJ, Cramer H. Yoga for Treating Headaches: a Systematic Review and Meta-analysis. *J Gen Intern Med* 2020;35:846-54. doi:10.1007/s11606-019-05413-9
90 Haller H, Lauche R, Sundberg T, Dobos G, Cramer H. Craniosacral therapy for chronic pain: a systematic review and meta-analysis of randomized controlled trials. *BMC Musculoskelet Disord* 2019;21:1. doi:10.1186/s12891-019-3017-y
91 Brønfort G, Haas M, Evans RL, Goldsmith CH, Assendelft WJJ, Bouter LM. WITHDRAWN: Non-invasive physical treatments for chronic/recurrent headache. *Cochrane Database Syst Rev* 2014;2014:CD001878.
92 Palmisani S, Al-Kaisy A, Arcioni R, et al. A six year retrospective review of occipital nerve stimulation practice--controversies and challenges of an emerging technique for treating refractory headache syndromes. *J Headache Pain* 2013;14:67. doi:10.1186/1129-2377-14-67
93 Chen YF, Bramley G, Unwin G, et al. Occipital nerve stimulation for chronic migraine--a systematic review and meta-analysis. *PLoS One* 2015;10:e0116786. doi:10.1371/journal.pone.0116786
94 Dodick DW, Silberstein SD, Reed KL, et al. Safety and efficacy of peripheral nerve stimulation of the occipital nerves for the management of chronic migraine: long-term results from a randomized, multicenter, double-blinded, controlled study. *Cephalalgia* 2015;35:344-58. doi:10.1177/0333102414543331
95 Tao H, Wang T, Dong X, Guo Q, Xu H, Wan Q. Effectiveness of transcutaneous electrical nerve stimulation for the treatment of migraine: a meta-analysis of randomized controlled trials. *J Headache Pain* 2018;19:42. doi:10.1186/s10194-018-0868-9
96 Ordás CM, Cuadrado ML, Pareja JA, et al. Transcutaneous Supraorbital Stimulation as a Preventive Treatment for Chronic Migraine: A Prospective, Open-Label Study. *Pain Med* 2020;21:415-22.
97 Silberstein SD, Calhoun AH, Lipton RB, et al, EVENT Study Group. Chronic migraine headache prevention with noninvasive vagus nerve stimulation: The EVENT study. *Neurology* 2016;87:529-38. doi:10.1212/WNL.0000000000002918
98 Stanak M, Wolf S, Jagoš H, Zebenholzer K. The impact of external trigeminal nerve stimulator (e-TNS) on prevention and acute treatment of episodic and chronic migraine: A systematic review. *J Neurol Sci* 2020;412:116725. doi:10.1016/j.jns.2020.116725
99 Lai YH, Huang YC, Huang LT, Chen RM, Chen C. Cervical Noninvasive Vagus Nerve Stimulation for Migraine and Cluster Headache: A Systematic Review and Meta-Analysis. *Neuromodulation* 2020;23:721-31. doi:10.1111/ner.13122
100 Lan L, Zhang X, Li X, Rong X, Peng Y. The efficacy of transcranial magnetic stimulation on migraine: a meta-analysis of randomized controlled trails. *J Headache Pain* 2017;18:86. doi:10.1186/s10194-017-0792-4
101 Yarnitsky D, Dodick DW, Grosberg BM, et al. Remote Electrical Neuromodulation (REN) Relieves Acute Migraine: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial. *Headache* 2019;59:1240-52. doi:10.1111/head.13551
102 Cascio Rizzo A, Paolucci M, Altavilla R, et al. Daith Piercing in a Case of Chronic Migraine: A Possible Vagal Modulation. *Front Neurol* 2017;8:624. doi:10.3389/fneur.2017.00624
103 Bhandari P, Ranjit E, Sapra A, Davis D, Brenham C. Daith Piercing: Wonder Treatment or Untested Fad?*Cureus* 2020;12:e6978. doi:10.7759/cureus.6978
104 Gaul C, Diener HC, Danesch U, Migravent® Study Group. Improvement of migraine symptoms with a proprietary supplement containing riboflavin, magnesium and Q10: a randomized, placebo-controlled, double-blind, multicenter trial. *J Headache Pain* 2015;16:516. doi:10.1186/s10194-015-0516-6
105 Sazali S, Badrin S, Norhayati MN, Idris NS. Coenzyme Q10 supplementation for prophylaxis in adult patients with migraine-a meta-analysis. *BMJ Open* 2021;11:e039358. doi:10.1136/bmjopen-2020-039358
106 Parohan M, Sarraf P, Javanbakht MH, Ranji-Burachaloo S, Djalali M. Effect of coenzyme Q10 supplementation on clinical features of migraine: a systematic review and dose-response meta-analysis of randomized controlled trials. *Nutr Neurosci* 2020;23:868-75. doi:10.1080/1028415X.2019.1572940
107 Martami F, Togha M, Seifishahpar M, et al. The effects of a multispecies probiotic supplement on inflammatory markers and episodic and chronic migraine characteristics: A randomized double-blind controlled trial. *Cephalalgia* 2019;39:841-53. doi:10.1177/0333102418820102
108 National Advisory Council for Complementary and Integrative Health. Butterbur. 2020. https://www.nccih.nih.gov/health/butterbur.
109 Abu-Arafeh I, Hershey AD, Diener HC, Tassorelli C, Clinical Trials Standing Committee and the Child and Adolescent Standing Committee of the International Headache Society. Guidelines of the International Headache Society for controlled trials of preventive treatment of migraine in children and adolescents, 1st edition. *Cephalalgia* 2019;39:803-16. doi:10.1177/0333102419842188
110 Winner PK, Kabbouche M, Yonker M, Wangsadipura V, Lum A, Brin MF. A Randomized Trial to Evaluate OnabotulinumtoxinA for Prevention of Headaches in Adolescents With Chronic Migraine. *Headache* 2020;60:564-75. doi:10.1111/head.13754
111 Shah S, Calderon MD, Crain N, Pham J, Rinehart J. Effectiveness of onabotulinumtoxinA (BOTOX) in pediatric patients experiencing migraines: a randomized, double-blinded, placebo-controlled crossover study in the pediatric pain population. *Reg Anesth Pain Med* 2021;46:41-8. doi:10.1136/rapm-2020-101605

