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Chronic migraine

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ABSTRACT

Chronic migraine is a disabling neurologic condition that affects 2% of the general population. Patients with chronic migraine have headaches on at least 15 days a month, with at least eight days a month on which their headaches and associated symptoms meet diagnostic criteria for migraine. Chronic migraine places an enormous burden on patients owing to frequent headaches; hypersensitivity to visual, auditory, and olfactory stimuli; nausea; and vomiting. It also affects society through direct and indirect medical costs. Chronic migraine typically develops after a slow increase in headache frequency over months to years. Several factors are associated with an increased risk of transforming to chronic migraine. The diagnosis requires a carefully performed patient interview and neurologic examination, sometimes combined with additional diagnostic tests, to differentiate chronic migraine from secondary headache disorders and other primary chronic headaches of long duration. Treatment takes a multifaceted approach that may include risk factor modification, avoidance of migraine triggers, drug and non-drug based prophylaxis, and abortive migraine treatment, the frequency of which is limited to avoid drug overuse. This article provides an overview of current knowledge regarding chronic migraine, including epidemiology, risk factors for its development, pathophysiology, diagnosis, management, and guidelines. The future of chronic migraine treatment and research is also discussed.

Introduction

Migraine is a neurologic condition characterized by attacks of headache; hypersensitivity to visual, auditory, olfactory, and cutaneous stimuli; nausea; and vomiting. Most people with migraine have "episodic migraine"—fewer than 15 days of headache each month. However, a subgroup of people with migraine has "chronic migraine," defined as at least 15 days of headache each month, including at least eight days a month on which the headache and associated symptoms are consistent with fully developed migraine attacks. Typically, chronic migraine develops after a slow increase in headache frequency over months to years, a process termed "migraine transformation." Chronic migraine is common, often affects people during their most productive years of life, exerts substantial individual and societal costs, and is associated with numerous comorbid disorders. Treatment includes avoidance of migraine triggers and risk factor modification, as well as drug and non-drug based treatments to prevent and abort migraine attacks.

SUMMARY POINTS

- Chronic migraine describes the migraine pattern in which a person has at least 15 headache days a month, including at least eight days a month with fully developed migraines
- Chronic migraine is a common and disabling neurologic disorder
- Patients with less frequent migraines (episodic migraine) should be counseled on avoiding risk factors associated with transformation to chronic migraine
- The treatment of chronic migraine includes avoidance of risk factors for chronic migraine, avoidance of migraine attack triggers, use of prophylactic and abortive drugs, and non-drug treatment
- The recognition and management of disorders that are comorbid with chronic migraine optimizes patient outcomes

SOURCES AND SELECTION CRITERIA

PubMed was searched for manuscripts published between 1950 and October 2013 using the following search terms: "chronic migraine" or "transformed migraine" or "refractory chronic migraine" or "chronic migraine" and "prevalence" or "chronic migraine" and "incidence" or "chronic migraine" and "treatment" or "chronic migraine" and "disability" or "chronic migraine" and "diagnosis" or "chronic migraine" and "pathophysiology" or "chronic migraine" and "comorbidity" or "chronic migraine" and "guidelines." The search was limited to the English language. In addition, the reference lists of identified manuscripts and the author's own files were searched for relevant publications. Manuscripts were selected for inclusion on the basis of the author's assessment of the paper's originality, as well as its importance and relevance to the topics included in this review.

This article uses the latest data to review the frequency of chronic migraine, risk factors associated with transformation to chronic migraine and reversion back to episodic migraine, the individual and societal burdens from chronic migraine, the pathophysiology of chronic migraine, and its diagnosis. Although few treatments have been adequately investigated specifically for chronic migraine, evidence based and experience based recommendations for treatment are discussed. This review concludes with recommended topics to discuss with patients, thoughts about the future of research and treatment, a summary of published guidelines on the diagnosis and treatment of chronic migraine, and a discussion of the design of chronic migraine clinical trials.

Epidemiology

Estimates of the prevalence of chronic migraine throughout the world range from 0% to 5.1%, with most general population studies reporting a prevalence of 1.4-2.2%.[1] The variation probably reflects true differences among populations and the use of different definitions. Data from the United States show that the prevalence of chronic migraine increases throughout adolescence, peaks in midlife, and then declines after age 50 years (fig 1).[2] The highest prevalence is in women aged 18-49 years.[2] In population based samples, chronic migraine accounts for about 8% of all migraine cases.[2] The proportion of migraineurs with a chronic migraine pattern increases slightly with age.

Transformation and reversion factors

Each year, about 2.5% of people with episodic migraine transform to chronic migraine.[3] Factors associated with an increased risk of transformation include obesity, snoring, sleep disorders, excessive caffeine intake, psychiatric disease, high frequency of headaches at baseline, frequent use of abortive migraine drugs, female sex, lower socioeconomic status, comorbid pain disorders, history of head or neck injury, and presence of cutaneous allodynia.[4-6] Major life changes, such as divorce, marriage, or change of employment status, also increase the risk of transformation to chronic migraine.[7]

Clinicians must be aware of modifiable risk factors associated with the development of chronic migraine so that they can counsel their patients to avoid these risk factors. Patients and clinicians must be especially aware of too frequent use of migraine abortive drugs ("medication overuse") as a risk factor because it is common in this clinical population. The prevalence of chronic migraine with medication overuse is 0.3-1.1% in the general population.[1] About half of people with chronic migraine who present to specialty headache clinics have medication overuse.[8] Estimates of medication overuse among people with chronic migraine in the general population vary widely—from one third to two thirds.[1]

The risk of developing chronic migraine depends on the frequency with which abortive drugs are used and the type of drug used. The highest risks are associated with barbiturates (odds ratio 1.7; critical frequency of five usage days/month) and opioids (odds ratio 1.4; critical frequency of eight usage days/month).[3] Overuse of migraine specific agents such as triptans is also associated with an increased risk of transformation, albeit a lower risk than that associated with overuse of butalbital and opiates.[9-11] Non-steroidal anti-inflammatory drugs (NSAIDs) might reduce the risk of transformation in patients with up to nine headache days a month but increase the risk in patients with 10-14 headache days a month.[3 12]

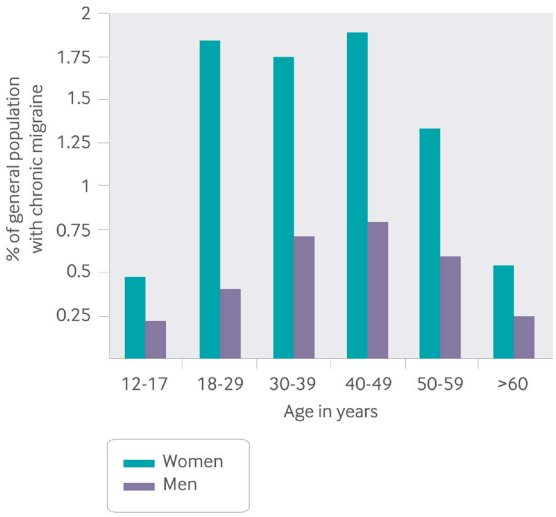

Fig 1 | Prevalence of chronic migraine in the United States according to age[2]

Fortunately, patients with chronic migraine often revert to episodic migraine. A general population study of 383 people with chronic migraine found that 33.9% had persistent chronic migraine during the two years after enrollment, 26.1% reverted to fewer than 10 headache days a month (low frequency episodic migraine), and 40% transitioned in and out of chronic migraine.[13] These data are consistent with results from other studies suggesting that chronic migraine is a "fluid" state, with many patients flowing in and out of a chronic migraine pattern over time.[6] Factors that may be associated with reversion of chronic migraine include lower baseline frequency of headaches (15-19 *v* 25-31 headache days/month), absence of allodynia, adherence to prophylactic drugs, withdrawal of overused abortive drugs, and physical exercise.[6 13]

Box 1 lists the risk factors associated with chronic migraine transformation and reversion.

