Migraine is a prevalent neurological disorder, but its prevalence is probably greater among practicing neurologists. I was about twelve years old when I had my “first and worst” headache – triggered, in retrospect, by eating an entire box of chocolates with my grandmother just hours earlier. There I was in the hotel room, a throbbing and ever-intensifying pain creeping over my left eyebrow toward the temple, curled in a ball, intensely nauseated, with a blanket over my head to block out light, and the sound of my parents’ voices only intensifying the agony I felt. If the pain hadn’t gone away with sleep, I am certain I would have also had my first head CT, and possibly my first lumbar puncture. Though we have all learned again and again the typical “red flags” for headache, any migraineur will have experienced at some point in life a “first,” and invariably a “worst.” Yet the needle in the haystack may be the aneurysm rupture, the obstructive hydrocephalus. Scarier still, severity of pain does not always match severity of disease – more often than not, the opposite is true. To a neurologist, a two-month history of personality changes and mild left-sided weakness with a dull, “two out of ten” headache is more frightening than a “ten out of ten” headache with nausea and vomiting in a young woman of childbearing age, especially if further history suggests a gradual onset, perimenstrual headaches, and a strong family history of migraine. Sorting through all those headaches invariably produces… headache. For many practitioners, the angst about headache is angst about missing a secondary cause. For others, it is the discomfort with treating chronic pain, or unpacking its psychosocial baggage. This issue of the Rhode Island Medical Journal aims to alleviate the provider’s headache, by shedding more light on headache – from accurate diagnosis to specific treatments.

**DR. NORMAN GORDON** has practiced general neurology in Rhode Island for more than 20 years; in Clinical Features of Migraine and Other Headache Disorders, he shares wisdom gleaned in his Miriam Hospital-affiliated private practice, illustrating the importance of making an accurate diagnosis as a crucial first step in the proper management of some common and uncommon primary headache disorders.

In Chronic Daily Headache: Challenges in Treatment, **DRS. JAY LEVIN AND MICHELLE MELLION** [of Rhode Island Hospital, The Neurology Foundation] provide a comprehensive review of one of the most tormenting conditions encountered by practitioners, touching on its diverse comorbidities, and treatment principles. By the end of the article, I assure you, the condition will be far less scary.

**DR. LUCY RATHIER** is a psychologist [of Lifespan Physicians Group] specializing in the behavioral treatment of medical conditions, particularly headache. Our article, A Biobehavioral Approach to Headache Management, provides the foundation for a collaborative, multifaceted approach to headache management, demonstrating a rationale for combining behavioral techniques with more typical medications – particularly for those headaches that have become chronic.

**DR. NIHARIKA MEHTA**, a specialist in obstetrical medicine at Women and Infants Hospital, has written an insightful case-based article, Headaches in the Pregnant Patient, which highlights challenges in diagnosing and treating headache in a pregnant patient – pregnant women being yet another anxiety-provoking population.

Pain is meant to signal the brain when something is wrong with the body. Yet in primary headache, that signal goes haywire, and the brain needs to be taught to stop listening to the false signal. Cut to two and a half years ago: pregnant with my daughter, I noticed an odd disturbance in my left peripheral vision – an alternating pattern of brightly lit, rainbow colors, shaped like a zigzag, with a glistening inner edge. It flashed on and off for fifteen minutes, then vanished completely. If it hadn’t been for my interest and knowledge of migraine, I might have panicked, inevitably intensifying the pain that followed. Instead, I waited it out. The descending pathways of my periaqueductal gray area kicked in, and I was fine. By linking clinical features and mechanisms with management strategies, we hope you will not be afraid to unpack the baggage – both physiologic and psychosocial – and appreciate that that the diagnosis and treatment of headache can be among the most rewarding in medicine.

**Author**

Julie Roth, MD, is a Neurologist at The Neurology Foundation, Providence, RI, and is Assistant Professor, Department of Neurology, the Warren Alpert Medical School of Brown University.
Clinical Features of Migraine and Other Headache Disorders

NORMAN GORDON, MD

INTRODUCTION

While the best recognized manifestation of migraine is headache, not all headaches presenting to physicians are migraine, and migraine disorder is not just a headache. Migraine is a complex and not fully understood process of cerebral dysfunction associated with a variety of symptoms uniting cortical depolarization, brainstem dysfunction, meningeal vasodilatation and excitation of sensory pain structures as remote as the cervical nucleus caudalis. This gives rise to the often seen myriad of symptoms, seeming somewhat disparate in this common disorder. I will attempt to explain at least some of the known and less well-known aspects of this fascinating disorder, including pathogenesis, management and treatment. I will also briefly discuss some of the lesser-known and often misdiagnosed headache syndromes.

Migraine without aura

About 75% of migraine occurs without aura, a phenomenon thought clinically related to the experimental phenomenon of cortical spreading depression of neuronal activity. However, even in migraine without aura, PET studies suggest that depolarization can occur in unilateral or bilateral occipital cortex or cortices.\(^1\)\(^2\) The headache of migraine is often unilateral and throbbing, accompanied by nausea, vomiting, photophobia, phonophobia (phonophobia), scalp hypersensitivity or hyperalgesia, and aggravated by movement and sensitivity to strong scents. It is commonly triggered by hormonal changes, atmospheric changes, sleep deprivation, hunger, alcohol, various vasoactive drugs and food additives and emotional events either positive, or more often, negative. Excessive stimulation by light, noise, strong scents and movement are both triggers and exacerbating factors. The prodrome of migraine can be characterized by dysphoria, fatigue with yawning, and other nonspecific symptoms that can precede the headache by hours or days. The headache itself typically lasts some hours and is then succeeded by postdromal fatigue, dulled senses, dysphoria or, conveniently termed, the ‘migraine hangover.’

