ABSTRACT

A variety of medications and treatment interventions, including antiepileptic drugs, tricyclic antidepressants, selective serotonin reuptake inhibitors, combined serotonin and norepinephrine reuptake inhibitors, β blockers, calcium channel antagonists, α2-adrenergic agonists, nonsteroidal anti-inflammatory drugs, muscle relaxants, occipital nerve blocks, and botulinum toxin type A injections, have been utilized in the prophylactic treatment of chronic daily headache (CDH). None of these currently possesses a strong scientific basis for such use, and none are approved by the US Food and Drug Administration for management of CDH. This article addresses the clinical management of the patient with CDH, and in particular, the patient with medication overuse headache, and describes findings from recent investigations of the more commonly prescribed prophylactic therapies, such as divalproex, topiramate, opioids, and botulinum toxin type A.


COMMON PROPHYLACTIC PRACTICES FOR CHRONIC DAILY HEADACHE*

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APPROACH TO THE PATIENT WITH CHRONIC DAILY HEADACHE

In attempting to formulate an approach to the patient who presents with CDH, consider a typical case: JR is a 45-year-old female with a long-standing prior history of episodic migraine (EM) who begins to experience relatively less intense but more pervasive head pain. For at least 1 year she has had some degree of headache on a daily basis. Four or 5 times monthly she has headache...
attacks reminiscent of her "old" migraine. Her headache frequency/severity profile is 30/7. Her Migraine Disability Assessment (MIDAS) questionnaire score is 90.

(Note: Over the past month: daily headache with 7 days of incapacitating head pain and MIDAS scores ranging from 0 [no disability] to 270 [maximum disability].)

The first step in the evaluation of any patient is to establish a diagnosis. Is the patient suffering from a primary or secondary headache disorder? In the great majority of cases, it will be the former: 90% to 95% of patients who present to medical attention—electively or emergently—with the chief complaint of headache have some variation of migraine. In the case of JR, she has a history of typical EM that has "transformed" into CDH. TM is the most commonly diagnosed primary headache disorder causing CDH. Secondly, it is important to try to establish when the patient first began experiencing CDH; most often this involves determining the point at which the patient's EM transformed into CDH. There are now some data suggesting that the duration of CDH and the timing of the transformation in relation to the present play a role in influencing prognosis. It may be useful to ask the patient, "Can you think of something that may have contributed to your headaches changing from episodic to daily?" For example, on occasion the female patient may recall that the month before she transformed she started to take an oral contraceptive pill (OCP). In such cases, changing the OCP formulation or discontinuing OCP use may have a positive impact on the patient's headaches. Similarly, it may be important to ask the patient if he or she can link the transformation to undue psychological distress, intrinsic hormonal change, head trauma, or another significant life event or medical disorder.

Perhaps more important than attempting to pinpoint a precipitating factor, such as the initiation of oral contraceptive use, may be identification of factors contributing to the primary headache disorder itself: so-called reinforcers that are adding fuel to the fire of this transformation process. For example, does the patient have a concomitant hormonal or sleep disorder? The latter may range from a condition as specific as sleep apnea, which can directly cause headaches or at least aggravate a preexisting headache disorder, to the less well-defined but far more common problem of chronically disrupted sleep (ie, difficulty falling asleep, nocturnal awakenings, or both). If a sleep disorder is present, it should be addressed and treated if the associated headache disorder is to be managed optimally. Fortunately, a variety of pharmacologic and nonpharmacologic therapies are now available to clinicians for management of the various forms of disrupted sleep.

Another factor contributing to CDH/TM may be the presence of concomitant mood disorder, such as anxiety or depression. If the patient reports depression, one should attempt to determine the depression's severity and character. If the depression is severe is the patient suicidal? What is the nature of the depression: deenergizing/fatiguing, anxious/agitated, or both? If deenergizing/fatiguing, the healthcare provider may want to consider prescribing a noradrenergic antidepressant. If anxious/agitated, a serotonergic agent may be more appropriate. Psychotherapy also should be considered. In addition, it is important to ask patients if they have pain involving other body regions (eg, the neck or lower back); many patients with CDH describe more diffuse pain, such as that experienced with fibromyalgia. Regardless of the site and etiology, coexisting chronic pain can trigger or aggravate chronic headache. Finally, medication overuse can be a potent reinforcer of chronic migraine. Medication overuse headache (MOH) represents a particularly difficult challenge to the healthcare provider who seeks to prescribe medication adequate to control acute headache intensifications but to avoid having the patient exacerbate his or her primary headache disorder through the excessive or inappropriate use of that medication. Because of its prevalence and profound effect on migraine, it is important to devote particular attention to MOH.

