The Cleveland Clinic Manual of Headache Therapy

Second Edition

Stewart J. Tepper
Deborah E. Tepper
Editors

Cleveland Clinic
Springer

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Preface to the Second Edition

To our readers,

The authors of the Cleveland Clinic Manual of Headache Therapy have been gratified by the response to our first edition, published in 2011. We have conversed with numerous colleagues about the utility of a basic Headache Manual centered on diagnosis and treatment with clinical pearls and summarizing tables.

We proceeded with this second edition for several reasons. First, the new *International Classification of Headache Disorders*, 3rd edition, is now available, and although it is in a beta form at the time of this writing, the changes are sufficiently significant to warrant a re-do of diagnostic parts of the Manual.

Second, a number of new formulations of medications have emerged, some already approved by the US FDA, some submitted, and others close to submission at the time we are putting this book together. Because these newer treatment options are present or imminent, a revised treatment section appears in order.

Finally, there are a number of clinical problems we did not cover in our first book. These include, specifically, problems around opioids and their implications and wean, and traumatic brain injury (TBI) and headaches associated with TBI. We have included these special topics in the new edition. We have also expanded several sections, and have added four new chapters and three new authors.

This manual is organized to address diagnosis in the first half and treatment in the second half. Parts I and II of this clinical manual cover the diagnosis of episodic and chronic primary headaches of adults in the office. Part III covers diagnosis of addiction and substance use and their relationship to headaches. Part IV covers diagnosis of secondary headaches, and Part V, diagnosis of pediatric headaches.

In the treatment half, Part VI covers treatment of episodic headaches in adults, and Part VII addresses treatment of chronic and refractory headaches in adults. Part VIII is devoted to treatment of major secondary headaches, and Part IX expands on treatment of pediatric headaches. Part X is devoted to special

topics in headache, including behavioral treatment, facial pain and neuralgias, women's issues, dizziness, traumatic brain injury and concussion, and nursing issues.

We thank our readers and our patients for the opportunity to learn, educate, and try our best to treat headache disorders effectively.

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Part I
Diagnosis of Episodic Primary Headaches

Chapter 1
Diagnosis of Migraine and Tension-Type Headaches

Stewart J. Tepper and Deborah E. Tepper

Introduction to Diagnosis

Headache diagnosis in the office is predicated on deciding if the patient's headache is primary or secondary. With this determination, the clinician will know how to proceed. Aiding diagnosis is the use of the *International Classification of Headache Disorders,* third edition, beta version (ICHD-3), published in 2013. Parts I and II of this clinical manual cover the diagnosis of primary headaches of adults in the office, Part III covers diagnosis of secondary headaches, and Part IV covers diagnosis of pediatric headaches. The remaining parts of the book cover treatment. A knowledge of basic headache epidemiology, some familiarity with ICHD-3, some shortcuts and clinical pearls, and recognition of when to be worried for the possibility of sinister headaches will equip the clinician with a route to satisfactory diagnosis (Table 1.1).

Epidemiology of Primary Headaches

Primary headaches are very common, and the headache usually encountered in the office is migraine. Outside the doctor's office, tension-type headache (TTH) is by far the most common diagnosis in the general population. But in clinical practice, when a patient complains of episodic headache, the diagnosis is usually migraine.

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Table 1.1 Steps to quick, correct diagnosis of headaches

1. Know basic epidemiology of primary and secondary headaches
2. SNOOP: a mnemonic for secondary workup (see Chaps. 5 and 6 in Part III of this book)
3. ICHD-3 criteria
4. Pattern recognition
5. Brief screeners
6. Impact/disability-based diagnosis

Table 1.2 Basics of epidemiology of migraine

1. Migraine occurs in 12% of the general population, 18% female, 6% male
2. When a patient complains of a stable pattern of episodic, disabling headache in the office, the likelihood of migraine or probable migraine is greater than 90%

Migraine occurs in about 12% of the US population, 18% of females, 6% of males, numbers established in three large US population-based studies from 1989 to 2007. Thus, unless there are red flags present, migraine is the likely diagnosis of an office patient with a stable pattern of episodic, disabling headache.

One study in 14 countries of primary care offices and nonheadache specialists established that when a patient complained of episodic headache, either as a chief complaint, secondary complaint, or checked "headache" off on the review of systems, the diagnosis was migraine or probable migraine (PM) in 94% of the patients. The remaining 6% were evenly divided between TTH and other types of headache. It is a pretty good bet that in the absence of concerns for secondary headache discussed in Part III, migraine should be the default diagnosis in patients complaining of a stable pattern of episodic, disabling headache in clinical practice (see Table 1.2).

Reminder on the Red Flags of Headache Diagnosis

As noted, diagnosis of secondary headaches will be covered in Part III of this book. However, it is worth stating at the beginning that a workup of patients with red flags is necessary before diagnosing primary headaches. When in doubt, investigate the atypical.

Dr. David Dodick, Professor of Neurology at the Mayo Clinic, first published the use of a mnemonic for red flags suggesting sinister or secondary headaches. His mnemonic, which will be repeated in Chap. 4, tells the clinician when to "snoop" for secondary headache and is adapted in Table 1.3.

If the red flags are not noted, it is time to decide which primary headache is presenting.

Table 1.3 The SNOOP mnemonic for red flags for secondary headache. (Adapted from Dodick 2003)

*S*ystemic symptoms (fever, weight loss) or
*S*econdary risk factors: underlying disease (HIV, cancer, autoimmune disease)
*N*eurologic symptoms or abnormal signs (confusion, impaired alertness or consciousness, focal exam)
*O*nset: sudden, abrupt, or split-second (first, worst)
*O*lder age onset: new-onset and progressive headache, especially at age > 50 (giant cell arteritis, cancer)
*P*attern change: first headache or different, change from
*P*revious headache history: attack frequency, severity, or clinical features
SSNOOPP

Table 1.4 Migraine without aura, ICHD-3 criteria

1. Having had more than five attacks, the patient should meet the following criteria
2. Headaches last from 4 to 72 h
3. Any two of the following four
(a) Moderate to severe intensity
(b) Throbbing quality
(c) Worsened by physical activity
(d) Unilateral location
4. The headaches need to have any one of the following:
(a) Nausea
(b) Photophobia and phonophobia
5. Secondary causes eliminated (normal exam, imaging, etc.)

Diagnosis Using the ICHD-3

The ICHD-3 provides validated international criteria for diagnosing headaches. Previously, the ICHD-2 was adopted by the National Institutes of Health (NIH), the Food and Drug Administration (FDA), the World Health Organization (WHO), and all major clinical professional organizations in the USA, including the American Academy of Neurology (AAN). The plan is for the ICHD-3 to be connected to future versions of the International Classification of Diseases (ICD) billing codes. Using the ICHD-3 can be very helpful; when a patient does not fit the ICHD-3 criteria for a given primary headache disorder, it is time to contemplate the possibility that a secondary headache exists.

The ICHD-3 of the International Headache Society (IHS) is an extensive, detailed document, 400 pages long, and many doctors use pattern recognition or other short cuts to diagnosis instead. Nonetheless, careful scrutiny of IHS criteria can be very useful, especially in more atypical headache disorder presentations. The ICHD-3 criteria for migraine without aura are summarized in Table 1.4.

A few clinical pearls help with using the ICHD-3 criteria. Although migraine is often suggested by the company it keeps (menstrual, stress, red wine, or weather triggers, history of motion sickness, family history), triggers are not included in the strict criteria for diagnosis.