Individual and societal effects

Individual and societal costs related to migraine are enormous. According to the Global Burden of Disease 2010 study, migraine accounts for about 1% of global disability adjusted life years and is the 30th leading cause of disability adjusted life years.[14] Annual direct and indirect costs from headache are estimated at $20bn (£12.2bn; €14.7bn) in the United States and annual costs from migraine are €27bn in Europe.[15 16]

As expected, chronic migraine results in substantially greater disability than episodic migraine. Compared with episodic migraine, people with chronic migraine have lower income, are less likely to be employed full time, and are more likely to be occupationally disabled.[17] A large population based study found that over a three month period, 57% of people with chronic migraine missed at least five days of

Box 1 | Factors associated with an increased risk for transformation and reversion of chronic migraine[3-7 13]

Transformation to chronic migraine
Obesity
Snoring
Sleep disorders
Excessive caffeine intake
Psychiatric disease
High baseline headache frequency
Overuse of migraine abortive drugs
Major life changes
Head or neck injury
Cutaneous allodynia
Female sex
Comorbid pain disorders
Lower socioeconomic status

Reversion to episodic migraine
Adherence to migraine prophylactic drugs
Lower baseline headache frequency
Absence of cutaneous allodynia
Physical exercise
Withdrawal of overused migraine abortive drugs

work or school compared with 24% of those with episodic migraine. In addition, 58% of those with chronic migraine and 18% with episodic migraine reported reduced productivity with household chores for at least five days over the three months.[18] About 25% of people with chronic migraine have very severe headache related disability according to scores on the migraine disability assessment scale, and about 90% have at least moderate levels of migraine related disability.[19 20] Compared with people with episodic migraine, those with chronic migraine are significantly more likely to have headaches of severe intensity and longer duration, whether treated or not; they are also more likely to have comorbid disorders.[20]

The use of healthcare resources is greater for patients with chronic migraine than for those with episodic migraine. People with chronic migraine visit primary care providers, specialists, and emergency departments more often. They are also admitted to hospital more often and require diagnostic tests and migraine drugs more often.[20 21] Annual total medical costs (direct and indirect) are 4.4 times greater in patients with chronic migraine ($7750) than in those with episodic migraine ($1757), with about 70% of the cost associated with chronic migraine being attributable to lost productive time.[22] In people with chronic migraine, an average of 4.6 hours of lost productive time per week is attributed to headache—0.8 hours of work absenteeism and 3.8 hours of presenteeism.[23]

Pathophysiology

The pathophysiology of chronic migraine and the mechanisms that result in transformation are not fully understood. However, the roles of atypical pain processing, central sensitization, cortical hyperexcitability, and neurogenic inflammation have been studied.

Atypical modulation of pain might play a role in transformation. Reduced inhibition of pain by regions of the descending pain modulatory pathway has been identified in chronic migraine.[24] In migraineurs, pain induced functional activation of pain inhibiting brainstem regions and the functional connectivity of brainstem pain modulatory regions are atypical.[25 26] Furthermore, the extent of these abnormalities correlates with the presence of cutaneous allodynia, a symptom of central sensitization.[25 26] It is postulated that recurrent migraine attacks lead to sensitization of the trigeminal system, which results in a reduced threshold for activation of this system, more frequent migraine attacks, and transformation to chronic migraine.[5] Cortical hyperexcitability might also contribute to transformation.[27-29] Transcranial magnetic stimulation studies of patients with chronic migraine suggest that the occipital cortex of these patients is hyperexcitable, even more so than in patients with episodic migraine.[30] The extent to which lack of cortical inhibition versus intrinsic cortical excitability contributes to this state is not clear.[31]

There is evidence that the structure and function of other pain processing regions in the brains of patients with migraine—for example, regions that participate in sensory discriminative, affective, and cognitive pain processing—are also atypical. Several studies have found positive correlations between the extent of these abnormalities and increasing frequency of headaches, suggesting that they are precursors to or biomarkers of transformation to chronic migraine.[32-35] Neuroimaging studies that have specifically studied patients with chronic migraine have found atypical pain processing and atypical structure of pain processing brain regions in this condition.[36-38]

Exuberant release of vasoactive neuropeptides such as calcitonin gene related peptide (CGRP) and the resultant neurogenic inflammation might also contribute to the pathophysiology of chronic migraine. A recent study found raised plasma concentrations of CGRP in migraineurs during the interictal phase of migraine compared with participants without migraine.[39] Furthermore, CGRP concentrations were higher in patients with chronic migraine than in those with episodic migraine. It is not clear whether high CGRP concentrations are the result of more frequent migraine attacks, thus serving as a potential biomarker of chronic migraine, or whether they are part of the process that leads to more frequent migraine attacks.

Diagnosis

History and examination

Diagnosis is made on the basis of the patient's symptoms and exclusion of other causes of frequent headache (box 2). The diagnostic process begins with a carefully obtained

Box 2 | Chronic migraine diagnostic criteria[40]

A: Headache (tension-type like or migraine like) on ≥15 days/month for >3 months and fulfilling criteria B and C
B: Occurring in a patient who has had ≥5 attacks of migraine with or without aura
C: On ≥8 days/month for >3 months, fulfilling any of the following:
- Migraine without aura diagnostic criteria
- Migraine with aura diagnostic criteria
- Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative

D: Not better accounted for by another headache diagnosis

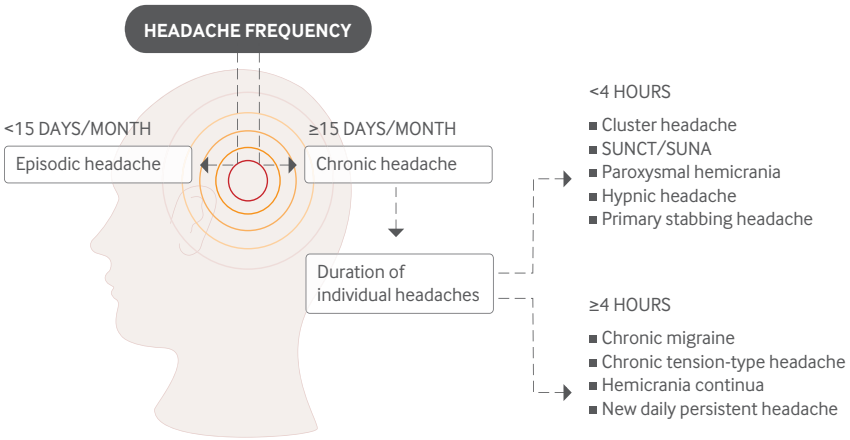

Fig 2 | Differentiating chronic migraine from other primary headaches. The differentiation of primary headaches is first made according to headache frequency. Headaches occurring on fewer than 15 days a month are considered "episodic," whereas those occurring on at least 15 days a month are considered "chronic." Chronic headaches can be subdivided according to the duration of individual headaches. Headaches shorter than four hours are considered "short duration," whereas those lasting at least four hours are "long duration." Chronic migraine is a chronic headache of long duration. SUNCT=short lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; SUNA=short lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms

headache history, to collect the information needed to determine the level of suspicion for a primary versus a secondary headache disorder and to assign a specific headache diagnosis. While collecting information about medical history and headache characteristics, the clinician is searching for "red flag" features that increase the likelihood of a secondary headache disorder and may thus lead to further diagnostic testing. Box 3 lists common red flags.

General physical and neurologic examinations are performed, with any potentially relevant abnormalities increasing the suspicion for a secondary headache disorder. In addition to the typical neurologic examination, the examination should include attention to the patient's neck and shoulders, temporal artery pulses, and temporomandibular joint. A funduscopic examination should be performed and the examiner should palpate over the occipital and supraorbital nerves in search of tenderness. Abnormal neurologic findings cannot be attributed to migraine without first considering other causes. Most patients will present with typical features of chronic migraine and normal examination findings, so will not need additional diagnostic testing. However, further diagnostic evaluation is warranted when the history and examination leave the clinician with concerns that a secondary headache disorder exists.

Box 3 | Red flags for a secondary headache disorder[41]

- Abnormal findings on neurologic examination
- Focal neurologic symptoms that are not consistent with typical migraine aura symptoms
- Systemic symptoms such as fevers, chills, and weight loss
- Rapid increase in headache frequency
- Orthostatic worsening of symptoms
- Exertional worsening of symptoms
- New onset headaches
- Thunderclap headaches (very severe headache that reaches maximum intensity in <1 min)
- Headaches in a patient with existing risk factors for a secondary headache (such as cancer or hypercoagulable state)
- Overuse of headache abortive drugs

Discussion of the indications for individual diagnostic tests is beyond the scope of this article. Tests that may be needed depend on the clinician's specific suspicions; they include blood tests, cervical spine imaging, sinus imaging, brain imaging, imaging of the brain arteries and venous sinuses, imaging of the cervical arteries, polysomnography, and lumbar puncture for cerebrospinal fluid analysis and measurement of opening pressure.

