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. 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. 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 $82,430 to $93,880. In Europe, the total cost is estimated to be as high as €95bn ($95bn; £82bn) annually.

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. Chronic migraine is associated with a change in nociception threshold, sensitization, and structural brain changes such as cortical thinning.

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”.
**STATE OF THE ART REVIEW**

**Box 1: PubMed search terms**

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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.” Chronic migraine must be distinguished from other headache conditions, including medication overuse headache (fig 1). Between 2.5% and 3% of patients with episodic migraine will progress to chronic migraine in the following year, 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.

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. 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.

**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. 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, and thunderclap headache. 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. 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, 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...
characteristics, risk factors, and comorbidities 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.

### Chronic migraine diagnostic criteria

**DESCRIPTION**

Headache occurring on ≥15 days/month for ≥3 months, which, on ≥8 days/month, has the features of migraine headache.

### Migraine without aura diagnostic criteria

**DESCRIPTION**

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

**DIAGNOSTIC CRITERIA**

- **A** 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/month 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 with aura diagnostic criteria

**DESCRIPTION**

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

**DIAGNOSTIC CRITERIA**

- **A** At least two attacks fulfilling criteria B and C
- **B** One or more of the following fully reversible aura symptoms:
  - 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

**DESCRIPTION**

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.

**DIAGNOSTIC CRITERIA**

- **A** Headache occurring on ≥15 days/month in a patient with a pre-existing headache disorder
- **B** Regular overuse for ≥3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache
- **C** Not better accounted for by another ICHD-3 diagnosis
Treatable risk factors for chronic migraine

- 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

Treatable risk factors for chronic migraine include but are not limited to caffeine intake, obesity, depression, sleep disorders, chronic pain conditions, analgesic overuse, stressors, and ineffective acute migraine treatment. These factors, among others, can contribute to the development and maintenance of chronic migraine.

Depression screening

- Skipping meals and fluids
- Sleep patterns: insomnia, obstructive sleep apnea
- Ineffective acute migraine treatment
- Stressors
- Analgesic overuse
- Depression
- Obesity
- Caffeine intake

Depression screening is crucial in identifying treatable risk factors for chronic migraine. Skipping meals and fluids, sleep patterns, ineffective acute migraine treatment, stressors, analgesic overuse, depression, obesity, and caffeine intake are all factors that can contribute to the onset and exacerbation of chronic migraine.

Treatable risk factors for chronic migraine are multifactorial, and clinicians should consider a comprehensive approach in their management. Identifying and addressing these risk factors can lead to improved outcomes for patients with chronic migraine.

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.

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). 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.

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,” 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. 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). 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. 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. 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. 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. 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). However, a subsequent systematic review...
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,
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, 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. 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. 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
  - Migraine Physical Function Impact Diary (MPFID)—measures the effect of symptoms on physical functioning over 24 hours
  - Migraine Disability Assessment (MIDAS)—measures symptoms over three months

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.

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. 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.

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 pranopanol to topiramate is ineffective for patients with chronic migraine. 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
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 55 A discussion of evidence based treatment, reviewing current chronic migraine guidelines, is included in the Guidelines section and summarized in table 1.

