

# Chronic Migraine in Women

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## CONTINUING MEDICAL EDUCATION

### LEARNING OBJECTIVES

After reading this article, the family physician will be able to:

1. Differentiate the clinical features and common comorbidities of chronic versus episodic migraine in women
2. Describe techniques to better assess migraine-related disability
3. Identify women with chronic migraine who are candidates for preventive therapy
4. Describe the efficacy and safety of pharmacologic options for abortive therapy
5. Describe the efficacy and safety of pharmacologic options for preventive therapy

### TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of chronic migraine in women.

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## INTRODUCTION

Primary headache disorders are the fifth leading cause of disability for women worldwide.<sup>1</sup> The annual prevalence of migraine in the United States is 18% for adult women and the lifetime prevalence is estimated to be 26%.<sup>2</sup> In women, the prevalence of chronic migraine (CM) is more than twofold higher

than in men.<sup>3</sup> Chronic migraine is and should be considered a complication of episodic migraine (EM) that extracts a significant human and social burden from those living with this condition. This is particularly true for women, since they experience a greater disease burden as demonstrated by greater headache-related disability and reduced productivity relative to men.<sup>3,4</sup>

While 70% of the migraine population is managed in a primary care setting, it is estimated that a quarter are dissatisfied or very dissatisfied with their care.<sup>5</sup> To a significant degree, this is due to a failure to adequately treat EM and institute effective preventive measures early to halt the progression of EM to CM.<sup>6</sup>

**CASE STUDY:** Rita is a 38-year-old woman who was diagnosed 12 years ago with migraine without aura. Her migraines responded to naproxen sodium until several years ago, at which time she was prescribed a triptan. Over the past 12 to 18 months, Rita has increasingly observed that her response to triptan therapy has been less robust, noting recurring headache within 1 to 2 days following triptan therapy. This mandated an additional dose of her triptan and naproxen sodium. When the headache is particularly debilitating, she also supplements her treatment with an over-the-counter headache combination product. Review of her headache diary shows that Rita now experiences 3 to 4 migraines fulfilling International Headache Society (IHS) criteria<sup>7</sup> per month, but with headache of moderate to severe intensity occurring on 12 to 15 days per month. She was prescribed topiramate 1 year ago, but it was discontinued because she experienced cognitive changes as the dose was increased.

The increasing frequency of Rita's migraine headaches and the growing lack of response to naproxen sodium and triptan therapy indicate that her diagnosis should be reevaluated and other possible contributory causes should be investigated. In addition, the subtype of migraine and treatment plan should be reassessed.

## DIFFERENTIATING EPISODIC MIGRAINE FROM CHRONIC MIGRAINE

It has only been within the past few years that consensus-based criteria for CM have become established and the clinical features of CM have been recognized. It was not until 2004 that a formal definition of CM was adopted by the IHS, with further refinement in 2005.<sup>7,8</sup> It should be made clear that other terms, such as chronic daily headache, transformed migraine, and medication overuse headache

(MOH), are not synonymous with CM. The recognition of CM as a migraine subtype, along with EM, underscored the clinical importance of CM.

### Episodic migraine

Episodic migraine is characterized by headache features that include unilateral location, pulsating quality, moderate or severe intensity, and aggravation by routine physical activity (TABLE). Nonheadache associated features include nausea and/or photophobia and phonophobia. Episodic migraine can be divided into migraine with or without aura. While many patients experience both, approximately 30% of migraines are associated with aura occurring prior to or during the headache phase of the attack.<sup>9</sup> Auras are considered a consequence of an electrical event in the brain called spreading cortical depression and consist of fully reversible focal neurological symptoms that are visual or sensory in nature. More importantly, EM is characterized by a return to normal baseline neurological function between each episode.