Differentiating chronic migraine from other primary headaches

Once it is known that the patient has a primary headache disorder, the specific headache type must be determined. Chronic migraine is one of several primary headaches that manifests with at least 15 headache days a month for at least three consecutive months. Chronic migraine can be differentiated from these other primary chronic headaches with a similar pattern by first considering the duration of individual headaches. Headaches that are shorter than four hours are considered "short" and ones that are longer than four hours are "long."[42] Chronic headaches of long duration are attributed to one of four diagnoses: chronic migraine, new daily persistent headache, hemicrania continua, or chronic tension-type headache. These four headache types are usually easy to differentiate from one another (fig 2).

New daily persistent headache is differentiated according to the manner in which the headache condition began. Unlike patients with chronic migraine, who typically develop the disease after a slow progression in headache frequency, patients with new daily persistent headache have continuous headache within the first 24 hours of headache onset. Although new daily persistent headache can have similar features to those seen in chronic migraine, the timing of onset differentiates it from chronic migraine.

Hemicrania continua is a continuous side locked headache of mild to moderate severity, with superimposed exacerbations of pain associated with ipsilateral cranial autonomic features (such as lacrimation, conjunctival injection, or rhinorrhea). Although mild to moderate cranial autonomic features can be present with migraine, the autonomic features of hemicrania continua are more common and more prominent. Occasionally it can be difficult to differentiate chronic migraine from hemicrania continua on the basis of symptoms alone. However, hemicrania continua is an "indometacin responsive" headache syndrome, meaning it is completely responsive to adequate doses of indometacin. Thus, a trial of indometacin is necessary for the formal diagnosis of hemicrania continua and helps to differentiate this condition from chronic migraine.[40]

Chronic tension-type headache is a "featureless" headache—it is not accompanied by migraine symptoms such as hypersensitivity to light and sound, nausea, or vomiting. In addition, the pain of tension-type headache is mild to moderate, whereas the pain of full-blown migraine attacks is moderate to severe. Notably, patients with chronic migraine

Box 4 | Medication overuse headache

- Headache occurs on at least 15 days/month in a patient with a pre-existing headache disorder
- Regular overuse* for longer than 3 months of one or more drugs that can be used for acute or symptomatic headache treatment
- Not better accounted for by another headache diagnosis

*Intake of ergotamine, triptans, opioids, combination analgesics (such as tablets that combine simple analgesics with opioids, butalbital, or caffeine), or drugs from multiple drug classes on at least 10 days/month. Intake of simple analgesics for at least 15 days/month.

Box 5 | Drug prophylaxis of chronic migraine*

Highest level evidence (≥2 randomized placebo controlled trials)
Topiramate
OnabotulinumtoxinA

Lower quality evidence (1 randomized study)
Sodium valproate
Gabapentin
Tizanidine
Amitriptyline

Lowest quality evidence (open label study)
Atenolol
Memantine
Pregabalin
Zonisamide

*The drugs listed have been studied specifically for prophylaxis in chronic migraine. However, drugs used for prophylaxis of episodic migraine are often used in chronic migraine, even in the absence of data supporting their use in this context.

often have days on which headaches resemble tension-type headache. They must, however, have at least eight days a month during which they experience full-blown migraine symptoms or are successfully treated with a triptan or ergot derivative for a presumed migraine before full expression of migraine features.[40]

Comorbid conditions

The identification and management of disorders that are comorbid with chronic migraine improve treatment outcomes. Chronic migraine is comorbid with sleep disorders, fatigue, other pain disorders, other neurologic disorders, psychiatric illness, cerebrovascular disease, cardiovascular disease, and gastrointestinal problems.[43-49] Compared with people with episodic migraine, patients with chronic migraine are twice as likely to have depression, anxiety, and other chronic pain. They are also significantly more likely to have bipolar disorder, respiratory illness (such as asthma and chronic obstructive pulmonary disease), heart disease, and vascular risk factors (such as hypertension and high cholesterol).[17]

Treatment

The main goals of treatment are to reduce the frequency of migraine attacks and to reduce migraine related disability while avoiding the overuse of migraine abortive drugs. These goals are achieved through a combination of avoiding migraine triggers, dealing with modifiable risk factors, and using pharmacologic and non-pharmacologic prophylaxis. Migraine abortive drugs are also needed, but their frequency of use must be limited to avoid overuse and medication overuse headache. Medication overuse is diagnosed if abortive drugs are used regularly for more than three months on 10 or more, or 15 or more, days a month, depending on the drug (box 4).[40]

Risk factor modification and trigger avoidance

As discussed above, several risk factors for the development of chronic migraine and for the reversion to episodic migraine have been identified. On the basis of clinical experience and emerging data, it is recommended that the management of chronic migraine includes providing the patient with advice regarding exposure to modifiable risk factors.[50-54] Depending on the individual patient, advice might include losing weight, participating in a regular exercise routine, avoiding caffeine, avoiding alcohol, avoiding stress or modifying the response to stressors, getting sufficient sleep, and avoiding overuse of migraine abortive drugs. Patients should be instructed to maintain a daily headache diary, an activity that helps patients track their migraine patterns and identify their migraine triggers. Once triggers are identified, measures should be taken to avoid exposure to them.

Prophylaxis

Drug with high quality evidence (≥2 randomized placebo controlled trials)

Data from relatively large randomized placebo controlled studies provide support for the use of topiramate and onabotulinumtoxinA (botulinum toxin type A) for prophylaxis in chronic migraine (box 5). Although many drugs used for prophylaxis in episodic migraine and chronic migraine are prescribed off label, onabotulinumtoxinA is the only one that is approved by the Food and Drug Administration for chronic migraine.

Topiramate has been studied for prophylaxis in three randomized placebo controlled clinical trials.[55-57] In the Silberstein study, 306 patients with a baseline of 17 migraine/migrainous days a month received topiramate at a mean dose of 86 mg/day (maximum dose 100 mg/day) or placebo. At 90 days, topiramate was superior to placebo for the primary efficacy endpoint of change from baseline in the mean number of monthly migraine/migrainous days (topiramate −6.4 days *v* placebo −4.7 days, P=0.01). A high dropout rate limits the quality of study results, with only 55.8% of the patients treated with topiramate and 55.2% of those treated with placebo completing the trial.

In the other two trials of topiramate, most patients overused migraine abortive drugs and sample sizes were relatively small.[55 57] Nonetheless, both found topiramate to be superior to placebo. In Diener and colleagues' study, after about three months of follow-up, 100 mg of topiramate reduced the mean number of monthly migraine days when compared with placebo. The treatment group (n=32) had 3.5 (standard deviation 6.3) fewer days with migraine a month (baseline headache frequency 15.5 (4.6) migraine days a month) compared with 0.2 (4.7) fewer days with migraine a month (baseline headache frequency 16.4 (4.4) migraine days a month; P<0.05 for comparison

between treatment groups) in the placebo group (n=27). In Silvestrini and colleagues' study, 28 patients with an average baseline headache frequency of 21 days a month were randomized 1:1 to low dose topiramate at 50 mg daily or placebo. During month two of treatment, participants receiving topiramate had fewer headache days than those receiving placebo (8.1 (8.1) *v* 20.6 (3.4); P<0.001). More common topiramate related side effects in these studies included weight loss, paresthesias, fatigue, difficulty concentrating, dry mouth, and nausea.

