REVIEW

CME CREDIT *EDUCATIONAL OBJECTIVE:* Readers will recognize the risk of developing medication overuse headache with increasing use of medications to treat acute migraine

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Breaking the cycle of medication overuse headache

ABSTRACT

When patients who have frequent, disabling migraines take medications to relieve their symptoms, they run the risk that the attacks will increase in frequency to daily or near-daily as a rebound effect comes into play. This pattern, called medication overuse headache, is more likely to happen with butalbital and opioids than with migraine-specific drugs, as partial responses lead to recurrence, repeat dosing, and, eventually, overuse. Breaking the cycle involves weaning the patient from the overused medications, setting up a preventive regimen, and setting strict limits on the use of medications to relieve acute symptoms.

KEY POINTS

Medication overuse headache can occur with as few as 5 days per month of treatment with butalbital or 8 days per month with opioids.

The features vary, but the most important is headache on 15 or more days per month, lasting at least 4 hours if untreated, for at least 3 consecutive months. Other common symptoms are morning headaches, neck pain, nonrestorative sleep, and vasomotor instability, all of which tend to improve with weaning from the overused medications.

Daily preventive treatment is indicated when patients have 10 or more headaches per month or severe disability from their attacks.

With treatment, the prognosis for medication overuse headache is good. However, patients need close follow-up to prevent recidivism.

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Some migraine patients fall into a trap by overusing the medications they take when they get their headaches, ending in a downward spiral of daily or near-daily headaches for which their medications become less and less effective.

This condition, called medication overuse headache, makes for a poor quality of life. It is often associated with nonrestorative sleep, neck pain, and vasomotor instability. Comorbid depression and anxiety are common and may complicate treatment. (Depression and anxiety, however, do not cause daily headaches.) Patients can also suffer from the physiologic and psychological consequences of the overused medications.

Fortunately, we can break the cycle.[1,2] Treatment involves completely weaning the patient from the overused medications and educating her or him to follow a new regimen of prophylaxis and acute treatment with clear limits on frequency of use. Nondrug treatments such as relaxation therapy, biofeedback, and cognitive behavioral therapy can be useful adjuncts.

CROSSING THE LINE: 15 HEADACHE DAYS A MONTH

Chronic daily headache

We define chronic daily headache as occurring on at least 15 days per month for at least 3 months in a row and lasting at least 4 hours if untreated.

Most patients start with episodic migraine, and many of them remember the period of transformation. Crossing the 15-day-per-month

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threshold changes the clinical presentation, prognosis, and treatment, all for the worse.

In a large population-based study,[3] 2.5% of patients who began with episodic migraine (headaches on fewer than 15 days per month) had "transformed migraine" (headaches on 15 or more days per month) 1 year later. The prevalence of chronic daily headache is almost 5% of the general population and may account for up to 70% of the initial diagnoses seen in headache centers.

The closer a patient is to having 15 headaches per month, the more likely she or he will cross the line.[4,5] Katsarava and colleagues[5] followed patients for 1 year in a neurology clinic in Germany and found that those starting the year with 6 to 9 headache days per month were 6.2 times more likely to develop chronic daily headache in the next year than those who began the year with 0 to 4 per month—and those starting with 10 to 14 headaches per month were 20 times more likely.

Medication overuse headache

Medication overuse headache is a subset of chronic daily headache, also occurring on 15 or more days per month but with the added criterion of medication overuse, ie, regular overuse for more than 3 months of at least one acute treatment drug:

- Ergotamine, triptans, opioids, or combination analgesic medications on 10 or more days per month on a regular basis for more than 3 months, or
- Simple analgesics or any combination of ergotamine, triptans, analgesics, or opioids on 15 or more days per month on a regular basis for more than 3 months without overuse of any single class alone.