### Chronic migraine

Chronic migraine often follows years after the onset of EM, and because of that, CM can be considered a complication of EM.<sup>7</sup> As headache frequency increases, migraines begin to lose their episodic nature and there is little or no time for neurological recovery between headaches.<sup>10</sup> Consequently, symptoms and disability are variable. This often leads to diagnostic uncertainty since patients typically report to their health care provider only their worst headache days as being migraine. Because the stereotypic nature of migraine observed in EM is less clear in CM, CM is measured in headache days rather than in attacks or episodes. CM is defined as  $\geq 15$  days of headache per month for more than 3 months, of which 8 or more headache days per month must fulfill the IHS criteria cited above for EM.<sup>11</sup> Other headache days may have features of tension-type or probable migraine and as such it is entirely possible that patients with CM experience more days with headache other than migraine than those that meet the IHS criteria for migraine.

Because the treatment need for CM is great, patients frequently overuse acute medication. This results often in another type of headache called MOH (previously called rebound headache). Medication overuse headache is particularly common with simple analgesics and triptans, as well as with caffeine, opioids, and barbiturates, although opioids and barbiturates are generally not recommended for management of EM or CM.<sup>12</sup>

In order to obtain an accurate understanding of headache days, it is valuable to ask patients how many days per month they are totally free of headache. The answer to this question is

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**TABLE** Selected clinical differences between episodic and chronic migraine

Feature	Episodic migraine	Chronic migraine
Headache frequency, days/month	<15	≥15
Experience severe headache pain, %	78.1%	92.4% <sup>a</sup>
Duration of headache without medication, mean hours	38.8	65.1 <sup>a</sup>
Duration of headache with medication, mean hours	12.8	24.1 <sup>a</sup>
Age, mean years (SD)	46.0 (13.8)	47.7 <sup>a</sup> (14.0)
Women, %	80.0	78.6
Occupationally disabled, %	11.1	20.0 <sup>a</sup>

Abbreviation: SD, standard deviation.

<sup>a</sup> $P < .05$

With kind permission from Springer Science+Business Media: *Curr Pain Headache Rep*, Defining the differences between episodic migraine and chronic migraine, volume 16, 2012, page 88, Katsarava Z, Buse DC, Manack AN, Lipton RB, Table 1.

often much more revealing than the number of migraine episodes per month.<sup>12,13</sup>

Relative to EM, headache-related disability is greater in CM and serves as an important issue to discuss with patients when assessing impact. However, headache-related disability can vary during a migraine attack, as well as from 1 attack to another. Results of the American Migraine Prevalence and Prevention study (N = 162,576) showed that, during a severe headache, 54% of patients with migraine experienced severe impairment or required bed rest, while 46% experienced only some or no impairment.<sup>14</sup>

Chronic migraine patients are less likely than patients with EM to be employed full-time, 2 to 3 times as likely to experience reduced occupational or household productivity, and 4 times as likely to experience missed family activities. The risk of anxiety, chronic pain, or depression is almost twice as high in patients with CM as with EM.<sup>13,15,16</sup> In addition, patients with CM have a 50% to 70% higher risk of asthma or chronic obstructive pulmonary disease, a 40% higher risk of heart disease and angina, and a 65% higher risk of stroke than patients with EM.<sup>13</sup> Compared with patients with EM, those with CM are more likely to have visited a primary care physician within the past 3 months (13.9% vs 26.2%;  $P < .001$ ) and have higher total mean headache-related costs during a 3-month period (\$383 vs \$1036;  $P < .001$ ).<sup>17</sup> These factors underscore the importance and value of a primary care physician's involvement in managing the patient with migraine.

Several risk factors for development of CM have been identified. These include frequent EM, poor response to acute migraine treatment, major stressors, depression, anxiety, snoring and sleep apnea, obesity, and overuse of acute treatment medications.<sup>18,19</sup> There are also associated nonmodifiable risk

factors such as older age, female gender, Caucasian race, low educational level/socioeconomic status, and head injury.<sup>12,13</sup>

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**CASE STUDY (continued):** Upon further questioning by her primary care physician, Rita states that she has only 4 or 5 days per month where she is truly headache-free. She is now using some form of acute medication 4 or 5 days per week. Rita is missing work and unable to care for her family for 24 to 36 hours during each of the 3 or 4 severe migraine attacks she experiences each month. Rita acknowledges feelings of depression and difficulty sleeping.

