

Diagnosis and Management of Chronic Daily Headache

Ivan Garza, M.D.,¹ and Todd J. Schwedt, M.D.²

ABSTRACT

Chronic daily headache (CDH) is a descriptive term that encompasses multiple headache diagnoses and affects ~4% of the general adult population. Chronic daily headache results in significant pain and suffering with substantial impact on quality of life, and enormous economic costs to society. Although most patients with primary CDH suffer from chronic migraine or chronic tension-type headache, other primary and secondary headache disorders can also manifest as a CDH syndrome. For CDH management to succeed, secondary headaches need to be ruled out with proper investigations when judged necessary. If the diagnosis of primary CDH is established, diagnosis of the specific CDH subtype is imperative to institute appropriate treatment. The diagnosis and management of distinct CDH entities, chronic migraine, chronic tension-type headache, new daily persistent headache, and hemicrania continua, are the primary forms of CDH and the emphasis of this review. Although, strictly speaking, medication overuse headache is a secondary form of CDH, it is also highlighted in this review given its frequent association with primary CDH.

KEYWORDS: Chronic, daily, headache, migraine, hemicrania

Chronic daily headache (CDH) is a descriptive term that encompasses several different headache diagnoses. Chronic daily headache affects 4% of the adult population in the United States and around the world.¹⁻³ The vast majority of CDH patients suffer from either chronic migraine or chronic tension-type headache. Chronic daily headache results in significant pain and suffering, reduction in quality of life, and enormous economic costs to society.^{4,5}

Scher has summarized the evidence from population-based studies related to risk factors influencing the incidence, prevalence, and prognosis of CDH.⁶ Major life changes (residence change, marital status, etc.) have been associated with the onset of CDH.⁷ Nonmodifiable factors that increase the risk for CDH

include female sex, low socioeconomic status, unmarried, history of head or neck trauma, and the presence of comorbid pain disorders. Modifiable risk factors for CDH include obesity, snoring and other sleep disorders, high caffeine intake, smoking, and overuse of abortive headache medications.⁶⁻⁹

Similar to all headache types, it is essential to exclude a secondary headache as the cause of CDH. Depending upon the clinical history and examination findings, further diagnostic testing may or may not be necessary. Although a complete list of causes for secondary CDH would be exhaustive, Table 1 summarizes common considerations.

If secondary headaches are ruled out, the clinician must determine the type of primary CDH the patient

¹Department of Neurology, Mayo Clinic, Rochester, Minnesota;

²Washington University Headache Center, Washington University School of Medicine, St. Louis, Missouri.

Address for correspondence and reprint requests: Ivan Garza, M.D., Assistant Professor, Department of Neurology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905 (e-mail: garza.ivan@mayo.edu).

Headache; Guest Editor, Jerry W. Swanson, M.D., F.A.C.P.

Semin Neurol 2010;30:154-166. Copyright © 2010 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel: +1(212) 584-4662.

DOI: <http://dx.doi.org/10.1055/s-0030-1249224>.

ISSN 0271-8235.

Table 1 Secondary Chronic Daily Headache

Medication-overuse headache
Cerebrovascular disease (cerebral venous sinus thrombosis, arteriovenous malformations, giant cell arteritis, subdural hematoma, etc.)
Altered CSF dynamics (spontaneous CSF leak, idiopathic intracranial hypertension, secondary intracranial hypertension)
Intracranial space-occupying lesions (neoplasms, others)
Posttraumatic
Infection (intra- or extracranial, sinusitis)
Musculoskeletal (cervical spine disorders, temporomandibular joint disorders)
Others

CSF, Cerebrospinal fluid.

has. Chronic migraine, chronic tension-type headache, new daily persistent headache, hemicrania continua, and medication overuse headache are discussed in this review. Although medication overuse headache is a secondary CDH, it is included here because of the important contribution to primary CDH.

CHRONIC MIGRAINE

Chronic migraine, which affects ~2% of the world population, places a substantial burden on individuals and societies.¹⁰ Chronic migraine results in poorer quality of life and causes significant disability.^{11,12} The World Health Organization considers chronic migraine to cause disability on par with the disability secondary to quadriplegia, dementia, and active psychosis.¹³ Direct and indirect costs from migraine are estimated at more than \$20 billion annually in the United States, much of which is due to chronic migraine.⁴ The average annual cost per person with chronic migraine is more than four times that associated with episodic migraine (\$7750 versus \$1757).¹⁴

Progression from episodic migraine (<15 headache days/month) to chronic migraine is referred to as “transformed migraine.” In population studies, 3% of those with infrequent episodic headaches transform to CDH each year; 6% transform to frequent episodic headaches.^{1,15} In clinic-based studies, 14% of those with episodic migraine transform to chronic migraine each year. Modifiable and nonmodifiable risk factors for this transformation have been described.^{15a}

A detailed discussion of migraine pathophysiology is discussed in the article by Dr. Cutrer in this issue. Interictal (between migraine) and longitudinal studies of chronic migraine will hopefully lead to an improved understanding of the pathophysiology and effects of transformation from episodic migraine to chronic migraine. Elevated concentrations of vasoactive neuropeptides in the cerebrospinal fluid of chronic migraine

patients suggest persistent activation of the trigemino-vascular system.¹⁶ Neurogenic inflammation may lead to central sensitization, a process implicated in the chronification of migraine. Functional and structural brain changes have been identified in migraine and are positively associated with increasing headache frequency and duration.¹⁷ Chronic migraine sufferers have increased iron deposition in the periaqueductal gray, putamen, globus pallidus, and red nucleus.^{18,19} They have reductions in gray and white matter density and volume in multiple regions of the brain.^{20–22} Migraine sufferers have inferior executive function and abnormal visual motion perception even when headache free.^{23,24}

Diagnosis

Chronic migraine patients tend to have mild to moderate headaches associated with mild migrainous features (e.g., photophobia, phonophobia) with superimposed more-severe headaches associated with more prominent migraine features (“full-blown” migraines). In some patients, environmental hypersensitivities persist even during headache-free periods.²⁵ This may include mild photophobia, phonophobia, motion-sensitivity, and cutaneous hypersensitivity/allodynia. Patients with chronic migraine have an increased frequency of comorbid psychiatric disorders, sleep disorders, fatigue, other pain, and gastrointestinal complaints. Recognition and treatment of these comorbidities can result in improved health, greater quality of life, and may potentially result in higher migraine treatment success rates. The following are the recently revised diagnostic criteria for chronic migraine²⁶:

1. Headache (tension-type and/or migraine) on ≥ 15 days per month for at least 3 months
2. Occurring in a patient who has had at least five attacks fulfilling criteria for migraine without aura
3. On ≥ 8 days per month for at least 3 months, headache has fulfilled criteria for pain and associated symptoms of migraine without aura (Criteria a and b below) or was treated and relieved by triptan(s) or ergot before the expected development of symptoms listed in Criteria a and b.
 - a. Has at least two of the following:
 - i. Unilateral location
 - ii. Pulsating quality
 - iii. Moderate or severe pain intensity
 - iv. Aggravation by or causing avoidance of routine physical activity
 - b. Has at least one of the following:
 - i. Nausea and/or vomiting
 - ii. Photophobia and phonophobia
4. No medication overuse and not attributed to another causative disorder

Treatment

The treatment of chronic migraine focuses on prophylactic therapies, which may include avoidance of migraine triggers, pharmacotherapy, physical therapy, biobehavioral therapy, and others. Simultaneous use of these different therapeutic modalities may be needed. Identification and treatment of comorbid disorders is also required for true treatment success. Acute headache medication use needs to be limited to avoid medication overuse headache. Although complete headache eradication is not a realistic expectation, significant reductions in headache frequency and/or severity are the goal of prophylactic therapy.

PHARMACOLOGIC PROPHYLAXIS

Prophylactic medications used to treat episodic migraine are also used for the prevention of chronic migraine. Thus, first-line prophylactic medications are from the following classes: antidepressants, antiepileptics, and antihypertensives. The prophylactic medications that have been specifically studied in clinical trials of patients with chronic migraine are illustrated in Table 2. Once an effective prophylactic medication is found, it is typically continued for 3 to 6 months prior to attempting discontinuation. An effective prophylactic medication is one that decreases headache frequency by at least 50%.