Two large randomized placebo controlled studies with identical study designs have investigated onabotulinumtoxinA for prophylaxis in chronic migraine.[58-61] In total, 1384 participants were randomized 1:1 to injections of onabotulinumtoxinA or placebo. Two thirds of subjects met criteria for overuse of abortive migraine drugs. Baseline headache frequency averaged nearly 20 days with headache per 28 days. A pooled analysis of the two trials found reductions in the mean change from baseline in number of headache days in participants treated with onabotulinumtoxinA and in those receiving placebo injections. However, onabotulinumtoxinA was significantly more effective than placebo at all time points from four weeks until 24 weeks after the first treatment. At the primary endpoint of 24 weeks, the mean reduction in headache days was 8.4 days per 28 days in the onabotulinumtoxinA group and 6.6 days per 28 days in the placebo group (P<0.001). More common onabotulinumtoxinA related side effects in these studies included neck pain, other musculoskeletal pain, injection site pain, eyelid ptosis, muscular weakness, and headache.

Drugs with lower quality evidence (1 randomized trial)

Sodium valproate was studied in a small randomized placebo controlled clinical trial in which 17 patients with chronic migraine received 500 mg sodium valproate twice daily, whereas 12 received placebo.[62] After three months, patients taking sodium valproate had significantly fewer headaches (5.2 *v* 22 headache days a month), whereas those receiving placebo had no change from baseline (22.3 headache days a month; P<0.05 for comparison between the two cohorts). Reported treatment related side effects included somnolence, tremor, impotence, and hair loss.

Gabapentin 2400 mg was investigated for prophylaxis in a study of 95 participants—22 with chronic migraine and 58 with "combination migraine and tension-type headache"—some of whom were "analgesic overusers."[63] Gabapentin was significantly better than placebo for the proportion of days free of headache (10% of days headache free at baseline *v* 26.6% of days headache free with gabapentin *v* 17.5% of days headache free with placebo; P<0.001 for comparison of gabapentin and placebo). Treatment outcomes for patients with migraine were not reported separately from those for patients with tension-type headache. Adverse events experienced by more than 5% of patients taking gabapentin included dizziness, somnolence, ataxia, and nausea.

Tizanidine (mean dose of 18 mg/day) was compared with placebo in a 1:1 randomized clinical trial of prophylaxis for frequent headaches in 92 participants who met criteria for efficacy analyses (at least eight weeks of double blind treatment without major protocol violations).[64] About 75% of participants had chronic migraine. Tizanidine was significantly superior to placebo for the primary endpoint of headache index (headache index = sum (headache days × average intensity × duration in hours)/28 days; P=0.0025). Post hoc analysis showed no differences in outcomes between patients with chronic migraine and those with migrainous or tension-type headaches. Tizanidine associated side effects included somnolence, dizziness, dry mouth, and asthenia.

Amitriptyline was compared with onabotulinumtoxinA for prophylaxis in a 1:1 randomized but non-blinded non-placebo controlled trial of 72 patients with chronic migraine.[65] Amitriptyline, at doses of 25-50 mg daily, had similar benefits to onabotulinumtoxinA. The number of days with pain was reduced by at least 50% in 72% of participants receiving amitriptyline and 67.8% of those taking onabotulinumtoxinA. Pain intensity was reduced by at least 3 points on a visual analog scale in 55.6% of patients receiving amitriptyline and 50% of those taking onabotulinumtoxinA. Lastly, the number of doses of analgesic given was reduced by least 50% in 71% of patients receiving amitriptyline and 77% of those taking onabotulinumtoxinA. Common side effects of amitriptyline included weight gain, dry mouth, somnolence, and constipation.

Open label studies provide lower quality but promising evidence for effective treatment of chronic migraine with atenolol, memantine, zonisamide, and pregabalin.[66-69]

Prophylaxis with a combination of drugs might be considered if the response to monotherapy is poor.[70] Published data in support of combining migraine prophylactic drugs are limited, and one study suggests that a combination of topiramate and propranolol is no more effective than topiramate alone for treating chronic migraine.[71] However, combination therapy is often used in clinical practice. The efficacy of this treatment approach requires further investigation. If combination therapy is used, drugs with differing mechanisms of action should be considered.

Drugs used for both episodic migraine and chronic migraine

Many drugs commonly used for treating episodic migraine are used for treating chronic migraine, despite the lack of evidence supporting their utility in this form of migraine. It is generally assumed that these drugs are effective in chronic migraine, but future investigations should test this assumption.

Non-drug treatments

Non-drug treatments such as physical therapy, behavioral therapy (for example, relaxation techniques, biofeedback, and cognitive behavioral therapy), massage, acupuncture, and physical exercise may be considered as adjuncts for the treatment of chronic migraine.[54 72-75] The choice of treatment should be guided by the needs of individual patients. For example, a patient with muscle tension in the neck and shoulders might benefit from physical therapy and massage, whereas someone with migraine related anxiety might be a good candidate for relaxation therapy.

Refractory chronic migraine

Despite use of best treatments, some patients with chronic migraine are refractory to conventional treatments. The prevalence of refractory chronic migraine in the general population is unknown, but about 5% of patents seen in specialty headache clinics are estimated to have refractory migraine, mostly refractory chronic migraine.[76] Before labeling a patient as having refractory migraine, it is important to assess the details of previous trials of treatment, including adherence to treatment, the maximum dose of drug used, and the duration for which the treatment was trialed. It is not uncommon for patients to consider themselves to have "failed" numerous drug treatments, when in reality they were not given adequate trials owing to the use of subtherapeutic doses or insufficient trial durations (or both).

Topics to discuss with patients

Active participation in treatment

The high frequency of symptoms in chronic migraine and the often unpredictable timing of severe migraine attacks can result in patients feeling that they have no control over their illness.[77 78] This can translate into patients taking a passive role in their treatment. It must be stressed to patients that treatment outcomes will be optimized only if they take an active role in their treatment. Active participation can include:

- Maintaining a headache and migraine trigger diary to identify migraine triggers and assess changes in migraine patterns over time
- Modifying lifestyle to minimize exposure to migraine triggers and risk factors
- Adhering to drug and non-drug based treatments.

Avoid drug overuse

Patients must be counseled about the negative effects of overusing abortive drugs. Until educated about drug overuse, most patients do not recognize that the frequent use of abortive migraine drugs can lead to headaches becoming more frequent and less responsive to other treatments for migraine. Clinicians should set limits on the average number of days a week that abortive migraine drugs can be used. On the basis of expert opinion, drug overuse is diagnosed in patients who have regularly used ergotamines, triptans, opioids, combination analgesics, or drugs from multiple classes on at least 10 days a month or simple analgesics on at least 15 days a month for at least three months (box 4).[40] For the successful avoidance of drug overuse, it is essential that the clinician works with the patient to find effective prophylactic treatments that reduce headache frequency. If drug overuse is present, treatment typically consists of patient education and counseling, withdrawal of the overused drug, and migraine prophylactic treatment.[79 80]

Be patient with prophylactic treatments

Patients with migraine often expect immediate results from new drugs. To improve adherence to treatment and reduce patient frustration, clinicians should make patients aware of the expected interval between starting a new drug and obtaining relief. Once the target dose is reached, six to eight weeks of treatment might be needed before maximum benefits are realized.

The goal is control

Patients should be advised that a realistic goal of treatment is to reduce the frequency and severity of their migraine symptoms and their migraine related disability. Unfortunately, the goal is not complete remission or cure of migraine.

Looking ahead

Research

An improved understanding of the pathophysiologic mechanisms involved in the transformation from episodic migraine to chronic migraine and reversion to episodic migraine is needed to develop methods of inhibiting transformation and supporting reversion. Several laboratories have developed animal models that reflect physiologic components of chronic migraine. It is hoped that such models will yield insights into mechanisms of chronic migraine transformation and reversion.[81-84]

A recent study in humans suggests that plasma concentrations of CGRP measured between migraine attacks might serve as a biomarker for chronic migraine.[39] Future studies should evaluate the utility of measuring concentrations of CGRP and other vasoactive neuropeptides to predict transformation, predict treatment responses, and assess early responses to migraine prophylaxis. Structural and functional neuroimaging biomarkers for predicting transformation and reversion and for predicting treatment response are also being sought. Structural measures (such as cortical thickness and volumetrics) and functional measures (such as regional activation and resting state functional connectivity) might help to advance our understanding of mechanisms involved in chronic migraine and help to identify chronic migraine biomarkers. Studies investigating genetic profiles that predispose people to developing chronic migraine are needed. Large, longitudinal, multicenter studies that collect detailed phenotypic, biologic, and neuroimaging data would greatly enhance the efficiency of chronic migraine research.

