CLINICAL PRACTICE

# Chronic Daily Headache

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*This* Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

**A 36-year-old woman with a long history of catamenial migraines had had a headache almost every day during the previous year. The background headache was mild but became severe and incapacitating at least twice a week, interfering with work and sleep. She took six to eight tablets containing a combination of aspirin, acetaminophen, and caffeine per day, with minimal relief. She had no fever, weight loss, diplopia, or tinnitus. Her headaches were not exacerbated by a Valsalva maneuver or positional change. Her physical examination was normal. How should she be evaluated and treated?**

## THE CLINICAL PROBLEM

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Chronic daily headache refers to the presence of a headache more than 15 days per month for longer than 3 months. Chronic daily headache is not a diagnosis but a category that contains many disorders representing primary and secondary headaches.[1,2] Secondary causes must be ruled out before the diagnosis of a primary headache disorder is made. Approximately 3 to 5 percent of the population worldwide[3-5] and 70 to 80 percent of patients presenting to headache clinics in the United States[6] have daily or near-daily headaches. The disability associated with this disorder is substantial and includes a diminished quality of life related to physical and mental health, as well as impaired physical, social, and occupational functioning.[7-9]

Risk factors for chronic daily headache as identified in population-based and clinic-based studies include obesity, a history of frequent headache (more than one per week), caffeine consumption, and overuse (more than 10 days per month) of acute-headache medications, including analgesics, ergots, and triptans.[10-14] Over half of all patients with chronic daily headache have sleep disturbances and mood disorders such as depression or anxiety, and these disorders can exacerbate the underlying headache.

Transformed migraine and medication-overuse headaches are among the most common and challenging of the chronic daily headache disorders and are the focus of this review (Table 1). The clinical features of primary chronic daily headache disorders are summarized in Table 2.[15] Primary chronic daily headache disorders are classified on the basis of the usual length of each episode — that is, prolonged (four hours or longer) or brief (less than four hours).[1]

## STRATEGIES AND EVIDENCE

### DIAGNOSIS

Before a primary headache can be diagnosed, secondary causes must be considered. The development of progressively frequent and severe headaches within a period

**Table 1. Criteria for Transformed Migraine and Medication-Overuse Headache.**

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|---|
| **Transformed migraine*** |
| Daily or almost daily (>15 days per month) head pain for >1 mo |
| Average headache lasting >4 hr per day (if untreated) |
| At least one of the following criteria: |
| History of any form of episodic migraine meeting IHS criteria† |
| History of increasing headache frequency with decreasing severity of migrainous features over a period of at least 3 mo |
| Headache at some time meets IHS criteria for migraine other than duration |
| Does not meet criteria for new daily persistent headache or hemicrania continua |
| **Medication-overuse headache[2]** |
| Headache present at least 15 days per month characterized by the development or marked worsening of pain during medication overuse and resolution of pain and reversion to previous episodic pattern (<15 days per month) within 2 mo after discontinuation of medication |
| **Definition of overuse of medication** |
| Regular overuse of a headache medication for >3 mo |
| Use of ergotamine, triptans, opioids, and combination analgesics >10 days per month |
| Use of simple analgesics ≥15 days per month |
| Total use of all headache medications ≥15 days per month |

* The criteria for transformed migraine are those of Silberstein et al.[1,2] These criteria have been used in clinical, population-based, and treatment studies during the past 10 years. The criteria for chronic migraine have not been field-tested or validated.

† The criteria of the International Headache Society (IHS) for migraine without aura[2] include at least five attacks that last 4 to 72 hours (untreated or unsuccessfully treated). The headaches must have at least two of the following characteristics: unilateral location, pulsating quality, moderate or severe pain intensity, and reason for avoidance of routine physical activity (e.g., walking or climbing stairs). During the headaches, at least one of the following must be present: nausea, vomiting, or both; photophobia and phonophobia; and no attribution to another disorder.

of three months, neurologic symptoms, focal or lateralizing neurologic signs, papilledema, headaches aggravated or relieved by assuming an upright or supine posture, headaches provoked by a Valsalva maneuver such as a cough or sneeze, systemic symptoms or fever, or a history of headache of sudden onset or onset after the age of 50 years should prompt a diagnostic evaluation with appropriate imaging.