Table 1.5 Clinical pearls on diagnosing migraine without aura

1. Migraine can be suggested by the company it keeps
   (a) Menstrual trigger
   (b) Red wine trigger
   (c) Weather trigger
   (d) Stress trigger
2. Location is not included in the diagnostic criteria
   (a) Neck pain in migraine is very common
   (b) Bilateral location occurs in at least 40 % of migraine
3. Migraine attacks vary between patients and in the same patient across time
4. Response to triptans and ergots is not diagnostic of migraine
5. Migraine has negative impact on patients in their daily activities. Tension-type headaches do not generally result in disability
6. Many migraine patients have either a family history of "headaches," personal histories of motion sickness, especially in childhood, or both
7. Ninety-four percent of patients complaining in the office to primary care doctors of stable, episodic headaches had migraine or probable migraine. Only 3 % had tension-type headache as the primary diagnosis

Location is not included in the diagnostic criteria. For example, neck pain, often thought to suggest TTH, is present in at least 75 % of migraine patients. Forty percent of migraine is bilateral. Bilateral maxillary pain, often thought to suggest "sinus headache," is a nonspecific symptom. In other words, do not make a diagnosis by location of pain alone.

Migraine is variable both inter- and intrapatient across time. Severity of migraine can be moderate, location can be bilateral, quality can be nonthrobbing, and nausea and aura can both be absent. Many migraine patients have either a family history of "headaches," personal histories of motion sickness, especially in childhood, or both.

Response to medication does not prove diagnosis. Meningitis and subarachnoid hemorrhage pain can transiently respond to migraine-specific treatments, such as triptans and ergots, so response to triptans is not conclusive for migraine diagnosis or even a primary headache disorder. Cluster headaches also respond to both triptans and dihydroergotamine.

Migraine adversely affects patients in their daily activities, while TTH does not generally result in disability. The ICHD-3 checklist can assure that the default primary episodic headache diagnosis is accurate. Clinical pearls on diagnosing migraine without aura are summarized in Table 1.5.

Pattern Recognition Diagnosis of Migraine

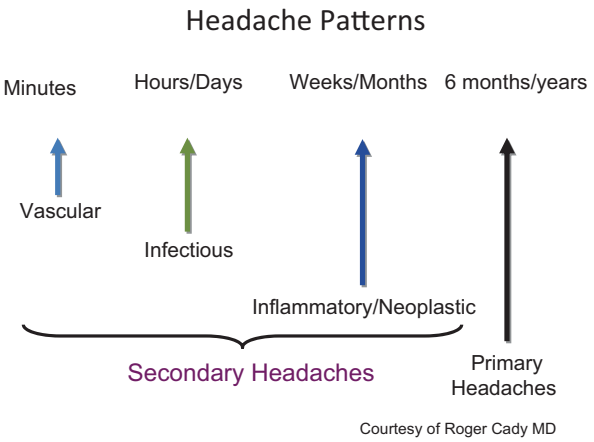
The duration of headache history can add to pattern recognition. Recent onset of headache should be of more concern (see Tables 1.6 and 1.7).

New and sudden headaches, often described as such as having thunderclap onset, raise the question of bleed. A presenting new headache of days' duration without a

Table 1.6 The aphorism of pattern recognition of migraine

• A patient presenting with a stable pattern of at least 6 months duration of episodic disabling headache has migraine until proven otherwise

Table 1.7 Headache patterns. (Courtesy of Roger Cady MD)



previous history of headaches raises the question of meningitis or encephalitis. New headaches of slow, progressive onset suggest neoplasm or vasculitis. And finally, the comfort of stable, episodic headaches of at least 6 months duration is the pattern of migraine.

Brief Screeners for Migraine Diagnosis

ID Migraine

Because some care providers find the ICHD-3 criteria too cumbersome, several brief screeners have been validated. The most important of these is ID Migraine, which consists of three questions: presence or absence of photophobia, presence or absence of nausea, and presence or absence of impact on activities. If the patient has the presence of 2/3 symptoms, ID Migraine has a sensitivity of 0.81 and a specificity of 0.75 (see Table 1.8).

Table 1.8 ID Migraine. (adapted from Lipton et al. 2003)

Yes or no answers
With your headaches
1. Do you have dislike of light?
2. Do you have nausea?
3. Do your headaches have impact on work, school, or recreational activities?
2/3 "yes" answers suggest migraine

Table 1.9 Migraine Disability Assessment Scale (MIDAS). (Adapted from Stewart et al. 1999)

MIDAS is a five-item questionnaire on headache disability which can be summarized as:

- "How many days in the last 3 months were you at least 50% disabled at work, home, school, or recreational activities?"
- Scores greater than 11 days suggest at least moderate disability and also suggest a diagnosis of migraine

Single Screener for Migraine: Nausea

Dr. Vincent Martin from the University of Cincinnati found that nausea alone, when associated with episodic headache, yields a sensitivity of 0.81 and a specificity of 0.83. So if your patient with a stable pattern of episodic disabling headache has nausea, that patient meets both 2/3 of the ID Migraine criteria and the single criterion. Brief screeners can be very useful at short-cutting to the diagnosis.

Impact-Based Diagnosis of Migraine

Impact is the third criterion of ID Migraine. Migraine is the recurring, episodic primary headache which causes disability and has impact. The impact of migraine is why the aphorism is for a stable pattern of at least 6 months of episodic, *disabling* migraine. TTH rarely has any impact at all.

Two screeners of disability or impact in episodic primary headache can indirectly suggest migraine. These are the Migraine Disability Assessment Scale (MIDAS) and the Headache Impact Test (HIT-6).

MIDAS uses a five-item questionnaire to ask the question, "How many days in the last 3 months were you at least 50% disabled by your headaches at work, home, school, or recreational activities?" (see Table 1.9). If the answer is greater than 11 days, migraine diagnosis is suggested.

HIT-6 uses questions in six domains to evaluate headache impact. If the HIT-6 score is greater than 60, migraine diagnosis is suggested.

Diagnosis of Tension-Type Headache

TTH was described by the late Dr. Fred Sheftell as the featureless headache. The diagnosis of TTH is made predicated on the fact that it is not migraine.

The ICHD-3 criteria for episodic TTH (ETTH) are summarized in Table 1.10.

The criteria for ETTH posit that it is not migraine: not unilateral, not throbbing, not severe, not worse with activity, no nausea, and generally no photophobia and no phonophobia. ETTH rarely causes any lasting impact. Patients rarely complain of it, and it is almost never seen in the office. As noted above, it is featureless. Also,

Table 1.10 Infrequent episodic tension-type headache, ICHD-3 criteria

1. At least ten episodes occurring less than once a month or less than 12 times per year average and fulfilling the following criteria
2. Headaches last from 30 min to 7 days
3. Headache has at least two of the following:
   (a) Not unilateral
   (b) Not throbbing
   (c) Mild or moderate intensity, not severe
   (d) Not aggravated by routine physical activity
4. Both of the following:
   (a) No nausea
   (b) No more than one of photophobia or phonophobia or neither
5. Not secondary

Table 1.11 Migraine without aura/(*episodic tension-type headache, ETTH*)

1. At least five (*ten*) attacks lasting 4–72 h (*30 min to 7 days*) with
2. At least two of the following four
   (a) Unilateral (*bilateral*)
   (b) Pulsating (*not pulsating*)
   (c) Moderate to severe intensity, inhibits or prohibits activities (*mild to moderate*). *Note, migraine has impact, not TTH!*
   (d) Physical activity aggravates (*does not aggravate*). *Note, migraine, not TTH has impact!*
3. At least one of the following
   (a) Nausea and/or vomiting (*no nausea or vomiting*)
   (b) Photophobia and phonophobia (*one or neither*)
4. Both have normal history, exam, or imaging test

note that the ICHD-3 criteria do not mention location or triggers, so ETTH is not diagnosed by a neck location or a stress trigger.

The ICHD-3 classification differentiates infrequent ETTH (episodes occurring on < 1 day per month on average, < 12 days per year) and frequent ETTH (occurring on ≥ 1 but < 15 days per month for at least 3 months, ≥ 12 and < 180 days per year). Some European headache clinicians think of patients with chronic daily headache (CDH) as having a background of ETTH punctuated by episodes of migraine, while American headache specialists believe that CDH is usually chronic migraine (see Chap. 4).