Another criterion is that the patient's headaches must worsen in some way (usually frequency) as the use of acute medications becomes more frequent.[6,7]

Medication overuse headache is the most common form of secondary chronic daily headache seen in headache practice,[8–10] and probably accounts for about half of cases of chronic daily headache.[11–13]

Different terminology confuses the issue

Many terms have been used to describe medication overuse headache in the past, such as analgesic-rebound headache (or just rebound headache), transformed migraine with medication overuse, and even chronic migraine. The lack of uniformity in terminology makes for confusion in the literature and difficulty in communicating with patients and colleagues. Some authors mean medication overuse headache when they say chronic daily headache.

Complicating this diagnostic confusion is a debate as to whether chronic daily headache in general should be treated as a primary or secondary headache disorder. Some European headache specialists insist on a strict division between primary and secondary daily headaches, and medication overuse headache is one of the latter. Many American specialists believe that chronic daily headache is a collective description or phenotype rather than a diagnostic category, and that it is usually associated with and exacerbated by medication overuse.[14,15] The International Classification of Headache Disorders uses the term "chronic migraine" for primary daily headache, and "medication overuse headache" for secondary daily headache or rebound.

Many American specialists approach the disorder clinically, treating chronic daily headache in the same way regardless of whether there is medication overuse. They cite randomized controlled trials of topiramate (Topamax) and onabotulinum toxin type A (Botox) that reported comparable benefit with these medications in patients with chronic daily headache with or without medication overuse.[16–18]

When patients complain that 'nothing works' for their headache, think about medication overuse headache

MORE IS LESS: THE PARADOX OF TREATING ACUTE HEADACHE

The clinical paradox and dilemma of treating acute episodic migraine is that more is less: the more days of acute treatment, the less well the migraines are controlled. And thus, the patient is likely to veer out of control.[3]

The compassion that motivates us to prescribe medications for acute episodic migraine must be tempered by the realization that too much of a good thing will result in its malignant transformation to medication overuse headache. Once this develops, preventive and migraine-specific acute medications are less effective, and patients need far more complex interventions.

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Complicating the dilemma, acute migraine-specific medications such as triptans and dihydroergotamine (Migranal) work better when taken early in migraine attacks, before central sensitization and allodynia develop with attendant photophonophobia and sensitivity to other stimuli. On the other hand, overuse will lead to medication overuse headache.

SYMPTOMS VARY

The symptoms of medication overuse headache vary in frequency, severity, location, quality, and associated features, both among patients and in the same patient. This is because the disease itself varies and also because of differences in the type and frequency of medication intake. Still, some features help to define this problem, and failing to recognize them may account for a widely held clinical feeling that these patients are "difficult."

History of episodic migraine. Generally, medication overuse headache does not occur in nonmigraineurs.

Headache on most days of the month. Whenever a migraineur starts having headaches on more days than not, the diagnosis of medication overuse should be considered.

Overuse of acute medications. The criteria (see above) allow for combining days of acute medication use. For example, if a patient takes a combination analgesic on 5 days and a triptan on 5 different days, that would still be enough days of acute treatment to trigger medication overuse headache.

Variable pain location is a particular characteristic of medication overuse headache. Although the location may differ from day to day (front or back, rostral or caudal, unilateral or bilateral), it is the quantity not the quality or location of the headaches that suggests the diagnosis.

A drug-dependent rhythm. Predictably, the headaches come on in the early morning or awaken the patient from sleep. This may be due to variable drug withdrawal.

Neck pain. Medication overuse headache frequently involves the neck, and patients often seek and receive treatments such as muscle relaxants or injections to the neck. When patients are weaned from their acute migraine medications, neck pain generally dissipates. The neck pain, however, can recur episodically with their remaining, now-episodic acute migraines. Neck pain associated with medication overuse headache is not usually a sign of a primary neck disorder; rather, it is a symptom of medication overuse headache itself.