Migraine aura

The aura is by far the most interesting aspect of migraine. The migraine aura usually precedes the headache and lasts 15 to 30 minutes. The most well recognized and common auras are visual and may be described by migraine sufferers as unilateral crescents, or expanding, jagged regions of shimmering light, leaving behind a scotoma. The terms fortification spectra, haloes, zigzags and scintillating scotomata are often used. Sensory auras of parasthesias, vertigo, as well as aphasias and motor hemiparesis are less frequently seen, but almost always have the same migratory nature of the visual aura. The mechanism of the aura is known to be spreading cortical neuronal depolarization demonstrated on PET scan, associated with subsequent hyperpolarization leading to the negative signs and symptoms such as the blind spot, hemi-anesthesia, and rarely hemiplegia.

The previously termed “Basilar Artery Migraine” is a migraine aura in which the deficits appear to be in a basilar artery distribution. This particular aura syndrome, the most striking of migraine auras, is associated with brainstem dysfunction, including bilateral visual loss, vertigo, dysthria, ataxia, tinnitus, hearing loss, global parasthesias, altered consciousness, and finally, syncope. Autonomic changes such as flushing, anhydrosis, ptosis, midryasis, pulse and blood pressure changes and diarrhea can occur. Other auras deserving mention are other episodic conditions – abdominal migraine, cyclic vomiting and episodic ataxia. These conditions are more common in children and eventually evolve into more typical migraine with and without aura, as they mature into adulthood.

Acephalgic migraine is aura without headache and is more prevalent with aging as the incidence of migraine headache recedes. Often, these auras are identical to auras that the patient may have experienced with typical headache in the past, but they may occur a priori. They are often described with the typical features of migraine aura, such as visual obscurations in one hemifield, lasting 15 to 30 minutes, but always need further evaluation like an MRI, and EEG because they do raise a red flag as a NEW phenomenon.\(^3\)\(^4\)

Migraine and stroke risk

There is evidence that the association between migraine with aura and stroke is real – however small – and likely related to contributing factors of smoking, oral contraceptive use, and age under 45.\(^4\)\(^5\) The incidence of small, nonspecific, white matter lesions on MRI is higher in migraine sufferers but of unclear clinical significance. However, white matter lesions are also seen in patients known to have microvascular or ischemic cerebral disease, among other conditions.
Treatment of migraine
The treatment of migraine consists of preventative and abortive therapy. Patients experiencing infrequent, episodic migraine responding to effective abortive treatment do not require prophylaxis. The goal of preventative treatment is to reduce not only the frequency but also the severity of the attacks. Prophylactic medications often potentiate the effect of abortive medications.

Preventative treatment
First-line prophylaxis does not necessarily involve the choosing of one or more of the many agents available, but rather education and lifestyle changes. Regular sleep, food, fluids and exercise are the mantra of headache hygiene. Identification and avoidance of obvious triggers is free, convenient and devoid of side effects. Preventative agents include beta blockers, calcium channel blockers, ACE inhibitors, Tricyclic antidepressants (TCAs), and NSAIDs. Anticonvulsants, considering a mechanism of action to inhibit spontaneous cortical depolarization, may make the most sense as first-line agents. Over the counter products such as feverfew, magnesium, riboflavin, CoQ10 and butterbur have all been somewhat supported by various, usually small clinical trials, but may be preferred by certain patients who are more favorably disposed to nontraditional methods. The American Academy of Neurology released guidelines in 2012 regarding the use of prophylactic and abortive migraine therapies, and included these supplements as having some data to support their use.

Migraine sufferers often respond to lower doses of preventative agents such as the anticonvulsants and TCAs than doses that are usually required to control epilepsy or depression. This tactic may minimize side effects and expense. Mention should be made of botulinum toxin, indicated for the treatment of chronic migraine (defined as greater than fifteen headache days per month) and administered every three months.

Abortive treatment
The most effective abortive treatment for migraine is the one that works. In other words, there is no clinical way to predict in advance a response to a particular migraine treatment. Any medication administered orally, as nasal spray, injection, patch, or rectally that not only aborts the headache, but also restores normal function within 1 to 2 hours, without unwanted side effects, can be an effective agent. Most of the abortive agents relieve the headache only. The prodrome, aura, and associated features dissipate either spontaneously or as a result of effective pain control. The triptan medications in all their forms are clearly the most effective agents, particularly when given as soon as possible in the migraine process, and in a dosage form appropriate for that individual. Oral agents in a patient who is vomiting may be useless, and in these patients, nasal sprays, injectables, or a patch is preferred. Triptans are serotonin 5-HT1B and D) agonists, and cause a degree of vasoconstriction in meningeal vessels, as well as other vascular beds, eliminating the pain caused by vasodilation. However, they are not expected to directly terminate the various sensitivities of migraine, the nausea or vomiting, or affective components such as irritability.

NSAIDs and Tylenol are often effective in early and milder migraine and can also be used safely in conjunction with triptans. Anti-emetics are effective adjuvant treatments and often used intravenously in appropriate settings such as the emergency room. Currently, the only ergot available is parenteral or nasal dihydroergotamine (DHE), a useful alternative to triptans, particularly in the emergency room, though this medication is subject to the same limitations in patients prone to vascular complications, and may cause nausea and vomiting itself. Dexamethasone and prednisone are particularly useful in the treatment of status migrainus, defined as a migraine occurring without remission for more than 72 hours. Opioids and other potent analgesics such as tramadol can be used as rescue medications but are sedating and usually do not restore normal activity within two hours as desired.