Topiramate Two randomized, double-blind, placebo-controlled studies are available.^{27,28} The larger of the two studies randomized 153 subjects to topiramate 100 mg daily and an equal number to placebo.²⁷ Those in the topiramate group experienced a reduction of 6.4 ± 5.8 headache days per month from a baseline of 17.1 ± 5.4 days, as compared with a reduction of 4.7 ± 6.1 days from a baseline of 17.0 ± 5.0 days in the placebo group ($p=0.10$). In the smaller of the two studies, 32 subjects were randomized to topiramate 100 mg daily and 27 were randomized to placebo.²⁸ Among all subjects, topiramate significantly reduced the mean number of monthly migraine days during the third month of therapy as compared with placebo ($p=0.02$).

Gabapentin Gabapentin has been studied as a prophylactic medication for chronic daily headache in a multicenter randomized placebo-controlled crossover study of 133 subjects (~85% with migraine).²⁹ Gabapentin 2400 mg per day was associated with a greater percentage of headache-free days (mean 26.6% vs. 17.5%, $p < 0.001$) and reductions in headache duration, severity, and analgesic use.

Tizanidine Tizanidine has been studied as an adjunctive prophylactic for chronic daily headache in a multicenter, randomized, blinded, placebo-controlled study.³⁰ One hundred thirty-six subjects (~3/4 with chronic migraine) were randomized to placebo or to tizanidine titrating up from 2 mg each night to the maximum tolerated dose, or 24 mg divided among three daily doses. The median tizanidine dosage was 20 mg per day. Subjects in the tizanidine group had significant reductions in headache index as compared with the placebo group.

Fluoxetine Sixty-four subjects with chronic migraine were randomized in a 16-week double-blind trial of fluoxetine.^{31,32} Subjects were treated with 20 mg daily and then increased to 40 mg daily if needed and as tolerated. Fluoxetine-treated subjects had significant improvements as compared with the placebo group in overall headache status, mood, and headache frequency.

Amitriptyline Thirty-nine transformed migraine subjects participated in a prospective double-blind study of amitriptyline versus amitriptyline plus fluoxetine.³² Although there were not significant differences in outcomes between the two treatment groups, subjects treated with amitriptyline (8–40 mg/day) and those treated with amitriptyline plus fluoxetine (8–20 mg/day) both had reductions in headache frequency and intensity.

Levetiracetam An open-label study of 36 transformed migraine subjects, with or without medication overuse, investigated the effect of levetiracetam.³³ At 3 months,

Table 2 Prophylactic Agents Studied Specifically in Chronic Migraine

Drug	Initial Dose (mg)	Typical Total Daily Dose (mg)	Common Side Effects	Serious Side Effects
Topiramate	25	100–200	Paresthesias, fatigue, weight loss	Acute angle closure glaucoma, metabolic acidosis, hyperthermia
Gabapentin	300	900–2400	Dizziness, somnolence, fatigue, edema	
Tizanidine	2	6–24	Somnolence, dry mouth, asthenia	Hepatitis
Fluoxetine	10–20	10–80	Insomnia, asthenia, tremor	Prolonged QT interval
Amitriptyline	10–25	50–150	Sedation, weight gain, constipation	Cardiac dysrhythmias
Levetiracetam	250	750–2000	Somnolence, asthenia	
Divalproex sodium	250–500	500–1500	Weight gain, tremor, nausea, alopecia	Pancreatitis, liver failure, thrombocytopenia
Memantine	5	5–20	Dizziness	

levetiracetam-treated subjects had reductions in headache frequency (24.9 days/month to 16.2 days/month; $p < 0.001$), disability (MIDAS dropped from 62.8 to 40.8; $p = 0.01$), and HIT-6 score (63.4 to 59.4; $p \leq 0.01$).

Valproate Two studies suggest valproate may be useful in the prophylaxis of chronic migraine. In an open-label study of 30 patients with intractable transformed migraine, patients were maintained on dosages between 1000 to 2500 mg.³⁴ A 50% or greater reduction in headache index was found in 67% of the subjects, headache-free days per month increased from 5.5 to 17.7, and days with significant disability declined from 22 per month to 8.5 per month. The second study was a chart review of 138 chronic daily headache patients (49 with transformed migraine) being treated with divalproex sodium monotherapy.³⁵ In the migraine patients, the mean decrease in migraine frequency was 65.2%.

Botulinum Toxin Although botulinum toxin type A appears to benefit a subset of patients with chronic migraine, no consistent or strong evidence is available yet to permit drawing conclusions on its efficacy in CDH (mainly transformed migraine).³⁶ Further study results are required and pending.

Memantine Memantine was recently reported to induce remission of chronic migraine.³⁷ An open-label study further suggests this drug may play a role in chronic migraine management.³⁸ Double-blind studies are required to establish memantine's role in chronic migraine treatment.

NONPHARMACOLOGIC THERAPY

Biofeedback, relaxation therapy, cognitive-behavioral therapy, and physical therapy may be useful as adjunctive treatments for chronic migraine. A controlled study of biofeedback showed associated decreases in oxidative stress and disability from migraine.³⁹ Cognitive-behavioral therapy may provide short-term and long-term reductions in headache burden.⁴⁰ Physical therapy is associated with significant reductions in migraine burden in some studies.⁴¹ Furthermore, a combination of physical therapy and biofeedback has been shown to provide greater relief than physical therapy alone.⁴²

Outcome

Patients with chronic migraine may revert back to episodic migraine. Reversion rates at one year range from 56 to 70% in population-based and specialty headache clinic-based samples, respectively.^{9,43} Predictors of reversion include withdrawal of overused medications, compliance with prophylactic medications, and regular physical exercise.

CHRONIC TENSION-TYPE HEADACHE

Chronic tension-type headache is considerably less prevalent than episodic tension-type headache.⁴⁴ A telephone survey obtained from 1993 to 1994 in Baltimore, Maryland, found an overall prevalence of 38.3% for episodic tension-type headache and a 1-year period prevalence of chronic tension-type headache of 2.2%.⁴⁴ Chronic tension-type headache increases in prevalence until the fourth decade of life and then decreases. Chronic tension-type headache is more prevalent in women compared with men and psychiatric disorders may be risk factors for its development.⁴⁴⁻⁴⁸

Although peripheral mechanisms apparently play a role in episodic tension-type headache pathophysiology, central mechanisms may play a larger role in chronic tension-type headache.^{49,50} Chronic tension-type headache sufferers had a general hypersensitivity to pain stimuli not seen in controls in a study of nociceptive processing.⁵¹ Central pain inhibition may be dysfunctional in chronic tension-type headache. Research using high-density electroencephalogram (EEG) brain mapping has found the supraspinal response to muscular pain to be abnormal in chronic tension-type headache sufferers.⁵² The reduced magnitude during and after induced tonic muscle pain in controls, but not in chronic tension-type headache patients, might be a consequence of impaired inhibition of the nociceptive input in chronic tension-type headache.⁵² Deficient diffuse noxious inhibitory control-like mechanisms, such as seen in generalized chronic pain like fibromyalgia, have been found in chronic tension-type headache.⁵³ Voxel-based morphometry and magnetic resonance imaging (MRI) have identified a significant gray matter decrease in regions involved in pain processing in chronic tension-type headache patients.⁵⁴

Diagnosis

Because it largely consists of head pain alone, tension-type headache is frequently called "the featureless headache."⁴⁹ Chronic tension-type headache typically evolves from episodic tension-type headache⁵⁵ and is usually bilateral, pressure-like in quality, and mildly to moderately intense. "Wearing a tight hat, wearing a tight band around the head, or wearing a heavy burden on the head" are frequent descriptions used by patients.⁵⁶ The following are current International Classification of Headache Disorders, 2nd edition (ICHD-2) criteria for chronic tension-type headache.⁵⁵

1. Headache occurring on ≥ 15 days per month on average for > 3 months (≥ 180 days per year) and fulfilling criteria 2-4
2. Headache lasts hours or may be continuous
3. Headache has at least two of the following characteristics:

- a. Bilateral location
- b. Pressing/tightening (nonpulsating) quality
- c. Mild or moderate intensity
- d. Not aggravated by routine physical activity such as walking or climbing stairs
4. Both of the following:
 - a. No more than one of photophobia, phonophobia, or mild nausea
 - b. Neither moderate or severe nausea nor vomiting
5. Not attributed to another disorder

Of note, the presence of migraine attacks superimposed on a background daily “tension-type” headache could suggest that chronic migraine may be the right diagnosis rather than chronic tension-type headache.⁵⁷

Treatment

Pharmacologic prophylaxis is the mainstay of treatment. Similar to chronic migraine, effective therapy is continued for at least 3 to 6 months prior to attempting discontinuation.⁵⁸ Table 3 summarizes prophylactic medications studied specifically in chronic tension-type headache.