Table. Medications/Procedures Commonly Used for CDH Therapy

<table>
<thead>
<tr>
<th>Tricyclic antidepressants</th>
<th>SSRI</th>
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<tr>
<td>β blockers</td>
<td>Venlafaxine</td>
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<tr>
<td>Verapamil</td>
<td>Tizanidine</td>
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<tr>
<td>Divalproex sodium</td>
<td>NSAID</td>
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<tr>
<td>Topiramate</td>
<td>Muscle relaxants</td>
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<tr>
<td>Gabapentin</td>
<td>Occipital nerve blocks</td>
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<tr>
<td>Zonisamide</td>
<td>Botulinum toxin type A</td>
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CDH = chronic daily headache; NSAID = nonsteroidal anti-inflammatory drugs; SSRI = selective serotonin reuptake inhibitors.
MEDICATION OVERUSE HEADACHE

There is compelling scientific evidence to indicate that medication overuse triggers (or at least reinforces) migraine transformation. In 1 study involving rats exposed to painful stimuli and treated with acetaminophen, investigators demonstrated that prolonged exposure to acetaminophen reverses the antinociceptive (ie, pain-protective) effect of the drug. Examining the rats’ brains, the investigators found that with prolonged acetaminophen administration, brain serotonin levels decreased, and 5-hydroxytryptamine (5HT2a) receptor densities increased. 5HT2a is a pronociceptive receptor that facilitates pain signaling.

A similar phenomenon has been noted in patients who overuse analgesics. The platelets of patients with MOH contain low levels of serotonin and high 5HT2a receptor densities, similar to what was discovered in the animal studies. When the patients reduced their use of the offending analgesic, the platelet serotonin levels began to rise, and the 5HT2a receptor density decreased.

The most common medications implicated in MOH may vary according to geographic area. For example, patients in the southeastern United States seem to favor so-called powders that contain a combination of acetaminophen, aspirin, and caffeine, which are available over the counter, and a prescription medication containing a combination of hydrocodone bitartrate and acetaminophen. Compounds containing butalbital (typically combined with caffeine and acetaminophen or aspirin) also can cause MOH, and because the patients may develop barbiturate dependence along with their worsening headache, these patients can be especially difficult to manage. Interestingly, some recent studies have suggested that the drug with the greatest propensity for inducing MOH at the lowest level of use frequency are the triptans. On the positive side, patients overusing triptans tend to improve more quickly with withdrawal of the offending triptan than do patients who are overusing an opioid, or even acetaminophen; the nontriptan overusers may take weeks or months to improve clinically.

Thus the clinical conundrum: on one hand, we are attempting to avoid reinforcing TM by our failure to treat acute intensifications aggressively, and on the other hand, how do we accomplish this without perpetuating MOH? One option may be to hospitalize patients with MOH for 2 to 4 weeks for detoxification coupled with treatment of intensifications with drugs believed to possess a low potential for causing MOH. This may not be cost effective, practical, or even possible for many patients (eg, the patient’s insurance carrier may not authorize hospitalization for this purpose). Another option is to attempt to strike a balance by advising patients to avoid using any 1 medication or class of medications more than 2 to 3 days per week, therefore constantly varying the acute medications utilized. However, evidence to support this approach is sparse at best.

