Medication-Overuse Headache

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ABSTRACT

Purpose of Review: Medication-overuse headache (MOH) is a chronic daily headache in which acute medications used at high frequency cause transformation to headache occurring 15 or more days per month for 4 or more hours per day if left untreated. MOH is a form of US Food and Drug Administration–defined chronic migraine. This review will describe (1) MOH clinical features and diagnosis, (2) pathophysiology and structural and functional MOH brain changes, and (3) prevention and treatment of MOH.

Recent Findings: MOH causes structural and functional brain changes. Any butalbital or opioid use increases the risk of transforming episodic into chronic migraine (sometimes referred to as chronification). The American Migraine Prevalence and Prevention Study demonstrated that transformation is most likely to occur with 5 days of butalbital use per month, 8 days of opioid use per month, 10 days of triptan or combination analgesic use per month, and 10 to 15 days of nonsteroidal anti-inflammatory use per month. Acute migraine treatment should be limited to 2 or fewer days per week, and opioids and butalbital should be avoided.

Treatment of MOH consists of combining prophylaxis, 100% wean of overused acute medications, and provision of new acute medications, strictly limiting use to 2 or fewer days per week. Wean can be done slowly in an outpatient setting or it can be done abruptly, sometimes requiring hospitalization with medicine bridges.

Summary: MOH development is linked to baseline frequency of headache days per month, acute medication class ingested, frequency of acute medications ingested, and other risk factors. Using less effective or nonspecific medication for severe migraine results in inadequate treatment response, with redosing and attack prolongation, frequently leading to chronification. Use of any barbiturates or opioids increases the transformation likelihood.

Patients with MOH can usually be effectively treated. The first step is 100% wean, followed by establishing preventive medications such as onabotulinumtoxinA or daily prophylaxis and providing acute treatment for severe migraine 2 or fewer days per week. Slow wean or quick termination of rebound medications can be accomplished for most patients on an outpatient basis, but some more difficult problems may need referral for multidisciplinary day hospital or inpatient treatments.

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Tepper discusses the unlabeled use of medications in the treatment of medication-overuse headache for which there are no US Food and Drug Administration (FDA)–approved medications. OnabotulinumtoxinA, a biologic, is FDA approved for chronic migraine, and medication-overuse headache is a subset of chronic migraine.

INTRODUCTION

Medication-overuse headache (MOH) is a secondary chronic daily headache (CDH), described by the International Classification of Headache Disorders, Second Edition (ICHD-II) as ''an interaction between a therapeutic agent used excessively and a susceptible patient [in which] overuse…[causes] headache in the headache-prone patient.''[1] Repeated acute medication use reaches a critical threshold, usually in a patient with episodic migraine (EM), and transformation to CDH

KEY POINT

■ The most important predictors for development of chronic migraine and medication-overuse headache are headache frequency and frequency of acute medication use.

ensues; the ''headache has developed or markedly worsened during medication overuse.''[2]

MOH is a subset of CDH, defined as headache, whether primary or secondary, occurring 15 or more days per month, 4 or more hours per day, for 3 or more months. In 2010, in the onabotulinumtoxinA prescribing information for chronic migraine (CM), the US Food and Drug Administration (FDA) defined CM as headache occurring 15 or more days per month for 4 or more hours per day.[3] The FDA definition of CM implies CDH and is an umbrella term, covering both primary and secondary daily headache, therefore including MOH.

MOH can be prevented with appropriate therapy. CDH is not a final end point, as patients with daily headache may revert to EM with the use of thoughtful, targeted intervention. MOH is rewarding to treat, and outcomes are generally good with adequate management and patient cooperation.

FREQUENT HEADACHE EPIDEMIOLOGY AND NATURAL HISTORY

CDH prevalence is 4% to 5%; the average annual incidence of new-onset CM in patients with EM is 2.5%.[4–7] CM is fluid; 57% of patients reverted to EM over 1 year, and 66% reverted over 2 years.[8,9] Thus, reevaluation of patients over time is useful, as clinical improvement often occurs gradually.

Factors associated with an increased transformation risk include white race, less education, previous marriage, obesity, diabetes, arthritis, top quartile of caffeine use, stressful life events in the previous year, head injury, snoring, high baseline headache frequency, and medication overuse.[8,10,11] Predictors for failure to revert to EM were less than a high school education, white race, previous marriage, higher baseline headache frequency (25 to 31 versus 15 to 19 headache days per month), and presence of baseline allodynia.

Quality of life is worse for patients with CM than EM, including missing more work or school, reduced productivity, more health care visits, and 4.4-fold higher health costs per patient-year.[7,12]

DIAGNOSIS

MOH diagnostic terminology has changed, but older diagnostic terms are still used. For years the terms ''rebound headache'' and ''transformed migraine''[13] were used interchangeably.[14,15] Transformed migraine included both primary and secondary CDH (**Table 5-1** and **Table 5-2**).[16]

The ICHD-II divided daily headaches into primary and secondary.[1] CM is a *primary* headache disorder that

TABLE 5-1 Transformed Migraine[a]

1. Chronic daily headache develops gradually, onset is not precipitous; it is not new daily persistent headache
2. One or more of the following:
   a. Prior history of episodic migraine
   b. Period of escalating headache frequency
   c. Concurrent superimposed attacks of episodic migraine

[a] Adapted from Silberstein SD, et al, Neurology.[15] © 1996, with permission from AAN Enterprises, Inc. *www.neurology.org/content/47/4/871.abstract?sid=5c777f95-b094-4735-a5dd-12a5b5e21573*.