PHARMACOLOGIC PROPHYLAXIS

Amitriptyline Amitriptyline is the drug of choice, typically at doses ranging from 25 mg to 100 mg per day.⁵⁰ This is the only antidepressant used in chronic tension-type headache that has demonstrated statistically significant benefit in several trials.⁵⁸ Amitriptyline has an estimated therapeutic gain of ~30% based on published trials.^{59,60}

Nortriptyline Nortriptyline has a more favorable side effect profile than amitriptyline.⁶¹ In a randomized placebo-controlled trial, patients with chronic tension-type headache who did not tolerate amitriptyline were switched to nortriptyline at doses of up to 75 mg/day.⁶² Both antidepressants produced larger reductions in headache, analgesic medication use, and headache-related disability than placebo.⁶²

Protriptyline Twenty-five adult female chronic tension-type headache sufferers were studied using protriptyline 20 mg every morning. Eighty-six percent had fewer headaches per month, and 73% had a $\geq 50\%$ reduction in headache attacks per month.⁶³ In contrast to the weight gain associated with other tricyclic antidepressants, patients lost slightly over three pounds during the study.⁶³ No placebo group was used.

Mirtazapine Bendsten studied mirtazapine in a randomized, double-blind, placebo-controlled, crossover trial. Mirtazapine 15 to 30 mg/day or placebo was given for 8 weeks separated by a 2-week washout period.⁶⁰ Mirtazapine reduced the area-under-the-headache curve by 34% more than placebo. The drug also reduced headache frequency, duration, and intensity significantly more than placebo. The efficacy of mirtazapine was similar to that of amitriptyline (a therapeutic gain of ~30%).^{59,60}

Topiramate In an open study, topiramate (daily dose 25 to 100 mg/day) resulted in a 50% reduction in headache frequency in 73% of 46 chronic tension-type headache patients at weeks 13 to 24.⁶⁴ Average headache intensity decreased from 6.13 to 2.07 on the visual analogue scale.⁶⁴ Randomized controlled trials are needed to define topiramate’s role in the management of chronic tension-type headache.

Sodium Valproate Sodium valproate (500 mg twice per day) was associated with greater reductions in pain frequency than placebo in 41 chronic tension-type headache subjects in a prospective, double-blind, randomized, placebo-controlled trial.⁶⁵ The Visual Analog Scale pain rating did not decrease in the active group.

Tizanidine Tizanidine (6 to 18 mg/day in divided doses) was found to be superior to placebo in a randomized, double-blind, crossover study in women with chronic tension-type headache.⁶⁶ A separate randomized, double-blind, parallel-group study, however, failed to demonstrate superiority to placebo.⁶⁷ To date, one

Table 3 Prophylactic Agents Studied in Chronic Tension-type Headache

Drug	Initial Dose (mg)	Typical Total Daily Dose (mg)	Common Side Effects	Serious Side Effects
Amitriptyline	10–25	25–100	Sedation, weight gain, constipation	Cardiac dysrhythmias
Nortriptyline	10–25	25–100	Sedation, weight gain, constipation	Cardiac dysrhythmias
Protriptyline	5–10	10–30	Sedation, weight change, constipation	Cardiac dysrhythmias
Mirtazapine	15	15–45	Somnolence, dry mouth	Neutropenia
Topiramate	25	100–200	Paresthesias, fatigue, weight loss	Acute angle closure glaucoma, metabolic acidosis, hyperthermia
Sodium valproate	250–500	500–1000	Weight gain, tremor, nausea, alopecia	Pancreatitis, liver failure, thrombocytopenia

cannot draw firm conclusions for the potential role of tizanidine in chronic tension-type headache.⁵⁸

Others Citalopram and paroxetine have not proven beneficial in chronic tension-type headache prophylaxis.^{59,68,69} Further research is needed to determine the potential efficacy of venlafaxine⁷⁰ and buspirone.⁷¹ There is no evidence for a beneficial effect of botulinum toxin in chronic tension-type headache.⁷²

COMPLEMENTARY/ALTERNATIVE TREATMENT

In chronic tension-type headache sufferers with coexistent depression, simultaneous treatment for both disorders has shown benefit.⁷³ Combination treatment is superior to pharmacotherapy or behavioral therapy alone.⁵⁸ Combination treatment with behavioral stress management was more likely to achieve clinically significant ($\geq 50\%$) reductions in headache index scores (64% of participants) than antidepressant medication (38% of participants), stress management therapy (35%), or placebo (29%) in a randomized placebo-controlled trial of 203 chronic tension-type headache subjects.⁶²

The potential role of acupuncture in chronic tension-type headache is yet to be defined. In one study, relaxation training induced the best benefit compared with acupuncture and physical training.⁷⁴ The potential role of hypnosis⁷⁵ and structured massage⁷⁶ remain to be determined. Other noninvasive physical treatments with some evidence in chronic tension-type headache prophylaxis include spinal manipulation, cranial electrotherapy, transcutaneous electrical nerve stimulation (TENS)/electrical neurotransmitter modulation combination, and automassage/TENS/stretching combination.⁷⁷

ACUTE PHARMACOLOGIC THERAPY

Simple analgesics and nonsteroidal antiinflammatory drugs (NSAIDs) remain as the pillar of abortive treatment in tension-type headache.⁵⁰ Acetaminophen/isometheptene/ dichloralphenazone frequently helps more severe episodes not responding to NSAIDs.

MEDICATION-OVERUSE HEADACHE

Medication-overuse headache frequently coexists with primary CDH and can preclude effective therapy of the latter. In some cases medication overuse headache may be responsible for the development or maintenance of a CDH syndrome⁷⁸; in other cases, medication overuse is the result of frequent headaches. Prophylactic medications for primary CDH are more likely to provide benefit following successful medication-overuse headache management.⁷⁹

The prevalence of medication-overuse headache in the general population is $\sim 1.5\%$.⁸⁰ The female to

male ratio is 3.5:1.⁸¹ In tertiary headache clinics throughout America, up to 50 to 80% of patients have medication-overuse headache.⁸⁰ By far, migraine is the most common primary headache disorder associated with medication-overuse headache. In a meta-analysis summarizing 29 studies, 65% of 2612 patients with chronic medication overuse headache had migraine, 27% had tension-type, and 8% had mixed or other type of primary headache.⁸¹

The risk for medication overuse headache development differs with individual substances. Opioids, butalbital-containing analgesics, and aspirin/acetaminophen/caffeine combinations are high risk; triptans are moderate risk; and NSAIDs are low risk.⁸² In a recent longitudinal population-based study, any use of barbiturates and opiates was associated with increased risk of transformed migraine.⁸³ Critical dose of opiate exposure was around 8 days per month, and the effect was more pronounced in men.⁸⁴ Critical dose of barbiturate exposure was around 5 days per month and the effect was more pronounced in women.⁸⁴ Triptans and NSAIDs induced migraine progression in those with high frequency of migraine at baseline (10–14 days per month), but not overall.⁸⁴

