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# Breaking the cycle of medication overuse headache

Care of this disorder can be complex—from ruling out another secondary cause of headache to supervising detox from abortives, providing preventives, and educating often-fearful patients.

## PRACTICE RECOMMENDATIONS

- › Avoid prescribing barbiturates or opioids for a headache disorder. **A**
- › Limit use of a headache-abortive medication to twice a week when starting a patient on the drug. **C**
- › Consider providing bridging therapy during detoxification of the overused medication. **C**
- › Do not provide a preventive medication without withdrawing the overused agent. **A**

### Strength of recommendation (SOR)

- A** Good-quality patient-oriented evidence
- B** Inconsistent or limited-quality patient-oriented evidence
- C** Consensus, usual practice, opinion, disease-oriented evidence, case series

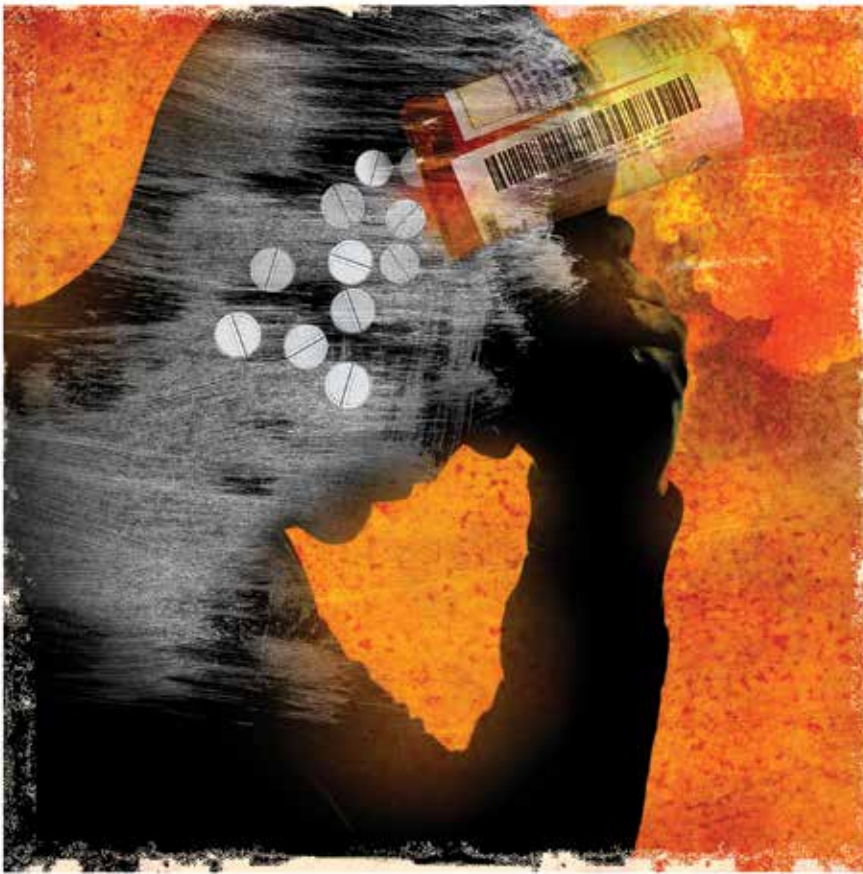
**M**edication overuse headache (MOH), a secondary headache diagnosis, is a prevalent phenomenon that complicates headache diagnosis and treatment, increases the cost of care, and reduces quality of life. Effective abortive medication is essential for the headache sufferer; when an abortive is used too frequently, however, headache frequency increases—potentially beginning a cycle in which the patient then takes more medication to abort the headache. Over time, the patient suffers from an ever-increasing number of headaches, takes even more abortive medication, and so on. In the presence of MOH, there is a reduction in pain response to preventive and abortive treatments; when medication overuse is eliminated, pain response improves.<sup>1</sup>

Although MOH is well recognized among headache specialists, the condition is often overlooked in primary care. Since headache is a top complaint in primary care, however, and prevention is a major goal in family medicine, the opportunity for you to recognize, treat, and prevent MOH is significant. In fact, a randomized controlled trial showed that brief patient education about headache care and MOH provided by a primary care physician can lead to a significant reduction in headache frequency among patients with MOH.<sup>2</sup>

This article reviews the recognition and diagnosis of MOH, based on historical features and current criteria; addresses risk factors for abortive medication overuse and how to withdraw an offending agent; and explores the value of bridging and preventive therapies to reduce the overall frequency of headache.

