CHRONIC DAILY HEADACHE (SJ WANG, SECTION EDITOR)

# Defining the Differences Between Episodic Migraine and Chronic Migraine

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**Abstract** Chronic migraine (CM) and episodic migraine (EM) are part of the spectrum of migraine disorders, but they are distinct clinical entities. Population-based studies have shown that those with CM demonstrate higher individual and societal burden because they are significantly more disabled than those with EM and have greater impaired quality of life both inside and outside the home. Proper diagnosis of both conditions requires clearly defined clinical criteria. Diagnosis enables the initiation of appropriate treatments and risk-factor modification, which ultimately improve functional status and quality of life for persons with migraine. Recognizing that both disorders are on the spectrum of migraine, this review serves as a guide to define the disease state of CM as distinct from EM in terms of clinical, epidemiological, sociodemographic, and comorbidity profiles.

**Keywords** Chronic migraine · Episodic migraine · Epidemiological profiles · Sociodemographics · Risk factors · Treatment · Chronic daily headache · Chronification · Diagnosis

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## Introduction

Migraine is a debilitating headache disorder. Including both episodic and chronic forms, it affects 14% of the population, and up to 18% of women [1, 2]. Migraine is currently ranked by the World Health Organization (WHO) as 19th among causes for years lived with disability [1]. Given the current barriers, improving diagnosis and optimizing treatment paradigms could substantially reduce this global burden.

Because there are no biological markers for migraine, diagnosis is based on clinical history and the exclusion of other headache disorders. Health care professionals apply clinical criteria to guide diagnoses and subsequent treatment. The definition of migraine without aura from the second edition of the International Classification of Headache Disorders (ICHD-2) requires all of the following symptoms: a) recurrent headaches (at least 5 lifetime attacks); b) untreated or unsuccessfully treated headache duration of 4 to 72 h; and c) at least two of the following pain characteristics: unilateral, pulsating, moderate or severe intensity, or aggravated by routine physical activity. In addition, the migraine attacks are associated with at least one of nausea/vomiting, photophobia, or phonophobia. Finally, other causes of headache must be excluded [3].

Episodic migraine (EM) is characterized by those with migraine who have 0 to 14 headache days per month, while chronic migraine (CM) is characterized by 15 or more headache days per month. Specifically, revised ICHD-2 (ICHD-2R) criteria define CM as headache on 15 or more days per month for 3 or more months, of which 8 or more days meet criteria for migraine without aura and/or respond to migraine-specific treatment, occurring in a patient with a lifetime history of at least five prior migraine attacks not attributed to another causative disorder and no medication overuse [4].

The relationship between EM and CM is complex. EM progresses to CM at the rate of 2.5% per year [5], and CM often remits to EM (2-year transition rate of 26%) [6]. The use of a frequency score of 15 or more days per month to classify CM is admittedly somewhat arbitrary. Nonetheless, these clinical definitions identify groups that differ in epidemiologic and symptom profiles, functional consequences and disabilities, indirect and direct costs, patterns of consultation and treatment, and rates of comorbidities. In addition, the patterns of treatment response for EM and CM differ, raising the possibility of both overlapping and distinct biological mechanisms.

Large observational studies have provided valuable information on the distinct clinical characteristics observed in CM and EM [7••, 8••, 9, 10••]. Much of the recently published data that highlight the epidemiological distinction between CM and EM have been generated by three large observational studies: the International Burden of Migraine Study (IBMS), the American Migraine Prevalence and Prevention (AMPP) study, and the German Headache Consortium (GHC) study. IBMS is a web-based, cross-sectional, multinational survey that identified and evaluated persons with CM and persons with EM [7••]. The AMPP study is a large United States (US) population–based, mail-based, longitudinal survey that identified 24,000 respondents with headache and followed them annually for 5 years (2004–2009) [8••]. The GHC study is a German population–based longitudinal survey where respondents completed questionnaires via mail ($n=4642$) or phone ($n=4708$) and were identified as either CM, high-frequency EM (9–14 headache d/mo), or low-frequency EM (0–8 headache d/mo) and then evaluated on an annual basis [10••].

