Diagnosis and treatment for chronic migraine

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Abstract: Migraine is a debilitating headache disorder that is underdiagnosed and undertreated worldwide, partially attributable to misdiagnosis and expectations of poor treatment outcomes. This article provides a review of chronic migraine, including pathophysiology, burden, diagnosis, and management, with special emphasis on the role of NPs.

Migraine is a disabling headache disorder that is underdiagnosed and undertreated worldwide, which may be partially attributed to misdiagnosis and patients' expectations of poor treatment outcomes.[1] The prevalence of migraine in the United States has been stable for over 20 years, around 11.7% to 13.2%.[2-4] Chronic migraine (CM) represents approximately 7.7% of individuals with migraine, with a U.S. prevalence of approximately 0.9%.[5] The purpose of this article is to provide a review of CM, including pathophysiology, burden, diagnosis, and management, with special emphasis on the role of NPs.

Keywords: chronic migraine, diagnosis, headache management, migraine

Headache disorders

The *International Classification of Headache Disorders,* 3rd edition (beta version) (ICHD-3b) includes diagnostic criteria for CM among the primary headache disorders, a category that includes migraine, tension-type headache, trigeminal autonomic cephalalgias, and other primary headaches.[6] Migraine is subclassified as migraine without aura, migraine with aura, and CM. Individuals with migraine without aura experience recurrent attacks with symptoms that include unilateral, pulsating pain of moderate/severe intensity, which worsens with routine physical activity and is accompanied by nausea and/or light/noise sensitivity.[6]

In addition to typical migraine symptoms, migraines with aura are distinguished by recurrent, slowly developing attacks with lateralized and reversible visual, sensory, speech/language, motor, brainstem, or retinal symptoms; attacks are accompanied or followed by headache and migraine symptoms.[6] This aura phenomenon may be explained by a propagating wave of depolarization followed by neural suppression, known as cortical spreading depression.

Clinical understanding and the definition of CM have evolved over time. In *ICHD-3b*, CM is broadly defined as migraines experienced greater than or equal to 15 days/month, noting that besides increased frequency, it is impossible to distinguish individual episodes of migraine in patients with CM from the headaches with migraine characteristics experienced less than 15 days/month in patients with episodic migraine (EM) (*see Distinguishing features of EM and CM*).[6]

As defined by *ICHD-3b*, secondary headache disorders are characterized by headaches caused by another condition (for example, head/neck trauma and comorbid medical conditions).[6] Headache disorders not qualifying as primary or secondary include painful cranial neuropathies, other facial pain, and other headache disorders.[6]

Risk factors for migraine progression

Given that attack frequency is the driving distinction between CM and EM, an individual patient may change categories; recently, the Chronic Migraine Epidemiology and Outcomes (CaMEO) study found that over a 3-month period, 3.4% of patients with EM progressed to CM, and 49.9% of patients with CM improved to EM in a large sample representative of U.S. patients receiving routine care.[7] Several nonmodifiable risk factors are associated with migraine chronification.[8] Epidemiologic studies repeatedly show that women have a higher CM prevalence than men, prevalence peaks in midlife for both genders, and is lower among adolescents and those older than 50.[5] CM is also highest among those with the lowest income, and full-time employment rates are lower among those with CM.[9] CM is also most prevalent among White and Hispanic individuals.[9]

Identified modifiable risk factors for migraine progression include high-frequency headache, medication overuse, poor treatment efficacy, comorbid pain, psychiatric comorbidities, obesity, excessive/habitual caffeine intake, sleep-related breathing disorders, and stress; risk mitigation interventions may prevent chronification.[10,11] Among individuals with EM, the odds of developing CM increase with headache frequency by nearly 25-fold for those with the highest versus lowest headache frequency.[12] Individuals with high-frequency headaches should treat them early during the attack, before the onset of sensitization, to decrease attack frequency and intensity.[13]