**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>
<thead>
<tr>
<th>Drug; category</th>
<th>Dosing, delivery, and frequency</th>
<th>Benefits</th>
<th>Adverse reactions and clinical considerations</th>
<th>Guidelines/consensus statements</th>
<th>Guideline/consensus recommendation*</th>
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<tbody>
<tr>
<td><strong>Antidepressants</strong></td>
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<tr>
<td>Amitriptyline; tricyclic antidepressant</td>
<td>10-100 mg PO QHS (initial dosing 10 mg increased by 10 mg weekly to goal dose). Pediatric dosing: 1 mg/kg/d</td>
<td>May help with insomnia and depression</td>
<td>Side effects: may cause QT prolongation, weight gain, constipation, dry mouth, sedation/fatigue. Contraindications: glaucoma, prostatic adenoma; use with caution in patients aged &gt;65 owing to increased risk of adverse side effects</td>
<td>Revised guidelines of the French Headache Society for the diagnosis and management of migraine in adults. Part 2: Pharmacological treatment 2021</td>
<td>Fair</td>
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<td>Latin American consensus on guidelines for chronic migraine treatment 2013</td>
<td>Included but noted not to be specifically studied for chronic migraine</td>
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<tr>
<td>Topiramate</td>
<td>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</td>
<td>May help with weight loss</td>
<td>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</td>
<td>Revised guidelines of the French Headache Society for the diagnosis and management of migraine in adults. Part 2: Pharmacological treatment 2021</td>
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<td>VA/DoD Clinical Practice Guideline for the Primary Care Management of Headache 2020</td>
<td>Recommended for episodic migraine only: weak</td>
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<td>Valproic acid</td>
<td>500-2000 mg (initial dose 300-500 mg; typical dosing range is 600-1000 mg)</td>
<td>May help with mood stabilization and seizure control</td>
<td>Side effects: weight gain, hair loss, nausea, acne, transaminits, 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</td>
<td>Revised guidelines of the French Headache Society for the diagnosis and management of migraine in adults. Part 2: Pharmacological treatment 2021</td>
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<td>Latin American consensus on guidelines for chronic migraine treatment 2013</td>
<td>Class 1, level B</td>
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<td><strong>Antihypertensives</strong></td>
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<td>Propranolol; β blocker</td>
<td>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)</td>
<td>May help with hypertension, anxiety or tremor</td>
<td>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</td>
<td>Revised guidelines of the French Headache Society for the diagnosis and management of migraine in adults. Part 2: Pharmacological treatment 2021</td>
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<td>VA/DoD Clinical Practice Guideline for the Primary Care Management of Headache 2013</td>
<td>Weak: migraine prevention, not chronic migraine specifically</td>
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<tr>
<td>Atenolol; β blocker</td>
<td>50-200 mg (100 mg) QAM</td>
<td>May help with tachycardia, hypertension, and some arrhythmias</td>
<td>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, ophthalmochromacyma</td>
<td>Revised guidelines of the French Headache Society for the diagnosis and management of migraine in adults. Part 2: Pharmacological treatment 2021</td>
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*Continued*
Drug category | Dosing, delivery, and frequency | Benefits | Adverse reactions and clinical considerations | 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


53

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


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


53

High

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, myasthenia gravis, amyotrophic lateral sclerosis


53

High

Fremanezumab

- 225 mg monthly or 675 mg, quarterly, subcutaneous
- Side effects: injection site reaction, immunologic antibody development. Not studied in patients with hypertension or in patients with history of hypertension or uncontrolled CVD


53

Medium

The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice 2021

22

Weak

Latin American consensus on guidelines for chronic migraine: a consensus statement from the European Headache Federation 2019

57

Medium

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
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. 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. A 2018 Cochrane review of botulinum toxins for the prevention of migraine included patients with chronic migraine. 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).

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. 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. 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). 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, 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.

### Table 1 | Continued

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<tr>
<th>Drug</th>
<th>Category</th>
<th>Drug</th>
<th>Dosing, delivery, and frequency</th>
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<td><strong>Antidepressants</strong></td>
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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). 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 the 70 mg dose and 2.4 (1.6 to 3.5; P=0.009) for the 140 mg dose.56 A randomized, double blind, placebo controlled trial of fremanezumab (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.70-74 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.75 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.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
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. 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. 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. 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.

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. 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. 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. 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.

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. Whereas one review included randomized controlled trials, prospective case controlled trials and single arm interventional trials, the other included only randomized controlled trials in which eTNS was compared against sham stimulation. 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 $0.04$; $P=0.117$).109 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, 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 0.39, 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 divalprox, 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 block114 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 lasmiditan),118 119 but discussion of this topic exceeds the scope of this review. Patients must be counselled 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).”52 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.53 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 etrizmab. Moderate evidence for topiramate and recent evidence for rimegeprat 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.

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Contributors: Both authors were involved in the development of the intellectual content, literature review, research, manuscript preparation, editing, and review.

Competing interests: We have read and understood the BMJ policy on declaration of interests and declare the following interests: none.

Provenance and peer review: Commissioned, externally peer reviewed.


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.

2019;35:909

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2020;35:846

2022;28:114

2015;132:270

2017;32:316


2020;133:664


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2019

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