Herein and with an emphasis on recent key findings, this article provides an update on the similarities and differences between CM and EM in their epidemiologic and symptom profiles, functional consequences and disabilities, indirect and direct costs, patterns of consultation and treatment, and rates of comorbidities.

## Epidemiology of Chronic Migraine Versus Episodic Migraine

### Prevalence

Epidemiologic studies in Europe and America estimate that 6% to 8% of men and 15% to 18% of women experience migraine each year [1]. Recent prevalence data from the US population–based AMPP study reported the 1-year gender-stratified prevalence for EM was 17.1% for women and 5.6% for men [11], and for CM was 1.3% for women and 0.5% for men [12]. CM prevalence rates also varied by age, and were highest for women (1.9%) and men (0.8%) in the

age range of 40 to 49 years. The authors also reported that CM represents 7.7% of the total migraine population [12].

Definitional variability of CM poses an epidemiological challenge; however, a recent systematic review summarizing 12 population-based studies using several definitions for frequent migraine determined the global prevalence of CM to be from 0.0% to 5.1% in the general population, with most estimates in the range of 1.4% to 2.2% [13•]. Most of the reviewed studies used the definition of chronic daily headache (≥ 15 headache/mo) with ICHD-1 migraine criteria [14] or the Silberstein-Lipton criteria for CM [15, 16]. None of these criteria matched the current ICHD-2R criteria [4, 13•], at least in part because of difficulties implementing the criteria.

### Symptom Profiles

The IBMS provides the most robust epidemiological data comparing the symptom profiles of CM and EM (Table 1) [7••]. Findings demonstrated that, on average, persons with CM had longer duration of headache attacks than those with EM, both treated (24.1 vs 12.8 h; $P<0.0001$) and untreated (65.1 vs 38.8 h; $P<0.0001$) [3, 4, 7••, 8••, 17]. In addition, chronic migraineurs were more likely to experience severe pain intensity than episodic migraineurs [7••]. These population findings are confirmed by clinic-based data. For example, the Phase 3 Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) clinical program [18] characterized 1384 individuals as chronic migraineurs. In a 28-day baseline period, headache occurred on 20 days on average, with 19 migraine days and 18 moderate/severe headache days [18].

### Sociodemographics

The AMPP study and the IBMS demonstrated different sociodemographic findings between persons with EM and CM [7••, 8••]. Both studies demonstrated that CM and EM were most common among females in their fourth decade of life, although those with CM were slightly older (AMPP: CM=41.7 y [mean] vs EM=40.2 y [mean], $P=0.005$; IBMS: CM=47.7 y [mean] vs EM=46.0 y [mean], $P=0.03$ [Table 1]) [7••, 8••]. CM also was most common among Caucasians (over 80%) [7••, 8••]. However, sociodemographic profiles for persons with CM differed from EM in that those with CM reported significantly lower household income levels, were less likely to be employed full time, and were more likely to be occupationally disabled (Table 1) [8••]. In the GHC study, chronic migraineurs also were found to have significantly higher body mass index (BMI; CM=25.9 mean BMI vs EM=24.1 mean BMI, $P<0.015$), have achieved lower levels of education, and were more likely to be smokers [10••].

**Table 1** Profiles of persons with chronic migraine and episodic migraine

| Patient profiles | Chronic migraine | Episodic migraine |
|---|---|---|
| Clinical characteristics[a, b, c] | | |
| Headache frequency, *d/mo* | ≥ 15 | < 15 |
| Severe headache pain,% | 92.4[*] | 78.1 |
| Duration of headache without medication, *mean h* | 65.1[*] | 38.8 |
| Duration of headache with medication, *mean h* | 24.1[*] | 12.8 |
| Sociodemographics[d] | | |
| Mean age, *y (SD)* | 47.7[*] (14.0) | 46.0 (13.8) |
| Race,% *Caucasian* | 90.7 | 87.3 |
| Women,% | 78.6 | 80.0 |
| Occupationally disabled,% | 20.0[*] | 11.1 |
| Household income,%< *$22,500/y* | 29.9[*] | 24.9 |
| Mean BMI, *n (SD)* | 29.8 (8.3) | 29.2 (7.9) |
| Resource utilization[c] | | |
| Primary care provider visits,% | 48.0[*] | 26.4 |
| Neurology/headache specialist visits,% | 23.8[*] | 8.0 |
| Comorbidities[d, e] | | |
| Depression[f],% | 30.2[*] | 17.2 |
| Anxiety,% | 30.2[*] | 18.8 |
| Obesity,% | 25.5[*] | 21.0 |
| Cutaneous allodynia,% | 68.3[*] | 63.2 |