The ICHD-3 also differentiates ETTH with and without pericranial tenderness. It is not clear that this distinction has any clinical importance at all.

Migraine vs. ETTH

Migraine can be distinguished from ETTH using Table 1.11, which lists the features of migraine without aura, followed by the characteristics of ETTH in parentheses and italics.

Table 1.12 Clinical pearls on the diagnosis of probable migraine

- A "probable" diagnosis in the ICHD-3 means that a primary headache disorder is missing one criterion
- Diagnosis of "probable" should trigger the clinician to consider the possibility that the patient has secondary headache, rather than a primary headache disorder, because the patient does not meet all of the IHS criteria for a given primary headache

Diagnosis of Probable Migraine

Probable migraine (PM) is the term used by the ICHD-3 for migraine missing one criterion. For example, a patient has more than five headaches lasting 24 h, which are bilateral, nonthrobbing, and of moderate intensity, worse with activity, with photophobia but no phonophobia, thus missing one of the "D" criteria.

The ICHD-3 instructs clinicians to diagnose based on the highest *complete* set of criteria, so that patients who meet criteria for both ETTH and PM should be diagnosed as having ETTH. However, there is a large group of clinicians who disagree and feel that the diagnosis should be based on the worst headache, namely migraine.

The diagnosis of "probable" should trigger the clinician to consider the possibility that the patient has secondary headache, rather than a primary headache disorder, because the patient does not meet all of the IHS criteria for a given primary headache. Think again about whether the patient merits a workup before assuming it is primary and treating (Table 1.12).

The Spectrum of Migraine

There is evidence that patients with migraine have a spectrum of episodic headaches across time. That is, some of their attacks will meet criteria for ETTH, some for PM, and some for migraine.

There is also evidence that the lower-level headaches of *migraineurs* respond to migraine-specific medications, such as triptans. However, ETTH attacks in people who *never get* migrainous headaches, the so-called pure ETTH, do not respond to triptans any better than placebo. The lower-level headaches of *migraineurs* behave as lower-level migraines, and their TTH are, in essence, phenotypically tension-type, but genotypically, and clinically, migraines.

Migraineurs thus have a spectrum of attacks, with clinical variability, but all of their attacks are likely manifestations of their migrainous disorder. People with "pure" TTH have no migrainous attacks and rarely complain of headaches in the doctor's office. Although TTH is more common than migraine, it is seldom the reason an individual seeks medical care.

Table 1.13 Organization of ICHD-3 migraine aura

1. Typical aura (≥1 aura spreads gradually over ≥5 min and/or ≥2 symptoms occur in succession and/or each aura lasts 5–60 min and/or ≥1 aura is unilateral)
   (a) Visual
   (b) Sensory
   (c) Speech and/or language
2. Brainstem aura
   (a) Typical aura meeting above criteria *plus*
   (b) At least two of the following brainstem symptoms: dysarthria, vertigo, tinnitus, hyperacusis, diplopia, ataxia, decreased level of consciousness, with each brainstem aura symptom lasting 5–60 min
3. Hemiplegic aura
   (a) Typical aura meeting above criteria *plus*
   (b) Fully reversible motor weakness lasting <72 h
4. Retinal aura: Fully reversible confirmed monocular visual phenomena meeting other criteria for typical aura

Chronic Migraine and Chronic TTH

Episodic migraine and TTH can transform into daily or nearly daily headache, and diagnosis of these chronic disorders will be described in Chap. 4.

Migraine with Aura

The ICHD-3 changed the organization of aura to make the entire system more logical. The criteria begin with a definition of aura as "recurrent attacks, lasting minutes, of unilateral fully reversible visual, sensory, or other central nervous system symptoms that usually develop gradually and are usually followed by headache and associated migraine symptoms." The auras are listed as visual, sensory, speech and/or language, motor, brainstem, or retinal. The first three types of aura are gathered under the term "typical," motor aura is "hemiplegic," basilar-type migraine is now "brainstem aura," and migrainous monocular visual change is "retinal" (Table 1.13).

Migraine with Typical Aura

Typical aura is defined as a reversible neurologic event, lasting from 5 to 60 min, in which headache occurs with the event or follows the aura within an hour. Aura only occurs in about 20% of migraineurs and often does not occur with each attack. In addition, the headache which accompanies aura does not always meet ICHD-3 criteria for migraine, and sometimes headache does not occur with aura at all.

Table 1.14 First pearl on precise diagnosis of aura

• Do not use the outdated, imprecise, and unacceptable terms "complicated migraine" or "complex migraine." They are not included in the ICHD-3

Table 1.15 Migraine with typical aura, ICHD-3 criteria

1. At least two attacks with the following
2. Aura must be a completely reversible visual, sensory and/or speech/language symptom or dysfunction with no motor symptoms such as weakness, no brainstem or posterior fossa symptoms and no retinal symptoms, suggested by retinal vasoconstriction
3. At least two of the following four
   (a) At least one aura symptom develops gradually over ≥5 min and/or different aura symptoms occur in succession over ≥5 min
   (b) Each aura symptom lasts 5–60 min. Duration can be 180 min with successive aura symptoms
   (c) ≥1 aura symptom is unilateral. Aphasia is considered unilateral, as language usually comes from a dominant hemisphere. The ICHD-3 states that dysarthria may or may not be considered unilateral
   (d) Headache occurs during the aura or follows the aura within 60 min
4. Not secondary

Table 1.16 Second pearl on precise diagnosis of aura

• If the visual aura is 5 -60 min long and not monocular, the diagnosis is typical aura without headache

The ICHD-3 criteria for typical aura are quite specific and include types of neurologic migrainous aura events that were previously called "complicated migraine" or "complex migraine" before the first ICHD. Neither term was included in the ICHD, and neither should be used in diagnosis of primary headaches (Table 1.14).

A diagnosis of typical aura requires at least two events as described in Table 1.15.

Typical aura can occur with migraine, with a headache that does not meet criteria for migraine, such as a TTH, and can occur with no headache following at all. The ICHD-3 now divides typical aura into two categories, that occurring with headache and that occurring without headache. Frequently, both aura without and with headache present over the course of a patient's lifetime. Rarely do patients have auras with every migraine headache.

Typical aura without headache has in the past been named "ocular migraine," "acephalic migraine," "migraine equivalents," and "late-life migraine accompaniments." These terms are no longer used. Late-life migraine accompaniments was a term coined by Dr. C. Miller Fisher for typical aura without headache, which commonly occurs in older patients (Table 1.16).

Typical aura symptoms can occur sequentially, with each one lasting up to an hour. This overall duration would have suggested a prolonged aura using old terminology, but now is simply described as "typical aura." There is no "prolonged aura" term in the ICHD-3. There is, however, a diagnosis of persistent aura without

Table 1.17 Persistent aura without infarction

1.	The present attack in a patient with migraine with aura is typical of previous aura except that one or more aura symptoms persist for ≥ 1 week
2.	Not secondary, no neuroimaging confirmation of stroke

infarction, defined as an aura lasting ≥ 1 week without neuroimaging confirmation of stroke in a person with a previous history of typical aura and with the persistent aura the same as the previous typical aura (see Table 1.17).

Migraine with Brainstem and Hemiplegic Auras

As noted above, the old terms "complicated migraine," "complex migraine," and "prolonged migraine" are no longer in use. Migraine with unusual aura is diagnosed either as typical aura with successive symptoms or as migraine with brainstem aura or hemiplegic migraine. The term migraine with brainstem aura replaced the terms basilar migraine and basilar-type migraine in ICHD-3.

Brainstem Aura

Note that typical aura and brainstem aura can never include weakness. Aura associated with weakness is either hemiplegic migraine or may not be migraine at all.