Further work is needed to delineate the diagnostic criteria for chronic migraine more accurately. The current diagnostic requirement of at least 15 headache days a month was set arbitrarily on the basis of expert consensus. Future studies should explore associations between the frequency of headache and physiologic, imaging, and phenotypic characteristics with the goal of refining criteria that differentiate episodic migraine from chronic migraine. These studies should also explore further subgrouping of patients with chronic migraine, such as differentiating patients who have constant, unremitting headache from those who have periods of freedom from headache.

Future drug treatments

New drugs that are more effective, better tolerated, and have fewer contraindications are needed. Several new classes of drug are under investigation for the abortive or prophylactic treatment of migraine. These include: CGRP antagonists, anti-CGRP antibodies, anti-CGRP receptor antibodies, 5-hydroxytryptamine type 1F (5HT-1F) receptor agonists, nitric oxide synthetase inhibitors, pituitary adenylate activating peptide (PACAP) receptor antago-

nists, transient receptor potential subfamily V member 1 (TRPV1) antagonists, and glutamate receptor antagonists (clinicaltrials.gov).[85] New methods of delivering existing migraine abortive drug are under study, including transdermal delivery of sumatriptan, a bidirectional nasal delivery system for sumatriptan, and oral inhalation of dihydroergotamine (clinicaltrials.gov).[86] In addition, drugs commonly used for treating episodic migraine should be tested for efficacy in chronic migraine in well designed randomized placebo controlled clinical trials.

Future non-drug treatments

Electrical stimulation of peripheral nerves and transcranial brain stimulation are of interest for the treatment of chronic migraine.

A supraorbital and supratrochlear percutaneous nerve stimulator is available over the counter.. A small, sham controlled study of this device (active stimulation n=34; sham stimulation n=33) in people with episodic migraine showed that 20 minutes of daily stimulation for three months resulted in 38% of patients having at least a 50% reduction in monthly migraine days (*v* 12.1% in the sham stimulation group, P=0.023).[87] The effectiveness of this stimulator in chronic migraine has yet to be investigated.

Occipital nerve stimulation through implanted stimulators continues to be investigated for the treatment of refractory chronic migraine. Several open label case series and two sham controlled clinical trials suggest that occipital nerve stimulation might provide some benefit for these patients.[88-92] However, the larger of the two sham controlled trials (the only one powered to test an a priori defined primary outcome) failed to show superiority of occipital nerve stimulation over sham stimulation for the primary outcome of at least a 50% reduction in average pain intensity with no increase in average headache duration.[92] Furthermore, adverse event rates, mostly as a result of lead migration, infection, and persistent stimulator related pain, have consistently been high in published reports. Further occipital nerve stimulation trials are currently under way (clinicaltrials.gov). Dual occipital and supraorbital nerve stimulation is also of interest.[93 94]

Sphenopalatine ganglion stimulation, vagal nerve stimulation, transcranial magnetic stimulation, and transcranial direct current stimulation have each shown early evidence of possible benefit for migraine treatment but require additional investigations to determine their safety and efficacy.[95-98]

Surgical deactivation of migraine trigger sites has been investigated in observational studies and a small controlled trial.[99-102] However, results from randomized controlled multicenter trials with long term follow-up have not been published. Therefore, there is currently insufficient evidence to support the use of such surgery for the treatment of migraine and it should be considered only within the context of clinical research trials.[103 104]

Chronic migraine guidelines

Chronic migraine diagnostic criteria

The newest diagnostic criteria for chronic migraine are available in the latest International Classification of Headache Disorders guideline.[40] These criteria should be used for assigning the diagnosis in all research studies and can help clinicians make a diagnosis in their patients.

Defining refractory chronic migraine

Guidelines for considering a patient with chronic migraine as "refractory" to treatment are available.[105-108] Such a definition is important for determining when it might be appropriate to recommend less well proved treatments or treatments that are still being investigated and are associated with greater risk (such as implanted stimulators). On the basis of expert consensus, the American Headache Society proposed the following definition for refractory chronic migraine:

- Headaches seriously interfere with function or quality of life despite modification of triggers, lifestyle factors, and adequate trials of drugs with established efficacy
- The patient did not respond to adequate trials of preventive drugs, alone or in combination, from at least two of four drug classes including β blockers, anticonvulsants, tricyclics, and calcium channel blockers
- The patient did not respond to adequate trials of abortive drugs, including both a triptan and dihydroergotamine intranasal or injectable formulation and either non-steroidal anti-inflammatory drugs or combination analgesics, unless contraindicated.

Management

Management guidelines specifically for chronic migraine are available from the Latin American and Brazilian Headache Societies, the German Migraine and Headache Society/German Society for Neurology, and the Austrian Headache Society/Swiss Headache Society.[109 110] Guidelines for the management of episodic migraine are available from the American Headache Society and American Academy of Neurology, Canadian Headache Society, the European Federation of Neurological Societies (EFNS), the Taiwan Headache Society, the Italian Society for the Study of Headache, headache specialists in India, and the Croatian Society for Neurovascular Disorders.[111-119] Although a comparison of guidelines is beyond the scope of this review, Loder and colleagues have published a comparison of the 2012 American Headache Society/American Academy of Neurology guidelines with the Canadian guidelines and the EFNS guidelines.[120] The European Headache Federation recently published a position statement on the use of neuromodulation for the treatment of chronic headaches.[121]

Clinical trial design for studies of chronic migraine

The International Headache Society clinical trials guidelines (2012) include guidance on conducting migraine clinical trials.[122] Guidelines for trials of prophylactic drugs for chronic migraine were published in 2008.[123] A series of papers was recently published that discusses important statistical considerations when studying the transformation and reversion of chronic migraine.[124-127]

Conclusions

Chronic migraine is a common neurologic condition that causes substantial pain, migraine hypersensitivity, and disability. Typically, chronic migraine develops after a slow

KEY RESEARCH QUESTIONS

What mechanisms underlie transformation from episodic migraine to chronic migraine?

What animal models are optimal for studying chronic migraine?

How can transformation to chronic migraine be best predicted and prevented at the level of the individual patient?

What are the safest and most effective treatments for chronic migraine?

increase in headache frequency over months to years. Clinicians and patients must be aware of modifiable risk factors associated with transformation to chronic migraine and reversion to episodic migraine. In addition to risk factor modification, treatment includes the avoidance of migraine attack triggers and the use of drug and non-drug abortive and prophylactic treatments.

Substantial advances have been achieved in defining chronic migraine, describing its pathophysiology, identifying risk factors associated with transformation and reversion, and identifying effective treatments. However, further work is needed within each of these areas. Animal models of chronic migraine, careful endophenotyping of patients, and advanced neuroimaging are likely to yield important additional insights. Furthermore, existing and new treatments for episodic migraine need to be studied in well designed clinical trials for their utility in treating chronic migraine.