CM development is associated with overuse of certain medications (notably opioids and barbiturates, but also serotonin 5-HT_1 receptor agonists [triptans] and nonsteroidal anti-inflammatory drug [NSAIDs]). The risk of CM development grows with the increasing number of acute medication days; however, for NSAIDs, the risk of migraine chronification is limited to patients experiencing 10 or more headache days per month.[14] Poor acute treatment efficacy and ineffective medication overuse can contribute to migraine chronification.[10] Analyses from the American Migraine Prevalence and Prevention (AMPP) study found that analgesic or NSAID users reported high treatment efficacy less frequently than triptan users.[10]

Comorbidities associated with migraine occur more frequently with CM. Prevalence of comorbid pain (for example, from chronic pain disorders, such as fibromyalgia, osteoarthritis, or chronic fatigue syndrome) increases with migraine frequency, as does the proportion of individuals reporting severe pain, even within EM and CM classifications.[7,9,15] Psychiatric comorbidities, including anxiety and depression, are common among individuals with CM and are risk factors for migraine chronification.[9,16] Patients presenting with migraine should be assessed for psychiatric comorbidities and given appropriate treatments for their condition.[13] The prevalence of CM increases with body mass index; obesity incidence is higher in this group compared with EM.[17] Data suggest weight reduction may reduce headache frequency; however, evidence-based recommendations are lacking.[13]

A case-control study of individuals with episodic (2–104 headache days per year; n=507) and chronic daily headache (greater than or equal to 180 headache days per year; n=206) determined the association between caffeine consumption (dietary and medicinal) and chronic daily headache.[18] Current caffeine consumption was higher among individuals with migraine than those with nonmigraine headaches, and high caffeine intake was associated with chronification.[18] Caffeine use induces withdrawal headache, defined in *ICHD-3b* as a headache that develops equal to

or less than 24 hours after cessation of regular (greater than 2 weeks) consumption of greater than or equal to 200 mg/day caffeine (approximately 2 cups of coffee) and that resolves 1 hour or less after a 100-mg caffeine intake or 7 days or less with continued abstinence.[6] Experts recommend slowly tapering off caffeine over several weeks to avoid withdrawal headache.[13]

Sleep-related breathing disorders (for example, snoring and sleep apnea) are also risk factors for chronification.[13] Encourage improved sleeping habits by suggesting weight loss, smoking cessation, decreased alcohol consumption, and avoiding sedative medications. Referral to a sleep specialist to diagnose and manage primary sleep disorders should be considered.

Stressful life events are also a risk factor for migraine chronification.[19] Major life events, such as changes in work, relationships, or residence; illness or death of a family member or friend; or personal stressful situations are associated with the development of chronic daily headache and migraine. Stress identification and modification, through counseling and mental healthcare provider referral, are integral to effective CM treatment.

Distinguishing features of EM and CM[6]

	EM	CM
Headache frequency	<15 days/month	≥15 days/month
Diagnosis	• Headaches lasting 4–72 hours • Unilateral • Pulsating • Moderate/severe intensity • Made worse with routine physical activity • Nausea and/or light/noise sensitivity	Same as EM, plus history of ≥15 headache days/month for the past 3 months with migrainous features ≥8 days/month
Risk factors for EM (+) and for EM progression to CM (++)		
Nonmodifiable		
Female gender	+	++
Middle age		++
Low income	+	++
White race	+	++
Hispanic ethnicity		++
Family history	+	
Modifiable		
High headache frequency		++
Barbiturate and/or opioid overuse	+	++
Comorbid pain disorders	+	++
Comorbid psychiatric disorders	+	++
Obesity	+	++
Excessive/habitual caffeine intake	+	++
Sleep-related breathing disorders	+	++
Stress	+	++
Comorbidities common with EM (+) and with EM progression to CM (++)		
Cardiovascular disease	+	++
Chronic pain	+	++
Fibromyalgia	+	++
Neurologic disorders	+	++
Nonheadache pain	+	++
Obesity	+	++
Psychiatric disorders	+	++
Respiratory disorders	+	++

Migraine pathophysiology

As migraine attacks increase in frequency, associated symptoms may decrease in severity and frequency.[20] This transition to more frequent attacks is thought to signify a change in underlying pathophysiology, which is attributed to a sensitized central nervous system (CNS). History and physical exam of patients with CM is notable for cutaneous allodynia, a clinical marker of central sensitization. Patients with cutaneous allodynia perceive normally innocuous stimuli as painful, consequent to hypersensitization of the CNS along the trigeminal nociceptive pathway.[21]