THERAPIES FOR CHRONIC DAILY HEADACHE

ANTIEPILEPTIC DRUGS

Although there is still no scientifically proven or US FDA-approved medication for the treatment of CDH, several drugs and therapies have been explored; of these, more than a few have shown some real promise. Our investigative group at the University of California, San Diego treated 75 chronic headache patients with the AED divalproex sodium. The patients were divided into 3 groups: frequent migraine (ie, ≥15 headache-days/month but not daily headaches), CDH/TM, and chronic tension-type headache (CTTH). All patients were treated in open-label fashion according to a uniform dosing regimen. Thirty-six patients (48%) reported a reduction of 50% or more in headache frequency, and responder rates were significantly higher in the 2 migraine groups: 11 (61%) of 18 among those patients with frequent migraine and 22 (51%) of 43 patients in the TM group, versus 3 (21%) of 14 patients with CTTH. These data suggest that prophylactic therapy with divalproex may be effective in selected patients with chronic migraine.

In another study, 33 patients with CDH/TM were managed according to a treatment algorithm involving the sequential administration of divalproex sodium, amitriptyline, amitriptyline plus phenelzeine, and methadone. If the patient failed one therapy, the next therapy in sequence was initiated. Twenty-two patients (67%) achieved a reduction of 50% or more in headache-days per month. Most positive treatment responses (17 of 22 patients; 77%) were attributed to divalproex sodium.

Another AED studied for its utility in patients with chronic migraine is topiramate. Although the results of a recently completed multicenter trial involving topiramate for treatment of chronic migraine are pending as of...
this writing, preliminary data have suggested the drug may be useful for this indication. Our investigative group at the University of South Alabama (USA) studied 170 patients with International Headache Society-defined migraine who were experiencing 15 or more days of headache per month and treated them with open-label topiramate according to a uniform dosing protocol.3

A positive treatment response was defined as a 50% or greater reduction in headache-days during the second treatment month relative to the patient’s pre-topiramate baseline. Nearly 39% (45 of 116 patients) who completed at least 60 days of treatment responded positively to topiramate. In the paired analysis, patients with CDH of more than 6 months-duration, patients who previously had tried and failed more than 3 prophylactic agents, and patients who previously had failed to respond to divalproex sodium were more likely to be nonresponders, but after multiple regression analysis, the only statistically significant predictor of a negative treatment response was CDH of more than 6 months’ duration ($P<.001$).

**CHRONIC OPIOID THERAPY**

Saper et al studied the utility of daily scheduled opioids of various types, ranging from methadone and sustained-release oxycodone to hydrocodone and meperidine, among 160 patients with chronic, intractable headaches.9 Seventy patients remained on the prescribed treatment for at least 3 years. Forty-one (26%) of the original 160 patients experienced a 50% or greater improvement in their headache index score (the primary outcome variable defined by the investigators). Problem drug behavior occurred in 50% of patients, usually involving dose violations. The authors concluded that although a not inconsequential minority of their patients with intractable headache were helped significantly by daily scheduled opioid therapy, 74% of those treated failed to respond or were withdrawn from the program for other reasons; in their opinion, this rendered such treatment a questionable choice for the patient with CDH. Our group at USA has completed a similar study that yielded a virtually identical result.10 The jury is still out regarding chronic opioid therapy for headache suppression. Such treatment clearly is beneficial for some patients and of no use to many others. In addition, conflicting data exist regarding the negative tardive consequences of long-term opioid use.11,12

**BOTULINUM TOXIN TYPE A THERAPY**

Botulinum toxin type A therapy has been evaluated for use in the suppression of chronic headache. Although studies have shown mixed results in the treatment of EM, the results of studies to date convey no benefit in CTTH; the results were promising from a recent multicenter trial involving subjects with CDH, the majority of whom had a history of migraine.13,14

Our USA group recently conducted an open-label study involving low-dose (ie, 25 U) botulinum toxin type A therapy for patients with frequent EM or CDH/TM.35 Six weeks after treatment, 41% of the patients reported a positive response (ie, ≥50% reduction in headache-days over the preceding month relative to their pretreatment headache frequency). As we found with topiramate, CDH was a predictor of a negative treatment response, especially if it had been present for more than 6 months.

**CONCLUSIONS**

In conclusion, optimal management of CDH requires accurate diagnosis, identification of or attention to CDH reinforcers, aggressive treatment of acute intensifications, and effective prophylactic therapy. Happily, various candidates for effective prophylactic therapy finally are emerging.

**REFERENCES**