Calcitonin G related peptide (CGRP) inhibitors and serotonin 1F receptor agonists are novel agents, which unfortunately in clinical trials have had either unacceptable adverse events, or other limitations despite showing efficacy, and none is at this time in a realistic pipeline.

Trigemino-Autonomic Cephalalgia (TAC)
Other interesting headache syndromes aside from migraine comprise a list that is far too extensive for the purposes of this article; however, some of these bear mentioning. The most familiar is cluster headache, which is characterized by brief [15-180 minutes] bouts of severe pain in the periorbital region, often accompanied by conjunctival injection, tearing, nasal congestion or rhinorrhea, eyelid edema, forehead and facial sweating, miosis, ptosis and or a sense of restless or agitation. Treatment involves inhaled high-flow nasal oxygen or triptan medications. Lesser known to the general practitioner are some other Trigemino-Autonomic Cephalalgias (TACs), a group of unilateral, severe, periorbital headaches associated with autonomic features. Of these, the two most interesting are Hemicrania Continua, and the chronic and episodic forms of Paroxysmal Hemicrania. Hemicrania continua is a unilateral, continuous headache which does vary in intensity without complete resolution. It affects the sexes equally; location is often peri-orbital but also may the entire hemicranium. It is unusual to be associated with the usual migraine accompaniments and in contradistinction, is frequently associated with autonomic features such as tearing, miosis, and ptosis. While typical response to triptans is poor, a unique response to indomethacin is diagnostic. Chronic and episodic paroxysmal hemi-cranias also involve peri-orbital pain, but are associated with autonomic features – predominantly parasympathetic – such
as redness, swelling and tearing. The attacks last between 5 and 30 minutes and occur more than five times a day. They are distinguished from cluster headaches, which usually last longer, and have the characteristic of often occurring after dark and fewer times per day. The pain is also described as stabbing and boring. This condition is more common in women, while cluster headache is more common in men. Again, the other remarkable distinguishing feature is an exquisite response to indomethacin at a dose of 75 mg a day or more.

The chronic form may last a year without remission, whereas the episodic form may remit for months at a time. Rarer forms of TACs include SUNCT [short-lasting unilateral neuralgiform headache with conjunctival injection and tearing]. Trigeminal neuralgia is an episodic facial pain syndrome and is not generally considered a headache disorder. Giant cell (temporal) arteritis should be excluded in elderly patients presenting with new onset of headache.

**SUMMARY**

Migraine disorder is not just a headache, but a relatively common and complex neurovascular syndrome, occurring in about 17% of women and 6% of men. The effects of migraine can be debilitating and disabling but can be effectively treated by a combination of non-pharmacological, lifestyle changes, pharmacological prophylaxis, and appropriate abortive treatment. Trigemino-Autonomic-Cephalgias are an interesting and less common group of primary headache disorders which, if recognized clinically, may respond to a unique set of treatments – including inhaled nasal oxygen (cluster headache) or a trial of indomethacin, which can be diagnostic as well.

**References**


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Chronic Daily Headache: Challenges in Treatment

JAY H. LEVIN, MD; MICHELLE MELLION, MD

INTRODUCTION

An overwhelming majority of men and woman living in the Western world will experience headaches at some point in their life. Astoundingly, the lifetime prevalence of headache for men and women in this part of the world is over 94%. Three to five percent of the global population has daily or near-daily headaches. Chronic daily headache (CDH) is not a single diagnosis, but rather a descriptive term for the presence of headaches occurring at least 15 days per month for at least 3 months.

Duration of headache attacks is a key factor in the diagnosis of specific CDH entities. Specifically, it is helpful to differentiate long duration (>4 hours) from short-duration (<4 hours) CDH (Table 1). Across the spectrum of CDH disorders, chronic migraine (CM), chronic tension-type headache (CTTH), and medication overuse headache (MOH) account for the vast majority of cases of CDH. Approximately half of people with headache on 15 or more days per month for more than 3 months have medication overuse headache (MOH).