Although the precise locus of sensitization and causal relationship between allodynia and migraine chronification is not identified, preclinical migraine models replicating allodynia symptoms suggest that recurring migraine attacks may induce central sensitization with resultant cutaneous allodynia.[22] CNS hypersensitization lowers the threshold for initiating a migraine attack, potentially increasing attack frequency and damaging the periaqueductal gray matter. This perpetuates the CM disease state with subsequent poor pain modulation and treatment refractoriness.[20,23]

The degree of headache-related burden associated with EM and CM varies. Because more than half of a chronic migraineur's days are spent with pain and symptoms, those with CM may experience increased headache-related burden across several domains (see *Burden of EM and CM*).

Headache-related disability

Multiple epidemiologic studies, including the CaMEO study, the International Burden of Migraine Study (IBMS), and the AMPP study reported higher rates of headache-related disability among individuals with CM than those with EM, as measured by the Migraine Disability Assessment (MIDAS) questionnaire.[5,9,16,24] The MIDAS is a patient-assessed, 5-item questionnaire that quantifies headache-related reduction or loss of activity among three domains: schoolwork/paid employment, household work/chores, and nonwork–related activities (family, social, and leisure). Higher scores are associated with greater disability. Greater disability associated with more severe disease can have a negative impact on functionality and activities of daily living, such as work, household chores, and social relationships.[9,25]

Family/work burden

The substantial disability associated with migraine affects work productivity, routine chores, and relationships—especially for those with CM.[24,26] In the CaMEO study, results from the Family Burden Module found migraineurs and their partners reported a pervasive and significant impact of migraine across the domains of reduced participation in family events, missed/cancelled events, financial impact, and interactions between migraineurs, their partners, and their children. In addition, impact severity increased with migraine frequency, and migraineurs consistently perceived the impact to be greater than their partners did.[27]

Quality of life

Detriments to quality of life are prevalent among those with CM and are commonly measured with the Migraine-Specific Quality of Life Questionnaire (MSQ) version 2.1.[9,28] The MSQ is a 14-item questionnaire that categorizes migraine-related detriment to activities of daily living across three domains: role restrictive, role preventive, and emotional functioning. Scores range from 0 to 100, where a higher score indicates a greater quality of life.[29,30]

In the PREEMPT clinical trials, participants (all with CM) had low baseline health-related quality of life scores, indicating that migraine restricted and prevented social and work-related activities and adversely affected emotions.[28] The IBMS Study found worse migraine-specific quality of life among those with CM than those with EM.[9]

Barriers to medical care

In CaMEO, less than 5% of individuals with CM and headache-related disability successfully overcame three identified barriers to medical care for their condition: consulting a healthcare professional (HCP), receiving an accurate diagnosis, and receiving minimal acute and preventive pharmacologic treatment.[31] CaMEO also found that individuals with CM who consulted a headache specialist were more likely to be diagnosed with CM than those consulting other types of HCP, although the diagnosis rate was still low (36.0%). The rate of CM diagnosis was 15.8% among patients who consulted nonheadache specialist prescribing HCPs.[32]

Healthcare resource utilization

Healthcare resource use is substantial, and higher for those with CM than EM.[33] The IBMS and AMPP studies found a higher frequency of HCP visits among those with CM.[9,34] The AMPP study found that those with CM reported a higher average frequency of use of most common headache-relieving drugs than those with EM.[34] Increased healthcare resource use translates into increased costs for those with CM.[34]

Epidemiologic studies show that women have a higher CM prevalence than men and prevalence peaks in midlife for both genders.

CM diagnosis/assessment

Patient history. A comprehensive patient history and physical/neurologic exam are important to rule out secondary causes of migraine (head trauma, systemic disease).[35] Attack frequency and duration are essential components of a migraine diagnosis; however, the number of headache-free days may provide a more accurate estimate.[36] Headache diaries are preferred to patient recall for capturing attack frequency and headache duration as well as other important factors, such as headache triggers and medication response.[36] Inquire about comorbidities, other areas of pain, HCPs consulted for pain/headache, and treatment history for a complete medical history.