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1 Natoli JL, Manack A, Dean B, Butler Q, Turkel CC, Stovner L, et al. Global prevalence of chronic migraine: a systematic review. *Cephalalgia* 2010;30:599-609.
2 Buse DC, Manack AN, Fanning KM, Serrano D, Reed ML, Turkel CC, et al. Chronic migraine prevalence, disability, and sociodemographic factors: results from the American Migraine Prevalence and Prevention Study. *Headache* 2012;52:1456-70.
3 Bigal ME, Serrano D, Buse D, Scher A, Stewart WF, Lipton RB. Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study. *Headache* 2008;48:1157-68.
4 Bigal ME, Lipton RB. Obesity is a risk factor for transformed migraine but not chronic tension-type headache. *Neurology* 2006;67:252-7.
5 Louter MA, Bosker JE, van Oosterhout WP, van Zwet EW, Zitman FG, Ferrari MD, et al. Cutaneous allodynia as a predictor of migraine chronification. *Brain* 2013;136:3489-96.
6 Scher AI, Midgette LA, Lipton RB. Risk factors for headache chronification. *Headache* 2008;48:16-25.
7 Scher AI, Stewart WF, Buse D, Krantz DS, Lipton RB. Major life changes before and after the onset of chronic daily headache: a population-based study. *Cephalalgia* 2008;28:868-76.
8 Davies P. Medication overuse headache: a silent pandemic. *Pain* 2012;153:7-8.
9 Evers S, Gralow I, Bauer B, Suhr B, Buchheister A, Husstedt IW, et al. Sumatriptan and ergotamine overuse and drug-induced headache: a clinicoepidemiologic study. *Clin Neuropharmacol* 1999;22:201-6.
10 Limmroth V, Katsarava Z, Fritsche G, Przywara S, Diener HC. Features of medication overuse headache following overuse of different acute headache drugs. *Neurology* 2002;59:1011-4.
11 Lipton RB, Serrano D, Nicholson RA, Buse DC, Runken MC, Reed ML. Impact of NSAID and triptan use on developing chronic migraine: results from the American Migraine Prevalence and Prevention (AMPP) study. *Headache* 2013;53:1548-63.
12 Starling AJ, Hoffman-Snyder C, Halker RB, Wellik KE, Vargas BB, Dodick DW, et al. Risk of development of medication overuse headache with nonsteroidal anti-inflammatory drug therapy for migraine: a critically appraised topic. *Neurologist* 2011;17:297-9.
13 Manack A, Buse DC, Serrano D, Turkel CC, Lipton RB. Rates, predictors, and consequences of remission from chronic migraine to episodic migraine. *Neurology* 2011;76:711-8.
14 Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380:2197-223.
15 Stovner LJ, Andree C. Impact of headache in Europe: a review for the Eurolight project. *J Headache Pain* 2008;9:139-46.
16 Stewart WF, Ricci JA, Chee E, Morganstein D, Lipton R. Lost productive time and cost due to common pain conditions in the US workforce. *JAMA* 2003;290:2443-54.
17 Buse DC, Manack A, Serrano D, Turkel C, Lipton RB. Sociodemographic and comorbidity profiles of chronic migraine and episodic migraine sufferers. *J Neurol Neurosurg Psychiatry* 2010;81:428-32.
18 Bigal ME, Serrano D, Reed M, Lipton RB. Chronic migraine in the population: burden, diagnosis, and satisfaction with treatment. *Neurology* 2008;71:559-66.
19 Buse D, Manack A, Serrano D, Reed M, Varon S, Turkel C, et al. Headache impact of chronic and episodic migraine: results from the American Migraine Prevalence and Prevention study. *Headache* 2012;52:3-17.
20 Stokes M, Becker WJ, Lipton RB, Sullivan SD, Wilcox TK, Wells L, et al. Cost of health care among patients with chronic and episodic migraine in Canada and the USA: results from the International Burden of Migraine Study (IBMS). *Headache* 2011;51:1058-77.
21 Blumenfeld AM, Varon SF, Wilcox TK, Buse DC, Kawata AK, Manack A, et al. Disability, HRQoL and resource use among chronic and episodic migraineurs: results from the International Burden of Migraine Study (IBMS). *Cephalalgia* 2011;31:301-15.
22 Munakata J, Hazard E, Serrano D, Klingman D, Rupnow MF, Tierce J, et al. Economic burden of transformed migraine: results from the American Migraine Prevalence and Prevention (AMPP) study. *Headache* 2009;49:498-508.
23 Stewart WF, Wood GC, Manack A, Varon SF, Buse DC, Lipton RB. Employment and work impact of chronic migraine and episodic migraine. *J Occup Environ Med* 2010;52:8-14.
24 Aurora SK, Barrodale PM, Tipton RL, Khodavirdi A. Brainstem dysfunction in chronic migraine as evidenced by neurophysiological and positron emission tomography studies. *Headache* 2007;47:996-1003; discussion 1004-7.
25 Moulton EA, Burstein R, Tully S, Hargreaves R, Becerra L, Borsook D. Interictal dysfunction of a brainstem descending modulatory center in migraine patients. *PLoS One* 2008;3:e3799.
26 Schwedt TJ, Larson-Prior L, Coalson RS, Nolan T, Mar S, Ances BM, et al. Allodynia and descending pain modulation in migraine: a resting state functional connectivity analysis. *Pain Med* 2014;15:154-65.
27 Aurora SK. Spectrum of illness: understanding biological patterns and relationships in chronic migraine. *Neurology* 2009;72(5 suppl):S8-13.
28 Aurora SK. Is chronic migraine one end of a spectrum of migraine or a separate entity? *Cephalalgia* 2009;29:597-605.
29 Aurora SK, Kulthia A, Barrodale PM. Mechanism of chronic migraine. *Curr Pain Headache Rep* 2011;15:57-63.
30 Aurora SK, Barrodale P, Chronicle EP, Mulleners WM. Cortical inhibition is reduced in chronic and episodic migraine and demonstrates a spectrum of illness. *Headache* 2005;45:546-52.
31 Diener HC, Dodick DW, Goadsby PJ, Lipton RB, Olesen J, Silberstein SD. Chronic migraine—classification, characteristics and treatment. *Nat Rev Neurol* 2011;8:162-71.
32 Kim JH, Suh SI, Seol HY, Oh K, Seo WK, Yu SW, et al. Regional grey matter changes in patients with migraine: a voxel-based morphometry study. *Cephalalgia* 2008;28:598-604.
33 Maleki N, Becerra L, Nutile L, Pendse G, Brawn J, Bigal M, et al. Migraine attacks the basal ganglia. *Mol Pain* 2011;7:71.
34 Schmitz N, Admiraal-Behloul F, Arkink EB, Kruit MC, Schoonman GG, Ferrari MD, et al. Attack frequency and disease duration as indicators for brain damage in migraine. *Headache* 2008;48:1044-55.
35 Valfre W, Rainero I, Bergui M, Pinessi L. Voxel-based morphometry reveals gray matter abnormalities in migraine. *Headache* 2008;48:109-17.
36 De Tommaso M, Losito L, Difruscolo O, Libro G, Guido M, Livrea P. Changes in cortical processing of pain in chronic migraine. *Headache* 2005;45:1208-18.
37 Mongini F, Keller R, Deregibus A, Barbalonga E, Mongini T. Frontal lobe dysfunction in patients with chronic migraine: a clinical-neuropsychological study. *Psychiatry Res* 2005;133:101-6.
38 Schwedt TJ, Schlaggar BL, Mar S, Nolan T, Coalson RS, Nardos B, et al. Atypical resting-state functional connectivity of affective pain regions in chronic migraine. *Headache* 2013;53:737-51.
39 Cernuda-Morollon E, Larrosa D, Ramon C, Vega J, Martinez-Camblor P, Pascual J. Interictal increase of CGRP levels in peripheral blood as a biomarker for chronic migraine. *Neurology* 2013;81:1191-6.
40 The International Classification of Headache Disorders, 3rd ed (beta version). *Cephalalgia* 2013;33:629-808.
41 Bigal ME, Lipton RB. The differential diagnosis of chronic daily headaches: an algorithm-based approach. *J Headache Pain* 2007;8:263-72.
42 Welch KM, Goadsby PJ. Chronic daily headache: nosology and pathophysiology. *Curr Opin Neurol* 2002;15:287-95.
43 Bigal ME, Kurth T, Santanello N, Buse D, Golden W, Robbins M, et al. Migraine and cardiovascular disease: a population-based study. *Neurology* 2010;74:628-35.