Most patients with transformed migraine and medication-overuse headache are women and have a history of episodic migraine that dates back to adolescence or early adulthood.[16,17] Patients often report a period of transformation that occurs over months or years in which headaches become more frequent, until a pattern of daily or near-daily headaches develops that clinically resembles a mixture of tension-type headache and migraine. This clinical phenotype explains why labels such as "mixed headache" and "tension–vascular headache" have been informally applied to this group of patients.

The overuse of acute-headache medications by patients with frequent headache may lead to medication-overuse headache, a syndrome of daily headaches that is induced and maintained by the very medications used to relieve the pain.[18,19] The prevalence in the population of chronic daily headache associated with the overuse of acute-headache medication was recently estimated to be 1.4 percent overall and was particularly high among women (2.6 percent), especially those over the age of 50 years (5 percent).[20] Overuse of acute-headache medications is reported by approximately 80 percent of the patients with transformed migraine who are seen in headache clinics,[21] but by fewer than a third of those with transformed migraine in the general population.[3] Furthermore, in a substantial proportion of patients, daily headache may continue once they stop overusing acute-headache medication. Therefore, the overuse of acute-headache

**Table 2. Other Types of Primary Chronic Daily Headache.***

| Disorder | Male:Female Ratio | Prevalence | Clinical Features |
|---|---|---|---|
| | | % | |
| Transformed migraine | 1:3 | 2 | Migraine with or without aura >15 days per month for >3 mo |
| Chronic tension-type headache | 1:1 | 2 | Mild-to-moderate severity; no migrainous symptoms; bilateral |
| New daily persistent headache | More common in women | Rare | Bilateral, persistent, moderately severe; may be preceded by viral infection; may resemble migraine or tension-type headache |
| Hemicrania continua | More common in women | Rare | Rare, unilateral, and constant exacerbations of severe headache; cranial autonomic symptoms; "ice-pick" pain; responsive to indomethacin by definition |
| Cluster headache | 3:1 | 0.4 | Cluster periods lasting 4–8 wk 1–3 times per year; daily headaches, often nocturnal, occurring 1–8 times per day, lasting about 1 hr on average, extremely severe, mostly periorbital or temporal, and associated with motor restlessness and autonomic symptoms (tearing, rhinorrhea) |
| Hypnic headache | 1:2 among the elderly (>60 yr of age) | 0.07 | Occurring daily but only during sleep; moderately severe; often bilateral; lasting about 1 hr; not associated with autonomic symptoms |
| Paroxysmal hemicrania | 1:2 | Rare | Headaches identical to cluster headaches except that attacks occur more often (>5 and up to 24 times per day) and are briefer (8–25 min); responsive to indomethacin by definition |
| Short-lasting, unilateral, neuralgiform headache with conjunctival injection and tearing syndrome | 3:1 | Rare | Headaches resembling cluster and paroxysmal hemicranias except that attacks occur more often (30–100 per day) and are much briefer (20–120 sec); may be mistaken for trigeminal neuralgia, except pain is strictly periorbital (V1) with cranial autonomic symptoms |

* Secondary causes require careful consideration and exclusion. These include medication-overuse headache, cervicogenic headache (pain referred from a source in the neck and perceived in one or more regions of the head, face, or both), intracranial hypertension or hypotension, intracranial infection (meningitis or sinusitis), space-occupying lesions, post-traumatic headache, arterial dissection, venous sinus thrombosis, and giant-cell arteritis. Prolonged (four hours or longer) chronic daily headache disorders include chronic migraine, chronic tension-type headache, hemicrania continua, and new daily persistent headache. Transient (less than four hours) disorders include cluster headache, hypnic headache, paroxysmal hemicrania, and the short-lasting, unilateral, neuralgiform headache with conjunctival injection and tearing syndrome.

medications is neither necessary nor sufficient to cause transformed migraine.

Patients with transformed migraine most often overuse acute-headache medications such as analgesics (especially analgesics that combine aspirin, acetaminophen, and caffeine and those that contain butalbital), opioids, ergotamine, or triptans or a combination of these medications.

The interval from the frequent intake of these medications to the development of medication-overuse headache has been reported to be shortest for triptans (1.7 years), longer for ergots (2.7 years), and longest for analgesics (4.8 years). It is unclear whether this observation relates to the pharmacologic characteristics of the medications.[22]

Although it is often difficult to be certain whether the overuse of acute-headache medication is the cause or the consequence of the daily headaches, accurate diagnosis and management require the withdrawal of such medications in all patients, especially in the light of the observation that their overuse may preclude the efficacy of preventive medications. If a pattern of episodic headaches (fewer than 15 days per month) recurs within 2 months after drug withdrawal, medication-overuse headache is diagnosed.[2] If headache continues to occur on at least 15 days per month despite the withdrawal of acute-headache medications, a diagnosis of transformed migraine is often made. Although this distinction is obviously arbitrary, the reduction in the frequency of headache after the withdrawal of medication is often dramatic in patients who have true medication-overuse headache.