Physical exam. New patients should receive a thorough physical exam to determine any deficits that may be contributing to the patient's headaches (hypertension, heart murmur, cervical dystonia). Continued follow-up care establishes improvement or decrements in contributing conditions. Refer patients to specialists as needed.

Role of imaging. Headache experts discourage imaging studies in patients with stable headaches meeting migraine criteria outlined in the *ICHD-3b*. Evidence has shown that the incidence of imaging findings is not different among patients with migraine and those without migraine, and

therefore, should not be used as a diagnostic tool.[37] Instead, migraine diagnosis relies upon a detailed patient history and medical/neurologic exams.[38]

Differential diagnosis. To diagnose CM, experts recommend initial elimination of secondary headache causes by identifying red flags, such as sudden symptom onset, worsening of preexisting headache in the absence of risk factors, and presence of systemic illness (cancer, HIV, lupus erythematosus, arteritis).[35,38,39] Applying *ICHD-3b* criteria then classifies symptoms as a primary headache disorder followed by the appropriate diagnosis within that classification.[38] Prevalence of headache subtypes (and in turn the frequency that one can be expected to encounter in these patients) can also aid in differential diagnosis.

While the prevalence of migraine has been reported to be 11.7%, other types of headache have much lower prevalence rates, including chronic tension-type headache (2%), cluster headache (0.4%), and hypnic headache (0.07%).[3] New daily persistent headache, hemicrania continua, and paroxysmal hemicrania all occur rarely.[35]

Treatment options

NPs can help their patients identify potential lifestyle adjustments in their treatment protocol to help reduce the risk of migraine progression (see *Treatment options for migraine*).[35,36] All patients with migraine should have access to acute pharmacologic treatments;[36] patients with CM also require preventive treatment.[31] The American Headache Society (AHS) provides recommendations for acute and prophylactic migraine medications (www.americanheadachesociety.org/professional_resources/practice_parameters_guidelines_and_classification).[40,41]

The AMPP study found a large underutilization of prophylactic migraine medication (indicated for 39% of migraineurs, but used by 12%), representing an area for great potential impact.[3] Only one drug, onabotulinumtoxinA, is approved specifically for CM prophylaxis. The safety and efficacy of onabotulinumtoxinA for CM prophylaxis have been demonstrated for up to nine treatment cycles.[42-44] OnabotulinumtoxinA has also been shown to improve patient quality of life, as early as 12 weeks (one treatment cycle).[28] All NPs qualify for training to perform onabotulinumtoxinA injections.[45] Even for NPs who do not inject, knowledge of the injection process can help educate patients regarding realistic treatment outcomes and appropriate provider referral for injection and/or other strategies for management.

Complementary and alternative treatment use is high among those with migraine/severe headache.[46] American

Burden of EM and CM[5,9,16,24,34]

	EM	CM
Headache-related disability		
Mean MIDAS* score (grade)	13.1–14.5 (III, moderate)	60.5–72.6 (IV-B, very severe)
Very severe disability (MIDAS* grade IV-B), % of patients	3.2–6.3	24.8–63.5
Family/work burden, % of patients: *≥5 days in past 3 months of*		
Missed school/work	2.2	8.2
Reduced productivity at work	18.2	58.1
Missed household work	24.3	57.4
Missed family activities	9.5	36.9
Quality of life: *MSQ† score, mean*		
Role function (preventive)	71.7	61.4
Role function (restrictive)	56.5	44.4
Emotional function	67.2	48.3
Healthcare resource utilization: *Mean number of visits per patient in past year*		
Primary care provider	0.72	2.42
Neurologist/headache specialist	0.22	1.06
ED	0.17	0.60
Hospital night	0.07	0.26

* Higher score indicates greater disability (little/no disability, Grade I: 0–5; mild disability, Grade II: 6–10; moderate disability, Grade III: 11–20; severe disability, Grade IV-A: 21–40; very severe disability, Grade IV-B: 41–270).
† Higher score indicates better quality of life

Treatment options for migraine[40,41-43,53]