44 Chen YC, Tang CH, Ng K, Wang SJ. Comorbidity profiles of chronic migraine sufferers in a national database in Taiwan. *J Headache Pain* 2012;13:311-9.
45 De Tommaso M, Sardaro M, Serpino C, Costantini F, Vecchio E, Prudenzano MP, et al. Fibromyalgia comorbidity in primary headaches. *Cephalalgia* 2009;29:453-64.
46 Kruit MC, van Buchem MA, Launer LJ, Terwindt GM, Ferrari MD. Migraine is associated with an increased risk of deep white matter lesions, subclinical posterior circulation infarcts and brain iron accumulation: the population-based MRI CAMERA study. *Cephalalgia* 2010;30:129-36.
47 Riedl A, Schmidtmann M, Stengel A, Goebel M, Wisser AS, Klapp BF, et al. Somatic comorbidities of irritable bowel syndrome: a systematic analysis. *J Psychosom Res* 2008;64:573-82.
48 Spector JT, Kahn SR, Jones MR, Jayakumar M, Dalal D, Nazarian S. Migraine headache and ischemic stroke risk: an updated meta-analysis. *Am J Med* 2010;123:612-24.
49 Teixeira AL, Costa EA, da Silva AA Jr, dos Santos IA, Gomez RS, Kummer A, et al. Psychiatric comorbidities of chronic migraine in community and tertiary care clinic samples. *J Headache Pain* 2012;13:551-5.
50 Verrotti A, Agostinelli S, D'Egidio C, Di Fonzo A, Carotenuto M, Parisi P, et al. Impact of a weight loss program on migraine in obese adolescents. *Eur J Neurol* 2013;20:394-7.
51 Hershey AD, Powers SW, Nelson TD, Kabbouche MA, Winner P, Yonker M, et al. Obesity in the pediatric headache population: a multicentre study. *Headache* 2009;49:170-7.
52 Narin SO, Pinar L, Erbas D, Ozturk V, Idiman F. The effects of exercise and exercise-related changes in blood nitric oxide level on migraine headache. *Clin Rehabil* 2003;17:624-30.
53 Pryse-Phillips WE, Dodick DW, Edmeads JG, Gawel MJ, Nelson RF, Purdy RA, et al. Guidelines for the nonpharmacologic management of migraine in clinical practice. Canadian Headache Society. *CMAJ* 1998;159:47-54.
54 Varkey E, Cider A, Carlsson J, Linde M. Exercise as migraine prophylaxis: a randomized study using relaxation and topiramate as controls. *Cephalalgia* 2011;31:1428-38.
55 Diener HC, Bussone G, Van Oene JC, Lahaye M, Schwalen S, Goadsby PJ. Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. *Cephalalgia* 2007;27:814-23.
56 Silberstein SD, Lipton RB, Dodick DW, Freitag FG, Ramadan N, Mathew N, et al. Efficacy and safety of topiramate for the treatment of chronic migraine: a randomized, double-blind, placebo-controlled trial. *Headache* 2007;47:170-80.
57 Silvestrini M, Bartolini M, Coccia M, Baruffaldi R, Taffi R, Provinciali L. Topiramate in the treatment of chronic migraine. *Cephalalgia* 2003;23:820-4.
58 Aurora SK, Dodick DW, Turkel CC, DeGryse RE, Silberstein SD, Lipton RB, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. *Cephalalgia* 2010;30:793-803.
59 Aurora SK, Winner P, Freeman MC, Spierings EL, Heiring JO, DeGryse RE, et al. OnabotulinumtoxinA for treatment of chronic migraine: pooled analyses of the 56-week PREEMPT clinical program. *Headache* 2011;51:1358-73.
60 Diener HC, Dodick DW, Aurora SK, Turkel CC, DeGryse RE, Lipton RB, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. *Cephalalgia* 2010;30:804-14.
61 Dodick DW, Turkel CC, DeGryse RE, Aurora SK, Silberstein SD, Lipton RB, et al. OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. *Headache* 2010;50:921-36.
62 Yurekli VA, Akhan G, Kutluhan S, Uzar E, Koyuncuoglu HR, Gultekin F. The effect of sodium valproate on chronic daily headache and its subgroups. *J Headache Pain* 2008;9:37-41.
63 Spira PJ, Beran RG. Gabapentin in the prophylaxis of chronic daily headache: a randomized, placebo-controlled study. *Neurology* 2003;61:1753-9.
64 Saper JR, Lake AE 3rd, Cantrell DT, Winner PK, White JR. Chronic daily headache prophylaxis with tizanidine: a double-blind, placebo-controlled, multicenter outcome study. *Headache* 2002;42:470-82.
65 Magalhaes E, Menezes C, Cardeal M, Melo A. Botulinum toxin type A versus amitriptyline for the treatment of chronic daily migraine. *Clin Neurol Neurosurg* 2010;112:463-6.
66 Calandre EP, Garcia-Leiva JM, Rico-Villademoros F, Vilchez JS, Rodriguez-Lopez CM. Pregabalin in the treatment of chronic migraine: an open-label study. *Clin Neuropharmacol* 2010;33:35-9.
67 Edvardsson B. Atenolol in the prophylaxis of chronic migraine: a 3-month open-label study. *Springerplus* 2013;2:479.
68 Pascual-Gomez J, Alana-Garcia M, Oterino A, Leira R, Lainez-Andres JM. [Preventive treatment of chronic migraine with zonisamide: a study in patients who are refractory or intolerant to topiramate]. *Rev Neurol* 2008;47:449-51.
69 Bigal M, Rapopot A, Sheftell F, Tepper D, Tepper S. Memantine in the preventive treatment of refractory migraine. *Headache* 2008;48:1337-42.
70 Peterlin BL, Calhoun AH, Siegel S, Mathew NT. Rational combination therapy in refractory migraine. *Headache* 2008;48:805-19.
71 Silberstein SD, Dodick DW, Lindblad AS, Holroyd K, Harrington M, Mathew NT, et al. Randomized, placebo-controlled trial of propranolol added to topiramate in chronic migraine. *Neurology* 2012;78:976-84.
72 Andrasik F. Behavioral treatment of migraine: current status and future directions. *Expert Rev Neurother* 2004;4:403-13.
73 Nestoriuc Y, Martin A. Efficacy of biofeedback for migraine: a meta-analysis. *Pain* 2007;128:111-27.
74 Pistoia F, Sacco S, Carolei A. Behavioral therapy for chronic migraine. *Curr Pain Headache Rep* 2013;17:304.
75 Yang CP, Chang MH, Liu PE, Li TC, Hsieh CL, Hwang KL, et al. Acupuncture versus topiramate in chronic migraine prophylaxis: a randomized clinical trial. *Cephalalgia* 2011;31:1510-21.
76 Irimia P, Palma JA, Fernandez-Torron R, Martinez-Vila E. Refractory migraine in a headache clinic population. *BMC Neurol* 2011;11:94.
77 Martin NJ, Holroyd KA, Penzien DB. The headache-specific locus of control scale: adaptation to recurrent headaches. *Headache* 1990;30:729-34.
78 Scharff L, Turk DC, Marcus DA. The relationship of locus of control and psychosocial-behavioral response in chronic headache. *Headache* 1995;35:527-33.
79 Hagen K, Albretsen C, Vilming ST, Salvesen R, Gronning M, Helde G, et al. Management of medication overuse headache: 1-year randomized multicentre open-label trial. *Cephalalgia* 2009;29:221-32.
80 Zeeberg P, Olesen J, Jensen R. Discontinuation of medication overuse in headache patients: recovery of therapeutic responsiveness. *Cephalalgia* 2006;26:1192-8.
81 Melo-Carrillo A, Lopez-Avila A. A chronic animal model of migraine, induced by repeated meningeal nociception, characterized by a behavioral and pharmacological approach. *Cephalalgia* 2013;33:1096-105.
82 Oshinsky ML, Gomonchareonsiri S. Episodic dural stimulation in awake rats: a model for recurrent headache. *Headache* 2007;47:1026-36.
83 Pusic AD, Grinberg YY, Mitchell HM, Kraig RP. Modeling neural immune signaling of episodic and chronic migraine using spreading depression in vitro. *J Vis Exp* 2011;(52). pii: 2910.
84 Stucky NL, Gregory E, Winter MK, He YY, Hamilton ES, McCarson KE, et al. Sex differences in behavior and expression of CGRP-related genes in a rodent model of chronic migraine. *Headache* 2011;51:674-92.
85 Silberstein SD. Emerging target-based paradigms to prevent and treat migraine. *Clin Pharmacol Ther* 2013;93:78-85.
86 Rapoport AM. The therapeutic future in headache. *Neurol Sci* 2012;33(suppl 1):S119-25.
87 Schoenen J, Vandersmissen B, Jeangette S, Herroelen L, Vandenheede M, Gerard P, et al. Migraine prevention with a supraorbital transcutaneous stimulator: a randomized controlled trial. *Neurology* 2013;80:697-704.
88 Oh MY, Ortega J, Bellotte JB, Whiting DM, Alo K. Peripheral nerve stimulation for the treatment of occipital neuralgia and transformed migraine using a c1-2-3 subcutaneous paddle style electrode: a technical report. *Neuromodulation* 2004;7:103-12.
89 Popeney CA, Alo KM. Peripheral neurostimulation for the treatment of chronic, disabling transformed migraine. *Headache* 2003;43:369-75.
90 Saper JR, Dodick DW, Silberstein SD, McCarville S, Sun M, Goadsby PJ. Occipital nerve stimulation for the treatment of intractable chronic migraine headache: ONSTIM feasibility study. *Cephalalgia* 2011;31:271-85.
91 Schwedt TJ, Dodick DW, Hentz J, Trentman TL, Zimmerman RS. Occipital nerve stimulation for chronic headache--long-term safety and efficacy. *Cephalalgia* 2007;27:153-7.
92 Silberstein SD, Dodick DW, Saper J, Huh B, Slavin KV, Sharan A, et al. Safety and efficacy of peripheral nerve stimulation of the occipital nerves for the management of chronic migraine: results from a randomized, multicenter, double-blinded, controlled study. *Cephalalgia* 2012;32:1165-79.
93 Hann S, Sharan A. Dual occipital and supraorbital nerve stimulation for chronic migraine: a single-center experience, review of literature, and surgical considerations. *Neurosurg Focus* 2013;35:E9.
94 Reed KL, Black SB, Banta CJ 2nd, Will KR. Combined occipital and supraorbital neurostimulation for the treatment of chronic migraine headaches: initial experience. *Cephalalgia* 2010;30:260-71.
95 Cecchini AP, Mea E, Tullo V, Curone M, Franzini A, Broggi G, et al. Vagus nerve stimulation in drug-resistant daily chronic migraine with depression: preliminary data. *Neurol Sci* 2009;30(suppl 1):S101-4.
96 Lipton RB, Pearlman SH. Transcranial magnetic simulation in the treatment of migraine. *Neurotherapeutics* 2010;7:204-12.
97 Teepker M, Hotzel J, Timmesfeld N, Reis J, Mylius V, Haag A, et al. Low-frequency rTMS of the vertex in the prophylactic treatment of migraine. *Cephalalgia* 2010;30:137-44.
98 Tepper SJ, Rezai A, Narouze S, Steiner C, Mohajer P, Ansarinia M. Acute treatment of intractable migraine with sphenopalatine ganglion electrical stimulation. *Headache* 2009;49:983-9.
99 Chepla KJ, Oh E, Guyuron B. Clinical outcomes following supraorbital foraminotomy for treatment of frontal migraine headache. *Plast Reconstr Surg* 2012;129:656e-62e.
100 Guyuron B, Kriegler JS, Davis J, Amini SB. Comprehensive surgical treatment of migraine headaches. *Plast Reconstr Surg* 2005;115:1-9.
101 Guyuron B, Kriegler JS, Davis J, Amini SB. Five-year outcome of surgical treatment of migraine headaches. *Plast Reconstr Surg* 2011;127:603-8.