Table 1. Spectrum of Chronic Daily Headache Disorders

<table>
<thead>
<tr>
<th>Long Duration Subtypes (&gt;4 hours)</th>
<th>Clinical Features</th>
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</thead>
<tbody>
<tr>
<td>Chronic Migraine (CM)</td>
<td>Migraine-like attacks (defined as disabling moderate to severe attacks of throbbing pain, typically unilateral, lasting 4-72 hours with associated nausea, vomiting, photophobia, or phonophobia) are superimposed on a daily or near-daily headache pattern, greater than 15 headache-days per month for more than 3 months.</td>
</tr>
<tr>
<td>Chronic Tension-Type Headache (CTTH)</td>
<td>Frequent episodes characterized by bilateral or tightening-quality pain of mild to moderate intensity lasting hours to days; pain is not associated with physical activity but may be associated with mild nausea, photophobia, or phonophobia. These headaches occur over 15 days per month for more than 3 months (or &gt;180 days per year).</td>
</tr>
<tr>
<td>Medication Overuse Headache (MOH; aka “Rebound Headache”)</td>
<td>Headache occurring 10 or more days per month for more than 3 months as a consequence of regular overuse of an acute or symptomatic headache medication. Common precipitants include triptans, acetaminophen, NSAIDs, narcotics, and combination-analgesics (ie. Hydrocodone-acetaminophen or Vicodin).</td>
</tr>
<tr>
<td>Hemicrania Continua</td>
<td>Persistent unilateral headache with associated ipsilateral conjunctival injection, lacrimaton, rhinorrhea, or ptosis lasting for over 3 months. It is marked by moderate to severe flairs. It is exquisitely sensitive to indomethacin.</td>
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<tr>
<td>New Daily Persistent Headache (NDPH)</td>
<td>Persistent headache, daily from its onset, which is clearly remembered. Pain may be migraine-like or tension-like and must be present for at least 3 months without remission. In the setting of abortive drug use, NDPH may only be diagnosed if the headaches clearly precedes the medication overuse. The diagnoses are not mutually exclusive.</td>
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<thead>
<tr>
<th>Short Duration Subtypes (&lt;4 hours)</th>
<th>Clinical Features</th>
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<tbody>
<tr>
<td>Chronic Cluster Headaches</td>
<td>Attacks marked by severe stabbing unilateral peri-orbital pain lasting 15-180 minutes, occurring up to 8 times daily. Episodic cluster headache becomes chronic when the cluster period occurs for over a year without at least 1 months remission.</td>
</tr>
<tr>
<td>Chronic Paroxysmal Hemicrania</td>
<td>Attacks of severe unilateral peri-orbital pain lasting 2-30 minutes occurring several times a day. Attacks are similar to cluster headaches, but are shorter and more frequent. Attacks are associated with conjunctival injection, lacrimation, rhinorrhea, or ptosis. They respond absolutely to indomethacin. Paroxysmal hemicrania becomes chronic when attacks occur for a year with remissions lasting less than a month.</td>
</tr>
<tr>
<td>Short-lasting, Unilateral, Neuralgiform headache attacks with Conjunctival injection and Tearing (SUNCT)</td>
<td>Headaches resembling cluster and paroxysmal hemicrania, diagnosed when a patient has 20 or more attacks of moderate to severe unilateral peri-orbital or temporal/trigeminal distribution stabbing pain lasting 1-600 seconds, often associated with conjunctival injection, lacrimation, rhinorrhea, and/or ptosis. SUNCT becomes chronic when the attacks occur near-daily without at least 1 months remission over the course of a year.</td>
</tr>
<tr>
<td>Hypnic Headache (aka “alarm clock headache”)</td>
<td>Headache attacks that develop only during sleep, cause awakening, and last for up to 4 hours per episode, at least 10 mornings per month for at least 3 months.</td>
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PATHOPHYSIOLOGY OF CHRONIC DAILY HEADACHE
The underlying mechanism of headache chronification, regardless of etiology, is not clear. The predominant theory in chronic migraine is that medication overuse induces a state of “latent sensitization” resulting in dysregulation of the central trigeminovascular pathways and neural adaptations, which subsequently decrease thresholds to triggers. The exact etiology of other chronic daily headaches, such as chronic tension-type headache, is also poorly understood. It has been proposed that peripheral pain pathways most likely play a role in episodic tension-type headache, whereas central pain pathways play a more important role in chronic tension-type headache. Increased pericranial tenderness induced by manual palpation is the most significant abnormal finding in patients with tension-type headache. The tenderness is typically present interictally and usually escalates during actual headache episodes.

DIAGNOSIS
A thorough history and neurological exam are sufficient to make the diagnosis of chronic daily headache. Examiners must keep in mind that the headache disorders often overlap. Understanding the various headache types and teasing out the dominant form(s) will help to guide appropriate treatment. Frequently, patients will present with more than one headache type, potentially necessitating diverse treatments. MOH is a common co-morbid condition that occurs in over 80% of patients with chronic migraine.

Adjunctive studies, such as neuroimaging or electroencephalography, should only be considered when there are changes in the headache history or new fociality on neurological examination. In the recent “Choosing Wisely” campaign, the American Headache Society (AHS) established that neuroimaging is not needed in patients with stable headache patterns. Patients presenting with headache and a normal neurological exam have a 0.4-0.9% chance of having a significant abnormality on neuroimaging, which is similar to that of the general population without headaches. In a large meta-analysis, an abnormal finding on neurological exam was the most robust predictor of intracranial pathology on neuroimaging. Patients with new focal findings on neurological exam are about 30% more likely to demonstrate pathological findings on neuroimaging. Red flags that should prompt immediate neuroimaging are summarized in Table 2. Since many of these potential etiologies for secondary headache may not be visible on head CT, the preferred imaging technique is MRI for non-emergency situations; the diagnostic yield of head CT was 2% compared to 5% for MRI. Because MRI was better at detecting abnormalities, the cost per abnormal finding of CT scans was $2409 compared to $957 for MRI.

EEG serves no role in the diagnosis of chronic daily headache. The American Academy of Neurology (AAN) recommends against the use of EEG for headaches in their recent “Choosing Wisely” campaign. The sensitivity of an EEG in detecting structural brain lesions is considerably lower than that of neuroimaging with CT or MRI. A normal EEG in a patient with evidence of structural abnormality may provide a false sense of security and delay more definitive neuroimaging. Conversely, an abnormal EEG (ie. mild focal slowing or questionable epileptiform activity) in a patient with a primary headache disorder may prompt additional unnecessary work-up and treatment. EEG therefore increases cost without adding benefit.

TREATMENT
Individuals presenting with chronic daily headache are among the most difficult and labor-intensive patients encountered in a neurologist’s practice. Treatment of CDH disorders is based on accurate diagnosis, exclusion of secondary causes, elimination of medication overuse, and modification of risk factors in a multidisciplinary fashion. We have outlined a general medical approach to CDH (Figure 1).