[*] Indicates statistical significance (*P*<0.05) between episodic and chronic migraine

[a] International Classification of Headache Disorders-2 [3]

[b] International Classification of Headache Disorders-2, revised [4]

[c] Blumenfeld et al. [7••]

[d] Buse et al. [8••]

[e] Bigal et al. [17]

[f] Measured by the Patient Health Questionnaire-9

*BMI* body mass index, *SD* standard deviation

## Individual Burden

CM has been shown to impose a greater emotional and social burden on the individual than EM in large observational studies using various validated tools [7••, 9, 19]. Using the Migraine-Specific Quality of Life (MSQ) questionnaire, which details how migraines limit daily performance, the IBMS showed individuals with CM consistently scoring worse in all categories by 6 to 13 points compared to individuals with EM [7••]. The 2009 AMPP study used the Headache Impact Test-6 (HIT-6) to assess headache impact on the lives of chronic migraineurs [19]. Conversion of HIT-6 scores to standard categories revealed that individuals with CM were much more likely to experience severe headache impact (72.9%) than those with EM (42.3%) [19]. Furthermore, those with CM had significantly higher odds of adverse headache impact than those with EM (OR 3.5; 95% CI, 2.77–4.41; *P*<0.0001) [19]. The AMPP study also evaluated disability and similarly showed that those with CM had a greater disability according to the Migraine Disability Assessment (MIDAS) questionnaire [9], which calculates a disability score based on reduced productivity (eg, missed days of school and work).

## Economic Burden

In the 2005 AMPP study data, CM respondents had lower household income levels, were nearly twice as likely to be occupationally disabled (CM 20.0% vs EM 11.1%; *P*<

0.001), and were less likely to be employed full time than EM respondents (CM 37.8% vs EM 52.3%; *P*<0.001) [8••]. In the 2006 AMPP study data, more than half of the individuals with CM missed at least 5 days of household work over a 3-month period, compared with only one quarter of those with EM [9]. Chronic migraineurs were three times more likely to report reduced productivity in household work than those with EM (58.1% vs 18.2%; *P*< 0.001) [9]. A minimum of 5 days of missed family activities was reported by 36.9% of those with CM and only 9.5% of those with EM (*P*<0.001) [9].

In another analysis of the 2005 AMPP study, chronic migraineurs were 19% less likely to be working for pay and lost 4.6 h per week from headache compared to 1.1 h by those with 3 or fewer headache days per month [20]. Although those with high-frequency migraine (10–14 headache d/mo) or CM only accounted for 9.1% of employed migraineurs, they represented 35% of the overall lost work time when considering medical leave and unemployment [20]. According to the 2006 AMPP study, those with CM have reported work or school productivity to be reduced by over 50% in the previous 3 months because of headaches [21].

From a societal perspective, CM is more costly per individual than EM [7••, 21, 22]. Both the AMPP study and IBMS found that those with CM had a statistically significant increase in resource utilization, as evidenced by markedly more primary care visits, specialist visits, emergency room visits, and hospitalizations compared to those with EM [7••, 21, 22]. Regarding US estimates, the

average per-person annual total costs were more than fourfold greater for those who had progressed to CM ($7750) compared with EM ($1757) [21].

Comorbidities

Those with various types of migraine share a range of comorbidities. Recent observational studies have provided insight into the distinct comorbidity profiles of those with CM versus EM. The IBMS demonstrated that those with CM were significantly more likely to report comorbidities for all groups than EM, notably in nonheadache pain (CM 39.1% and EM 18.4%; $P<0.0001$), psychiatric disorders (CM 46.3% and EM 28.5%; $P<0.0001$), and vascular disease events (CM 8.2% and EM 3.3%; $P<0.0001$) [7••].