EM	CM
Lifestyle	
• Avoid triggers • Exercise to reduce obesity • Minimize stress • Practice good sleeping habits • Reduce/eliminate caffeine • Seek treatment for comorbidities • Set regular meal times	Same as EM
Acute	
Level A*	
• Analgesics (acetaminophen) • Ergots (dihydroergotamine nasal spray, pulmonary inhaler) • NSAIDs (aspirin, diclofenac, ibuprofen, naproxen) • Opioids (butorphanol nasal spray) • Triptans (almotriptan; eletriptan; frovatriptan; naratriptan; rizatriptan; sumatriptan oral, nasal spray, patch, SC; zolmitriptan nasal spray, oral) • Drug combinations (acetaminophen/aspirin/caffeine, sumatriptan/naproxen)	Same as EM
Level B†	
• Antiemetics (I.V. chlorpromazine, I.V. droperidol, I.V. metoclopramide, I.V./IM prochlorperazine) • Ergots (dihydroergotamine [I.V., IM, SC], ergotamine/caffeine) • NSAIDs (flurbiprofen, ketoprofen, ketorolac [I.V., IM]) • Other (I.V. magnesium sulfate) • Combinations (codeine/acetaminophen, tramadol/acetaminophen)	Same as EM
Preventive	
Level A*	
• Antiepileptic drugs (divalproex sodium, valproate sodium, topiramate) • Beta-blockers (metoprolol, propranolol, timolol) • Triptans (frovatriptan)	Topiramate, onabotulinumtoxinA
Level B†	
• Antidepressants (amitriptyline, venlafaxine) • Beta-blockers (atenolol, nadolol) • Triptans (naratriptan, zolmitriptan)	Same as EM
Complementary/alternative	
• Mind/body strategies (behavioral/psychological approaches, biofeedback, breathing exercises, meditation, yoga) • Manual therapies (acupuncture, chiropractic, massage) • Physical methods (aerobic exercise, neck exercise) • Nutraceuticals (butterbur, feverfew, magnesium, riboflavin, coenzyme Q_{10}, B vitamins)	Same as EM

* Established efficacy. † Probably effective.
Note: Level of evidence does not necessarily correlate with FDA regulatory approval.

Academy of Neurology/AHS guidelines recommend (Level A evidence: medications with established efficacy) butterbur for migraine prevention, and recommend considering (Level B: medications that are probably effective) feverfew, magnesium, and riboflavin.[47] Other expert-recommended nutraceutical options include coenzyme Q_{10} and B vitamins.[48]

Not all patients will respond favorably to treatment; patients with severe baseline pain, long headache duration, nausea, psychologic disorders (anxiety, depression), and acute medication overuse often have poor treatment response.[49-52] A detailed patient history should alert the NP to any of these characteristics so they may be addressed and treatment adjusted accordingly.

NP role in patient management

NPs knowledgeable about diagnostic criteria for EM and CM and evidence-based treatment strategies reduce two barriers critical to positive patient outcomes.[36] With CM, complete pain relief may not be achievable; therefore, NPs play a key role in educating patients regarding treatment adherence and expectation management.[36] Counseling patients regarding medication options, reducing medication overuse, lifestyle choices, trigger management, and the importance of keeping a detailed diary of headache intensity, frequency, and duration is essential.

Collaboration between NPs, headache specialists, mental health providers, and pain specialists ensures that comorbid disorders are addressed in conjunction with headaches, with timely follow-up to address new symptoms or changes in headache. Special consideration should be given to patients with hemiplegic migraine, migraine with aura, and mixed migraine, as well as pregnant women with migraine.

Future directions

CM represents an area of growing interest and research with increasing

knowledge of the burden it places on individuals and society. Novel biologic drugs targeting calcitonin gene-related peptide are in early clinical development for CM treatment.[54] Ongoing migraine databases collect information on populations that cannot be studied in controlled trials; databases may collect enough information to demonstrate that certain treatments in these populations are safe. Evolving patient support systems include websites where clinicians, family, and friends can offer empathetic feedback in a virtual extension of face-to-face patient groups. The authors believe that NPs are well positioned to provide increased support and improved outcomes for patients with CM. NP

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