The diagnosis of migraine with brainstem aura requires the following: (1) the attacks must include a typical aura, (2) the attack also includes an aura with at least two brainstem or posterior fossa symptoms, (3) there can be no motor weakness, (4) the duration of each aura symptom is 5–60 min, and (5) headache occurrs during the aura or following the aura within an hour (see Tables 1.18 and 1.19).

Hemiplegic Migraine

Hemiplegic migraine diagnosis is contingent on the presence of at least two attacks with typical aura *and* motor weakness as well. The duration of the typical aura remains 5–60 min, while the motor weakness lasts < 72 h, without residual.

Many spells are erroneously attributed to migraine when they are unexplained and weakness is present. Remaining true to the ICHD-3 criteria, requiring typical aura with reversible weakness avoids that diagnostic error (see Tables 1.20 and 1.21).

Diagnosis of familial hemiplegic migraine (FHM) requires at least one first- or second-degree relative to be diagnosed with FHM, otherwise the diagnosis becomes sporadic hemiplegic migraine. Multiple genes have been cloned to explain the

Table 1.18 Migraine with brainstem aura, ICHD-3 criteria

1. At least two attacks with the following
2. A typical aura occurs with completely reversible visual, sensory and/or speech/language symptoms or dysfunction with no motor symptoms, such as weakness, and no retinal symptoms suggested by retinal vasoconstriction
3. The patient also has an aura consisting of at least two of the following brainstem or posterior fossa reversible symptoms, but *no motor weakness*
   (a) Dysarthria
   (b) Vertigo
   (c) Tinnitus
   (d) Hypacusis or phonophobia
   (e) Double vision
   (f) Ataxia
   (g) Decreased level of consciousness
4. Each aura symptom lasts ≥5 min up to 60 min, but they can be sequential
5. Headache begins during the aura or follows aura within 60 min
6. Not secondary

Table 1.19 Key pearls on diagnosing brainstem aura

- The patient must have a history of migraine with aura, meaning a history of at least two attacks including typical aura
- Each attack must include a typical aura
- The attack also includes an aura with at least two brainstem or posterior fossa symptoms
- There can be no motor weakness
- The duration of each aura symptom is 5–60 min
- Headache occurs during the aura or following the aura within an hour

Table 1.20 Hemiplegic migraine, ICHD-3 criteria

1. At least two attacks with the following
2. Typical aura and completely reversible motor weakness
3. At least 2/4 of the following
   (a) Duration of typical aura onset is at least 5 min, and the typical aura symptoms can occur sequentially
   (b) Duration of typical aura is 5–60 min although the typical auras can be additive when sequential, so up to 3 h. Motor weakness lasts less than < 72 h
   (c) At least one aura symptom is unilateral
   (d) Headache occurs during the aura or follows the aura within an hour
4. Not secondary

pathogenesis of FHM. The ICHD-3 lists three validated gene mutations triggering hemiplegic migraine, CACNA-1A (FHM-1), ATP1A (FHM-2), and SCN1A (FHM-3), and diagnosis of these causative mutations can be obtained by blood screening. The three gene mutations all result in excess glutamate in the synapse, increasing neuronal excitability postsynaptically, probably by activating the *N*-methyl-D-aspartate (NMDA)–glutamate receptor. There is also a classification in the IHCD-3 for FHM from other loci, anticipated for future discoveries.

Table 1.21 Key pearls on diagnosing hemiplegic migraine

- The patient must have a history of migraine with aura, meaning a history of at least two attacks including typical aura
- Each attack must include a typical aura lasting 5–60 min
- The attack also includes an aura with reversible motor weakness lasting 5 min to < 72 h
- Headache occurs during the aura or following the aura within an hour

Table 1.22 Retinal migraine, ICHD-3 criteria

1. At least two attacks with
2. Fully reversible monocular
   a. Positive visual changes (e.g., scintillations)
   b. Negative visual changes (e.g., blindness)
3. Confirmation by ≥ 1 of
   a. Clinical visual field exam
   b. Patent drawing of monocular visual change after careful instruction
4. ≥ 1 of
   a. Aura spreads gradually over ≥ 5 min
   b. Aura lasts 5–60 min
   c. Headache occurs with aura or within 60 min of its end
5. Not secondary, so other causes of transient monocular blindness have been eliminated

Retinal Migraine

Retinal migraine is defined by the ICHD-3 as "repeated attacks of monocular visual disturbance, including scintillations, scotomata, or blindness, associated with migraine headache." This could be due to neuronal activation in the retina or to vascular change, but is monocular. The criteria require *monocular* positive or negative visual changes otherwise meeting criteria for a migraine aura with clinical confirmation, listed in Table 1.22. For clinical pearls on diagnosing migraine with aura, see Table 1.23, and for a review of the clinical pearls on migraine with brainstem aura and hemiplegic migraine see Table 1.24.

Episodic Syndromes that may be Associated with Migraine (Previously Called Childhood Periodic Syndromes that are Commonly Precursors of Migraine)

These syndromes (recurrent gastrointestinal disturbance, cyclical vomiting syndrome, abdominal migraine, and benign paroxysmal vertigo) will be covered in Chap. 8.

Table 1.23 Clinical pearls on migraine with aura

- Typical aura can be visual, hemisensory, and/or an alteration of speech or language. Events lasting 5–60 min can follow each other successively, that is, up to 3 h, and still be diagnosed as typical aura
- Typical aura now requires at least one of

1. At least one aura symptom spreads gradually over at least 5 min, and/or at least two symptoms occur in succession
2. Duration of the aura is at least 5–60 min
3. At least one aura symptom is unilateral. Aphasia is considered unilateral
4. Headache occurs with the aura or within 1 h

- Aura can occur with migraine headache, with nonmigraine headache, and without headache. ICHD-3 divides typical aura into that with headache and that without
- Primary reversible migrainous aura should be diagnosed as typical, brainstem, hemiplegic, retinal, or persistent without infarction
- Help the patient distinguish between monocular symptoms (retinal aura) or homonomous symptoms (typical aura). Positive cortical phenomena, such as seeing zigzag fortification spectra seen in typical aura, take the symptom out of the eye to the visual cortex. Typical aura is far more common!

Table 1.24 Review of the clinical pearls on migraine with brainstem aura and hemiplegic migraine

- There is no ICHD-3 term of: complex migraine, complicated migraine, acephalic migraine, ocular migraine, or migraine equivalent. Avoid these terms as they are meaningless
- Brainstem aura is diagnosed by having at least two episodes with a *typical aura* and at least two symptoms of brainstem or posterior fossa dysfunction lasting 5–60 min, with headache or followed by headache within an hour
- There is never motor weakness in migraine with brainstem aura
- Neither migraine with brainstem aura nor hemiplegic migraine can be diagnosed without the typical aura component
- Hemiplegic migraine diagnosis requires at least two episodes of *typical aura* lasting 5–60 min, with motor weakness lasting < 72 h with headache or followed by headache within an hour
- Hemiplegic migraine cannot be diagnosed without the typical aura component
- *Note well*: Neither migraine with brainstem aura nor hemiplegic migraine can be diagnosed by ICHD-3 criteria without at least two identical attacks of a typical aura meeting ICHD-3 criteria, lasting 5–60 min, in addition to the target aura of brainstem symptoms of 5–60 min, or motor weakness lasting < 72 h, and a headache with the aura or within 60 min of the aura

Complications of Migraine

The ICHD-3 lists the following as complications of migraine: status migrainosus, persistent aura without infarction (already covered above), migrainous infarction, and migraine aura-triggered seizure.