TABLE 5-2 Silberstein-Lipton Chronic Daily Headache Classification System, 1994[a]

Daily or near-daily headache lasting >4 hrs/d for >15 d/mo
1. Transformed migraine with or without medication overuse
2. Chronic tension-type headache with or without medication overuse
3. New daily persistent headache with or without medication overuse
4. Hemicrania continua with or without medication overuse

[a] Adapted from Silberstein SD, et al, Headache.[16] © 1994, with permission from John Wiley & Sons, Inc. *onlinelibrary.wiley.com/doi/10.1111/j.1526-4610.1994.hed3401001.x/pdf*.

does not include MOH, which is a *secondary* headache disorder in the 2006 ICHD-II Revised (ICHD-IIR) (**Table 5-3**).[2] The question of whether to be a "lumper" of both primary and secondary daily headaches by phenotype, as suggested by the FDA, with CM being CDH including MOH, or a "splitter" into primary daily headache disorders and secondary ones, as laid out in the ICHD-IIR, remains a diagnostic decision for every clinician.

The FDA definition of CM includes both secondary and primary CDH types and does not require gradual onset, previous migraine diagnosis, number of migrainous days, or duration of CDH. Specifically, the FDA defines CM as headache occurring 15 or more days per month, with each headache lasting 4 or more hours per day.

For simplicity's sake, the FDA definition of CM will be used in this article. If the 2006 ICHD-IIR primary CM criteria are used, this will be explicitly stated in the text.

In order to diagnose MOH based on the 2004 ICHD-II criteria, the patient must revert to episodic headache after being weaned from overused medications. The diagnosis cannot be made when the patient is in rebound. However, some patients do not revert to episodic headache after prolonged medication overuse, possibly because their pain regulatory system is permanently damaged by prolonged acute medication exposure.

In addition, the 2004 criteria describe different clinical presentations of daily headache as caused by different medication classes. For example,

TABLE 5-3 Chronic Migraine Criteria From the 2006 International Classification of Headache Disorders, Second Edition, Revised[a]

A. Headache (tension-type and/or migraine) on ≥15 d/mo for ≥3 months
B. Occurring in a migraine patient
C. On ≥8 d/mo for ≥3 months headache has fulfilled:
1. Criteria for migraine without aura and/or
2. Treated and relieved by triptan(s) or ergot
3. No medication-overuse headache or secondary cause

[a] Adapted from Headache Classification Committee; Olesen J, et al, Cephalalgia.[2] © 2006, with permission from SAGE. *cep.sagepub.com/content/26/6/742.abstract*.

KEY POINTS

- The ICHD-II defines chronic migraine as a primary chronic daily headache that does not include medication-overuse headache, which is a secondary daily headache.
- The FDA defines chronic migraine as headache occurring 15 days or more per month with each headache lasting 4 or more hours per day.
- When diagnosing chronic migraine, clearly state whether ICHD-IIR criteria are being used, thus excluding medication-overuse headache (MOH), or whether the FDA definition is being used, which can include MOH.

KEY POINTS

- The more diagnoses promulgated and the more medications tried and found ineffective, the more likely the diagnosis of medication-overuse headache.
- Consider medication-overuse headache likely in a patient with daily or near-daily headache. Rebound should be the default diagnosis; when in doubt, think medication-overuse headache.
- Medication-overuse headache has circadian periodicity, with onset in the morning.

triptan overuse supposedly creates daily migrainous headaches, and ergots ostensibly cause daily tension-type headaches.[1] ICHD-IIR criteria remove the need for reversion to episodic headache to make the MOH diagnosis, and they also eliminate the differing clinical characteristics linked to overuse of different medications (**Table 5-4**).[2]

Clinical Presentations

The clinical manifestations of headache in MOH can change over time in the same patient and are often quite different between patients. This can cause patients to assume they have different types of headache or to describe only the most severe headaches, and the variability can lead even the most astute diagnostician to an incorrect diagnosis.

Differences in presentation for MOH are presumed to be caused by the changing amounts and types of acute medications ingested by patients and variable withdrawal over time. However, certain clinical similarities in patients with MOH are helpful in diagnosis.

Most patients with MOH have episodic headache history. Transformation is usually described as a gradual increase in frequency and severity.

Frequency and type of acute medications. Different medication types are more likely to precipitate MOH. Consumption of acute medications more than 2 days per week with high headache frequency is likely to lead to MOH. Some medications cause transformation of MOH from episodic to chronic at very low frequencies of use, eg, butalbital at 5 days per month. Combinations of medications are more likely to accelerate MOH.