## What defines MOH?

Typically, MOH is a chronification of a primary headache disorder. However, in patients with a history of migraine who are undergoing treatment for another chronic pain condition with an opioid or other analgesic, MOH can be induced.<sup>3</sup> An



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increase in the frequency of headache raises the specter of a concomitant increase in the level of disability<sup>4</sup>; psychiatric comorbidity<sup>5</sup>; and more headache days, with time lost from school and work.

The Migraine Disability Assessment (MIDAS) questionnaire, a validated instrument that helps the provider (1) measure the impact that headache has on a patient's life and (2) follow treatment progress, also provides information to employers and insurance companies on treatment coverage and the need for work modification. The MIDAS score is 3 times higher in patients with MOH than in patients with episodic migraine.<sup>6,7</sup>

The annual associated cost per person of MOH has been estimated at \$4000, resulting in billions of dollars in associated costs<sup>8</sup>; most of these costs are related to absenteeism and disability. After detoxification for MOH, annual outpatient medication costs are reduced by approximately 24%.<sup>9</sup>

#### Efforts to solve a common problem create another

Headache affects nearly 50% of the general population worldwide,<sup>10</sup> accounting for about 4% of primary care visits<sup>11</sup> and approximately

20% of outpatient neurology consultations.<sup>12</sup> Although inpatient stays for headache are approximately half the duration of the overall average hospital stay, headache accounts for 3% of admissions.<sup>13</sup> According to the Global Burden of Disease study, tension-type headache, migraine, and MOH are the 3 most common headache disorders.<sup>10</sup> Headache is the second leading cause of disability among people 15 to 49 years of age.<sup>10</sup>

The prevalence of MOH in the general population is 2%.<sup>7,14,15</sup> A population-based study showed that the rate of progression from episodic headache (< 15 d/mo) to chronic headache ( $\geq$  15 d/mo) in the general population is 2.5% per year<sup>16</sup>; however, progression to chronic headache is 14% per year in patients with medication overuse. One-third of the general population with chronic migraine overuses symptomatic medication; in US headache clinics, roughly one-half of patients with chronic headache overuse acute medication.<sup>6</sup>

#### Definitions and diagnosis

MOH is a secondary headache diagnosis in the third edition of the International Classification of Headache Disorders (ICHD-3)

➤  
The time it takes to develop medication overuse headache is shortest with triptans, followed by ergots, then analgesics.

(TABLE 1),<sup>17</sup> which lists diagnostic criteria for recognized headache disorders.

■ **Terminology.** MOH has also been called *rebound headache*, *drug-induced headache*, and *transformed migraine*, but these terms are outdated and are not formal diagnoses. Patients sometimes refer to substance-withdrawal headaches (not discussed in this article) as rebound headaches, so clarity is important when discussing headache with patients: namely, that MOH is an exacerbation of an existing headache condition caused by overuse of abortive headache medications, including analgesics, combination analgesics, triptans, barbiturates, and opioids.

MOH was recognized in the early 1950s and fully differentiated as a diagnosis in 2005 in the second edition of the ICHD. The disorder is subcategorized by offending abortive agent (TABLE 2<sup>17</sup>) because the frequency of analgesic use required to develop MOH differs by agent.

■ **Risk factors for MOH and chronification of a primary headache disorder.** There are several risk factors for developing MOH, and others that contribute to increasing headache frequency in general (TABLE 3<sup>5,14,18-23</sup>). Some risk factors are common to each. All are important to address because some are modifiable.

■ **Pathophysiology.** The pathophysiology and psychology behind MOH are largely unknown. Physiologic changes in pain processing and functional imaging changes have been demonstrated in patients with MOH, both of which are reversible upon withdrawal of medication.<sup>23</sup> Genetic factors and changes in hormone and neurotransmitter levels are found in MOH patients; this is not the case in patients who have an episodic headache pattern only.<sup>24</sup>

■ **Presentation.** Diagnostic criteria for MOH do not include clinical characteristics. Typically, the phenotype of MOH in a given patient is similar to the underlying primary headache<sup>25</sup>—although this principle can be complicated to tease out because these medications can suppress some symptoms. Diagnosis of a primary headache disorder should be documented along with the diagnosis of MOH.

Medication overuse can exist without MOH: Not every patient who frequently uses an abortive medication develops MOH.