Table 1.25 Status migrainosus, ICHD-3 criteria

1. The present attack in a patient with migraine without aura is typical of previous attacks except for its duration
2. Headache has both of the following features
(a) Unremitting for > 72 h
(b) Severe intensity
3. Not secondary

Table 1.26 Migrainous infarction, ICHD-3 criteria

1. The present attack in a patient with migraine with aura is *typical of previous attacks except that one or more aura symptoms persists for > 60 min*
2. Neuroimaging demonstrates ischemic infarction in the relevant area
3. Not secondary (no other stroke etiologies)

Status Migrainosus

This is simply a migraine that will not quit and commonly occurs in migraineurs at some point in their life. The ICHD-3 criteria are a migraine duration that exceeds 72 h, with pain or associated features that are "debilitating." Many menstrually related migraines (MRM) go longer than 3 days, so conventionally typical long menstrual migraines are excluded from this diagnosis (see Table 1.25).

Migrainous Infarction

Migraine and stroke, both being common, often occur together. Stroke risk is increased in migraine with aura patients, with the risk greatest in women under the age of 45. However, it is very rare that migraine actually appears to cause stroke, an event in which the stroke evolves out of the migraine.

This type of event, a true migrainous infarction, is so infrequent that the ICHD-3 criteria are very strict. The stroke must occur in a patient with previously established aura, and in the same distribution as the aura. Further, the ICHD-3 requires imaging confirmation of the stroke (see Table 1.26), although clinically objective evidence of the stroke, for example reflex asymmetry, a Babinski, or a pronator drift, should suffice.

Secondary causes for stroke occurring in a migraine need to be scrupulously eliminated. The rarity of true migrainous infarction cannot be overstressed (Table 1.27).

Migraine Aura-Triggered Seizure (Migralepsy)

As with migrainous infarction, migraine aura-triggered seizures can occur, but are very unusual. The seizure, when triggered by migraine with aura, must occur during

Table 1.27 Key pearls on migrainous infarction

- Migrainous infarction requires that the stroke occurs in the territory of *previously established aura in a patient with migraine with aura*
- In addition, by ICHD-3 criteria, the stroke must be imaged *in this previously established territory*
- In addition, secondary causes must be scrupulously ruled out
- So beware of this diagnosis: it is very, very rare!

Table 1.28 Migraine aura-triggered seizure (migralepsy), ICHD-3 criteria

1. Patient must have migraine with aura
2. The seizure occurs during or within 1 h after a migraine aura

Table 1.29 Menstrual Migraine, ICHD-3 beta appendix definitions

1. Both forms of menstrual migraine occur only as migraine without aura
2. *Pure menstrual migraine:* Attacks occur exclusively on days −2 to +3 of menstruation in at least 2/3 menstrual cycles *and at no other times of the cycle*
3. *Menstrually related migraine without aura:* Attacks occur on days −2 to +3 of menstruation in at least 2/3 menstrual cycles and *additionally at other times of the cycle*

the migraine or within an hour of the migrainous aura, and once again, secondary causes must be excluded (see Table 1.28).

A critical part of the diagnosis of migraine aura-triggered seizure is that by criteria, the seizure can only be triggered in a patient with migraine with aura, not in migraine without aura. This makes the diagnosis even more rare.

Menstrual Migraine

Menstrual migraine is only defined in the appendix of the ICHD-3 beta, but the current definitions are widely accepted and adopted. Menstrual migraine occurs in about 2/3 of women, and is just a migraine with a menstrual trigger. Hormonal issues and headache will be covered more extensively in Chap. 21.

There are two forms of menstrual migraine, but it is not clear that the differences are clinically meaningful. The usual form is referred to as menstrually-related migraine (MRM), in which attacks occur both during the menses and outside the menses. Pure menstrual migraine (PMM) attacks occur only during menses and not outside the menses. Both forms require that the menstrual attacks be migraine without aura.

For the purpose of diagnosis, the first day of flow is numbered +1, and to be a menstrual migraine the attack must begin between day −2 and +3. Menstrual migraines must occur in 2/3 of periods (see Table 1.29).

Clinically, menstrual migraines are often longer and more severe than non-menstrual migraines, so identifying them can help with planning a treatment regimen. There is a validated test for menstrual migraine, the Menstrual Migraine

Table 1.30 Menstrual Migraine Assessment Tool (MMAT), a quick screener for menstrual migraine. (Tepper et al. 2008)

Q1: Do you get headaches during your period?
Q2: Do your menstrual headaches get severe?
Q3: Do you get dislike of light during your menstrual headaches?
2/3 yes answers strongly suggest menstrual migraine

Assessment Test (MMAT), which consists of just three questions, presence or absence of attacks during menses, presence or absence of severe attacks, and presence or absence of photophobia. With 2/3 of these present, the sensitivity of MMAT for menstrual migraine is 0.94 and the specificity is 0.74, so it is well worth using in clinical practice for identifying menstrual migraine (see Table 1.30).

Conclusions on Diagnosis of Migraine and Tension-Type Headache

- A patient complaining of a stable pattern of at least 6 months of episodic, disabling headache likely has migraine
- The presence of nausea with long-established episodic headaches strongly suggests migraine
- Location does not determine diagnosis; migraine usually is accompanied by neck pain
- Triggers do not determine diagnosis; the most common trigger for migraine is stress
- TTH is featureless and without impact; patients almost never complain of tension-type headaches in the office
- Most patients with migraine have a spectrum of attacks, from attacks that appear like tension-type headaches to attacks that appear like PM (missing one migraine criterion) to ICHD-3 migraine, and all three levels of headache are likely forms of migraine responding to triptans
- Typical aura can be visual, sensory, or as an alteration of speech or language, or all three sequentially
- Both brainstem aura and hemiplegic aura attacks also require the presence of typical aura
- Migrainous infarction and migraine aura-triggered seizures are both rare and occur only in patients with established migraine with aura
- Menstrual migraine occurs from day −2 to +3, often with severe intensity and photophobia

Suggested Reading

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Chapter 2
Diagnosis of Trigeminal Autonomic Cephalalgias

Mark J. Stillman

Introduction

The trigeminal autonomic cephalalgias (TACs) refer to a specific group of primary headaches characterized by unilaterality, associated cranial autonomic features, and specific duration of pain. The major TACs as listed by the International Classification of Headache Disorders, third edition, beta version (ICHD-3) are listed in Table 2.1 and, to differentiate them, the Other Primary Headache disorders (covered in Chap. 3) are listed in Table 2.2.

The term "probable" is used in the ICHD-3 to mean a headache is missing one ICHD-3 criterion to make the diagnosis. Probable TACs are under ICHD number 3.5. The probable headaches are excluded from our tables for simplicity, utility, and clarity.

Remember that if the patient is missing a single criterion, the headache diagnosis becomes "probable." As discussed in Chap. 1, when a patient is missing a criterion, the possibility of a secondary cause increases, and serious consideration should be given to doing a careful workup for secondary causes. Essentially, a probable diagnosis should raise your suspicions for sinister etiology.

Diagnostic Features of the TACs: How to Make the Diagnosis

As with any other painful condition, making a correct diagnosis is 90 % of the battle and helps direct proper therapy. This is particularly important with the TACs, as some of these headaches can be differentiated by a response to certain medications, such as indomethacin.