Circadian periodicity. MOH generally occurs in the morning. Patients may be awakened from sleep by headache or have onset fairly quickly upon arising, probably due to nocturnal withdrawal.

Pain location and the neck. Patients with MOH have variable quality, intensity, and location of daily headaches. They describe different headaches as front, back, right, left, unilateral, or bilateral and have many explanations for this variability. It is not the quality of headaches but rather the quantity that makes the MOH diagnosis.

Neck pain occurs in more than two-thirds of patients with EM, but its presence in MOH is striking. MOH is frequently misdiagnosed as tension-type or cervicogenic headache and patients are given neck interventions, which are often ineffective. Completing a wean from medications often dramatically ameliorates the neck pain.

TABLE 5-4 Medication-Overuse Headache Criteria From the International Classification of Headache Disorders, Second Edition, Revised[a]

A. Headache ≥15 d/mo
B. Regular overuse for >3 months of ≥1 acute/symptomatic treatment drugs:
   1. Ergotamine, triptans, opioids, or combination analgesic medications on ≥10 d/mo on a regular basis for >3 months
   2. Simple analgesics or any combination of ergotamine, triptans, or analgesics opioids on ≥15 d/mo on a regular basis for >3 months without overuse of any single class alone
C. Headache developed or markedly worsened during medication overuse

[a] Adapted from Headache Classification Committee; Olesen J, et al, Cephalalgia.[2] © 2006, with permission from SAGE. *cep.sagepub.com/content/26/6/742.abstract*.

Autonomic and vasomotor symptoms. Many patients with MOH report vasomotor instability, rhinorrhea, nasal stuffiness, postnasal drip, and ocular or gastrointestinal symptoms, likely caused by withdrawal and most evident in opioid rebound. Sinus symptoms are frequently attributed to sinus headaches. Patients self-medicate with decongestants, exacerbating MOH. Care providers prescribe antibiotics, worsening antibiotic resistance. Dysautonomic symptoms almost always improve after wean.

Comorbid depression and anxiety. The odds ratio for comorbid depression and anxiety in patients with EM is 4 to 5 and even higher in patients with CM, and the co-occurrence of depression and anxiety can lead clinicians to think a patient's problem is primarily psychiatric. Trying to treat depression or anxiety without a wean will be unsuccessful as a strategy for treating MOH. Frequent use of nonsteroidal anti-inflammatory drugs (NSAIDs) or analgesics such as ibuprofen interferes with serotonergic antidepressant efficacy, an example of how rebound medications nullify or reduce efficacy in prevention.[17] It may not be possible to reverse the psychiatric problems until overused medications are eliminated.

Sleep. Patients with MOH generally have a nonrestorative sleep disturbance, possibly related to depression or drug withdrawal. Caffeine consumption, increased by caffeine-containing combination analgesics, can further disturb sleep. Generally, MOH sleep disturbance, as with MOH neck pain, is not a sign of primary sleep or neck disorder and improves dramatically with wean and treatment.

Reduced effectiveness of all treatments. Reduced effectiveness of both acute and preventive treatments occurs in patients with rebound before wean.[15] Patients often present with many unsuccessful trials of multiple medication classes. After wean, even when an episodic pattern has not been reestablished, prophylactic treatment can be much more effective.[2]

PATHOPHYSIOLOGY

MOH is associated with both structural and functional brain changes, gray matter volume reduction, and areas of hypometabolism and hypermetabolism.[18,19] Repeated migraine episodes may result in free radical formation and iron byproduct deposition in basal ganglia and brainstem nuclei on fMRI.[20–22]

Chronic opioid use increases peripheral expression of calcitonin gene-related peptide and dynorphin, enabling activation of excitatory glutamate receptors and neurotoxicity manifested by neuronal apoptotic cell damage and death. Descending pain facilitation persists long after opioid discontinuation and may be a cause of irreversible dysregulation in MOH, in which a patient cannot revert to EM following wean.[23]

Srikiatkhachorn and colleagues[24] studied animal neuronal changes with chronic analgesic exposure. They speculated that repeated episodes of peripheral vasodilation and neurogenic inflammation during migraine attacks sensitize nociceptors.

Patients who undertreat migraine obtain partial relief, then have recurrence of the same attack and repeat treatment during an attack, which can last for days. If the frequency of attacks and the acute medication dose are high enough, transformation of the migraines from episodic to chronic begins.

FREQUENCY, TYPE, AND DURATION OF ACUTE MEDICATION AND GENESIS

The American Migraine Prevalence and Prevention population-based study followed 8219 patients with EM for up to 6 years for MOH development. Any use of barbiturates and opiates was found to be

KEY POINTS

- Medication-overuse headache is often accompanied by neck pain and vasomotor instability; these symptoms generally improve after a wean of rebound medications.
- In true high-dose secondary medication-overuse headache, as opposed to primary ICHD-IIR chronic migraine, remission without wean is unlikely. The adage is, ''There is no spontaneous remission from rebound.''
- Medication-overuse headache is associated with both structural and functional brain imaging changes.
- Pro-nociceptive expression of calcitonin gene-related peptide, dynorphin, and glutamate can manifest in neuronal cell damage and death in medication-overuse headache.