## TREATMENT

### *Nonpharmacologic Therapy*

Although data are lacking from controlled trials, clinical experience suggests that lifestyle modifications such as limiting or eliminating caffeine consumption, engaging in regular exercise, and establishing regular mealtimes and sleep schedules can be beneficial for some patients. Depression, anxiety, and sleep disturbances should be addressed.[23] Training in relaxation techniques and

**Table 3. Preventive Medications Used in Cases of Transformed Migraine or Medication-Overuse Headache.***

| Medication Class and Drug | Target Daily Dose | Titration Period | Common Side Effects |
|---|---|---|---|
| **Antidepressants** | | | |
| Tricyclic antidepressants such as amitriptyline | 50–100 mg | 1–2 mo | Weight gain, dry mouth, constipation, palpitation, drowsiness, dizziness, fatigue |
| Selective serotonin-reuptake inhibitors such as fluoxetine | 20–60 mg | 1 mo | Anorexia, insomnia, anxiety, tremor, asthenia, dizziness, somnolence |
| **Anticonvulsants** | | | |
| Divalproex | 500–2000 | 2–4 wk | Nausea, somnolence, dizziness, vomiting, tremor, alopecia, weight gain |
| Gabapentin | 900–3600 mg | 1–2 mo | Dizziness, somnolence, ataxia, abnormal thinking, peripheral edema, weight gain, incoordination |
| Topiramate | 50–200 mg | 1–2 mo | Paresthesia, difficulty with word-finding and concentration, weight loss |
| **$\alpha_2$-Adrenergic agonists** | | | |
| Tizanidine | 8–20 mg | 1–2 mo | Dry mouth, somnolence, asthenia, dizziness, constipation, hypotension, bradycardia |
| **Neurotoxin** | | | |
| Botulinum toxin type A | 25–260 U every 3 mo | Injection every 3 mo | Weakness of injected muscle, ptosis, neck pain |

* All the listed agents (except divalproex) have been studied in at least one randomized trial involving patients with a primary chronic daily headache (more than 15 days per month). However, these were not studies specifically of patients with transformed migraine or medication-overuse headache. Most of the patients in some studies and all the patients in other studies had a history of migraine; none of the studies evaluating these therapies uniformly used the definition of the International Headache Society for chronic migraine or the criteria of Silberstein et al.[1] for transformed migraine. Overuse of acute-headache medications was present in a substantial proportion of patients in several studies. This table is not intended to be exhaustive. No medications are approved by the Food and Drug Administration for the prevention of headache in patients with transformed migraine or medication-overuse headache.

biofeedback may be beneficial, although data to support these interventions come from patients with chronic tension-type headache, rather than transformed migraine.[24] Patients should be provided with support and close follow-up, particularly during the first eight weeks after treatment is initiated.

*Preventive Medications*

Randomized trials of the use of preventive medications in chronic daily headache are scarce.[25-34] In a single trial involving the tricyclic amytriptyline, the reported response rates (the percentage of patients whose frequency of headache is reduced by more than 50 percent) have exceeded 50 percent. Response rates superior to those achieved with placebo have also been reported for gabapentin (36 percent, as compared with 11 percent for placebo), topiramate (71 percent, as compared with 11 percent), and botulinum toxin type A (54 percent, as compared with 38 percent).[25,30,31] However, available studies are limited by small numbers of patients, the failure to account for the overuse of acute-headache medications, the concomitant use of other preventive medications, the lack of a specific diagnosis, or a combination of these factors.

Nonetheless, on the basis of these data and clinical experience, several potential preventive therapies are being used in patients with transformed migraine (Table 3). Given the high rate of associated sleep and mood disorders in these patients, sedating antidepressants such as amitriptyline may be particularly useful, although data are lacking to compare this category of drugs with a placebo or other preventive medications.

Preventive medications are generally titrated to the minimal effective or maximal tolerated dose over a period of one or two months. This target dose is maintained for at least two months; if the patient has a response (more than a 50 percent reduction in the number of days on which headache occurs), the medication is continued for at least three to six months. At that point, clinical experience suggests that it is reasonable to attempt to taper and discontinue the medication, after consultation with the patient.