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Table 2.1 The major trigeminal autonomic cephalalgias (TACs), ICHD-3

ICHD-3 number, name (abbreviation)
3.1 Cluster headache (CH)
3.1.1 Episodic cluster headache (ECH)
3.2.1 Chronic cluster headache (CCH)
3.2 Paroxysmal hemicrania (PH)
3.2.1 Episodic paroxysmal hemicrania (EPH)
3.2.2 Chronic paroxysmal hemicrania (CPH)
3.3 Short-lasting unilateral neuralgiform headache attacks (SUNHA)
3.3.1 Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)
3.3.1.1 Episodic SUNCT
3.3.1.2 Chronic SUNCT
3.3.2 Short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA)
3.3.2.1 Episodic SUNA
3.3.2.2 Chronic SUNA
3.4 Hemicrania continua (HC)

Table 2.2 The major Other Primary Headaches, ICHD-3 (covered in Chap. 3)

ICHD-3 number, name (abbreviation)
4.1 Primary cough headache
4.2 Primary exercise headache
4.3 Primary headache associated with sexual activity
4.4 Primary thunderclap headache (PTH)
4.5 Cold-stimulus headache
4.5.1 Headache attributed to external application of a cold stimulus
4.5.2 Headache attributed to ingestion or inhalation of a cold stimulus
4.6 External-pressure headache
4.6.1 External-compression headache
4.6.2 External-traction headache
4.7 Primary stabbing headache
4.8 Nummular headache
4.9 Hypnic headache
4.10 New daily persistent headache (NDPH)[a]

[a] Also covered in Chap. 4

Table 2.3 Clinical pearls on probable headaches

- If a patient is missing a single criterion for an ICHD-3 diagnosis, the headache diagnosis becomes "probable"
- When a patient is missing a criterion, the possibility of a secondary cause increases, and serious consideration should be given to doing a careful workup for secondary causes
- A probable diagnosis should raise your suspicions for sinister etiology

Table 2.4 Duration of the TACs

- Hemicrania continua (HC): Continuous pain with exacerbations daily or several times a week lasting hours to days each
- Cluster headache (CH) attacks: 15–180 min
- Paroxysmal hemicrania (PH) attacks: 2–30 min
- Short-lasting unilateral headache attacks (SUNHA); short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)/Short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA) attacks): 1–600 s

Table 2.5 Initial clinical pearls on diagnosis of TACs

- Agitation is a common feature for both CH and HC, and is not listed as a criterion for PH or SUNHA in ICHD-3
- When no autonomic features are present and cluster is suspected, ask about agitation
- Unilateral photophonophobia is often present in TACs, especially HC
- Make sure the patient has had a very good MRI. Diagnosis of a TAC should provoke a workup for a hypothalamic or pituitary lesion; as many as 10% of patients with TACs will have an abnormality of this region or the posterior fossa
- Within SUNHA, SUNA is just SUNCT without a red eye or tearing
- SUNHA is in a different location (V1) compared to trigeminal neuralgia (TN; V2–3). SUNHA, unlike TN, is associated with autonomic features
- A woman with frequent CH-like attacks should make the clinician think of paroxysmal hemicrania (PH)

Duration of TACs

Wags have stated that the longer the name of the paroxysmal TAC, the shorter the duration. Hemicrania Continua (HC) is continuous. Eighty-five percent of Cluster Headache (CH) attacks last between 15 and 180 min. Paroxysmal Hemicrania (PH) attacks are between 2 and 30 min. And the duration of Short-lasting Unilateral Headache Attacks (SUNHA), including Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing (SUNCT) and Short-lasting Unilateral Neuralgiform headache attacks with cranial Autonomic symptoms (SUNA), is measured in seconds (1-600 s).

The current ICHD-3 criteria for the diagnosis of the TACs are listed in the subsequent tables. As noted above, the TACs are grouped into Section 3 of the ICHD-3, and while these headaches are similar in many ways, the response to medications can vary markedly. Each will be discussed separately, but not before some points are made. These clinical pearls on TACs are listed in Table 2.5.

In both HC and CH, if the autonomic features are not manifested, an equally important criterion listed is the sense of restlessness and inability to sit still during an attack. There is a minority of patients who, during an HC exacerbation or a cluster attack, will not manifest obvious ipsilateral sympathetic paresis (miosis, ptosis, Horner's) or parasympathetic discharge (conjunctival tearing, rhinorrhea, etc.). In such cases, the patient must report (or a companion must report) that the patient

will rock, pace, or otherwise appear agitated. One of my cluster patient's wife told me that the patient was groaning and holding his involved eye; next to him on the pillow was a handgun! This degree of agitation is not required or listed for PH or SUNHA.

Never underestimate the severity of the pain of CH! CH is called the "suicide headache" for good reason.

As many as 50% of patients with TACs will refer their symptoms of photophonophobia to the ipsilateral, painful side, in contrast to migraineurs, who usually complain of bilateral light and sound sensitivity. HC, in particular, manifests unilateral photophonophobia in at least half of patients, and ipsilateral photophonophobia should make the clinician think seriously about a TAC diagnosis.

The diagnosis of a TAC should provoke a workup for a hypothalamic or pituitary lesion; as many as 10% of patients with TACs, in particular SUNHA, will have an abnormality of this region or the posterior fossa on a good imaging study, in particular SUNHA. If the clinician has not visualized a magnetic resonance imaging (MRI) with and without contrast as part of the workup, repeating one should be considered.

SUNA is simply a SUNHA without the red eye or tearing, so SUNA and SUNCT are very similar. Neither is indomethacin responsive; both tend to respond to antiepilepsy drugs such as lamotrigine or gabapentin.

Trigeminal neuralgia (TN) does not manifest autonomic features and is only rarely in V1, so location and associated autonomic features distinguish SUNHA from TN, even when the duration of attacks is similar. In addition, SUNHA is usually heralded by stabs of pain, sometimes in a sawtooth pattern, not seen in TN.

A woman with frequent cluster-like attacks, especially if not terribly agitated, should make the clinician think of PH rather than CH, due to gender alone. After ruling out secondary causes, an indomethacin trial may be indicated.

Diagnosis of Cluster Headache

CH, the most common of the TACs, are generally more common in males, starting as early as the second decade. CH can persist well into life, as far as into the seventh decade. They are called clusters because they tend to cluster at the same time(s) of the year, with cycles or periods of daily attacks lasting for weeks to months in the episodic variety, and remissions lasting for months to years. This is considered to be a reflection of the relationship of these headaches with circadian and circannual periods and the effect of light–dark cycles on the suprachiasmatic nucleus of the hypothalamus, by way of the retinal–hypothalamic–pineal pathways.

Approximately 85% of all CHs are *episodic*; the cluster period or cycle, as it is called, spontaneously remits, and there will be freedom from CH attacks for a month or longer each year in episodic cluster headache (ECH).

The remaining cluster sufferers have *chronic* clusters in which they will have headaches daily or near daily and will not be free from a CH attack for any period of a month or more in a given year. Chronic cluster headache (CCH) may start de novo, but generally evolves from the episodic variety.

Table 2.6 Diagnostic criteria for cluster headache, ICHD-3

A. ≥5 attacks fulfilling B–D
B. Severe or very severe unilateral orbital, supraorbital, or temporal headache attacks, untreated lasting for 15–180 min
C. Either or both of the following
   1. At least one of the following symptoms or signs, ipsilateral to the headache
      A) Parasympathetic activation
         a. Conjunctival injection or lacrimation
         b. Nasal congestion and/or rhinorrhea
         c. Eyelid edema
         d. Forehead and facial sweating
         e. Forehead and facial flushing
      B) Sympathetic paresis
         f. Horner's or partial Horner's (miosis, ptosis)
      C) Miscellaneous
         g. Sensation of fullness in the ear
   2. A sense of restlessness and agitation
D. The attacks have a frequency QOD to 8/day during an active period
E. Secondary causes excluded

Episodic cluster headache (ECH)
- At least two cluster periods lasting 7 days to 1 year, separated by pain-free periods lasting ≥1 month

Chronic cluster headache (CCH)
- Attacks occur for >1 year without remission or with remission for <1 month

Probable cluster headache: attacks missing one criterion

Table 2.7 Clinical pearls on diagnosing cluster

- Attacks are short, sharp, and severe (triple S; SSS) and occur with an average frequency of 1–3/day
- Attacks manifest parasympathetic activation and sympathetic paresis with agitation
- Attacks occur with alarm clock periodicity
- Circadian and circannual periodicity are seen frequently in CH, but usually not the other TACs
- Cluster patients in cycle rarely, if ever, drink alcohol, due to the severity of the trigger
- Smoking and obstructive sleep apnea are common in cluster patients
- In about one-third of the cluster patients, there can be low-level ipsilateral interictal pain, making it sometimes difficult to differentiate from HC, but the intensity of the continuous pain is generally worse in HC

Most cluster attacks are severe and retro-orbital. They are not throbbing; rather, they are described as burning, boring, stabbing, or tearing. Attacks are short, sharp, and severe (triple S; SSS).