### Treatment is multifaceted—and can become complex

Mainstays of treatment of MOH are education about the disorder and detoxification from the overused agent, although specific treatments can differ depending on the agent involved, the frequency and duration of its use, and a patient's behavioral patterns and psychiatric comorbidities. Often, a daily medication to prevent headache is considered upon, or after, withdrawal of the offending agent. The timing of introducing a preventive might impact its effectiveness. Some refractory cases require more intensive therapy, including hospitalization at a specialized tertiary center.

But before we look at detoxification from an overused agent, it's important to review one of the best strategies of all in combatting MOH.

#### First and best strategy: Avoid onset of MOH

■ **Select an appropriate abortive** to reduce the risk of MOH. With regard to specific acute headache medications, some nuances other than type of headache should be considered. Nonsteroidal anti-inflammatory drugs (NSAIDs) are recommended as abortive therapy by the American Headache Society for their efficacy, favorable adverse effect profile, and low cost. NSAIDs are protective against development of MOH if a patient's baseline headache frequency is < 10/mo; at a frequency of 10 to 14 d/mo, however, the risk of MOH increases when using an NSAID.<sup>6</sup> A similar effect has been seen with triptans.<sup>16</sup> Longer-acting NSAIDs, such as nabumetone and naproxen, have been proposed as less likely to cause MOH, and are even used as bridging therapy sometimes (as long as neither of these was the overused medication).<sup>26</sup>

The time it takes to develop MOH is shortest with triptans, followed by ergots, then analgesics.<sup>27</sup>

Prospective cohort studies<sup>6,16</sup> have shown that barbiturates and opioids are more like-

ly to induce MOH; for that reason, agents in these analgesic classes are almost universally avoided unless no other medically acceptable options exist. Using barbiturate-containing compounds or opioids > 4 d/mo exponentially increases the likelihood of MOH.

Promising preclinical data demonstrate that the gepant, or small-molecule calcitonin gene-related peptide (CGRP) receptor antagonist, class of medications used as abortive therapy does not induce medication overuse cutaneous allodynia.<sup>28</sup>

**■ Provide education.** Primary prevention of MOH involves (1) increasing patients' awareness of how to take medications appropriately and (2) restricting intake of over-the-counter abortive medications. Often, the expert recommendation is to limit abortives to approximately 2 d/wk because more frequent use places patients at risk of further increased use and subsequent MOH.

A randomized controlled trial in Norway compared outcomes in 2 groups of patients with MOH: One group was given advice on the disorder by a physician; the other group was not provided with advice. In the "business-as-usual" group, there was no significant improvement; however, when general practitioners provided simple advice (lasting roughly 9 minutes) about reducing abortive medication use to a safe level and cautioned patients that they would be "feeling worse before feeling better," headache days were reduced by approximately 8 per month and medication days, by 16 per month.<sup>2</sup>

A subsequent, long-term follow-up study<sup>29</sup> of patients from the Norway trial<sup>2</sup> who had been given advice and education showed a relapse rate (ie, into overuse of headache medication) of only 8% and sustained reduction of headache days and medication use at 16 months.

**■ Offer support and other nondrug interventions.** A recent review of 3 studies<sup>23</sup> recommended that extra support for patients from a headache nurse, close follow-up, keeping an electronic diary that provides feedback, and undertaking a short course of psychotherapy can reduce medication overuse and prevent relapse.

**TABLE 1**  
**Diagnostic criteria for medication overuse headache<sup>17</sup>**

Headache that occurs ≥ 15 d/mo in a patient with a pre-existing headache disorder
Regular overuse for > 3 mo of ≥ 1 drugs that can be taken for acute or symptomatic (or both) treatment of headache <sup>a</sup>
Headache that is not better accounted for by another diagnosis in The International Classification of Headache Disorders, 3rd edition <sup>17</sup>

<sup>a</sup> Patients should be coded for 1 or more subtypes of **8.2 Medication-overuse headache** according to the specific medication(s) overused and the criteria for each subtype, as follows:

- A patient who fulfills criteria for **8.2.2 Triptan-overuse headache** and criteria for a subtype of **8.2.3 Non-opioid analgesic-overuse headache** should receive both codes. Exception: A patient overuses a combination-analgesic medication, which is coded **8.2.5 Combination-analgesic-overuse headache** and not according to each constituent of the combination-analgesic medication.
- A patient who uses multiple drugs for acute or symptomatic treatment of headache might do so in a manner that constitutes overuse, even though no individual drug or class of drug is overused; such a patient should be coded **8.2.6 Medication-overuse headache attributed to multiple drug classes not individually overused**.
- A patient who is clearly overusing multiple drugs for acute or symptomatic treatment of headache but cannot give an adequate account of the names or quantities of those drugs is coded **8.2.7 Medication-overuse headache attributed to unspecified or unverified overuse of multiple drug classes** until better information is available. Almost all such cases necessitate follow-up using a diary.