KEY POINTS

- Patients with vascular disease and migraine should receive daily preventive therapy to reduce frequency, severity, and duration of migraines because acute medication options are limited, triptans and ergots are contraindicated, and the potential for medication-overuse headache with overuse of acute medications is high.
- Use of nonsteroidal anti-inflammatory drugs, combined analgesics, and triptans should be limited to 2 or fewer days per week, even when alternated.
- Ask the patient to use a headache diary to accurately record the frequency of attacks.
- An acute sustained pain-free response (''one and done'') is the best way to prevent transformation into medication-overuse headache.

associated with increased MOH risk. The odds ratio for developing MOH in individuals using butalbital for more than 1 year was 2.06 and for opioids was 1.48.[6,25]

Butalbital was associated with chronification at 5 days of use per month and opioids were associated with chronification at 8 days of use per month. At low frequencies (5 or fewer days of use per month), NSAIDs appeared protective against MOH, whereas at high frequencies (10 to 15 days per month), they were provocative for CM. Triptans were associated with transformation at 10 days of use per month.

Two additional points on transformation: first, it is far more likely that MOH/CM will be triggered by overuse in a patient with a history of EM than in a patient without migraine history. Three well-known studies demonstrate the likelihood of transformation in patients with EM using acute medications for other purposes. In one of the initial descriptions of MOH, weaned patients again experienced MOH when using analgesics for other purposes.[26] Wilkinson and colleagues'[27] study of patients with inflammatory bowel disease found that only the patients with EM developed CM with frequent opioid use to control bowel movements. Finally, Bahra and colleagues[28] noted that most patients with arthritis in a rheumatology clinic who developed MOH were patients with EM. The brain does not recognize for what disorder the acute medication is being used; if the patient has EM, the likelihood of transformation increases with the frequency of acute medication intake.

Second, as noted previously, the two most important factors in chronification are frequency of baseline headache and frequency of acute medication use. No one knows where one ends and the other begins because as frequency escalates so does acute medication use. The marked increase in likelihood of transformation begins at around 10 days of headache per month. The likelihood of chronification also accelerates at 10 days of acute treatment per month, with the exception of barbiturates and opioids, which escalate the likelihood at 5 and 8 days per month, respectively. Thus, the interplay between frequency and acute medication use is complex, intertwined, and difficult to separate, making use of a headache diary in clinical practice critical.

PREVENTION

Preventing MOH is always better than treating it once it is established. Prevention of MOH should be a primary goal when treating EM. Headache diaries are crucial to record number of headache days, treatments, and treatment response. Clinical decisions cannot be made without quantitative data, and relying on patient recall is inadequate.

Prevent transformation to CM by aiming for a sustained pain-free response with acute treatment, defined as pain free within 2 hours of treatment, without recurrence of the same attack, without a repeat dose of the acute treatment, and without rescue treatment—''one and done.''

Patients are more likely to achieve sustained pain-free response with triptans, dihydroergotamine, or NSAIDs. Optimal dosing, administering treatment early in the attack (preferably less than 30 minutes into an attack), and adding an NSAID to the triptan all increase the likelihood of a sustained pain-free response.

Limiting both the number of headache days per month and the number of acute treatment days per month to less than 10 decreases the likelihood of transformation to MOH/CM. The addition of prevention as headache days or treatment days increase may help

prevent chronification. A balance exists between baseline frequency and headache impact or disability; the higher either goes, the quicker prophylaxis should be added. If the impact of headaches is higher, the baseline frequency of headaches at which daily prevention should be added is lower. In a responder, daily prevention at an optimal dose for at least 2 to 3 months should lower migraine frequency by 50% or more.

TREATMENT

MOH treatment involves four steps: (1) 100% weaning off overused medications, (2) establishing preventive medication and/or behavioral or nondrug preventive strategies, (3) providing acute medications with limits to prevent further overuse, and (4) educating patients and families (**Table 5-5**).

An evaluation of the patient's MOH based on the duration and severity of the headache attacks, the number of overused medications consumed and their doses, and comorbid medical and psychiatric conditions is necessary to formulate a treatment plan (**Table 5-6**).

Wean

Old evidence. Clinicians have noted that most patients do not improve without wean, and that those who begin prevention at the same time as detoxification do better than those given prophylaxis without wean.[15,29] Wean with no prophylaxis reestablished EM in about 60% of patients.[15] Patients given preventive daily medication and behavioral treatment while detoxified improved more than those with any one of these interventions alone or no interventions.[15,29,30]

More recent evidence. Two randomized controlled trials of topiramate for CM included patients who had MOH. Topiramate in MOH without wean was less effective than in patients without MOH.[31,32]

In the regulatory CM trials for onabotulinumtoxinA, patients who were taking opioids and barbiturates were mostly excluded, as were patients without any headache-free days in a given month.[33,34] Post hoc analyses found that onabotulinumtoxinA did have effect on MOH without wean.