Education is a key element in treating CDH. Taking the time to communicate with patients about reasonable expectations from available treatments for CDH is necessary in order to begin to manage this complicated and frustrating medical problem. Patients need to understand that treatment will take time and that their headaches will likely not disappear immediately, if ever. As physicians, we need to partner with our patients in their treatment, not only managing medications that can help with treatment, but also advising them about behavioral and lifestyle changes that are necessary for successful management.

Lifestyle changes to modify risk factors play an important role in headache prevention. Clinicians must help patients identify headache triggers and address risk factors such as excessive caffeine use, poor sleep habits, maladaptive coping mechanisms to stress, unhealthy diet, and lack of exercise. Moderation of caffeine intake, improved sleep hygiene, stress management, healthy diet, and aerobic exercise all are important in successful management of chronic headaches. A trained psychologist may help promote strategies to modify these risk factors. Patients with comorbid conditions such as depression and anxiety would be ideal candidates for biobehavioral therapy. Referral to a sleep specialist may reveal undiagnosed sleep apnea. Physical therapy may

Table 2. Red flags in patients with Chronic Daily Headache

| New focal signs on neurological exam |
| New onset HA pattern in a patient > 50 years of age |
| Change in established headache pattern |
| Drowsiness, confusion, cognitive impairment |
| Weight loss |
| Known HIV+ |
| Fever, stiff neck |
Thorough history and neurological examination
• Identify headache triggers and address risk factors
• Identify red flags and exclude secondary causes of headaches (neuroimaging when necessary; MRI is typically more sensitive to exclude headache etiologies overlooked on head CT)

Figure 1.

Management of CDH with or without MOH

Comprehensive Treatment Regimen
• Patient education and lifestyle modifications
• Biobehavioral therapy may help
• Address comorbid depression and anxiety
• Biobehavioral therapy may help
• Taper or eliminate overused analgesics
• Initiate pharmacological prevention
• Set realistic goals with patients
• Close follow-up in outpatient clinic with referral to headache specialist if particularly complex or refractory to treatment

prove to be beneficial, especially in conjunction with other multidisciplinary treatment modalities. Techniques such as relaxation training, biofeedback, stress management, and cognitive-behavioral therapy have proven efficacy in treating patients with CDH. Behavioral management is discussed in depth by Rathier and Roth in the current issue of the Journal.

It is essential to taper or eliminate overused analgesics. Both the AAN and AHS recommend against the routine use of opioid or butalbital-containing medications. Reducing the 1.4% prevalence of MOH by 50% could save the US health care system approximately $15 billion annually in health care costs and lost productivity. Opiates may contribute to MOH with frequency of use as few as 8 days per month, thereby leading to chronication of the very headaches they were originally intended to treat. These medications should be tapered over a course of a few weeks. Simple analgesics and triptans may be abruptly discontinued. Patients must be counseled about the role of medication-overuse in perpetuating their daily headache cycle. They also need to be counseled that their headaches may worsen initially as they reduce their medication usage, but they may be reassured that after this withdrawal period they will likely be restored to a more episodic, less chronic headache pattern. As with any lifestyle modification, analgesic overuse will require patience on the part of the practitioner and perseverance on the part of the patient. Cognitive-behavioral therapy (CBT) may help challenge maladaptive thoughts and promote wellness strategies.

Pharmacological approaches to chronic daily headache management are often required in conjunction with nonpharmacologic options. Nearly 40% of patients with migraines need preventative therapy, but only 3-13% currently take these medications. There are a myriad of medications for patients with CDH. The American Academy of Neurology (AAN) and American Headache Society (AHS) have developed guidelines regarding pharmacological prevention of chronic migraine and other chronic daily headache disorders with both conventional medications and herbal remedies.

Even after eliminating medication-overuse and instituting appropriate prophylactic pharmacological measures, up to 40% of patients may suffer a relapse after initial successful treatment. CDH is a difficult spectrum of disorders to treat. It is essential to educate patients, manage their expectations, and set goals for treatment. Rather than expecting to be completely pain-free, more realistic goals may include decreasing headache intensity, restoring daily functioning, and improving quality of life. Behavioral therapy may augment medical therapy to maximize success.

Table 3. Pharmacological Prevention of Chronic Migraine and other Chronic Daily Headaches (Adapted from AAN/AHS Guidelines)

<table>
<thead>
<tr>
<th>Level A: Medications with well-established efficacy</th>
<th>Level B: Probable efficacy</th>
<th>Level C: Possible efficacy</th>
</tr>
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<tbody>
<tr>
<td>Valproate</td>
<td>Amitriptyline</td>
<td>Lisinopril</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Venlafaxine</td>
<td>Candesartan</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Atenolol</td>
<td>Clonidine</td>
</tr>
<tr>
<td>Timolol</td>
<td>Nadolol</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>NSAIDs^</td>
<td>Co-Q10</td>
</tr>
<tr>
<td>Butterbur (petasites)</td>
<td>Magnesium</td>
<td>Estrogen</td>
</tr>
<tr>
<td>OnabotulinumtoxinA</td>
<td>Feverfew (MIG-99)</td>
<td>Ciproheptadine</td>
</tr>
<tr>
<td></td>
<td>Riboflavin (Vit B2)</td>
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<td></td>
<td>Histamine SC</td>
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CONCLUSIONS

Treating patients with CDH is extremely challenging. Taking the time to perform a detailed history, neurological examination, and review medication utilization is critical in order to determine appropriate management. Treatment starts with educating patients about their condition, tapering overused analgesics, and setting realistic goals during an ongoing dialogue between clinician and patient. A comprehensive approach to preventative therapy, both pharmacologically and non-pharmacologically, will enable
patients to reach their goals. Although CDH is difficult to manage, the partnership formed with patients to cope with this condition can be exceptionally rewarding for the clinician and life-changing for the patient.