Similarly, the AMPP study [8••] revealed that those with CM were about twice as likely to be depressed (CM 30.2% vs EM 17.2%; OR 2.0; 95% CI, 1.67–2.40; $P<0.001$) as determined by self-report on the Patient Health Questionnaire-depression module (PHQ-9) [23] and to have anxiety based on self-report of a physician's diagnosis (CM 30.2% vs EM 18.8%; OR 1.8; 95% CI, 1.51–2.15; $P\leq0.001$ [Table 1]). Chronic pain disorders also were more than twice as frequent among persons with CM (31.5% vs 15.1%; OR 2.5; 95% CI, 2.08–2.97; $P\leq0.001$) as well as specific pain disorders like arthritis (CM 33.6% vs EM 22.2%; OR 1.7; 95% CI, 1.43–2.05; $P\leq0.001$). In addition, the CM population also had higher rates of cardiovascular and respiratory comorbidities, such as hypertension, high cholesterol, stroke, emphysema or chronic obstructive pulmonary disease, and asthma [8••].

## Onset and Risk Factors for Progression from Episodic Migraine to Chronic Migraine

Epidemiological and clinical observations support the progression of EM to CM [24] Progression from EM to CM occurs in about 2.5% of those with EM annually [5]. Because not all those with EM progress to CM, it is important to identify those at high risk for progression. Risk factors can be broken into two categories: those that are easily modified and those that are not readily modifiable (eg, age, female sex, Caucasian race, low educational level/ socioeconomic status, and head injury) [25]. Identification of modifiable risk factors for progression to CM, such as obesity, depression, and medication overuse, is important because physicians can implement approaches through behavioral and pharmacologic interventions to help the patient maintain a stable, healthy lifestyle, thus reducing the risk of CM [26]. Below are brief discussions of potential modifiable risk factors and their associations with the transition between EM and CM.

Modifiable Risk Factors

Studies have linked obesity to frequent headache [26]. Although obesity (defined as having BMI>30) is not a risk factor for the development of EM, it is a risk factor for progression of EM to CM [26]. One large population-based study reported that the prevalence of CM ranged from 0.9% in normal-weighted persons to 1.6% in the obese population (OR 1.7 [1.2–2.4]) and 2.5% in the morbidly obese population (OR 2.2 [1.5–3.2]) [27].

Depression, anxiety, and chronic pain disorders all have been associated with CM at higher rates than with EM [8••]. It has been difficult to determine the causal relationship between depression and migraine because there is a bidirectional relationship between the two disorders; thus, those experiencing either migraine or depression are at increased risk for developing the other [28]. To explain this relationship, two possible hypotheses are depression as a risk factor for CM onset or depression as a consequence of CM [29]. However, recently presented results support a casual rather than consequential relationship between depression and the onset of CM. Adjusted longitudinal modeling of the AMPP study data aimed to assess the role of depression as a predictor of new onset of CM among persons with EM and concluded that, among persons with EM, severe depression was associated with an about 1.28-fold increased risk of the subsequent onset of CM the following year, even after controlling for factors of headache-related disability and headache-day frequency [29]. Additionally, the effects of depression, anxiety, and obesity are additive, such that migraine-related disability increases when obese individuals have comorbid depression or anxiety compared to non-depressed obese migraineurs [30, 31].

Stressful life events such as divorce, moving, employment changes, or problems with children have been considered a risk factor for chronic daily headache [32]. Results from the frequent headache epidemiology study demonstrated that, compared to episodic headache control patients, those with chronic daily headache had more major life changes in the year before or the same year as the onset of chronic daily headache [32].