Multiple mechanisms may be involved in the development of medication-overuse headache.⁸⁵ Development of medication-overuse headache appears to be restricted to those with underlying headache disorders as it does not develop de novo in those without headaches who overuse the same medications.^{85,86} Neurophysiologic studies have shown facilitation of trigeminal and somatic nociceptive systems in medication-overuse headache, mainly mediated at a supraspinal level.⁸⁷ This suggests central sensitization (a process also involved in migraine pathophysiology) may also be involved in medication-overuse headache pathophysiology. Studies using 18-fluorodeoxyglucose positron emission tomography (18-FDG PET) have identified reversible metabolic changes in pain processing structures and persistent orbitofrontal hypofunction in migraine patients with coexistent medication overuse headache.⁸⁸ Chronic morphine exposure results in increased descending facilitation from the rostral⁸⁸ ventromedial medulla and increased excitatory neurotransmission at the dorsal horn.⁸⁹ Sometimes, substance addiction may be the base for medication overuse headache. Others appear to be treating pain and a comorbid anxiety disorder with the same medication (e.g., opiates).⁹⁰ Out of 895 patients with medication overuse headache studied in a prospective fashion, 68% met three of five substance-dependence criteria according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* versus 20% in those without medication-overuse headache.⁹¹ Fear of headache, anticipatory anxiety, obsessive drug-taking behaviors, and psychological drug dependence may also help induce and then sustain medication-overuse headache.⁹⁰

Diagnosis

As discussed earlier, medication-overuse headache patients typically have a primary headache disorder that increased in frequency and led to increased analgesic consumption and then medication-overuse headache. It is not uncommon for patients to take frequent analgesics solely to prevent a severe analgesic-withdrawal headache.⁸⁵ Medication overuse headache varies in its characteristics (severity, location, type) and is frequently associated with nausea, asthenia, and cognitive difficulties (impaired memory, poor concentration, irritability).⁸⁰ If a CDH sufferer is taking analgesics more than 2 to 3 days per week on average, medication-overuse headache should always be suspected. The following are current ICHD-2 diagnostic criteria for medication overuse headache. Please note that the type of medication overused is important for proper diagnosis.⁸⁰

1. Headache present on ≥ 15 days/month
2. Regular overuse for > 3 months of one or more acute/symptomatic treatment drugs
 - a. Ergotamine, triptans, opioids, or combination analgesic medications on ≥ 10 days/month on a regular basis for > 3 months
 - b. Simple analgesics or any combination of ergotamine, triptans, analgesic opioids on ≥ 15 days/month on a regular basis for > 3 months without overuse of any single class alone
3. Headache has developed or markedly worsened during medication overuse

Treatment

Abrupt drug withdrawal remains the treatment of choice when dangerous physical withdrawal is not a concern.⁸⁵ Proper management of medication-overuse headache should include the following steps:

1. Patient education
2. Withdrawal of offending medication
3. "Bridging" aimed at symptomatic relief during medication withdrawal
4. Establish new acute and preventive headache treatment regimen
5. Follow-up and headache reassessment
6. Relapse prevention

Patient Education

Patients with medication-overuse headache need to understand that as long as they are overusing analgesics, headache preventives may be less effective or not effective at all.^{79,89} They need to be educated on why analgesic overuse is detrimental. The majority of medication-overuse headache patients benefit from drug withdrawal. Benefit may be from the withdrawal alone

or from a "reparative" change from treatment failure to favorable response to medical management.^{79,92}

Withdrawal of the Offending Medication

During analgesic withdrawal, headaches frequently exacerbate before starting to improve.⁸⁹ Nausea, vomiting, restlessness, anxiety, and sleep disturbances may also occur during withdrawal.^{85,89} Withdrawal symptoms usually last 2 to 10 days (mean 3.5 days),⁸⁵ but can endure for 2 to 4 weeks.⁸⁹ Although many physicians prefer inpatient programs for withdrawal,⁸⁵ most patients can be managed on an outpatient basis.⁸⁹ A recent prospective, randomized trial in patients with migraine and superimposed medication-overuse headache showed that simple, strong advice was as effective as structured inpatient and outpatient detoxification programs in achieving medication withdrawal.⁹³ The mean success rate of withdrawal treatment at 1 to 6 months was 72.4% in a meta-analysis.⁸⁵

Bridging

The goal of "bridging" is to provide symptomatic relief during acute medication withdrawal. No clear guidelines or consensus recommendations exist.⁹⁴ Bridging recommendations are based on case series, retrospective chart reviews, prospective uncontrolled studies, and expert opinion.⁸⁹ Some studies support the use of corticosteroids; others do not.⁹⁵ Further randomized, placebo-controlled trials are needed to clarify the potential role of corticosteroids in medication-overuse headache management.⁹⁶ Antiemetics are often prescribed in addition to the following published strategies.

ORAL

Naproxen 500 mg twice a day until withdrawal is complete⁹⁷

Naproxen sodium 550 mg twice a day for 2 to 4 weeks⁸⁹

Naproxen sodium 550 mg twice a day for 1 week, then once a day for 1 week⁸⁹

Prednisone 60 mg/day, decrease by 20 mg every 2 days (total 6 days)⁹⁸

Prednisone 100 mg for 5 days⁹⁶

INJECTED

Intravenous (IV) methylprednisolone 100 to 200 mg every 12 hours for 2 to 3 days^{89,99}

IV or intramuscular (IM) dexamethasone 8 to 20 mg/day, tapering over 2 to 3 days⁹⁸

IV hydrocortisone 100 mg every 6 hours for 24 hours; every 8 hours for 24 hours; then every 12 hours for 24 hours⁹⁸

Repetitive IV dihydroergotamine (DHE; inpatient): IV metoclopramide 10 mg, followed by 0.5 mg IV DHE.

Doses adjusted based on headache severity and side effects¹⁰⁰

Continuous IV DHE (inpatient): 3 mg of DHE in 1000 mL of normal saline at 42 mL/h by IV infusion pump, totaling 3 mg of DHE administered at constant rate over 24 hours¹⁰¹

Subcutaneous DHE (outpatient): 1 mg twice a day for 1 week followed by 0.5 mg twice a day for 1 week, or 1 mg twice a day for 1 week followed by 1 mg every day for 1 week⁸⁹

IV valproate sodium: loading dose of 15 mg/kg followed by daily maintenance of 5 mg/kg every 8 hours for 12 to 48 hours¹⁰²

IV prochlorperazine starting with 5 mg to 10 mg every 8 hours, with dosage adjustment according to efficacy and side effects until headache-free⁹⁹

Establish Appropriate Headache Prevention

Whether pharmacologic prophylaxis should be started at the time of medication withdrawal remains an ongoing dispute.¹⁰³ Because most patients will require long-term preventives, the authors recommend starting such treatment at the time of withdrawal. Preventives are chosen according to the type of underlying primary headache disorder.

Follow-up and Headache Reassessment

Once the overused medications have been withdrawn, patients frequently return to a pattern of intermittent headaches. These headaches need to be classified and treated accordingly.

Relapse Prevention

Most relapses occur in the first year following withdrawal.¹⁰⁴ In general, avoidance of opiates and/or butalbital for the regular management of primary headache disorders is recommended. Limitations for the frequency of analgesic intake should be explained: triptan or combination analgesic use should be limited to 9 or fewer days a month on average and NSAIDs to 15 or fewer days a month to prevent medication-overuse headache relapse.¹⁰⁵ The identification and management of comorbidities (anxiety, etc.) that may contribute to medication overuse headache development and preservation are of paramount importance to prevent medication overuse headache relapse.⁹⁰

NEW DAILY PERSISTENT HEADACHE

New daily persistent headache, one of the most treatment refractory headaches, is a headache that begins one day and typically does not remit.¹⁰⁶ New daily persistent

headache affects women more than men with reported ratios of 1.3:1 and 2.5:1.0 and can essentially affect all age groups.^{107–109} Peak age of onset is in the second and third decades for women and the fifth decade in men.¹⁰⁹ Overall mean age of onset is 35 years of age.¹⁰⁸ Although new daily persistent headache is estimated to occur infrequently in the general population, the exact frequency is unknown.¹⁰⁸ In headache clinics, however, ~1 in 10 CDH patients have new daily persistent headache.¹¹⁰

The etiology of new daily persistent headache is not well understood. Although the nature of the associations is unclear, infection, flu-like illness, surgery, and stressful life events may precede new daily persistent headache.¹⁰⁹ How these may result in new daily persistent headache is unknown and in many patients, no precipitating factors exist.¹⁰⁸ Possible associations between new daily persistent headache and Epstein-Barr virus (EBV), herpes simplex virus (HSV), and cytomegalovirus (CMV) have been suggested but remain unproven.^{109,111–114}