Because those taking opioids and barbiturates and those with continuous MOH were for the most part not included, the studies excluded the most difficult MOH/CMs. Most importantly, the studies did not examine whether the patients would have done better with a wean in addition to onabotulinumtoxinA, and because the studies were not initially powered to evaluate onabotulinumtoxinA for MOH specifically, the MOH outcomes were post hoc.

Physicians have a fundamental responsibility to wean patients from medication overuse. Overuse of medication is deleterious to a patient's overall health and can lead to severe medical consequences, including gastrointestinal bleeding, analgesic nephropathy, barbiturate-worsened depression, and, of course, CM. MOH, especially rebound from scheduled medications, causes frequent conflict with the care provider and staff over prescriptions,

TABLE 5-5 Medication-Overuse Headache Treatment Steps

1. Completely (100%) wean off overused medications
2. Establish preventive medication and/or behavioral or nondrug preventive strategies
3. Provide acute medications with limits to prevent further overuse
4. Educate patient and family

KEY POINTS

- If the frequency of headache days reaches 10 days per month or the impact of migraine is very high, add preventive medication.
- Wean is crucial in the treatment of medication-overuse headache.

TABLE 5-6 Medication-Overuse Headache Treatment Options

- ▶ **Outpatient Alone**
- ▶ **Infusion Therapy**
  - Outpatient
  - Inpatient
- ▶ **Integrated Program**
  - Day hospital
  - Inpatient program
- ▶ **All of the Above With or Without OnabotulinumtoxinA**

their amount, their refills, and their suspicious disappearances, impairing therapeutic alliance.

In every patient with rebound, physicians should address the wean up front in the first steps taken. Prevention and wean should be added at the same time.

There are four levels of wean (**Table 5-7**).

Outpatient treatment. Most patients with MOH can be treated as outpatients. Prevention is added, wean is undertaken, a quit date for overused medications is set, and acute medications are provided with limits. Education is pivotal, and behavioral and nonpharmacologic strategies brought to bear. Wean is done either slowly over 4 to 6 weeks or abruptly with a bridge to blunt withdrawal symptoms.

Take time to educate. When appropriate, patients need reassurance that they are not addicts, and differentiating abuse from overuse and dependence is important. Explain that treatment takes time and return visits are necessary. Encourage the patient to bring family and friends into the treatment program.

Psychologists can counsel patients for anticipatory anxiety; provide biofeedback, relaxation therapy, and cognitive-behavioral therapy; and help shift the locus of control to the patient. Again, other nonpharmacologic treatments such as regular lifestyle habits, aerobic exercise, trigger avoidance, and active patient participation can be useful. MOH can also occur in children and can be managed in a similar manner as adults but with greater emphasis on behavioral approaches. **Case 5-1** discusses a patient who can be approached using several of these options.

Slow wean. Slow wean steps are the following: (1) establish prevention early; (2) slowly wean overused medications

TABLE 5-7 Four Levels of Wean

1. Conventional outpatient slow wean, simultaneous onabotulinumtoxinA initiation, or slow addition of preventive medications; migraine-specific acute medications provided with strict limits
2. Conventional outpatient quick discontinuation with bridging medications, quick onabotulinumtoxinA initiation, or preventive medications (bridge[a], with no tapering of rebound medications)
3. Medical model: infusions as the bridge and quick onabotulinumtoxinA initiation or preventive medications either in infusion suite or inpatient
4. Multidisciplinary program: day hospital or inpatient wean with multidisciplinary team using infusions as the bridge and quick onabotulinumtoxinA initiation or preventive medications

[a] Bridge can be oral or IV.

Case 5-1

A healthy 40-year-old man had headaches meeting ICHD-II criteria for episodic migraine without aura through his twenties at a rate of 1 to 2 per month. He used a variety of medications to treat these attacks, including combinations of aspirin/acetaminophen (APAP)/caffeine [Excedrin]), dichloralphenazone/APAP/isometheptene, and butalbital/APAP/caffeine. These combination analgesics gave him partial relief but not a pain-free response. His headaches always recurred and required retreatment, and the length and frequency of his migraines increased gradually to 1 to 2 per week, then to more often than not. The gradual transformation of his migraines from episodic migraine to chronic migraine resulted in his current medication regimen:

- 7 days per month of two tablets of APAP/caffeine (Excedrin) per day
- 3 days per month of two capsules of dichloralphenazone/APAP/isometheptene per day
- 3 days per month of butalbital/APAP/caffeine
- 3 days per month of hydrocodone 5 mg/APAP

Comment. Two key questions must be asked in approaching treatment for this man, namely:

(1) Can this man be treated as an outpatient?

(2) If so, should treatment be slow wean or abrupt discontinuation?

The answer is that this man can be treated either way. He can stop his medications abruptly because he is not at risk for barbiturate or narcotic withdrawal. He could be given a long-acting nonsteroidal anti-inflammatory drug (NSAID) bridge such as twice-daily naproxen or nabumetone, although he is in partial NSAID rebound from Excedrin, which contains 250 mg aspirin, 250 mg acetaminophen, and 65 mg caffeine. He would be started on onabotulinumtoxinA or daily prophylaxis with a tricyclic antidepressant, antiepileptic drug, or beta-blocker during the bridge, and he would be given a triptan for use 2 or fewer days per week at the end of the bridge along with maintaining his prevention.