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## MANAGEMENT OF CHRONIC MIGRAINE

It must be realized that because CM was recognized as a migraine subtype only a few years ago, the comprehensive management of patients with CM is unclear. Few clinical trials of pharmacologic therapies have been conducted in patients meeting the definition of CM. Those that have been done involve preventive therapy for CM. Beyond this limited information, the management of patients with CM draws on experience treating other migraine subtypes, particularly EM, although its applicability to CM is relatively unproven.

Managing CM successfully requires patients to actively participate in decisions related to their management. As a largely self-managed chronic disease, the appropriate use (and avoidance of overuse) of medications ultimately rests with the patient. The health care provider has a critical role in therapeutic decision making and appropriate prescribing, as well as educating the patient regarding the risks of medications, including avoiding their overuse.

Another principle of management is that the focus of treatment should be on the whole patient and not solely on the

migraine episodes. Consequently, in addition to considering severity of illness, comorbidities, and prior response to medications, treatment should be individualized to include the patient's needs, preferences, and values. This underscores the central role of primary care in management of the migraine patient.

There are 4 components of treatment: patient education and support, nonpharmacologic therapy, pharmacologic therapy, and ongoing assessment. A key aspect of patient education is to discuss a patient's treatment expectations in order to create alignment in establishing realistic therapeutic goals. These goals need to be important to the patient and the time to achieve them should be realistic. A clinical benefit with preventive therapies, for example, often takes 2 to 3 months. Although not discussed in this article, incorporating appropriate nonpharmacological therapies, such as diet, sleep hygiene, exercise, and use of complementary and alternative therapies such as acupuncture, is generally helpful.<sup>20-22</sup>

### Pharmacologic treatment of chronic migraine

The overarching goals of pharmacologic treatment for CM are to reduce the headache burden and improve functioning and quality of life, while avoiding treatment-related side effects and complications. To achieve these goals, both acute and preventive measures need to be utilized. Acute or abortive therapies are utilized by patients with migraine to stop the attack once begun. This is often problematic in patients with CM as the need for acute treatment—and the risk of MOH—are high. Consequently, building therapeutic strategies for the spectrum of attacks, rather than defining a patient's profile, is important.<sup>23</sup> This is accomplished by providing appropriate drugs and formulations to match the treatment needs of each patient. For almost all patients with CM, preventive therapies are appropriate.<sup>24</sup> Regular follow-up involving review of the patient's headache diary provides an opportunity to refine and optimize treatment efforts. The use and evaluation of preventive care may be guided by headache assessment tools such as the Headache Impact Test<sup>25</sup> or the Migraine Disability Assessment questionnaire.<sup>26</sup>

### Selecting abortive treatment

Patients with CM have significant need for abortive medications and are at high risk for MOH. Thus, treatment needs to be patient-specific and the health care provider needs to provide the best therapeutic choice for the specific presentations of migraine that the patient experiences. For example, since an early morning migraine is often associated with nausea, providing an oral medication is unlikely to be effective. Therefore, an injectable or nasal spray is more likely to achieve a better outcome and ultimately, less medication utilization. Gastric stasis or gastric atony is common in migraine patients, resulting in poor absorption of oral medications. Such

patients often have an inconsistent response to oral medications. On the other hand, a person with migraine that has a definite mild headache phase will likely respond well to early intervention with a triptan or nonsteroidal anti-inflammatory drug (NSAID). Another factor to consider in selecting treatment is the patient's treatment dynamics. Some patients, for example, "wait to see" if the headache attack will merit use of a prescription medication. Others reserve their prescription medication in case they have a worse headache in the future.

Patients with CM often need more than 1 formulation of abortive medication; a wide variety is available. Migraine-specific medications such as triptans, dihydroergotamine, and ergotamine target 5-HT<sub>1B/1D</sub> receptors on blood vessels and pain-sensing nerves. 5-HT<sub>1B/1D</sub> receptor agonists are generally the most effective agents available in aborting the attack and related symptoms.<sup>27</sup> Among the 5-HT<sub>1B/1D</sub> receptor agonists, sumatriptan is the most effective abortive treatment for migraine.<sup>28,29</sup> Sumatriptan tablets are commonly used, but are less effective than the nasal spray or especially, injectable formulations.<sup>30</sup> Consequently, sumatriptan tablets are more likely to be overused and cause MOH.