References

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Effective long-term management of patients with headaches can be challenging because these disorders are complex with heterogeneous triggers, expression, and impact.\(^1\) While the biomedical model has led to important discoveries in the pathophysiological mechanisms of headache, the model has limitations, including the marked varied individual responses to identical treatments.\(^1\) Headache has both sensory (e.g., pain location, intensity, and quality) and affective (e.g., depression, anxiety, distress) components.\(^5\) The pain experience involves the interconnectivity of physical vulnerabilities (e.g., genetics), psychological predispositions (e.g., prior learning history), biological changes, psychological issues, and biopsychosocial contexts that influence an individual’s evaluation of and response to headache.\(^1\) As a result, effective treatment of headache cannot rely solely on regulating the chemical and electrical signals within the pain pathways associated with headache, but must also address their cognitive, affective, and behavioral components.

Typically, nonpharmacologic treatment for headache has been considered an option when the patient’s presentation fell outside the normative patient experience. As headache has begun to be conceptualized as a chronic disease,\(^4\) treatment also needs to reflect this conceptualization. Hence, a comprehensive, multidisciplinary treatment program to prevent headache is appropriate. The biobehavioral approaches with the strongest efficacy include cognitive behavioral therapy [CBT], relaxation training, biofeedback, and stress management.

**BIOLOGICAL BASIS FOR MIGRAINE AND PRIMARY HEADACHE DISORDERS**

The pathophysiology of migraine is complex, melding a genetic predisposition\(^2\) with a cascade of events that have been described over nearly one century. For many years, migraines were thought to be a purely vascular headache, and the aura of migraine was felt to be due to cerebral vasomotor phenomena resulting in ischemia. In the 1940s, when Leao first described his theory of cortical spreading depression (CSD), an electrical signaling phenomenon involving the cortex of the brains of rabbits, a new postulated mechanism for migraine was born. Since then, fMRI studies in humans have demonstrated that neuronal signaling in CSD is the physiological basis of migraine aura, though it is unknown whether it is this event or another – originating in deep, subcortical structures such as the brainstem – is the first in the migraine cascade.\(^6-9\) The throbbing pain of migraine is triggered by subsequent activation of the trigeminal vascular system, mediated by a neurogenic inflammatory response, release of nociceptive neuropeptides such as calcitonin gene related peptide (CGRP), neurokinin A, substance P, among others. Nausea and irritability occur through stimulation of the chemoreceptor trigger zone, and autonomic activation results in fluctuating levels of catecholamines.\(^3\) Central pain processing pathways are subsequently activated in the thalamus, periaqueductal gray (PAG) matter of the midbrain, and the posterior hypothalamus, and a process known as central sensitization contributes to the aversion to stimuli – including sound, light, motion. For some, even light touch can be painful.

The clinical picture of migraine is the result of neurovascular dysregulation, and the many prescription and over-the-counter treatments target nociceptive and inflammatory pathways (such as NSAIDs) or stabilize and constrict cerebral blood vessels [triptans, ergots, and others]. Prophylactic agents also operate on central and peripheral pathways, stabilizing blood vessels and autonomic activation (beta blockers and calcium channel blockers), acting on ion channels and neuronal receptors [anticonvulsant medications], or regulating levels of neurotransmitters [SSRIs, TCAs]. Each medicine works by interrupting a single link in the cascade; however, no pharmacological treatments operate specifically on central sensitization, or treat the affective component of the pain, both of which may be larger complaints for patients than the pain itself. Non-pharmacologic strategies for headache treatment and prevention are a way to reduce brain-derived autonomic and nociceptive dysregulation, through behavioral “revamping” of these dysfunctional systems. Behavioral treatments in particular are evidence-based, and complementary to medical treatments, providing comprehensive care for a complex condition.

**BIOBEHAVIORAL TREATMENTS FOR HEADACHE AND MIGRAINE**

Biobehavioral techniques focus on managing the physiological, cognitive, and affective components of stress. These techniques facilitate skill development aimed towards increasing the patient’s ability to cope with pain and reduce headache-related distress.\(^30\) A review of biobehavioral treatments consistently show that biofeedback, relaxation, and CBT [including stress management] produce a 30-60% reduction in migraine activity. The US Headache Consortium\(^11\) assigned the following treatments “Grade A” evidence [multiple...
well-designed randomized clinical trials that yielded a consistent pattern of findings: relaxation training, thermal biofeedback combined with relaxation training, electromyographic biofeedback, and CBT (for prevention of migraine). Individuals with clinical depression or anxiety, those with moderate-severe headache-related disability, difficulty managing triggers (including stress), having other significant psychological issues (e.g., history of abuse/maltreatment), or preference for biobehavioral approaches are all ideal candidates for biobehavioral intervention.11

Stress and Headache
Stress results from an interaction between the perception of an event as threatening to one’s well-being and an individual’s physiologic, cognitive, and affective response to the situation. When individuals experience a situation they view as “stressful,” the individual’s response elicits various physiologic changes including cerebral vasoconstriction and neurogenic inflammation. Stress increases sympathetic arousal and may increase neuronal hyperexcitability.