The use of preventive medications in patients with headaches thought to be due to overuse of acute-headache medications is more controversial. Some investigators believe that most patients who overuse these medications have medication-overuse headache and that withdrawal of the overused medications alone will allow the headache to revert to an episodic pattern, without the need for preventive therapy.[35] However, given the relatively poor long-term success rates after the withdrawal of medication alone, other investigators recommend preventive therapy in such patients in an attempt to reduce the frequency and severity of the withdrawal headaches, as well as the potential for relapse, which can occur during or after the withdrawal period.

The use of daily opioid therapy in patients with chronic daily headache is controversial. A recent prospective study with an initial cohort of 160 patients who were prescribed daily opioid therapy reported the outcomes among 70 patients with medically refractory chronic daily headache who continued this therapy for at least three years.[36] Only 41 of the original 160 patients (26 percent) had greater than 50 percent improvement in a headache index that took into account the frequency and severity of headaches each week. Fifty percent of the patients had "problem drug behavior" (defined as "lost" prescriptions, seeking medication from other sources, and most commonly, dose violations). Most of these patients (74 percent) either did not show marked improvement or were dropped from the program because of problem drug behavior. These data from a highly specialized center with very close follow-up underscore the low efficacy of long-term opioid therapy and the high risk of misuse in this patient population.

## WITHDRAWAL FROM ACUTE-HEADACHE MEDICATION

No controlled studies have yet assessed the efficacy of withdrawal of medication alone. Treatment strategies for patients with transformed migraine associated with overuse of acute-headache medication are therefore based on case series, prospective uncontrolled studies, controlled trials involving patients with unspecified chronic daily headache, and clinical experience. Withdrawal studies are confounded by the addition of preventive medications, behavioral techniques, lifestyle modifications, and acute-headache medications, all of which may influence the frequency and severity of headaches. Nonsteroidal antiinflammatory drugs and dihydroergotamine mesylate (unlike ergotamine tartrate) are generally considered to have a low risk of medication-overuse headache and are often used to treat breakthough headaches during the withdrawal period. It is unclear whether the rarity of overuse of acute-headache

medication associated with dihydroergotamine reflects a pharmacologic mechanism or whether the rarity is explained by the more limited use of this medication, which requires parenteral administration, as compared with ergotamine tartrate, which is taken orally.

In general, most patients can be treated on an outpatient basis (Table 4). Simple analgesics, ergotamine, triptans, and most combination analgesics can be discontinued abruptly, whereas opioids and butalbital-containing analgesics should be tapered over a period of one month. To minimize the potential for troublesome or serious withdrawal symptoms from analgesics containing barbiturates and opioids, some experts have drawn on clinical experience to recommend a short (two to six weeks), tapering course of phenobarbital or clonidine for patients who have been using such agents.

A prospective study demonstrated that withdrawal symptoms and headaches generally resolved within four days after the cessation of triptan, whereas fewer than 20 percent of patients reported being free of headache within four days after the discontinuation of analgesics.[22] Withdrawal from ergotamine tartrate and combination analgesics may cause severe headache, nausea, vomiting, hypotension, and tachycardia that can last several days to weeks.

A recent double-blind, placebo-controlled study evaluated the effect of 100 mg of prednisone for five days on the duration of severe withdrawal headache in 20 patients with presumed medication-overuse headache.[37] There was a significant reduction in the number of hours of severe withdrawal headache in the active-treatment group (18.1 vs. 36.7 hours, $P=0.04$), which confirmed earlier observations from uncontrolled studies. In a 12-week open-label study, a single bedtime dose of tizanidine ranging from 2 to 16 mg (average, 3.6) in combination with a single morning dose of a nonsteroidal antiinflammatory drug resolved chronic daily headache in 34 of 55 patients (62 percent).[38]

Inpatient treatment may be necessary if the patients are not successful in decreasing their use of acute-headache medications, if the amount of barbiturate or opioid makes withdrawal on an outpatient basis unsafe, or if there are serious coexisting medical or psychiatric conditions.[39] Although there is a paucity of controlled trials to guide inpatient therapy, a meta-analysis of uncontrolled inpatient studies demonstrated that 81 percent of patients had a decreased severity or frequency of headache of at least 50 percent after two months of follow-up and that 61 percent had such an improvement after one to four years of follow-up.[39]