Cluster attacks are manifested by parasympathetic activation (scleral injection, lacrimation, diaphoresis, nasal stuffiness, and/or rhinorrhea). Less common is a Horner's or partial sympathetic paresis with ptosis and/or miosis. As noted above, agitation is the rule, and cluster attacks are generally shorter than 3 h in duration. Major diagnostic criteria for CH are listed in Table 2.6.

There is a circadian alarm clock periodicity to the attacks, attacks occurring at the same time of day or night, and a circannual periodicity with the cluster periods

occurring at the same time of year, often with the changing of the clocks for daylight savings time. The periodicity feature of CH, extremely useful in diagnosis and not usually seen in the other TACs, is not included in the ICHD-3 criteria.

Attacks can be precipitated by alcohol, fumes such as gasoline fumes, excessive exercise, and napping. Cluster patients in cycle rarely, if ever, drink alcohol. Cluster patients are commonly smokers, however.

In about 30% of cluster and PH patients, a low-level pain can persist ipsilaterally interictally. The patients describe this as a "ghost pain" between attacks. The continuous pain of HC is generally more severe, averaging 6–7/10 in intensity.

Diagnosis of the Paroxysmal Hemicranias

The Paroxysmal Hemicranias (PH) are defined by an absolute response to indomethacin. The headaches are similar in quality to cluster pain, but the pain is shorter lasting and more frequent during any given day.

As with CH and HC, there are both *episodic* and *chronic* PH subforms. Episodic Paroxysmal Hemicrania (EPH) occurs in periods lasting 1 week to a year, and its occurrence is separated by pain-free periods lasting 1 month or longer (remissions). When cycles of attacks of PH last more than 1 year without remissions lasting 1 month or longer, the headache qualifies as Chronic Paroxysmal Hemicrania (CPH). This distinction is identical to that in CH.

EPH is more rare than CPH, the opposite of CH, where the episodic subform is more common. In EPH, the disorder occurs equally in males and females, while in CPH there is a female predominance. CH always has a male predominance, regardless of subform.

Attacks of PH can be less severe than CH, but in the same location. The attacks are quite short, up to 30 min only, allowing for 15 min of overlap with CH attacks. The usual duration of a PH attack is 14 min, so it is usually easy to tell from SUNHA or TN. SUNHA attacks are from 1 s to 10 min, but average duration is 50 s. However, there is an overlap of a 2–10-minute duration between SUNHA and PH, so indomethacin can be the important distinguishing feature, as SUNHA does not respond to indomethacin. TN attacks are much shorter, there are no autonomic features, and are usually in V2–3, while PH is in V1.

More than half of the time, PH attacks occur more than five times per day by ICHD-3 criteria, so attacks usually occur more frequently in PH than CH. The frequency of CH attacks can be up to eight times per day, so the frequency of the two disorders can overlap, but this is rare. In general, CH attacks occur one to three times daily, and PH attacks occur with a mean frequency of eight times per day. SUNHA attacks can occur hundreds of times per day.

Patients are less frequently agitated in PH than with CH. Agitation is not a diagnostic criterion for PH, but is for CH.

There is no circadian or circannual periodicity. PH attacks occur at random.

Table 2.8 Diagnostic criteria for paroxysmal hemicrania, ICHD-3

A. ≥ 20 attacks fulfilling B–E
B. Attacks of severe unilateral orbital, supraorbital, or temporal pain lasting 2–30 min
C. Headache is accompanied by ≥ one of the following:
   1. Ipsilateral conjunctival injection or lacrimation
   2. Ipsilateral nasal congestion or rhinorrhea
   3. Ipsilateral eyelid edema
   4. Ipsilateral forehead and facial sweating
   5. Ipsilateral forehead and facial flushing
   6. Sensation of fullness in the ipsilateral ear
   7. Ipsilateral miosis and/or ptosis
D. Attacks have a frequency of > 5/day for > 50 % of the time, although periods with lower frequency can occur
E. Absolute responsiveness to therapeutic doses of indomethacin
F. Secondary causes excluded

Episodic Paroxysmal Hemicrania (EPH)
- At least two PH periods lasting 7 days to 1 year, separated by pain-free periods lasting ≥ 1 month

Chronic Paroxysmal Hemicrania (CPH)
- Attacks occur for > 1 year without remission or with remission for < 1 month

Table 2.9 Clinical pearls on diagnosing paroxysmal hemicrania

- Since cluster is a disease of men, think PH when you see a woman who reportedly has CH
- EPH occurs equally in men and women. CPH is more common in women
- If the cluster is refractory, especially if there is no response to subcutaneous sumatriptan or O2, think PH
- If there is no alarm clock periodicity or agitation, think PH
- If attack frequency is high (> 5/day) or attack duration is short (30 min), think PH over CH
- If you think PH, try an indomethacin trial before proceeding with CH treatment
- There is an overlap in duration of attacks between CH, PH, and SUNHA, so once again, indomethacin may be the way to the diagnosis of PH

Finally, and most importantly, the diagnosis of PH is made by absolute responsiveness to indomethacin. If you have ruled out secondary causes and think the patient could have PH, try an indomethacin course first before treating as if it is cluster.

Diagnosis of SUNHA (SUNCT and SUNA)

In the third edition of the ICHD, the category SUNHA includes the two recognizable forms of SUNCT and SUNA. SUNCT and SUNA are very brief headaches with prominent cranial autonomic features that can deceive the clinician because they can be triggered by cutaneous stimuli, similar to TN. These headaches are characterized by paroxysms of short-lasting (1–600 s) stabbing tic-like pain. Average duration of each attack is around 50 s. The duration of these severe attacks was expanded from 5–240 s in ICHD-2 to 1–600 s in ICHD-3.

Table 2.10 Diagnostic criteria for SUNHA (SUNCT/SUNA), ICHD-3

A. ≥ 20 attacks fulfilling B–D
B. Attacks of unilateral orbital, supraorbital, or temporal moderate to severe stabbing or pulsating pain, lasting 1–600 s and occurring as single stabs, series of stabs, or in a sawtooth pattern
C. Pain is accompanied ipsilaterally by ≥ one of the following
   1. Ipisilateral conjunctival injection or lacrimation[a]
   2. Ipsilateral nasal congestion or rhinorrhea
   3. Ipsilateral eyelid edema
   4. Ipsilateral forehead and facial sweating
   5. Ipsilateral forehead and facial flushing
   6. Sensation of fullness in the ipsilateral ear
   7. Partial Horner's: ipsilateral miosis and/or ptosis
D. Attack frequency of ≥ one/day for ≥ 50 % of the time when the disorder is active
E. Secondary causes excluded

- SUNCT: Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing
- SUNA: Short-lasting Unilateral Neuralgiform headache attacks with cranial Autonomic symptoms

[a] The absence of conjunctival injection and tearing but the presence of other cranial autonomic features suggests SUNA

Table 2.11 Clinical pearls on SUNHA

- Pain is maximal in V1 distribution, unlike trigeminal neuralgia (TN)
- There are autonomic features invariably, unlike TN
- As in TN, cutaneous triggers are common in SUNHA, but unlike TN, movement of the neck can also be a trigger in SUNHA
- Moderate to severe intensity
- Pain is stabbing, burning, electric-like
- Brief paroxysms of pain lasting 1–600 s each (mean 50 s)
- Attacks peak within 2–3 s
- Attack frequency varies from 1/day to 30/hour
- No latency or refractory period
- Stabs are the rule, either alone, as a herald for an attack, or in a sawtooth pattern
- SUNHA is not indomethacin responsive and usually responds to lamotrigine or gabapentin
- Remember: SUNHA is rare, which is why the workup is crucial! The most common secondary cause is a pituitary lesion

The attacks can present with isolated stabs of pain in the orbit or the temporal region or anywhere in the head, and can occur hundreds of times a day. SUNCT/SUNA can alternately present with groups of stabs (sawtooth pattern) separated by complete or incomplete resolution of the pain. A single stab can herald an attack. There may be periods of remission, or there may be no days of remission.