102 Guyuron B, Reed D, Kriegler JS, Davis J, Pashmini N, Amini S. A placebo-controlled surgical trial of the treatment of migraine headaches. *Plast Reconstr Surg* 2009;124:461-8.
103 Loder E, Weizenbaum E, Frishberg B, Silberstein S. Choosing wisely in headache medicine: the American Headache Society's list of five things physicians and patients should question. *Headache* 2013;53:1651-9.
104 Mathew PG. A critical evaluation of migraine trigger site deactivation surgery. *Headache* 2014;54:142-52.
105 Bussone G. Clinical considerations on chronic migraine, pharmacoresistance and refractoriness. *Neurol Sci* 2010;31(suppl 1):S83-5.
106 D'Amico D, Leone M, Grazzi L, Bussone G. When should "chronic migraine" patients be considered "refractory" to pharmacological prophylaxis? *Neurol Sci* 2008;29(suppl 1):S55-8.
107 Schulman EA, Lake AE 3rd, Goadsby PJ, Peterlin BL, Siegel SE, Markley HG, et al. Defining refractory migraine and refractory chronic migraine: proposed criteria from the refractory headache special interest section of the American Headache Society. *Headache* 2008;48:778-82.
108 Schulman EA, Peterlin BL, Lake AE 3rd, Lipton RB, Hanlon A, Siegel S, et al. Defining refractory migraine: results of the RHSIS survey of American Headache Society members. *Headache* 2009;49:509-18.
109 Giacomozzi AR, Vindas AP, da Silva AA Jr, Bordini CA, Buonanotte CF, Roesler CA, et al. Latin American consensus on guidelines for chronic migraine treatment. *Arq Neuropsiquiatr* 2013;71:478-86.
110 Straube A, Gaul C, Forderreuther S, Kropp P, Marziniak M, Evers S, et al. [Therapy and care of patients with chronic migraine: expert recommendations of the German Migraine and Headache Society/German Society for Neurology as well as the Austrian Headache Society/Swiss Headache Society]. *Nervenarzt* 2012;83:1600-8.
111 Treatment Guideline Subcommittee of the Taiwan Headache Society. [Treatment guidelines for preventive treatment of migraine]. *Acta Neurol Taiwan* 2008;17:132-48.
112 Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, et al. EFNS guideline on the drug treatment of migraine—revised report of an EFNS task force. *Eur J Neurol* 2009;16:968-81.
113 Holland S, Silberstein SD, Freitag F, Dodick DW, Argoff C, Ashman E. Evidence-based guideline update: NSAIDs and other complementary treatments 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;78:1346-53.
114 Pringsheim T, Davenport W, Mackie G, Worthington I, Aube M, Christie SN, et al. Canadian Headache Society guideline for migraine prophylaxis. *Can J Neurol Sci* 2012;39(2 suppl 2):S1-59.
115 Ravishankar K, Chakravarty A, Chowdhury D, Shukla R, Singh S. Guidelines on the diagnosis and the current management of headache and related disorders. *Ann Indian Acad Neurol* 2011;14(suppl 1):S40-59.
116 Sarchielli P, Granella F, Prudenzano MP, Pini LA, Guidetti V, Bono G, et al. Italian guidelines for primary headaches: 2012 revised version. *J Headache Pain* 2012;13(suppl 2):S31-70.
117 Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the quality standards subcommittee of the American Academy of Neurology. *Neurology* 2000;55:754-62.
118 Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman E. 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.
119 Vukovic Cvetkovic V, Kes VB, Seric V, Solter VV, Demarin V, Janculjak D, et al. Report of the Croatian Society for Neurovascular Disorders, Croatian Medical Association. Evidence based guidelines for treatment of primary headaches—2012 update. *Acta Clin Croat* 2012;51:323-78.
120 Loder E, Burch R, Rizzoli P. The 2012 AHS/AAN guidelines for prevention of episodic migraine: a summary and comparison with other recent clinical practice guidelines. *Headache* 2012;52:930-45.
121 Martelletti P, Jensen RH, Antal A, Arcioni R, Brighina F, de Tommaso M, et al. Neuromodulation of chronic headaches: position statement from the European Headache Federation. *J Headache Pain* 2013;14:86.
122 Tfelt-Hansen P, Pascual J, Ramadan N, Dahlof C, D'Amico D, Diener HC, et al. Guidelines for controlled trials of drugs in migraine: third edition. A guide for investigators. *Cephalalgia* 2012;32:6-38.
123 Silberstein S, Tfelt-Hansen P, Dodick DW, Limmroth V, Lipton RB, Pascual J, et al. Guidelines for controlled trials of prophylactic treatment of chronic migraine in adults. *Cephalalgia* 2008;28:484-95.
124 Houle TT, Turner DP, Houle TA, Smitherman TA, Martin V, Penzien DB, et al. Rounding behavior in the reporting of headache frequency complicates headache chronification research. *Headache* 2013;53:908-19.
125 Houle TT, Turner DP, Smitherman TA, Penzien DB, Lipton RB. Influence of random measurement error on estimated rates of headache chronification and remission. *Headache* 2013;53:920-9.
126 Lipton RB, Penzien DB, Turner DP, Smitherman TA, Houle TT. Methodological issues in studying rates and predictors of migraine progression and remission. *Headache* 2013;53:930-4.
127 Turner DP, Smitherman TA, Penzien DB, Lipton RB, Houle TT. Rethinking headache chronification. *Headache* 2013;53:901-7.