Concomitant depression and anxiety are comorbid with episodic migraine, but appear to be more common with medication overuse headache. Treating the depression or anxiety does not restore an episodic pattern of migraine; weaning from the overused medications remains the most important intervention. A frequent clinical error is to diagnose and treat the psychiatric issues without recognizing medication overuse as the primary problem.

Nonrestorative sleep is almost always reported by patients with medication overuse headache. This is often due to the caffeine contained in combination analgesics or to excessive dietary caffeine intake, but it may also be part of the daily acute drug withdrawal syndrome. The sleep problems are also associated with the concomitant depression. Sleep often improves after weaning from the offending substance or substances. As with neck pain, patients do not have a primary sleep disorder—the sleep disturbance is a symptom of medication overuse headache.

Vasomotor instability. Autonomic features are commonly associated with medication overuse headache. Rhinorrhea, nasal stuffiness, and lacrimation are features of medication withdrawal, especially from opioids, and are frequently attributed to sinus disease or "sinus headaches." Many patients undergo unnecessary sinus procedures or are given antibiotics, decongestants, and other wrong medications for incorrect diagnoses. Decongestants can cause and exacerbate medication overuse headache, so they need to be withdrawn. The sinus features generally remit when the overused migraine medications are eliminated.

Preventive medications are less effective or ineffective until the acute medications are withdrawn. Thus, prescribing prevention without weaning is usually futile, and the patients are often dismissed as having a refractory problem. At the same time, migraine-specific acute treatments, ie, triptans and ergots, are

Hierarchy of risk (in descending order):
Butalbital
Opioids
Triptans
NSAIDs

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usually also less effective. When patients complain that "nothing works," either preventively or acutely, medication overuse headache should spring to mind.

Weaning from overused medications can restore the efficacy of previously ineffective treatments at the same time that a patient is restored to an episodic headache pattern. Thus, complete weaning is the pivotal clinical intervention. Clinically, there is no spontaneous remission from rebound without absolute detoxification, maintained for months.[9,19–22]

Other diagnoses entertained. The more diagnoses suggested for daily headache, and the more treatments tried unsuccessfully, the more likely the diagnosis is actually medication overuse headache. Because this condition is protean, patients and caregivers alike make more and more fanciful diagnoses such as allergies, cervicogenic headache, temperomandibular disorder, occipital neuralgia, chronic Lyme disease, and systemic candidiasis. A useful strategy is to assume that daily headache is likely due to medication overuse. And since medication overuse headache is generally treatable, patients labeled as having refractory headaches often are dramatically improved by appropriate intervention.

WHY ARE MIGRAINEURS SO SUSCEPTIBLE?

Medication overuse headache occurs primarily in people with a history of episodic migraine, but the unique susceptibility of migraineurs is not fully understood.

Structural changes in the brain?

Episodic migraine attacks appear to be generated in the upper brainstem. This region in turn activates a set of peripheral pain mechanisms, ie, meningeal inflammation and vasodilation. The peripheral pain processes turn on afferent circuits that carry the pain signals to the lower brainstem, where these signals are integrated. Finally, the central signals ascend the brainstem, stimulating autonomic nuclei that account for nausea and other vasomotor changes, proceed through the thalamus, and terminate in the cortex where pain is perceived. Thus, migraine without aura consists of three steps—a central generator, a set of peripheral pain mechanisms, and a series of steps culminating in central integration. (Aura involves other steps, not outlined here.)

A possible explanation of why migraine becomes chronic is that a yo-yo effect of repeated migrainous pain processes, followed by repeated medication, results in structural changes. These propagate central sensitization with a lowered threshold for activation of all of the central processing of head pain.

This set of disturbances may occur due to undertreatment of migraine pain. With inadequate pain control, headaches recur, and the process repeats until damage occurs. Evidence for this is seen in up-regulation of excitatory serotonin receptors when analgesics are repetitively given to laboratory animals.[23]

A pure withdrawal phenomenon?