112 Negro A, Delaruelle Z, Ivanova TA, et al, European Headache Federation School of Advanced Studies (EHF-SAS). Headache and pregnancy: a systematic review. *J Headache Pain* 2017;18:106. doi:10.1186/s10194-017-0816-0

113 Saldanha IJ, Cao W, Bhuma MR, et al. Management of primary headaches during pregnancy, postpartum, and breastfeeding: A systematic review. *Headache* 2021;61:11-43. doi:10.1111/head.14041

114 Govindappagari S, Grossman TB, Dayal AK, Grosberg BM, Vollbracht S, Robbins MS. Peripheral Nerve Blocks in the Treatment of Migraine in Pregnancy. *Obstet Anesthes Dig* 2015;35:211-210.1097/01.aoa.0000472732.97231.f3 .

115 Wong HT, Khalil M, Ahmed F. OnabotulinumtoxinA for chronic migraine during pregnancy: a real world experience on 45 patients. *J Headache Pain* 2020;21:129. doi:10.1186/s10194-020-01196-1

116 Wijeratne T, Tang HM, Crewther D, Crewther S. Prevalence of Migraine in the Elderly: A Narrated Review. *Neuroepidemiology* 2019;52:104-10. doi:10.1159/000494758

117 Berk T, Ashina S, Martin V, Newman L, Vij B. Diagnosis and Treatment of Primary Headache Disorders in Older Adults. *J Am Geriatr Soc* 2018;66:2408-16. doi:10.1111/jgs.15586

118 Evers S, Áfra J, Frese A, et al, European Federation of Neurological Societies. EFNS guideline on the drug treatment of migraine--revised report of an EFNS task force. *Eur J Neurol* 2009;16:968-81. doi:10.1111/j.1468-1331.2009.02748.x

119 Worthington I, Pringsheim T, Gawel MJ, et al, Canadian Headache Society Acute Migraine Treatment Guideline Development Group. Canadian Headache Society Guideline: acute drug therapy for migraine headache. *Can J Neurol Sci* 2013;40(Suppl 3):S1-80. doi:10.1017/S0317167100118943

120 Tassorelli C, Diener HC, Dodick DW, et al, International Headache Society Clinical Trials Standing Committee. Guidelines of the International Headache Society for controlled trials of preventive treatment of chronic migraine in adults. *Cephalalgia* 2018;38:815-32. doi:10.1177/0333102418758283

121 Sacco S, Braschinsky M, Ducros A, et al. European headache federation consensus on the definition of resistant and refractory migraine : Developed with the endorsement of the European Migraine & Headache Alliance (EMHA). *J Headache Pain* 2020;21:76. doi:10.1186/s10194-020-01130-5

122 Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman E, Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology* 2012;78:1337-45. doi:10.1212/WNL.0b013e3182535d20