Contraindications, adverse events, and cost are important considerations in treatment selection. It is also important to keep in mind that the ineffectively treated migraine has a significant cost associated with it in terms of increased medical utilization, impact at home and in the workplace, and most of all, to the individual.<sup>31</sup>

Non-migraine-specific medications can also be highly effective and should be provided as a therapeutic tool based on their efficacy, rather than on convenience, availability, or cost. Treatment that is most likely to rapidly, safely, and completely abort a migraine attack and provide sustained normal functioning for the patient should be selected. One ineffective approach is to stage acute treatment or arbitrarily begin with 1 medication and add another if the first is ineffective. This approach often does little more than add attack-related disability and increase the likelihood of therapeutic failure. Instead, it is often best to combine acute treatments at the outset based on what is likely to be effective, including nonprescription analgesics, prescription NSAIDs, antiemetics, and triptans.

**CASE STUDY (continued):** Rita's primary care provider diagnosed her with CM and MOH. She was started on amitriptyline to improve sleep, treat depression, and as preventive therapy to reduce migraine frequency. She is instructed to slowly titrate the dose to 75 mg at bedtime. In addition, Rita is provided with specific acute treatment strategies. She is advised to initiate treatment early when the pain is escalating, but still mild to moderate. She was provided with subcutaneous sumatriptan as first-line treatment for migraine associated with nausea and for rescue and advised to not use sumatriptan more than

2 days per week. She is provided with diclofenac potassium to use on alternate days if needed, but also fewer than 2 days per week. Goals are established to improve acute treatment outcome and reduce the overall quantity of acute medications being used. She agrees to return in 2 weeks for a follow-up visit.

### Preventive treatment

Preventive therapy is of central importance in the management of patients with CM. Preventive therapy is appropriate in those: (1) who experience  $\geq 2$  attacks/month that produce disability that lasts  $\geq 3$  days/month; (2) who have a contraindication to or failure of abortive treatments; (3) who use an abortive medication  $> 2$  times per week; or (4) with an uncommon migraine condition, such as hemiplegic migraine, migraine with prolonged aura, or migrainous infarction.<sup>32</sup> In addition, preventive therapy should be utilized in those with comorbidities and those with increasing frequency of EM to prevent the transformation into CM.

A wide variety of medications that work as preventive treatment for EM have also been utilized as preventive therapy for CM. However, their efficacy in CM is uncertain, as few have actually been studied in CM. Two medications that have been evaluated specifically as preventatives in patients with CM are topiramate and onabotulinumtoxinA. Only onabotulinumtoxinA has been approved by the US Food and Drug Administration (FDA) for the indication of CM.

### Topiramate

The efficacy of topiramate as preventive therapy for CM has been studied in 306 patients with CM.<sup>33</sup> Topiramate 100 mg/day was associated with a 5.8 day reduction in headache days per month compared with 4.7 days for placebo ( $P = .067$ ). Significant improvements were observed in patient disability and quality of life. For example, 69% of patients treated with topiramate experienced a 25% or greater reduction in the number of headache days per month compared with 52% of placebo-treated patients ( $P = .005$ ). Reductions were observed with topiramate compared with placebo in worst daily severity of migraine ( $P = .016$ ), severity of photophobia ( $P = .032$ ), as well as frequency of vomiting ( $P = .018$ ), photophobia ( $P = .038$ ), phonophobia ( $P = .010$ ), unilateral pain ( $P = .015$ ), pulsatile pain ( $P = .023$ ), and pain worsened by physical activity ( $P = .047$ ).

### OnabotulinumtoxinA

Used in conditions such as spasticity for more than 2 decades, onabotulinumtoxinA inhibits the vesicular release of acetylcholine from neurons, resulting in partial chemical denervation of the muscle. In animals and trigeminal cell cultures, onabotulinumtoxinA blocks vesicular release of calcitonin gene-related peptide through the same synaptosomal-associated protein of

25 kDa (SNAP-25) mechanisms occurring in motor neurons.<sup>34,35</sup> Both of these mechanisms may have relevance to the efficacy of onabotulinumtoxinA in migraine.