Diagnosis

The vast majority of patients (up to 82%) can vividly recall the exact date the headache started.¹⁰⁹ In most, ~80%, the pain is continuous.^{108,109} Pain intensity tends to be moderate, although many patients experience severe pain.¹⁰⁹ Clinical features vary significantly. Headaches may have primarily migraine features (photophobia, nausea, etc.) or be “featureless” and reminiscent of chronic tension-type headache.^{107–109} Secondary headache disorders, including those due to spontaneous cerebrospinal (CSF) leaks and cerebral venous sinus thrombosis, need to be ruled out.^{55,106} MRI of the brain with gadolinium and magnetic resonance venography (MRV) should be considered. Clinical judgment guides further investigations, if any. Current ICHD-2 diagnostic criteria for new daily persistent headache are as follows:⁵⁵

1. Headache for >3 months fulfilling Criteria 2 through 4
2. Headache is daily and unremitting from onset or from <3 days from onset
3. At least two of the following pain characteristics:
 - a. Bilateral location
 - b. Pressing/tightening (nonpulsating) quality
 - c. Mild or moderate intensity
4. Not aggravated by routine physical activity, such as walking or climbing stairs
5. Both of the following:
 - a. No more than one of photophobia, phonophobia, or mild nausea
 - b. Neither moderate or severe nausea nor vomiting
6. Not attributed to another disorder

Of note, although the above criteria reflect essentially a chronic tension-type headache phenotype, migrainous features are frequently reported.¹¹⁵ Diagnostic criteria will likely be modified as knowledge about this disorder expands.

Treatment

New daily persistent headache can endure for many years (even decades) and can be disabling. Despite proper treatment, the headache frequently does not abate.¹⁰⁶ Takase found treatment to be very effective in 27%, moderately effective in 3%, mildly effective in 20%, and not effective in 50% of 30 new daily persistent headache sufferers.¹⁰⁸ In agreement with other headache specialists,¹¹⁶ we recommend classifying the dominant headache phenotype, whether it is migraine or tension-type, and treat with preventives accordingly.

New daily persistent headache has been reported to take one of the following courses: a self-limited one typically resolving without treatment within several months, or a refractory course resistant to aggressive treatment.⁵⁵ Although most patients are headache free at 2 years in some series, in others (and in practice) new daily persistent headache may be refractory to treatment for many years.^{106–109,113}

HEMICRANIA CONTINUA

Hemicrania continua is a one-sided continuous headache of moderate severity with superimposed severe exacerbations of pain often associated with ipsilateral autonomic symptoms. The frequency of hemicrania continua in the general population is unknown.¹¹⁷ Hemicrania continua may begin at any age, but peaks in the third decade of life.¹¹⁸ It is twice as common in women than men.¹¹⁹

The pathophysiology of hemicrania continua is incompletely understood. However, a PET study of seven patients with hemicrania continua showed significant activation of the contralateral posterior hypothalamus and ipsilateral rostral pons during baseline pain that were blocked by administration of indomethacin.¹²⁰ PET in one patient with hemicrania continua without autonomic features, who had dorsal pontine activation but no hypothalamic activation, suggests that the hypothalamus may play a role in autonomic activation, perhaps via disinhibition of the trigeminal-autonomic reflex.¹²¹

Diagnosis

Hemicrania continua is a unilateral headache that is continuous in nature. Continuous pain is generally moderate in intensity. There are superimposed severe attacks of pain that last minutes to several days classically associated with autonomic features (lacrimation, miosis,

etc.).¹²² Although not fulfilling the diagnostic criteria,⁵⁵ a subgroup of patients with continuous one-sided headaches completely responsive to indomethacin do not have autonomic symptoms.¹²³ Mild migrainous features may be present, and some patients develop superimposed headaches consistent with migraine headaches.¹²⁴ Ipsilateral ocular discomfort or an ocular foreign body sensation and a superimposed stabbing headache (“jabs and jolts”) are often reported.¹¹⁸ ICHD-2 diagnostic criteria are as follows:⁵⁵

1. Headache for >3 months fulfilling Criteria 2 through 4
2. All of the following characteristics:
 - a. Unilateral pain without side-shift
 - b. Daily and continuous, without pain-free periods
 - c. Moderate intensity, but with exacerbations of severe pain
3. At least one of the following autonomic features occurs during exacerbations and ipsilateral to the side of pain:
 - a. Conjunctival injection and/or lacrimation
 - b. Nasal congestion and/or rhinorrhea
 - c. Ptosis and/or miosis
4. Complete response to therapeutic doses of indomethacin
5. Not attributed to another disorder

Secondary headaches mimicking primary hemicrania continua (including response to indomethacin) have been reported, including internal carotid artery dissection, unruptured aneurysm, pineal cyst, pituitary tumor, ipsilateral mesenchymal tumor of the sphenoidal bone involving the clinoid process at the base of the skull, lung adenocarcinoma, and pontine stroke.^{125–130} Diagnostic studies must therefore be ordered as necessary.

If hemicrania continua is suspected, an oral indomethacin test can be used for the diagnosis of hemicrania continua. One of several methods is as follows: 50 mg twice per day for 3 days, 50 mg three times per day for 3 days, 50 mg four times per day for 3 days. Indomethacin response is typically fast. In a prospective study of 12 hemicrania continua patients, complete pain relief was obtained within 48 hours in all cases, within 24 hours in 10 of the patients, and within 8 hours in nine.¹³¹ Completion of the test without headache resolution is considered a failed trial.

Treatment

Due to absolute response to indomethacin, it is the treatment of choice for hemicrania continua. The appropriate dose will vary among patients. The initial dose is that dose which results in resolution of headache, determined during the diagnostic indomethacin trial. Oral doses ranging from 25 mg to 300 mg per day

have been reported effective. However, given adverse side effects of indomethacin, the lowest effective dose is the desired dose. Periodic attempts to decrease the dose should be made. Potential side effects from indomethacin are numerous. Administration of indomethacin with food can reduce gastrointestinal side effects. Treatment with gastric mucosal protectants, such as proton-pump inhibitors, may also decrease this risk and is common practice. Many of these potential side effects are dose-related. Approximately one of three patients report side effects attributable to indomethacin therapy.¹³² Contraindications to treatment with indomethacin and/or discontinuation due to intolerance have led to the search for alternative therapies. There have been case reports of efficacy with melatonin, topiramate, verapamil, cox-2 inhibitors, gabapentin, botulinum toxin type A, and occipital nerve stimulation.^{119,133–138}