There are five ways that stress can potentially contribute to the expression and maintenance of headache episodes: 1. Predisposer – Stress contributes to headache onset or expression in a person with a preexisting vulnerability; 2. Precipitant – Stress precipitates individual headache episodes; 3. Exacerbator – Stress exacerbates the progression of headache, including transformation from an episodic to chronic condition; 4. Perpetuator – Stress worsens headache-related disability and quality of life; and 5. Consequence – Headache can serve as a stressor.12 After a stressful period, there may be a letdown phase that can as a result trigger a headache.

Co-morbid Psychiatric Disorders and Headache
Depression and anxiety are more common among patients with headache relative to the general population. Depression and anxiety are especially prevalent among those with chronic migraine, with more than half experiencing depression and nearly one-third experiencing anxiety. Experiencing depression or anxiety is associated with more severe migraines, increased disability, reduced adherence, increased medication use, and lower efficacy for actively managing migraine. In fact, psychological distress may play a greater role in the progression of headache from episodic to chronic than medication overuse.

The prevalence and impact of abuse and maltreatment is beginning to receive greater attention within the headache community. PTSD occurs more commonly in those with migraine (whether episodic or chronic) than in those without migraine. The trauma impairs their ability to cope with various aspects of life, including how to manage headaches. Given a history of trauma, the individual would be well-served by including a psychological evaluation in treatment plan.

Cognitive-Behavioral Therapy (CBT)
CBT, a Grade A treatment for headache prevention,13 utilizes both cognitive and behavioral headache management strategies. Cognitive strategies focus on identifying and challenging maladaptive thoughts, beliefs, and responses to stress.14 Cognitive strategies for headache management focus on enhancing self-efficacy (i.e., patients’ beliefs in their ability to succeed or accomplish a certain task),14 encouraging patients to adopt an internal locus of control (i.e., a belief that the mechanism for change lies within oneself as opposed to an external locus of control or the belief that only the health-care provider, medication, or medical procedures have the power for change),15 and eliminating catastrophizing (a hopeless and overwhelming way of thinking), all of which predict poor treatment outcomes.16

Behavioral strategies include replacing behaviors that may maintain or exacerbate headaches with wellness strategies. Modifiable risk factors for migraine progression include medication overuse, obesity, caffeine overuse, snoring, depression, and stressful life events. Behavioral treatment includes education in wellness activities as a means of enhancing self-management of headaches. For example, patients can benefit from making lifestyle behavior changes designed to help them maintain a healthy weight and achieve a state of physical well-being (i.e., proper nutrition and eating habits, reduced consumption of caffeine, regular physical activity). Interventions that encourage patients to improve sleep hygiene, quit smoking, reduce alcohol intake, and reduce use of sedative medications may also be provided by a psychologist. CBT may also provide the patient with strategies to avoid triggering a headache, improve overall coping, and help the headache sufferer manage co-morbid symptoms of depression and anxiety.

Relaxation Training and Biofeedback
Relaxation techniques possess Grade A evidence for their use.16 The focus is on helping patients minimize physiologic responses to stress and decrease sympathetic arousal. The classic procedure, progressive muscle relaxation training, first published in 1938, involves tensing and relaxing various muscle groups while attending to the resulting contrasting sensations.17 Other relaxation techniques include visual or guided imagery, cue-controlled relaxation, diaphragmatic breathing, hypnosis, and self-hypnosis.16,18

Biofeedback has also received Grade A evidence for its use.19-21 It involves monitoring physiological processes that the patients may not be consciously aware and/or do not believe they voluntarily controls. Digital processes take the patients’ physiological information and convert it into a signal that patients receive in either visual or auditory form. Through biofeedback training, patients develop increased awareness of physiological functions associated with headache and stress and learn to control their physiologic states.23-24 Various relaxation skills, such as diaphragmatic breathing or visualization to elicit the “relaxation response”25 are often incorporated into biofeedback training.19 To achieve the benefits from relaxation and biofeedback, patients may
use any techniques or tools that help them quiet the mind and calm the body [e.g., meditation, prayer, yoga, pleasant music, guided relaxation]. To achieve maximum benefit of these techniques, patients must be motivated to consistent practice in order to lower their baseline of stress and tension.

Cost-Effectiveness of Behavioral Treatment

Recent research found that the most expensive behavioral treatment method – individual sessions with a psychologist in clinic – cost more than pharmacologic treatment with $6-a-day drugs in the first months. However, at about five months, individual sessions become competitive in cost. After a year, they are less expensive than all methods except treatment with drugs costing 50 cents or less a day. Overall, group therapy and minimal-contact behavioral treatment were cost-competitive with even the least expensive medication treatment in the initial months. At one year, they become the least-expensive headache treatment choice.

SUMMARY

Headaches are more than just a series of changes in neurophysiology and neurochemistry. They also involve individuals experiencing pain and attempting to manage the impact of that pain on their lives. As a result, headache is best conceptualized in a biopsychosocial framework, as involving physiologic, cognitive, affective, and behavioral phenomena. Although pharmacologic treatment alone is considered a basis of involved in migraine management and prevention, many individuals with headache will benefit from multidisciplinary treatment.

References


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Headache disorders are highly prevalent throughout the world, and have a female predominance. More than 80% of women in the reproductive age group experience headache at some point, making it a common occurrence in pregnancy. The International Headache Society broadly categorizes headaches as primary or secondary. As is the case in the non-pregnant population, primary headaches (such as migraine headaches, tension headaches and cluster headaches, chronic daily headaches or medication overuse headaches) account for majority of the cases of headache seen in pregnancy. Secondary headaches are headaches attributable to another underlying cause. Certain causes of secondary headaches deserve special consideration in pregnancy as they might be either unique to pregnancy or be exacerbated by physiologic changes of the gravid state.