The efficacy and safety of onabotulinumtoxinA in patients with CM have been investigated in 2 prospective, randomized, multicenter clinical trials: the Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) trials.<sup>36,37</sup> In both PREEMPT trials, patients were randomized to onabotulinumtoxinA 155 to 195 units or placebo every 12 weeks for 2 cycles. In the PREEMPT 1 trial ( $N = 679$ ), the mean change in number of headache episodes, the primary efficacy endpoint, was similar for onabotulinumtoxinA and placebo ( $-5.2$  vs  $-5.3$ , respectively;  $P = .344$ ), although the numbers of headache days ( $P = .006$ ) and migraine days ( $P = .002$ ) were lower with onabotulinumtoxinA.<sup>36</sup> In the PREEMPT 2 trial ( $N = 705$ ), the mean change in frequency of headache days per 28 days, the primary efficacy endpoint, was significantly improved with onabotulinumtoxinA compared with placebo ( $-9.0$  vs  $-6.7$ , respectively;  $P < .001$ ).<sup>37</sup> In the subset of patients with CM and MOH, a planned pooled analysis showed greater improvement in number of headache days and all secondary endpoints.<sup>38</sup>

A planned pooled analysis of all patients included in PREEMPT 1 and 2 showed that, with the exception of frequency of acute headache pain medication intake, improvements in all secondary endpoints were significantly greater with onabotulinumtoxinA than placebo.<sup>39</sup> Secondary endpoints included frequency of migraine days, frequency of moderate/severe headache days, number of cumulative hours of headache on headache days, proportion of patients with severe ( $\geq 60$  points) Headache Impact Test scores, frequency of headache episodes, and frequency of migraine episodes. Most adverse events were mild or moderate in severity and resolved without sequelae. The most frequently reported adverse events leading to discontinuation were neck pain (0.6%), muscular weakness (0.4%), headache (0.4%), and migraine (0.4%) in the onabotulinumtoxinA group.

OnabotulinumtoxinA has been compared with topiramate as preventive therapy in a randomized, double-blind, pilot study involving 59 patients with CM.<sup>40</sup> Following 12 weeks of treatment, significant improvement in the treatment responder rate and all secondary endpoints, including quality of life, was observed in patients treated with either onabotulinumtoxinA or topiramate, with no difference between groups. These efficacy results as preventive therapy are similar to an earlier pilot study in 60 patients treated with onabotulinumtoxinA (maximum 200 units/3 months) or topiramate 100 mg/day over 9 months.<sup>41</sup> Adverse events with onabotulinumtoxinA were generally characterized by weakness in muscle groups in the local vicinity of injection sites around the head and neck (especially eyebrow/eyelid and forehead/neck), while those with topiramate

generally involved systemic effects such as cognitive deficits, paresthesias, loss of appetite, and weight loss. Treatment-related discontinuation occurred in 7.7% of patients treated with onabotulinumtoxinA and 24.1% of patients treated with topiramate.<sup>41</sup>

**CASE STUDY (continued):** Rita returns in 3 months. She is sleeping better and her mood is improved, but she continues with 18 headache days per month. She has reduced her work absenteeism with use of subcutaneous sumatriptan and diclofenac potassium, but continues with significant migraine-related disability at home. Rita and her primary care provider discuss the need for modifying her preventive treatment plan and agree to a trial of at least 2 injection cycles of onabotulinumtoxinA. Rita is reminded of the importance of not overusing her abortive medications and is provided with additional diaries to track her acute treatment successes and failures as well as the number of headache days she experiences.

## SUMMARY

Chronic migraine is a frequent, severely disabling headache that often evolves from EM. Treatment should be individualized with consideration of the patient as a whole person rather than just the headaches. Many options have been used for acute and preventive pharmacologic management, although good scientific and clinical evidence is limited to a few options. Evidence supports the efficacy and tolerability of both topiramate and onabotulinumtoxinA for prevention of CM headaches. However, only onabotulinumtoxinA is approved by the FDA for preventive treatment of CM. ●

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