REFERENCES

- Scher AI, Stewart WF, Liberman J, Lipton RB. Prevalence of frequent headache in a population sample. *Headache* 1998;38(7):497–506
- Lu SR, Fuh JL, Chen WT, Juang KD, Wang SJ. Chronic daily headache in Taipei, Taiwan: prevalence, follow-up and outcome predictors. *Cephalalgia* 2001;21(10):980–986
- Wang SJ, Fuh JL, Lu SR, et al. Chronic daily headache in Chinese elderly: prevalence, risk factors, and biannual follow-up. *Neurology* 2000;54(2):314–319
- Stewart WF, Ricci JA, Chee E, Morganstein D, Lipton R. Lost productive time and cost due to common pain conditions in the US workforce. *JAMA* 2003;290(18):2443–2454
- Lipton RB, Stewart WF, Scher AI. Epidemiology and economic impact of migraine. *Curr Med Res Opin* 2001;17 (Suppl 1):s4–s12
- Scher AI, Midgette LA, Lipton RB. Risk factors for headache chronification. *Headache* 2008;48(1):16–25
- Scher AI, Stewart WF, Buse D, Krantz DS, Lipton RB. Major life changes before and after the onset of chronic daily headache: a population-based study. *Cephalalgia* 2008;28 (8):868–876
- Scher AI, Stewart WF, Lipton RB. Caffeine as a risk factor for chronic daily headache: a population-based study. *Neurology* 2004;63(11):2022–2027
- Scher AI, Stewart WF, Ricci JA, Lipton RB. Factors associated with the onset and remission of chronic daily headache in a population-based study. *Pain* 2003;106(1-2): 81–89
- Castillo J, Muñoz P, Guitera V, Pascual J. Kaplan Award 1998. Epidemiology of chronic daily headache in the general population. *Headache* 1999;39(3):190–196
- Guitera V, Muñoz P, Castillo J, Pascual J. Quality of life in chronic daily headache: a study in a general population. *Neurology* 2002;58(7):1062–1065
- D'Amico D, Usai S, Grazi L, et al. Quality of life and disability in primary chronic daily headaches. *Neurol Sci* 2003;24(Suppl 2):S97–S100
- Harwood RH, Sayer AA, Hirschfeld M. Current and future worldwide prevalence of dependency, its relationship to total population, and dependency ratios. *Bull World Health Organ* 2004;82(4):251–258
- Munakata J, Hazard E, Serrano D, et al. Economic burden of transformed migraine: results from the American Migraine Prevalence and Prevention (AMPP) Study. *Headache* 2009;49(4):498–508
- Katsarava Z, Schneeweiss S, Kurth T, et al. Incidence and predictors for chronicity of headache in patients with episodic migraine. *Neurology* 2004;62(5):788–790
- Lipton RB. Tracing transformation: chronic migration classification, progression, and epidemiology. *Neurology* 2009;72(5 Suppl):S3–S7
- Sarchielli P, Alberti A, Floridi A, Gallai V. Levels of nerve growth factor in cerebrospinal fluid of chronic daily headache patients. *Neurology* 2001;57(1):132–134
- Schwedt TJ, Dodick DW. Advanced neuroimaging of migraine. *Lancet Neurol* 2009;8(6):560–568
- Welch KM, Nagesh V, Aurora SK, Gelman N. Periaqueductal gray matter dysfunction in migraine: cause or the burden of illness? *Headache* 2001;41(7):629–637
- Kruit MC, Launer LJ, Overbosch J, van Buchem MA, Ferrari MD. Iron accumulation in deep brain nuclei in migraine: a population-based magnetic resonance imaging study. *Cephalalgia* 2009;29(3):351–359
- Schmitz N, Admiraal-Behloul F, Arkink EB, et al. Attack frequency and disease duration as indicators for brain damage in migraine. *Headache* 2008;48(7):1044–1055
- Valfrè W, Rainero I, Bergui M, Pinessi L. Voxel-based morphometry reveals gray matter abnormalities in migraine. *Headache* 2008;48(1):109–117
- Rocca MA, Ceccarelli A, Falini A, et al. Brain gray matter changes in migraine patients with T2-visible lesions: a 3-T MRI study. *Stroke* 2006;37(7):1765–1770
- Schmitz N, Arkink EB, Mulder M, et al. Frontal lobe structure and executive function in migraine patients. *Neurosci Lett* 2008;440(2):92–96
- Granziera C, DaSilva AF, Snyder J, Tuch DS, Hadjikhani N. Anatomical alterations of the visual motion processing network in migraine with and without aura. *PLoS Med* 2006;3(10):e402
- Ashkenazi A, Mushtaq A, Yang I, Oshinsky ML. Ictal and interictal phonophobia in migraine—a quantitative controlled study. *Cephalalgia* 2009;29(10):1042–1048
- Olesen J, Bussone MG, Diener HC, et al; Headache Classification Committee. New appendix criteria open for a broader concept of chronic migraine. *Cephalalgia* 2006; 26(6):742–746
- Silberstein SD, Lipton RB, Dodick DW, et al; Topiramate Chronic Migraine Study Group. Efficacy and safety of topiramate for the treatment of chronic migraine: a randomized, double-blind, placebo-controlled trial. *Headache* 2007;47(2):170–180
- Diener HC, Bussone G, Van Oene JC, Lahaye M, Schwalen S, Goadsby PJ; TOPMAT-MIG-201(TOP-CHROME) Study Group. Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. *Cephalalgia* 2007;27(7):814–823
- Spira PJ, Beran R; GAustralian Gabapentin Chronic Daily Headache Group. Gabapentin in the prophylaxis of chronic daily headache: a randomized, placebo-controlled study. *Neurology* 2003;61(12):1753–1759
- Saper JR, Lake AE III, Cantrell DT, Winner PK, White JR. Chronic daily headache prophylaxis with tizanidine:

- a double-blind, placebo-controlled, multicenter outcome study. *Headache* 2002;42(6):470-482
31. Saper JR, Silberstein SD, Lake AE III, Winters ME. Double-blind trial of fluoxetine: chronic daily headache and migraine. *Headache* 1994;34(9):497-502
 32. Krymchantowski AV, Silva MT, Barbosa JS, Alves LA. Amitriptyline versus amitriptyline combined with fluoxetine in the preventative treatment of transformed migraine: a double-blind study. *Headache* 2002;42(6):510-514
 33. Rapoport AM, Sheftell FD, Tepper SJ, Bigal M. Levetiracetam in the preventive treatment of transformed migraine. *Curr Ther Res* 2005;66:212-221
 34. Mathew NT, Ali S. Valproate in the treatment of persistent chronic daily headache. An open label study. *Headache* 1991;31(2):71-74
 35. Freitag FG, Diamond S, Diamond ML, Urban GJ. Divalproex in the long-term treatment of chronic daily headache. *Headache* 2001;41(3):271-278
 36. Naumann M, So Y, Argoff CE, et al; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Assessment: Botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2008;70(19):1707-1714
 37. Spengos K, Theleritis C, Paparrigopoulos T. Memantine and NMDA antagonism for chronic migraine: a potentially novel therapeutic approach? *Headache* 2008;48(2):284-286
 38. Bigal M, Rapoport A, Sheftell F, Tepper D, Tepper S. Memantine in the preventive treatment of refractory migraine. *Headache* 2008;48(9):1337-1342
 39. Ciancarelli I, Tozzi-Ciancarelli MG, Spacca G, Di Massimo C, Carolei A. Relationship between biofeedback and oxidative stress in patients with chronic migraine. *Cephalalgia* 2007;27(10):1136-1141
 40. Martin PR, Forsyth MR, Reece J. Cognitive-behavioral therapy versus temporal pulse amplitude biofeedback training for recurrent headache. *Behav Ther* 2007;38(4):350-363
 41. Lockett DM, Campbell JF. The effects of aerobic exercise on migraine. *Headache* 1992;32(1):50-54
 42. Marcus DA, Scharff L, Mercer S, Turk DC. Non-pharmacological treatment for migraine: incremental utility of physical therapy with relaxation and thermal biofeedback. *Cephalalgia* 1998;18(5):266-272, discussion 242
 43. Seok JI, Cho HI, Chung CS. From transformed migraine to episodic migraine: reversion factors. *Headache* 2006;46(7):1186-1190
 44. Schwartz BS, Stewart WF, Simon D, Lipton RB. Epidemiology of tension-type headache. *JAMA* 1998;279(5):381-383
 45. Lavados PM, Tenhamm E. Epidemiology of tension-type headache in Santiago, Chile: a prevalence study. *Cephalalgia* 1998;18(8):552-558
 46. Russell MB, Levi N, Saltyte-Benth J, Fenger K. Tension-type headache in adolescents and adults: a population based study of 33,764 twins. *Eur J Epidemiol* 2006;21(2):153-160
 47. Bendtsen L, Jensen R. Tension-type headache: the most common, but also the most neglected, headache disorder. *Curr Opin Neurol* 2006;19(3):305-309
 48. Juang KD, Wang SJ, Fuh JL, Lu SR, Su TP. Comorbidity of depressive and anxiety disorders in chronic daily headache and its subtypes. *Headache* 2000;40(10):818-823
 49. Fumal AS. Chronic tension-type headache. In: Goadsby PJ, Dodick DW, eds. *Chronic Daily Headache for Clinicians*. 1st Ed. Hamilton, Ontario: BC Decker Inc; 2005:57-64
 50. Mathew NT. Tension-type headache. *Curr Neurol Neurosci Rep* 2006;6(2):100-105
 51. Bendtsen L, Jensen R, Olesen J. Decreased pain detection and tolerance thresholds in chronic tension-type headache. *Arch Neurol* 1996;53(4):373-376
 52. Buchgreitz L, Egsgaard LL, Jensen R, Arendt-Nielsen L, Bendtsen L. Abnormal pain processing in chronic tension-type headache: a high-density EEG brain mapping study. *Brain* 2008;131(Pt 12):3232-3238
 53. Pielsticker A, Haag G, Zaudig M, Lautenbacher S. Impairment of pain inhibition in chronic tension-type headache. *Pain* 2005;118(1-2):215-223
 54. Schmidt-Wilcke T, Leinisch E, Straube A, et al. Gray matter decrease in patients with chronic tension type headache. *Neurology* 2005;65(9):1483-1486
 55. Headache Classification Subcommittee of the International Headache Society. *The International Classification of Headache Disorders, 2nd Edition*. Cephalalgia 2004;24(Suppl 1):1-160
 56. Jensen R, Becker WJ. Symptomatology of chronic tension-type headaches. In: Olesen J, Ramadan NM, Tfelt-Hansen P, Welch KMA, eds. *The Headaches*. 3rd ed. Philadelphia: Lippincott Williams and Wilkins; 2006:693-699
 57. Bigal ME, Lipton RB. Tension-type headache: classification and diagnosis. *Curr Pain Headache Rep* 2005;9(6):423-429
 58. Lenaerts ME. Pharmacoprophylaxis of tension-type headache. *Curr Pain Headache Rep* 2005;9(6):442-447
 59. Bendtsen L, Jensen R, Olesen J. A non-selective (amitriptyline), but not a selective (citalopram), serotonin reuptake inhibitor is effective in the prophylactic treatment of chronic tension-type headache. *J Neurol Neurosurg Psychiatry* 1996;61(3):285-290
 60. Bendtsen L, Jensen R. Mirtazapine is effective in the prophylactic treatment of chronic tension-type headache. *Neurology* 2004;62(10):1706-1711
 61. Garza I, Swanson JW. Prophylaxis of migraine. *Neuropsychiatr Dis Treat* 2006;2(3):281-291
 62. Holroyd KA, O'Donnell FJ, Stensland M, Lipchik GL, Cordingley GE, Carlson BW. Management of chronic tension-type headache with tricyclic antidepressant medication, stress management therapy, and their combination: a randomized controlled trial. *JAMA* 2001;285(17):2208-2215
 63. Cohen GL. Protriptyline, chronic tension-type headaches, and weight loss in women. *Headache* 1997;37(7):433-436
 64. Lampl C, Marecek S, May A, Bendtsen L. A prospective, open-label, long-term study of the efficacy and tolerability of topiramate in the prophylaxis of chronic tension-type headache. *Cephalalgia* 2006;26(10):1203-1208
 65. Yurekli VA, Akhan G, Kutluhan S, Uzar E, Koyuncuoglu HR, Gultekin F. The effect of sodium valproate on chronic daily headache and its subgroups. *J Headache Pain* 2008;9(1):37-41
 66. Fogelholm R, Murros K. Tizanidine in chronic tension-type headache: a placebo controlled double-blind cross-over study. *Headache* 1992;32(10):509-513
 67. Murros K, Kataja M, Hedman C, et al. Modified-release formulation of tizanidine in chronic tension-type headache. *Headache* 2000;40(8):633-637