For more information on the classification of medication overuse headache, see: <https://ichd-3.org/8-headache-attributed-to-a-substance-or-its-withdrawal/8-2-medication-overuse-headache-moh/>.<sup>17</sup>

**If MOH develops, initiate withdrawal, introduce a preventive**

**■ Withdraw overused medication.** Most current evidence suggests that withdrawal of the offending agent is the most effective factor in reducing headache days and improving quality of life. A randomized controlled trial compared the effects of (1) complete and immediate withdrawal of an abortive medication with (2) reducing its use (ie, limiting intake to 2 d/wk), on headache frequency, disability, and quality of life.<sup>30</sup> There was a reduction of headache days in both groups; however, reduction was much greater at 2 months in the complete withdrawal group than in the restricted intake group (respectively, a 41% and a 26% reduction in headache days per month). This effect was sustained at 6 and 12 months in both groups. The study confirmed the results of earlier research<sup>2,15</sup>: Abrupt withdrawal leads to reversion to an episodic pattern at 2 to 6 months in approximately 40% to 60% of patients.

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TABLE 2

Medication overuse headache subcategories by offending abortive agent<sup>17</sup>

Subgroup of abortive medication	Extent of abortive medication use
<ul style="list-style-type: none"> <li>• Ergotamine (or ergot alkaloids)</li> <li>• Combination analgesics (≥ 2 analgesics or an analgesic combined with caffeine)</li> <li>• Opioids</li> <li>• Triptans</li> </ul>	≥ 10 d/mo
Nonopioid analgesic overuse headache <ul style="list-style-type: none"> <li>• Acetaminophen</li> <li>• Acetylsalicylic acid</li> <li>• Nonsteroidal anti-inflammatory drugs</li> <li>• Other</li> </ul>	≥ 15 d/mo

More studies are needed to determine the most appropriate treatment course for MOH; however, complete withdrawal of the causative drug is the most important intervention.

■ **Consider withdrawal plus preventive treatment.** Use of sodium valproate, in addition to medication overuse detoxification, led to a significant reduction in headache days and improvement in quality of life at 12 weeks but no difference after 24 weeks, compared with detoxification alone in a randomized, double-blind, placebo-controlled study.<sup>31</sup>

A study of 61 patients showed a larger reduction (by 7.2 d/mo) in headache frequency with any preventive medication in addition to medication withdrawal, compared to withdrawal alone (by 4.1 d/mo) after 3 months; however, the relative benefit was gone at 6 months.<sup>32</sup>

A study of 98 patients compared immediate and delayed initiation of preventive medication upon withdrawal of overused abortive medication.<sup>33</sup> Response was defined as a > 50% reduction in headache frequency and was similar in both groups; results showed a 28% response with immediate initiation of a preventive; a 23% response with delayed (ie, 2 months after withdrawal) initiation; and a 48% response in both groups at 12 months.

Collectively, these studies suggest that adding a preventive medication at the time of withdrawal has the potential to reduce headache frequency more quickly than withdrawal alone. However, after 3 to 6 months,

the outcome of reduced headache frequency is the same whether or not a preventive medication is used—as long as the offending agent has been withdrawn.

■ **Do preventives work *without* withdrawing overused medication?** Patients with MOH often show little or no improvement with addition of a preventive medication only; their response to a preventive improves after withdrawal of the overused medication. Patients without previous headache improvement after addition of a preventive, who also did not improve 2 months after withdrawal, then demonstrated an overall reduction in headache by 26% when a preventive was reintroduced after withdrawal.<sup>2</sup>

■ **The research evidence for preventives.** Medications for headache prevention have not been extensively evaluated specifically for treating MOH. Here is what's known:

- Flunarizine, amitriptyline, and beta-blockers usually are ineffective for MOH.<sup>24</sup>
- Results for topiramate are mixed: A small, double-blind, placebo-controlled chronic migraine study in Europe showed that, in a subgroup of patients with MOH, topiramate led to a small but significant reduction (3.5 d/mo) in headache frequency, compared to placebo.<sup>27</sup> A similar study done in the United States did not show a significant difference between the active-treatment and placebo groups.<sup>34</sup>

TABLE 3

Risk factors for increasing headache frequency<sup>5,14,18-23</sup>

Headache chronification <sup>a</sup>	Medication overuse headache <sup>a</sup>
Allodynia <sup>21</sup>	Baseline attack frequency 7-14 d/mo <sup>19</sup>
Asthma, chronic bronchitis, sinusitis <sup>21</sup>	Body mass index > 30 <sup>23</sup>
Baseline attack frequency ≥ 10-15 d/mo <sup>20</sup>	Chronic noncephalic pain <sup>19</sup>
Chronic noncephalic pain <sup>21</sup>	Family history of medication overuse headache <sup>14</sup>
Depression, anxiety <sup>19,21</sup>	Female <sup>14,19,22</sup>
Family history of migraine or substance abuse <sup>18</sup>	Gastrointestinal complaints <sup>18,19</sup>
Female <sup>18,19</sup>	Insomnia <sup>19</sup>
Gastrointestinal complaints <sup>18,19</sup>	Low education <sup>18,19</sup>
Hypertension <sup>18</sup>	Low socioeconomic status <sup>14</sup>
Low education <sup>18,19</sup>	Married <sup>14</sup>
Married <sup>18</sup>	Obsessive-compulsive disorder, anxiety disorder, mood disorder <sup>5,19</sup>
Medication overuse <sup>21</sup>	Physical inactivity <sup>19</sup>
Menopause <sup>18</sup>	Primary headache is migraine <sup>18</sup>
No migraine remission during pregnancy <sup>18</sup>	Sedative-hypnotic use <sup>18,19</sup>
Not using an oral contraceptive <sup>18</sup>	Sick leave > 2 wk in the previous year <sup>19</sup>
Primary headache is nonmigrainous <sup>19</sup>	Smoking <sup>19</sup>
Snoring, obstructive sleep apnea, insomnia <sup>19,21</sup>	Whiplash injury <sup>19</sup>
Unemployed <sup>18</sup>	Younger <sup>b</sup> age <sup>19</sup>
Whiplash injury <sup>19</sup>	

<sup>a</sup> Items in red are risk factors common to chronification and medication overuse.

<sup>b</sup> Compared to patients with chronic daily headache without medication overuse.

- Findings regarding onabotulinumtoxinA are intriguing: In a posthoc analysis of onabotulinumtoxinA to treat chronic migraine, patients with MOH who did not undergo detoxification had an 8 d/mo greater reduction in headache, compared to placebo.<sup>35</sup> However, when compared to placebo in conjunction with detoxification, onabotulinumtoxinA demonstrated no benefit.<sup>36</sup>
- Newer CGRP antagonist and CGRP receptor antagonist monoclonal antibodies are successful preventive medications that have demonstrated a reduction in acute medication use days per month and headache days per month<sup>37</sup>; these compounds have not been compared to withdrawal alone.

**Reducing the severity**

**and duration of withdrawal symptoms**

Withdrawal from overused abortive head-

ache medications can lead to worsening headache, nausea, vomiting, hypotension, tachycardia, sleep disturbances, restlessness, anxiety, and nervousness. Symptoms usually last 2 to 10 days but can persist for as long as 4 weeks; duration of withdrawal symptoms varies with the medication that is being overused. In patients who have used a triptan, for example, mean duration of withdrawal is 4.1 days; ergotamine, 6.7 days; and NSAIDs, 9.5 days.<sup>23</sup> Tapered withdrawal is sometimes recommended with opioids and barbiturates to reduce withdrawal symptoms. It is unclear whether starting a preventive medication during withdrawal assists in reducing withdrawal symptoms.<sup>38</sup>

■ **Bridging therapy** to reduce symptoms of withdrawal is often provided despite debatable utility. Available evidence does not favor one agent or method but suggests some strategies that could be helpful:

- **A prednisone taper** has a potential role during the first 6 days of with-

➤ **Reduce the risk of medication overuse headache by selecting an appropriate abortive; NSAIDs are recommended for their efficacy, favorable adverse effect profile, and low cost.**

drawal by reducing rebound headache and withdrawal symptoms<sup>39</sup>; however, oral prednisolone has been shown to have no benefit.<sup>40</sup>