Another alternative would be to taper his medications slowly over 4 to 6 weeks. He could be given onabotulinumtoxinA at the beginning of the taper, or a tricyclic, antiepileptic drug, or beta-blocker could be introduced slowly over the month so that when he is off the rebound medications he will be on therapeutic prophylaxis. He should be given a quit date in week 5, and at that time instructed not to take any further rebound medications and not to treat low-level headaches. He would use a triptan for severe migraine 2 or fewer days per week. He should keep a headache diary.

KEY POINT

- OnabotulinumtoxinA, at 155 units in a fixed dose/sites protocol, is the only FDA approved treatment for chronic migraine.

over weeks; (3) set a quit date for rebound medications; (4) provide acute medications as needed 2 or fewer days per week; and (5) provide education, psychological counseling, and nondrug therapies (**Table 5-8**).

The only FDA-approved preventive medication for CM is onabotulinumtoxinA. Thus, on-label treatment of MOH would require onabotulinumtoxinA as the prophylaxis selected at the beginning of the wean. The FDA-approved Phase 3 Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) protocol for onabotulinumtoxinA administration is 155 units injected in fixed sites.[33,34]

KEY POINTS

- Barbiturate/butalbital withdrawal is potentially fatal.
- Patient intake of scheduled medications such as barbiturates, opioids, and benzodiazepines should be checked against state registries. Ask specifically whether the patient purchases butalbital off the Internet.

TABLE 5-8 Slow Outpatient Wean Approach for Medication-Overuse Headache

1. Slowly taper overused medications/caffeine over 4 to 6 weeks.
2. Add preventive medications slowly over 4 to 6 weeks.
   - OnabotulinumtoxinA: FDA approved for CM
     - 155 units, fixed dose/sites per PREEMPT protocol and taper overused medications
   - Tricyclic antidepressants: amitriptyline (Level B recommendation for EM),[35] nortriptyline, and doxepin by consensus effective in EM:
     - 10 mg every night at bedtime; increase by 10 mg/wk to target dose of ~50 mg every night at bedtime
   - Beta-blockers: propranolol, FDA approved for EM, not CM; Level A recommendation for metoprolol; Level B recommendation for nadolol[35]
     - For nadolol, begin with 40 mg and increase by 40 mg/wk to 80 mg
   - Antiepileptic drugs
     - Topiramate[a]: FDA approved for EM, not CM
       - 25 mg every night at bedtime, increase by 25 mg/wk to target dose of 100 mg every night at bedtime
     - Valproate[b]: FDA approved for EM, not CM
       - 250 mg every night at bedtime, increase by 250 mg to target dose of 500 mg to 1 g every night at bedtime, all in extended-release dose
3. Set a quit date, generally in week 4, after which the patient should no longer treat low-level headaches with previously overused rebound medications or newly provided acute migraine-specific medication.
4. Provide migraine-specific acute treatment for severe migraines to be used ≤ 2 d/wk. Never use the same medication or class of medications that is being weaned, and if possible change classes of acute medication.
5. In refractory weans, a steroid course can be helpful.

[a] Topiramate should be used with caution in women of childbearing age, as its pregnancy category was switched to D because of increased risk of oral cleft birth defects among infants exposed to topiramate during pregnancy.

[b] Valproate should not be used in women of childbearing age because of the risk of polycystic ovaries in the patient and the risk of neural tube defects in the fetus. Valproate should not be used in patients withdrawing from butalbital or benzodiazepines with liver induction.

FDA = US Food and Drug Administration; CM = chronic migraine; PREEMPT = Phase 3 Research Evaluating Migraine Prophylaxis Therapy; EM = episodic migraine.

Rapid wean (cold turkey) with bridge. Quick discontinuation of rebound medications can be dangerous or disabling and should only be done with patients using 3 or fewer tablets per day of barbiturates, benzodiazepines, opioids, or caffeine-containing analgesics. Fatal or life-threatening barbiturate withdrawal from butalbital has occurred. Patients can obtain drugs not prescribed by their provider through the Internet, increasing withdrawal risk.[36] Physicians who practice in a state with a scheduled medication registry for patients (eg, in Ohio, OARRS; in Kentucky, KASPER; in Michigan, MAPS; in Indiana, INSPECT) should look up and quantify use before abrupt discontinuation if they are reasonably sure the patient is not Internet sourcing.

Medications are then abruptly stopped and prophylaxis immediately started. An advantage of this protocol is that the overused medication is stopped from

the beginning so the patient is separated from the problem immediately. Also, wean is not prolonged.

A 5- to 10-day oral or IV bridge is used during withdrawal to reduce withdrawal symptoms and to treat headache. Prevention is added promptly and should be in place when the bridge is stopped. At the end of withdrawal, migraine-specific acute medication is prescribed to be used 2 or fewer days per week. Triptans or ergots should not be used in patients with vascular disease. The bridge must also be tolerated, eg, no NSAID or steroid use in patients with dyspepsia.