68. Langemark M, Olesen J. Sulpiride and paroxetine in the treatment of chronic tension-type headache. An explanatory double-blind trial. *Headache* 1994;34(1):20–24
69. Holroyd KA, Labus JS, O'Donnell FJ, Cordingley GE. Treating chronic tension-type headache not responding to amitriptyline hydrochloride with paroxetine hydrochloride: a pilot evaluation. *Headache* 2003;43(9):999–1004
70. Adelman LC, Adelman JU, Von Seggern R, Mannix LK. Venlafaxine extended release (XR) for the prophylaxis of migraine and tension-type headache: A retrospective study in a clinical setting. *Headache* 2000;40(7):572–580
71. Mitsikostas DD, Gatzonis S, Thomas A, Ilias A. Buspirone vs amitriptyline in the treatment of chronic tension-type headache. *Acta Neurol Scand* 1997;96(4):247–251
72. Schulte-Mattler WJ, Martinez-Castrillo JC. Botulinum toxin therapy of migraine and tension-type headache: comparing different botulinum toxin preparations. *Eur J Neurol* 2006; 13(Suppl 1):51–54
73. Walker Z, Walker RW, Robertson MM, Stansfeld S. Antidepressant treatment of chronic tension-type headache: a comparison between fluoxetine and desipramine. *Headache* 1998;38(7):523–528
74. Söderberg E, Carlsson J, Stener-Victorin E. Chronic tension-type headache treated with acupuncture, physical training and relaxation training. Between-group differences. *Cephalalgia* 2006;26(11):1320–1329
75. Melis PM, Rooimans W, Spierings EL, Hoogduin CA. Treatment of chronic tension-type headache with hypnotherapy: a single-blind time controlled study. *Headache* 1991;31(10):686–689
76. Quinn C, Chandler C, Moraska A. Massage therapy and frequency of chronic tension headaches. *Am J Public Health* 2002;92(10):1657–1661
77. Bronfort G, Nilsson N, Haas M, et al. Non-invasive physical treatments for chronic/recurrent headache. *Cochrane Database Syst Rev* 2004;(3):CD001878
78. Bigal ME, Rapoport AM, Sheftell FD, Tepper SJ, Lipton RB. Transformed migraine and medication overuse in a tertiary headache centre—clinical characteristics and treatment outcomes. *Cephalalgia* 2004;24(6):483–490
79. Mathew NT, Kurman R, Perez F. Drug induced refractory headache—clinical features and management. *Headache* 1990;30(10):634–638
80. Dodick D, Freitag F. Evidence-based understanding of medication-overuse headache: clinical implications. *Headache* 2006;46(Suppl 4):S202–S211
81. Kavuk I, Katsarava Z, Selekler M, et al. Clinical features and therapy of medication overuse headache. *Eur J Med Res* 2004;9(12):565–569
82. Smith TR, Stoneman J. Medication overuse headache from antimigraine therapy: clinical features, pathogenesis and management. *Drugs* 2004;64(22):2503–2514
83. Bigal ME, Serrano D, Buse D, Scher A, Stewart WF, Lipton RB. Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study. *Headache* 2008;48(8):1157–1168
84. Bigal ME, Lipton RB. Excessive acute migraine medication use and migraine progression. *Neurology* 2008;71(22):1821–1828
85. Diener HC, Limmroth V. Medication-overuse headache: a worldwide problem. *Lancet Neurol* 2004;3(8):475–483
86. Lance F, Parkes C, Wilkinson M. Does analgesic abuse cause headaches de novo? *Headache* 1988;28(1):61–62
87. Ayzenberg I, Obermann M, Nyhuis P, et al. Central sensitization of the trigeminal and somatic nociceptive systems in medication overuse headache mainly involves cerebral supraspinal structures. *Cephalalgia* 2006;26(9): 1106–1114
88. Fumal A, Laureys S, Di Clemente L, et al. Orbitofrontal cortex involvement in chronic analgesic-overuse headache evolving from episodic migraine. *Brain* 2006;129(Pt 2):543–550
89. Boes CJ, Black DF, Dodick DW. Pathophysiology and management of transformed migraine and medication overuse headache. *Semin Neurol* 2006;26(2):232–241
90. Saper JR, Hamel RL, Lake AE III. Medication overuse headache (MOH) is a biobehavioural disorder. *Cephalalgia* 2005;25(7):545–546
91. Fuh JL, Wang SJ, Lu SR, Juang KD. Does medication overuse headache represent a behavior of dependence? *Pain* 2005;119(1-3):49–55
92. Zeeberg P, Olesen J, Jensen R. Discontinuation of medication overuse in headache patients: recovery of therapeutic responsiveness. *Cephalalgia* 2006;26(10):1192–1198
93. Rossi P, Di Lorenzo C, Faroni J, Cesarino F, Nappi G. Advice alone vs. structured detoxification programmes for medication overuse headache: a prospective, randomized, open-label trial in transformed migraine patients with low medical needs. *Cephalalgia* 2006;26(9):1097–1105
94. Obermann M, Katsarava Z. Management of medication-overuse headache. *Expert Rev Neurother* 2007;7(9): 1145–1155
95. Bøe MG, Mygland A, Salvesen R. Prednisolone does not reduce withdrawal headache: a randomized, double-blind study. *Neurology* 2007;69(1):26–31
96. Diener HC. How to treat medication-overuse headache: prednisolone or no prednisolone? *Neurology* 2007;69(1): 14–15
97. Mathew NT. Amelioration of ergotamine withdrawal symptoms with naproxen. *Headache* 1987;27(3):130–133
98. Krymchantowski AV, Barbosa JS. Prednisone as initial treatment of analgesic-induced daily headache. *Cephalalgia* 2000;20(2):107–113
99. Lu SR, Fuh JL, Juang KD, Wang SJ. Repetitive intravenous prochlorperazine treatment of patients with refractory chronic daily headache. *Headache* 2000;40(9): 724–729
100. Silberstein SD, Schulman EA, Hopkins MM. Repetitive intravenous DHE in the treatment of refractory headache. *Headache* 1990;30(6):334–339
101. Ford RG, Ford KT. Continuous intravenous dihydroergotamine in the treatment of intractable headache. *Headache* 1997;37(3):129–136
102. Schwartz TH, Karpitskiy VV, Sohn RS. Intravenous valproate sodium in the treatment of daily headache. *Headache* 2002;42(6):519–522
103. Katsarava Z, Jensen R. Medication-overuse headache: where are we now? *Curr Opin Neurol* 2007;20(3):326–330
104. Katsarava Z, Muessig M, Dzagnidze A, Fritsche G, Diener HC, Limmroth V. Medication overuse headache: rates and predictors for relapse in a 4-year prospective study. *Cephalalgia* 2005;25(1):12–15
105. Garza I, Swanson JW. Answers to frequently asked questions about migraine. *Mayo Clin Proc* 2006;81(10):1387–1391, quiz 1392