- **Alone, IV methylprednisolone** seems not to be of benefit; however, in a retrospective study of 94 patients, IV methylprednisolone plus diazepam for 5 days led to a significant reduction in headache frequency and drug consumption that was sustained after 3 months.<sup>41</sup>
- **Celecoxib** was compared to prednisone over a 20-day course: a celecoxib dosage of 400 mg/d for the first 5 days, tapered by 100 mg every 5 days, and an oral prednisone dosage of 75 mg/d for the first 5 days, then tapered every 5 days. Patients taking celecoxib had lower headache intensity but there was no difference in headache frequency and acute medication intake between the groups.<sup>42</sup>

■ **Other strategies.** Using antiemetics and NSAIDs to reduce withdrawal symptoms is widely practiced, but no placebo-controlled trials have been conducted to support this strategy.

Patients in withdrawal might be more likely to benefit from inpatient care if they have a severe comorbidity, such as opioid or barbiturate use; failure to respond to, tolerate, or adhere to treatment; or relapse after withdrawal.<sup>38</sup>

Cognitive behavioral therapy, exercise, a headache diary, and biofeedback should be considered in every patient's treatment strategy because a multidisciplinary approach increases adherence and leads to improvement in headache frequency and a decrease in disability and medication use.<sup>43</sup>

#### **Predictors of Tx success**

A prospective cohort study determined that the rate of MOH relapse is 31% at 6 months, 41% at 1 year, and 45% at 4 years, with the highest risk of relapse during the first year.<sup>44</sup> Looking at the correlation between type of medication overused and relapse rate, the research indicates that

- triptans have the lowest risk of relapse,<sup>44</sup>

- simple analgesics have a higher risk of relapse than triptans,<sup>22,44</sup> and
- opioids have the highest risk of relapse.<sup>22</sup>

■ **Where the data don't agree.** Data on combination analgesics and on ergots are conflicting.<sup>22</sup> In addition, data on whether the primary type of headache predicts relapse rate conflict; however, migraine might predict a better outcome than tension-type headache.<sup>22</sup>

#### **To recap and expand: Management pearls**

The major goals of headache management generally are to rule out secondary headache, reach a correct diagnosis, reduce overall headache frequency, and provide effective abortive medication. A large component of reducing headache frequency is addressing and treating medication overuse.

■ **Seek to understand the nature of the patient's headache disorder.** Components of the history are key in identifying the underlying headache diagnosis and ruling out other, more concerning secondary headache diagnoses. The ICHD-3 is an excellent resource for treating headache disorders because the classification lists specific diagnostic criteria for all recognized headache diagnoses.

Medication withdrawal—with or without preventive medication—should reduce the frequency of MOH in 2 or 3 months. If headache does not become less frequent, however, the headache diagnosis might need to be reconsidered. Minimizing the use of abortive medication is generally recommended, but reduction or withdrawal of these medications does not guarantee that patients will revert to an episodic pattern of headache.

Treating withdrawal symptoms is a reasonable approach in some patients, but evidence does not support routinely providing bridging therapy.

■ **Apply preventives carefully.** Abortive medication withdrawal should generally be completed before initiating preventive medication; however, over the short term, starting preventive therapy while withdrawing the overused medication could assist in reducing headache frequency rapidly. This strategy

can put patients at risk of medication adverse effects and using the medications longer than necessary, yet might be reasonable in certain patients, given their comorbidities, risk of relapse, and physician and patient preference. A preventive medication for an individual patient should generally be chosen in line with recommendations of the American Academy of Neurology<sup>45</sup> and on the basis of the history and comorbidities.

■ **Provide education**, which is essential to lowering barriers to success. Patients with MOH must be counseled to understand that (1) a headache treatment that is supposed to be making them feel better is, in fact, making them feel worse and (2) they will get worse before they get better. Many patients are afraid to be without medication to use as needed. It is helpful to educate them on the different types of treatments (abortive, preventive); how MOH interferes with headache prophylaxis and medication efficacy; how MOH alters brain function (ie, aforementioned physiologic changes in pain processing and functional imaging changes<sup>23</sup>); and that such change is reversible when medication is withdrawn. **JFP**

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➤ **Inpatient care of withdrawal might be beneficial when a patient has a severe comorbidity; does not respond to, tolerate, or adhere to treatment; or relapses after withdrawal.**



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