Traditionally, acute medication overuse (generally defined as use of medications on more than 10 or 15 d/mo, depending on the class) [5] has been considered a risk factor for poor migraine prognosis [33, 34]. Recent epidemiological data have shown that intake of (overuse or use of) certain classes of medication increase the risk of CM in those who already have EM. Specifically, follow-up data from respondents in the 2006 AMPP study demonstrated that those with EM in 2005 had an increased risk of developing CM when they used compounds that contained barbiturates (OR 2.06; 95% CI, 1.3–3.1) and opiates (OR 1.98; 95% CI, 1.4–2.8) [5]. The use of triptans or NSAIDs

was not associated with increased risk for developing CM [5]. These findings support other population-based [35–37] and clinic-based studies [34] in chronic daily headache.

Another possible risk factor for progression to CM is the consumption of caffeine. A population-based study that investigated caffeine consumption among participants in a general health survey determined that high medicinal (first-choice medication containing caffeine) or dietary (287 mg/d) consumption of caffeine before chronic daily headache onset was a modest risk factor (OR 1.5; $P=0.05$), with an increase in women (OR 1.9; $P=0.006$) and those who were under 40 years (OR 3.4; $P<0.001$) [38].

Risk-factor modification, such as decreasing headache frequency with behavioral and pharmacological treatment; weight loss management; avoiding medication overuse and caffeine consumption; and screening and treating depression and other psychiatric comorbidities, remains a component to optimizing care [26].

## Patterns of Treatment Response

### Acute Treatment

Acute medication is often required because migraine attacks are associated with severe and disabling features and usually are accompanied by other symptoms of sensory disturbance (eg, light and sound sensitivity) [39]. Because the clinical distinction between CM and EM is based primarily on the frequency of headache and migraine days rather than the attack features or symptoms, both populations use acute therapies (eg, analgesics and NSAIDs) or migraine-specific agents with vasoconstrictor properties (eg, triptans and ergot derivatives) [9, 39]. Although the patterns of treatment response to acute medication are similar between EM and CM, there are emerging differences driven by the frequency of use, response, and overall satisfaction [9]. It is important to treat CM and EM patients at the earliest onset of symptoms; however, those with CM have a less robust response to triptans than those with EM [40•]. Additionally, medication overuse of acute therapies containing barbiturates and opiates is a risk factor and an important consideration, particularly for CM [5]. It is critical to limit and monitor the use of these compounds when treating migraine and to educate patients on the risks associated with the progression to CM due to medication overuse.

### Preventive Treatment

As our understanding of the clinical, epidemiological, and pathophysiological differences between EM and CM develops, it becomes highly likely that we will find the patterns of treatment or treatment response to preventive therapies to be different between the two migraine groups. Indeed, the recognition of the two disease states within the ICHD-2 guidelines is designed to facilitate the optimal treatment paradigm and the development of therapies specifically targeted at either EM or CM.

Several classes of drugs are available for migraine prevention, including antihypertensives, antiepileptics, and antidepressants [39]. Specifically, antihypertensive agents available for migraine treatment are β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers. Common choices of antiepileptics include topiramate, valproate, and gabapentin. In addition, tricyclic antidepressants are commonly used [39].

Many of these therapies also are used in the prevention of CM; however, of the aforementioned EM therapies, only topiramate has demonstrated efficacy in CM patients through randomized placebo-controlled trials [41, 42]. Additionally, while efficacy has not been demonstrated in EM, onabotulinumtoxin A injections [43] have demonstrated safety and efficacy in CM patients in randomized, double-blind, placebo-controlled studies [18, 44, 45]. Less-studied agents in CM preventive treatment include gabapentin, pregabalin, fluoxetine, tizanidine, zonisamide, and memantine [46].

## Conclusions

Migraine is a highly debilitating disease in both its episodic and chronic forms, with the latter imposing more substantial individual and socioeconomic burden as described by various population-based studies [7••, 9, 10••, 21]. Through identification of risk factors for progression to CM, clinicians can educate patients about modifiable risk factors and can begin appropriate selected therapy in a timely manner. As research continues to demonstrate, CM is a distinct disorder with clinico-epidemiological profiles and therapeutic response patterns different from that of EM. Clear definition and enhanced recognition of these two disease states can better facilitate the development of therapies specifically targeted at either EM or CM.

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