Also possible is that medication overuse headache is just a complex dependence-and-withdrawal phenomenon. Thus, the cyclical use of various medications results in withdrawal headaches and a set of symptoms, including disturbed sleep, morning headache, and vasomotor signs of withdrawal. Arguing against its being a pure withdrawal phenomenon is that daily use of analgesics or opioids generally does not cause daily headache in nonmigraineurs.[24]

Prescribing prevention without detoxification is usually futile

HOW MUCH MEDICATION USE IS TOO MUCH?

For an episodic migraine condition to transform into a chronic one, medications need to be taken on only a modest number of days per month: 5 to 10, depending on the type of medication.

A pivotal study[3] found that butalbital combinations were most likely to cause medication overuse headache, needing to be taken on merely 5 or more days per month to cause it in migraineurs. Opioids caused it if taken 8 or more days per month, and triptans if taken 10 or more days per month. Nonsteroidal anti-inflammatory drugs (NSAIDs) actually protected against transformation to daily headache if used 5 or fewer days per month, but caused medication overuse headache if used 10 or more days per month.

Thus, there was a hierarchy of risk, with butalbital being the worst, opioids in the mid-

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dle, and NSAIDs and triptans the least risky. None of the agents had to be taken daily to trigger medication overuse headache.

PREVENTION IS THE BEST TREATMENT

The best approach to medication overuse headache is to prevent it while the patient still has episodic migraine.

Outcomes are better with triptans or ergots

Undertreatment of migraine leads quickly to overuse of symptomatic medications, and from there to medication overuse headache.

Outcomes of episodic migraine are better when triptans or ergots (which are migraine-specific) are used first-line in patients with disabling migraine and no vascular contraindications. Patients who start with nonspecific treatment and step up to a more specific treatment when lower-level medications fail have less favorable outcomes in terms of migraine relief and disability time than those treated with triptans from the beginning.[25]

To put this in perspective, if a patient takes an acute medication, gets only partial relief (not a pain-free response) at 2 hours and then takes another pill, or gets a recurrence and takes another pill, the likelihood of prolonging an attack and using more medications goes up. If a patient takes a triptan and gets a sustained pain-free response, the attack is truncated and the medication usage reduced. Therefore, migraine-specific acute treatments are more likely to not be overused.

Detoxification is the pivotal clinical intervention

Daily preventive medication, if necessary

As noted above, if the number of headache days exceeds 10 per month, the likelihood of developing daily headache escalates steeply. Thus, patients with 10 or more days of headache per month should be prescribed preventive medications to be taken daily to reduce the frequency, severity, and duration of attacks. Preventive treatment may also increase the efficacy of the acute treatments.

The drugs used for preventive treatment are different than those used for acute treatment and are not likely to cause medication rebound headache. However, they are not very effective. Those that have the best evidence of efficacy are beta-blockers, tricyclic antidepressants, and anticonvulsants; calcium channel blockers and NSAIDs are also popular. This topic has been reviewed in detail elsewhere.[26,27]

REVERSING MEDICATION OVERUSE HEADACHE

If a patient already has medication overuse headache, the clinician is faced with the problem of weaning her or him from the overused medication while establishing a reasonable regimen of prophylaxis and acute medications with limits.

For the most part, these tasks can be accomplished in a series of clinic visits. However, some patients have such severe comorbid medical and psychiatric illnesses that outpatient treatment is impossible. For them, a day hospital or inpatient program with infusion capabilities is often useful.

Outpatient treatment of medication overuse headache

Outpatient treatment of medication overuse headache involves:

Educating patients about the genesis of the problem and reassuring them that you are not accusing them of being an addict. Most patients who develop medication overuse headache are habituated inadvertently, and this needs to be made clear, along with the overall plan and the likely prognosis.