TABLE 5-9 Abrupt Wean With Bridge[a,b]

1. Day 1
   - Abrupt termination of acute rebound medications
   - Initiate a 7- to 10-day therapeutic bridge
     - The following bridges have been described (none is FDA approved for this purpose):
       - NSAIDs can be used repetitively and in a scheduled manner
         - Nabumetone 750 mg/d
         - Naproxen 500 mg twice daily
       - Steroids can be used
         - Dexamethasone 4 mg twice daily for 4 days, then once daily for 4 days
         - Prednisone 60 mg to 100 mg every day (days 1 and 2), taper over a week
       - Triptans can be used repetitively and in a scheduled manner
         - Sumatriptan 25 mg 3 times daily for 10 days or until 24 hours headache free, whichever comes first
         - Naratriptan 2.5 mg twice daily for 2 weeks
       - Ergots
         - DHE nasal spray 2 to 3 times daily for 3 to 7 days
         - Methylergonovine 0.2 mg 2 to 3 times daily for 7 to 10 days
2. Beginning Day 1
   - Start daily prophylaxis over 2 days, limited by tolerability (eg, exclude topiramate). Among preventive agents, it should be possible to rapidly add one of the following:
     - OnabotulinumtoxinA
       - 155 units, fixed dose/sites, FDA-approved PREEMPT protocol
     - Tricyclics
       - Amitriptyline or nortriptyline 25 mg at bedtime on day 1, 50 mg at bedtime (day 2)
     - Beta-blockers
       - Metoprolol 25 mg on day 1, 50 mg on day 2
       - Nadolol 40 mg on day 1, 80 mg on day 2
3. At the end of the bridge, provide migraine-specific treatment such as a triptan, strictly limiting use to $\leq$ 2 d/wk
4. If the patient has difficulty and steroids were not used as the bridge, an additional steroid run may be helpful

FDA = US Food and Drug Administration; NSAID = nonsteroidal anti-inflammatory drug; DHE = dihydroergotamine; PREEMPT = Phase 3 Research Evaluating Migraine Prophylaxis Therapy.

[a] Data from Drucker P, Tepper SJ, Headache.[38] *onlinelibrary.wiley.com/doi/10.1046/j.1526-4610.1998.3809687.x/abstract;jsessionid=614FF8EA6A36F3F34633A9C64C1260C8.d02t02.*

[b] Data from Krymchantowski AV, Moreira PF, Cephalalgia.[39] *cep.sagepub.com/content/23/10/982.abstract*.

KEY POINTS

- Patients with long durations of medication-overuse headache, significant comorbidities, high doses of overused medications, narcotic or barbiturate overuse, or those who have been unsuccessful in previous outpatient programs should be referred to interdisciplinary headache programs.
- Butalbital is generally weaned with a 100-mg butalbital equals 30-mg phenobarbital conversion.

Inpatient or outpatient infusions are often used as a bridge. This medical model for higher-level bridging is appropriate if comorbidity is not too severe. The usual protocol in patients with no vascular disease involves some adaptation of the Raskin protocol of repetitive IV dihydroergotamine[37] (**Table 5-9**).[38,39]

Prospective randomized studies on steroids as the bridge have been equivocal. Higher steroid doses are more effective.[40]

Multidisciplinary Programs

Referral to an interdisciplinary headache program is necessary when patients have been unsuccessful with outpatient treatment, have long MOH/CM duration, have multiple medical and psychiatric comorbidities, and/or are using high medication doses that would be difficult or hazardous to withdraw from without more rigorous and structured interventions. The more difficult the patient's clinical situation, the more necessary a multidisciplinary program with parenteral infusion options.

For some patients, even a day hospital program is not safe. The patient may have dangerous weans, risky behaviors, and unstable medical conditions. In any of these circumstances, inpatient treatment becomes imperative.

The interdisciplinary program, whether day hospital or inpatient, should be formally structured and involve multiple medical subspecialties, such as neurology, primary care, psychology, skilled nursing, infusions, and physical therapy. High-dose narcotics, barbiturates, and benzodiazepines require special weaning skills. Generally, patients are weaned as quickly as is safe, with all modalities on hand.

Minimal information on butalbital use in migraine is available. The elimination half-life of butalbital is 61 hours (range, 35 to 88 hours). Elimination is not complete within 24 hours. The analgesic half-life is short at 4 to 6 hours. Butalbital accumulates inexorably with frequent administration.[41,42] As noted previously, butalbital withdrawal is dangerous. Butalbital is generally weaned

TABLE 5-10 Multidisciplinary Treatment for Medication-Overuse Headache[a,b]

1. Abruptly discontinue overused medications when safe, or quickly taper if necessary.
   Use caution when discontinuing benzodiazepines or barbiturates
   a. For barbiturates: Phenobarbital should be used to prevent barbiturate-withdrawal syndrome and seizures
   b. 100 mg butalbital = 30 mg phenobarbital
2. Initiate parenteral bridge therapy: repetitive IV dihydroergotamine[c] (Raskin protocol) coadministered with IV neuroleptics ± valproate, ketorolac, steroids, and/or ondansetron.
3. Initiate preventive medications rapidly. This can be onabotulinumtoxinA with or without daily prophylaxis.
4. Provide interdisciplinary education and treatment.
5. Discharge on prophylaxis and acute medications with strict limits of use ≤2 d/wk.