Case: A 22 y.o. gravida 1, at 28 wks gestation presents for daily headaches which began after 16 weeks gestation. Headaches are present when she wakes up in the morning and tend to decrease but not resolve with acetaminophen. She has no prior h/o headaches and is otherwise healthy. Pertinent features in exam include a BMI of 37, BP 128/88 and a normal neurologic exam (including fundoscopy).

What is the differential diagnosis of new onset headache in the second half of pregnancy?
Pregnancy is associated with a physiologic increase in blood volume and vasodilatation, that peaks around 26–28 weeks gestation. Previously asymptomatic arteriovenous malformations (AVMs) or aneurysms can therefore present at this time with headaches or cerebrovascular accidents. Sinus headaches are also more frequently seen in pregnancy due to this increased vascularity and mucus production, resulting in sinus congestion. In patients presenting with prolonged debilitating headaches, worse with supine position, idopathic intracranial hypertension (pseudotumor cerebri) is an important consideration. This condition is often encountered in pregnancy, since it is known to particularly affect obese women of childbearing age. In patients with pituitary adenomas, particularly macroadenomas, tumor growth can occur with pregnancy progression, and may present as headache. Pregnancy is a hypercoagulable state and although ischemic stroke is rare, cerebral vein thrombosis can be seen in pregnancy, particularly in the third trimester and postpartum period. Finally, preeclampsia, which can complicate 5–10% of pregnancies, characterized by hypertension and proteinurria, can also present with headache. Preeclampsia headaches tend to be vascular in nature and often accompanied by visual disturbances.

What investigations, if any, should be performed in this patient? What radiologic testing can be performed safely in pregnancy?
Common things being common, most patients who present with headaches in pregnancy have benign headaches and do not need investigations. However, some investigations might be necessary when ruling out secondary causes. Preeclampsia is a multisystem pregnancy-specific disorder characterized by hypertension and proteinurria. Clinical symptoms of preeclampsia include headache which can be present irrespective of high blood pressure. Other associated abnormalities include thrombocytopenia, liver and renal dysfunction and occasionally pulmonary edema. When considering preeclampsia in the differential, the following investigations are recommended; a complete blood count (looking for hemo-concentration and thrombocytopenia), liver enzymes (AST and ALT), creatinine and a urine protein to creatinine ratio looking for proteinurria.

A CT scan can safely be performed with minimal radiation risk to the fetus, regardless of gestational age. Magnetic resonance imaging (MRI) carries no radiation risk and has been used in pregnancy without any documented adverse pregnancy outcomes. An MRA and MRV should be considered when suspecting AVM’s or cerebral vein thrombosis. Similarly, a lumbar puncture can be safely performed in pregnancy at any gestational age. Opening pressure is not affected by the gravid state.

Case (continued): The patient did not have preeclampsia and was treated with acetaminophen and caffeine for symptomatic relief. She was also placed on metoprolol 12.5 mg po twice daily for prophylaxis and at a follow-up visit 4 weeks later reported improvement.

How are headaches best managed in pregnancy?
Although both patients and providers are wary of using medications during pregnancy, sometimes with severe or frequent disabling headaches, treatment becomes necessary. Table 1 lists some medication that can be safely used for treatment of tension/migraine headaches in pregnancy.
Case (Conclusion): She returned at 37 wks. gestation with severe intractable headache, borderline hypertension and labs suggestive of preeclampsia. She was started on a magnesium sulfate drip and a decision was made to induce labor. On postpartum day 7, after an uneventful delivery, she returned with a severe persistent headache and generalized malaise. Slight weakness in the right leg was noted. An MRV showed right sagittal vein thrombosis. She was started on low molecular weight heparin and subsequently transitioned to oral anticoagulation, with planned treatment duration of 6 months.

In summary, headaches are a common complaint in pregnancy, especially in the first half. Although common etiologies prevail, it is important to consider the “zebras” in diagnosis and perform an evaluation as indicated. Some causes of headache can cause substantial morbidity to mother and fetus if undiagnosed, therefore necessary radiologic testing should not be withheld. There are several treatment options available for a pregnant woman, and pregnancy should not preclude the institution of an appropriate regimen to help her remain relatively symptom free.

### Table 1. Headache Medications, and Their Use In Pregnancy

<table>
<thead>
<tr>
<th>Class of meds</th>
<th>Use in pregnancy justifiable in most circumstances</th>
<th>Use in pregnancy justified in some circumstances</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medications for acute relief of headache</td>
<td>Acetaminophen Metoclopramide Promethazine Prochlorperazine Caffeine</td>
<td>Ibuprofen Butalbital Sumatriptan Opioids</td>
<td>Occasional use of NSAIDs, including ibuprofen, prior to 20 wks gestation is acceptable. Use during late pregnancy is avoided due to concerns about premature ductal closure. Safety data for Sumatriptan in pregnancy is still evolving but available data is reassuring.</td>
</tr>
<tr>
<td>Medications for preventive therapy</td>
<td>Amitriptyline Nortriptyline Metoprolol Magnesium Verapamil</td>
<td></td>
<td>Propranolol and atenolol use in pregnancy may be associated with fetal growth restriction. For most patients, the risk of antiepileptic medications for headache prevention in pregnancy outweighs the benefit.</td>
</tr>
</tbody>
</table>

1 From Micromedex, accessed Mar 21, 2014

### References


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