Weaning from the overused medications can be done gradually, tapering the drugs over 4 to 6 weeks, during which preventive medications are introduced. Alternatively, the discontinuation of rebound medications can be done abruptly, with transitional medications (eg, corticosteroids, NSAIDs, dihydroergotamine, or triptans) used as a bridge to blunt withdrawal, during which the prophylaxis is established (TABLE 1).

Establishing daily preventive medications. The prophylactic regimen can be established either before or during the weaning.

Providing acute medications, with limits. At a certain point in the weaning, advise the patient not to treat low-level headaches, and provide a triptan or dihydroergotamine to use for severe attacks, no more than twice weekly and less than 10 days per month. If the pa-

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TABLE 1

Two approaches to weaning from overused headache medications

Slow weaning
Consider adding preventive medications in anticipation of weaning

Taper medication weekly, eg, four butalbital tablets per day during the first week, three per day during the second week, and so on

Or add preventive medication during the weaning, eg, nortriptyline (Pamelor) 10 mg at bedtime during the first week, 20 mg during the second week, up to 50 mg (not approved by the US Food and Drug Administration [FDA] for migraine, but listed in consensus guidelines)

Alternative: topiramate (Topamax) 25 mg at bedtime during the first week, 50 mg during the second week, up to 100 mg (FDA-approved)

Thus, at the end of 5 weeks, the patient is off the overused medication and is on preventive therapy, such as nortriptyline 50 mg

'Cold turkey' with bridge
Abruptly discontinue the overused drug, if safe to do so (eg, three or more narcotic or barbiturate tablets/day)

Give corticosteroids or nonsteroidal anti-inflammatory drugs, triptans, or dihydroergotamine (not FDA-approved for use in this manner) daily for 5 to 7 days or until the patient is headache-free for 24 hours

"Ramp up" prophylaxis quickly, eg, give nortriptyline 25 mg at bedtime the first night, 50 mg the second night, and then maintain that dosage

Alternative: propranolol (Inderal LA) 60 mg at bedtime the first night, 120 mg the second night, and consider higher dosing to 160–240 mg if blood pressure permits, then maintain that dosage (FDA-approved)

Thus, at the end of 1 week, patient is off the overused medications and is on preventive therapy

Then provide acute medications (triptans or dihydroergotamine) for severe migraine no more than 2 days per week, fewer than 10 days/month: writing this on the prescription helps remind the patient not to exceed the limit

tient is in triptan rebound, dihydroergotamine would be the choice.

Instructing the patient to keep a headache diary to follow adherence and outcomes.

Psychology consultation can be very helpful to teach patients behavioral techniques to deal with anticipatory anxiety during the weaning.

Multidisciplinary programs with infusion capability

Some patients need a more intensive approach to restore an episodic migraine pattern. Examples: those on very high doses of narcotics or barbiturates, those with comorbid medical illnesses that limit both acute and preventive treatments, and those with severe and complicating comorbid psychiatric illnesses.

Multidisciplinary programs are available, with specialists in neurology, primary care, psychology, and physical and occupational therapy providing treatment. Patients check into the hospital or a "day hospital," where they can also receive intravenous infusions to get through the weaning. The goal is to shift the locus of control back to patients as they revert from daily headache to episodic migraine. Patient education is crucial.

OUTCOMES ARE GOOD

There is much good news about medication overuse headache.

It can be prevented with careful monitoring of acute medication outcomes and number of headache days. Prophylaxis should be used when treating high-frequency or very disabling migraine.

Most patients improve when weaned and treated with preventive medications. "Recov-

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ery" means at least 3 months off the overused medications. In studies, more than half of patients who underwent treatment for medication overuse headache remained better and had an episodic pattern of headache 5 years later.[26]

Unfortunately, the initial improvement often seen with patients after weaning and being given preventive medication (72%–85% of patients improve) in the first year is often followed by preventable relapse, so it is very important to follow up with patients regularly.[28–32]

Helping restore a patient's quality of life is an outcome rewarding to primary care provider and specialist alike.

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