However, relapse is common after the withdrawal of acute-headache medications, both in patients who were no longer experiencing chronic daily headache after medication withdrawal and in those who continued to have chronic daily headache but who were initially successful in decreasing their intake of acute-headache medications. One large, prospective study indi-

**Table 4. Suggested Treatment of Transformed Migraine or Medication-Overuse Headache.**

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| Education, support, and close follow-up for 8–12 wk |
| Lifestyle modifications (quitting smoking, eliminating caffeine consumption, exercising, eating regular meals, and establishing regular sleep schedule) |
| Behavioral therapy (relaxation therapy, biofeedback) |
| Abrupt withdrawal of overused medications for acute headache, except barbiturates or opioids* |
| Prednisone (100 mg for 5 days [optional]) |
| Acute-headache treatment (for moderate or severe headache) |
| Nonsteroidal antiinflammatory drugs (e.g., 500 mg of naproxen sodium) |
| Dihydroergotamine (1 mg) intranasally, subcutaneously, or intramuscularly |
| Antiemetics (10–20 mg of metoclopramide, 10 mg of prochlorperazine, or 4–8 mg of ondansetron) |
| Preventive therapy |

* For butalbital overuse, taper the drug over a period of two to four weeks; if there is concern about the possibility of withdrawal syndrome, provide a tapering course of phenobarbital (30 mg twice daily for two weeks, followed by 15 mg twice daily for two weeks). For opioid overuse, taper the drug over a period of two to four weeks; if there is concern about the possibility of withdrawal syndrome, provide clonidine (transdermal therapeutic system patch for one to two weeks).

cated a relapse rate of 38 percent in the first year and a rate of 42 percent after four years.[40,41] In another report, 60 percent of the patients continued to have chronic daily headache and were overusing acute-headache medications four years after the initial withdrawal of the medication.[42]

## AREAS OF UNCERTAINTY

The mechanisms by which headache becomes daily and sometimes continuous remain unclear. Repeated attacks of migraine in susceptible persons may lead to a state of chronic central sensitization of trigeminal-pain pathways, resulting in continuous headache. The overuse of analgesics, especially opioids, may also sensitize central-pain pathways. Randomized, controlled trials of different treatment strategies that can be used to inform therapy for patients with transformed migraine or medication-overuse headache are lacking. The role of novel treatments for certain subtypes of chronic daily headache also remains uncertain. Occipital-nerve stimulation has shown some promise in individual patients with chronic migraine, but controlled trials are needed.[43]

## GUIDELINES

There are no formal recommendations from the American Academy of Neurology or the American Headache Society for the management of transformed migraine or medication-overuse headache. However, consensus guidelines of the American Academy of Neurology for the management of chronic migraine recommend "guarding against medication overuse headache by avoiding acute headache medication escalation and initiating preventive medication in patients with frequent headache or in those who overuse acute therapies."[42]

## CONCLUSIONS AND RECOMMENDATIONS

Most patients with chronic daily headache have a history of episodic migraine and overuse acute-headache medications. A careful history-taking and examination should rule out features suggestive of a secondary cause. The presentation of the patient in the vignette is consistent with a diagnosis of transformed migraine resulting from overuse of acute-headache medication. Although, strictly speaking, the diagnosis of medication-overuse headache requires the withdrawal of the overused medication and an evaluation of the frequency of headache after two months of follow-up, patients tend to tolerate this approach poorly. Thus, in this case, in combination with abruptly discontinuing the patient's overused medications, I would treat her with 60 mg of prednisone for five days to minimize withdrawal headaches and other symptoms, even though only limited data are available to support the use of this approach.

Although data are lacking from randomized trials of patients with transformed migraine or medication-overuse headache to guide the use of preventive therapy, I would also recommend starting therapy with amitriptyline (10 mg) at bedtime and increasing the dose in increments of 10 mg until the frequency of the headaches begins to decline or dose-limiting side effects occur, with monthly follow-up for the first three months. On the basis of clinical experience, I would also encourage the patient to limit or eliminate caffeine consumption, exercise regularly, and maintain a regular sleep schedule. Moderate or severe headaches that occur after the withdrawal of overused acute-headache medication could be treated with a nonsteroidal antiinflammatory agent or intranasal or parenteral dihydroergotamine; antiemetics are helpful for headache-induced or drug-induced nausea. If the patient were to make good progress and have a marked reduction in the frequency of headache for three to six months, it would be reasonable to try to taper the dose of amitriptyline gradually. However, she should be reminded that the need to use acute-headache medications for more than two days per week indicates the need to resume a preventive medication.

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