106. Rozen TD. New daily persistent headache. *Curr Pain Headache Rep* 2003;7(3):218–223
107. Vanast WJ. New daily persistent headaches definition of a benign syndrome. *Headache* 1986;26:317–320 (Abstract)
108. Takase Y, Nakano M, Tatsumi C, Matsuyama T. Clinical features, effectiveness of drug-based treatment, and prognosis of new daily persistent headache (NDPH): 30 cases in Japan. *Cephalalgia* 2004;24(11):955–959
109. Li D, Rozen TD. The clinical characteristics of new daily persistent headache. *Cephalalgia* 2002;22(1):66–69
110. Bigal ME, Sheftell FD, Rapoport AM, Lipton RB, Tepper SJ. Chronic daily headache in a tertiary care population: correlation between the International Headache Society diagnostic criteria and proposed revisions of criteria for chronic daily headache. *Cephalalgia* 2002;22(6):432–438
111. Diaz-Mitoma F, Vanast WJ, Tyrrell DL. Increased frequency of Epstein-Barr virus excretion in patients with new daily persistent headaches. *Lancet* 1987;1(8530):411–415
112. Hamada T, Ohshima K, Ide Y, Sakato S, Takamori M. A case of new daily persistent headache with elevated antibodies to Epstein-Barr virus. *Jpn J Med* 1991;30(2):161–163
113. Meineri P, Torre E, Rota E, Grasso E. New daily persistent headache: clinical and serological characteristics in a retrospective study. *Neurol Sci* 2004;25(Suppl 3):S281–S282
114. Santoni JR, Santoni-Williams CJ. Headache and painful lymphadenopathy in extracranial or systemic infection: etiology of new daily persistent headaches. *Intern Med* 1993;32(7):530–532
115. Rozen TD. New daily persistent headache. In: Goadsby PJ, Dodick DW, eds. *Chronic Daily Headache for Clinicians*. 1st Ed. Hamilton, Ontario: BC Decker Inc.; 2005:209–215
116. Goadsby PJ, Boes C. New daily persistent headache. *J Neurol Neurosurg Psychiatry* 2002;72(Suppl 2):ii6–ii9
117. Rossi P, Faroni J, Tassorelli C, Nappi G. Diagnostic delay and suboptimal management in a referral population with hemicrania continua. *Headache* 2009;49(2):227–234
118. Peres MF, Silberstein SD, Nahmias S, et al. Hemicrania continua is not that rare. *Neurology* 2001;57(6):948–951
119. Dodick D. Hemicrania continua: diagnostic criteria and nosologic status. *Cephalalgia* 2001;21(9):869–872
120. Matharu MS, Cohen AS, McGonigle DJ, Ward N, Frackowiak RS, Goadsby PJ. Posterior hypothalamic and brainstem activation in hemicrania continua. *Headache* 2004;44(8):747–761
121. Irimia P, Arbizu J, Prieto E, Fernández-Torrón R, Martínez-Vila E. Activation of the brainstem but not of the hypothalamus in hemicrania continua without autonomic symptoms. *Cephalalgia* 2009;29(9):974–979
122. Matharu MS, Boes CJ, Goadsby PJ. Management of trigeminal autonomic cephalgias and hemicrania continua. *Drugs* 2003;63(16):1637–1677
123. Marmura MJ, Silberstein SD, Gupta M. Hemicrania continua: who responds to indomethacin? *Cephalalgia* 2009;29(3):300–307
124. Bigal ME, Tepper SJ, Rapoport AM, Sheftell FD. Hemicrania continua: comparison between two different classification systems. *Cephalalgia* 2002;22(3):242–245
125. Eross EJ, Swanson JW, Dodick DW. Hemicrania continua: an indomethacin-responsive case with an underlying malignant etiology. *Headache* 2002;42(6):527–529
126. Antonaci F, Sjaastad O. Hemicrania continua: a possible symptomatic case, due to mesenchymal tumor. *Funct Neurol* 1992;7(6):471–474
127. Valença MM, Andrade-Valença LP, da Silva WF, Dodick DW. Hemicrania continua secondary to an ipsilateral brainstem lesion. *Headache* 2007;47(3):438–441
128. Rogalewski A, Evers S. Symptomatic hemicrania continua after internal carotid artery dissection. *Headache* 2005;45(2):167–169
129. Peres MF, Zukerman E, Porto PP, Brandt RA. Headaches and pineal cyst: a (more than) coincidental relationship? *Headache* 2004;44(9):929–930
130. Levy MJ, Matharu MS, Meeran K, Powell M, Goadsby PJ. The clinical characteristics of headache in patients with pituitary tumours. *Brain* 2005;128(Pt 8):1921–1930
131. Pareja J, Sjaastad O. Chronic paroxysmal hemicrania and hemicrania continua. Interval between indomethacin administration and response. *Headache* 1996;36(1):20–23
132. Pareja JA, Caminero AB, Franco E, Casado JL, Pascual J, Sánchez del Río M. Dose, efficacy and tolerability of long-term indomethacin treatment of chronic paroxysmal hemicrania and hemicrania continua. *Cephalalgia* 2001;21(9):906–910
133. Rozen TD. Melatonin responsive hemicrania continua. *Headache* 2006;46(7):1203–1204
134. Peres MF, Silberstein SD. Hemicrania continua responds to cyclooxygenase-2 inhibitors. *Headache* 2002;42(6):530–531
135. Schwedt TJ, Dodick DW, Hentz J, Trentman TL, Zimmerman RS. Occipital nerve stimulation for chronic headache—long-term safety and efficacy. *Cephalalgia* 2007;27(2):153–157
136. Camarda C, Camarda R, Monastero R. Chronic paroxysmal hemicrania and hemicrania continua responding to topiramate: two case reports. *Clin Neurol Neurosurg* 2008;110(1):88–91
137. Burns B, Watkins L, Goadsby PJ. Treatment of hemicrania continua by occipital nerve stimulation with a bion device: long-term follow-up of a crossover study. *Lancet Neurol* 2008;7(11):1001–1012
138. Garza I, Cutrer F. Pain relief and persistence of dysautonomic features in a patient with hemicrania continua responsive to botulinum toxin type A. *Cephalalgia* 2009; June 10 (Epub ahead of print)