[a] Data from Raskin NH, Neurology.[37] *www.neurology.org/content/36/7/995.full.pdf+html?sid=630000f9-4cb4-4885-bbf9-d3e4cccc0a49*.
[b] Data from Loder E, Biondi D, Headache.[43] *onlinelibrary.wiley.com/doi/10.1046/j.1526-4610.2003.03171.x/abstract*.
[c] IV aspirin in Germany.

with a 100-mg butalbital equals 30-mg phenobarbital conversion.[43]

Because butalbital is often used by patients for anxiolysis, a consultation with a psychologist or psychiatrist would be appropriate, as well as consideration of instituting anxiolytics with randomized controlled data suggesting that they treat both migraine and depression, such as venlafaxine. OnabotulinumtoxinA can be administered during these programs, with or without other daily prevention, but always with a complete wean (**Table 5-10**).[37,43]

Many multidisciplinary programs, both inpatient and outpatient, are available to help patients exit MOH. Several institutions across the country provide either day hospital or inpatient multidisciplinary programs. **Case 5-2** describes a patient who would do best with an interdisciplinary program approach.

PROGNOSIS

In the general population, as noted, CM generally reverts to lower frequencies of headache over 2 years. Thus, tapering prophylactic medication after 1 year of stability is a good idea. For example, after 1 year of treatment, onabotulinumtoxinA can be allowed to wear off over 3 months for reevaluation of headache frequency.

Most weaned patients with MOH revert to EM or improve and show better response to prophylaxis. Improvement is maximized by combining prevention and wean. A meta-analysis by Zed and colleagues reported that 45% to 60% of patients improved with wean alone by 1 year; 72% to 85% improved with wean plus prophylaxis. At 3 to 5 years, 50% to 66% maintained improvement.[44] Relapse rates ranging from 19% to almost 71% suggest strong need for patient follow-up.

Frequent acute medication use alone does not guarantee that a patient will develop CM, and EM is usually a precursor. Some susceptibility is necessary for developing MOH. Wean alone does not guarantee a reversion to EM, probably

KEY POINTS

- Because butalbital is often used by patients for anxiolysis, prepare to treat anxiety in butalbital withdrawal.
- Two-thirds of those with chronic migraine in the general population experience remission by 2 years.

Case 5-2

A 52-year-old man presented to his neurologist with daily headache and a failed back syndrome. His medical history was notable for episodic migraine that escalated to chronic migraine in the setting of morphine 30 mg/d to 60 mg/d and hydrocodone 10 mg/aspirin/acetominophen [APAP] use (6 to 10 per day). He stated that the morphine was for the back pain, whereas the hydrocodone/APAP was for his headaches. His back still hurt, but headaches were now his main concern.

A prednisone course was ineffective. He had no response to amitriptyline, propranolol, valproate, or topiramate. His insurance refused to authorize onabotulinumtoxinA. He was unsuccessful at narcotic reduction because of his back pain. He also had coronary artery disease.

Comment. This patient will need a multidisciplinary program. He would benefit from a pain medicine specialist to help manage his back pain with nonhabituating medications. The narcotics will require special expertise in wean. The migraine and back pain will both need daily preventive medications. He will need strategies and acute medications with limits for his reestablished episodic migraine, which most likely will return as his headache pattern once the opioids are weaned. A straight medical model or outpatient approach is not appropriate for this patient because of his comorbid conditions.

because some patients develop permanent alterations in pain regulatory pathways. Most MOH/CM patients improve with wean and prevention, however, so this is a very gratifying disorder to treat.

CONCLUSIONS

MOH development is linked to baseline frequency of headache days per month, class of acute medications ingested, frequency of acute medication use, as well as other risk factors. Using less effective or nonspecific medication for severe migraine results in an inadequate treatment response, with redosing and prolongation of attacks, and thus frequently leads to transformation of the headaches from episodic to chronic. Any use of barbiturates or opioids increases transformation likelihood.

Patients with MOH can usually be effectively treated. Wean is the first step in a treatment approach that also involves establishing preventive medications such as onabotulinumtoxinA or daily prophylaxis and providing acute treatment for severe migraine 2 or fewer days per week. Wean must be 100%. Slow wean or quick termination of rebound medications can be accomplished for most patients in an outpatient setting, but some with more difficult problems may need referral for multidisciplinary day hospital or inpatient treatments.

The FDA has approved one CM treatment, onabotulinumtoxinA, in an evidence-based, fixed dose/sites, 155-unit protocol. Other treatments are unapproved, less well studied, and are likely less effective and more toxic.

MOH usually signals that a patient has EM and that with proper treatment reversion to an improved and episodic pattern can be achieved. Working with patients to achieve this end, to shift the locus of control to them, and to help them take their lives back is a clinical opportunity for neurologists.

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