Unlike TN, which as noted above, SUNHA attacks might resemble because of cutaneous triggers and duration, SUNHA attacks generally do not exhibit a refractory period. Also, TN occurs < 5 % of the time in V1; SUNCT/SUNA pain is usually in V1. Time to peak for SUNHA is about 2–3 s. SUNHA attacks are longer in duration (typically 30–120 s) than TN (typically 1–3 s). SUNCT, as the names infers, is

associated with both conjunctival injection (redness) and tearing, and there may be other ipsilateral autonomic signs. SUNA may have conjunctival injection or tearing but not both together, and other autonomic features occur.

Secondary headaches may masquerade as SUNHA, including brainstem strokes, arteriovenous malformations, pituitary tumors, arterial dissections of the vertebral artery, or demyelination. It is therefore mandatory to investigate all suspected cases of SUNCT/SUNA or to personally review high-quality imaging if it has been performed.

There have been several small case series of SUNCT being cured by resection of pituitary tumors. The pathophysiology and explanation for these cures is mysterious.

Remember, SUNHA is rare. Be vigilant in a search for secondary causes.

Unfortunately, SUNHA does not respond to indomethacin as do PH and HC. Treatment for SUNCT/SUNA will be discussed in Chap. 11, but is usually lamotrigine or gabapentin.

Pathophysiology of the TACs: What you Need to Know

There is now a substantial body of evidence that the spectrum of TACs and the Other Primary Headaches are related in their pathophysiological origin, as one would suspect, since they generally share many clinical features. Recent advances with positron emission tomography (PET) scanning and functional MRI have demonstrated areas of activation in the posterior hypothalamus for all of the TACs during the headache phase. In addition, the expected areas of the cortical and subcortical pain matrix show activity in response to the pain. Table 2.12 displays the areas of hypothalamic activation.

HC offers a mirror image of CH and migraine functional imaging. Cluster manifests activation in the ipsilateral hypothalamus, HC the contralateral hypothalamus. Some scientists feel that migraine manifests activation in the contralateral upper brainstem, HC the ipsilateral upper brainstem.

Anatomically, there are reciprocal connections between the posterior hypothalamus and the trigeminal nucleus caudalis (TNC), the site of origin of the second order nociceptive neuron. In the last decade, there have been more than 50 patients who have had implantation of deep brain stimulators (DBS) in the ipsilateral hypothalamus for drug refractory CH and other TACs. There are no controlled studies of DBS for TACs, except to note that turning off working stimulators without patient knowledge has resulted in return of headaches.

For CH, in 60% of patients there has been a greater than 50% decrease in the frequency of headaches, and in 30% there has been a complete response with DBS. However, there has been one death and several transient ischemic attacks (TIAs) and strokes in the course of implanting DBS for CH.

It is now apparent that stimulation of this hypothalamic site promotes the relief of the headache and does not stimulate the pain, suggesting that the posterior hypothalamus is a key area of modulation for cluster and TAC pain. This is discussed further, along with other stimulation approaches, in Chap. 12 on treatment of the TACs and other primary headaches.

Table 2.12 Areas of hypothalamic stimulation seen with the TACs

Headache	Hypothalamic activation area (with respect to side of pain)
Cluster headache	Ipsilateral posterior hypothalamus
Paroxysmal hemicrania	Contralateral hypothalamus
Hemicrania continua	Contralateral hypothalamus and ipsilateral upper brainstem
SUNCT	Ipsilateral or bilateral hypothalamus
SUNA	Absent in patients with extraocular autonomic phenomena

Table 2.13 Differential points among the paroxysmal TACs. (Adapted from Goadsby et al. 2010)

Features	Cluster headache	Paroxysmal hemicrania	SUNCT/SUNA
Gender (M/F)	3–6/1	1/1	1.5/1
Pain quality	Stab/sharp/throb/poker	Stab/sharp/throb/poker	Stab/sharp/throb/poker
Severity	Very severe	Severe–very severe	Severe
Distribution	V1 > C2 > V2 > V3	V1 > C2 > V2 > V3	V1 > C2 > V2 > V3
Attack frequency	Every other day–8/day	Mean 11; up to 30/day	Mean 100; >100/day
Attack length	15–180 min	2–30 min	1–600s
Migraine features			
Nausea	50%	40%	25%
Photo-/phonophobia	65%	65%	25%
Triggers			
Alcohol	Yes	Yes	No
Nitroglycerin	Yes	Yes	No
Cutaneous	No	No	Yes
Agitation/restlessness	90%	80%	65%
Episodic/chronic	9/1	1/2	1/9
Circadian/circannual periodicity	Yes	No	No
Treatment efficacy			
Oxygen	70%	None	None
Sumatriptan subcutaneously	90%	20%	10% or less
Indomethacin	Almost none	100%	None

M male, *F* female, *C* cervical, *V* trigeminal

The Paroxysmal TACs: Telling Them Apart

CH, PH, and SUNHA constitute the paroxysmal TACs, in that the minority of patients have continuous pain, and the continuous pain is generally not severe. HC, on the other hand, is a continuous TAC. Table 2.13 outlines major points that help differentiate the paroxysmal TACs from one another.

Table 2.14 Hemicrania Continua (HC), ICHD-3 criteria

A. Unilateral continuous CDH for > 3 months with moderate to severe exacerbations
B. At least one of the following ipsilateral to the side of pain
   1. Conjunctival injection
   2. Lacrimation
   3. Nasal congestion
   4. Rhinorrhea
   5. Ptosis
   6. Miosis
   7. Eyelid edema
   8. Forehead or facial sweating or flushing
   9. Sense of fullness in the ear
   10. Restlessness or agitation or worsening of pain with movement
C. Complete response to therapeutic doses of indomethacin, with a trial up to at least 225 mg/day
D. Not secondary
E. Remitting subtype: Interruptions of pain for ≥ 1 day without treatment
F. Unremitting subtype: continuous pain with no remission periods of pain for ≥ 1 day for ≥ 1 year

Hemicrania Continua

HC is one of four primary daily headaches, covered in Chap. 4. However, it is a TAC as well, and since ICHD-3 classifies it in the TAC section, it is also covered here. HC is a continuous, side-locked, generally moderate (6/10 intensity) headache associated with cranial autonomic symptoms, with periodic severe intensity exacerbations. By definition, this headache is indomethacin responsive. Because HC has these qualifying autonomic characteristics, it is categorized as a trigeminal autonomic cephalalgia or TAC in ICHD-3, the only TAC that is continuous most of the time. However, as noted above, agitation can substitute as a diagnostic criterion for the autonomic features, or also can occur with them.

The ICHD-3 criteria for HC are quite specific, but there are detailed descriptions of patients with this syndrome suggesting that clinical presentations can be more variable. Still, most have a dramatic indomethacin response.

The official criteria are that the headache be strictly one-sided and continuous for at least 3 months. Periodic exacerbations occur in which the pain becomes moderate to severe (usually severe), and autonomic features such as ipsilateral lacrimation, conjunctival injection, ptosis, miosis, nasal stuffiness, or rhinorrhea occur. The response to indomethacin is incorporated in the diagnosis, and the criteria specify "complete response."

Cittadini and Goadsby described in detail 39 patients with HC, and added a number of common clinical features, in addition to the ICHD-3 criteria. The daily baseline side-locked headache of HC can be mild, although they described the continuous headache as averaging 6/10 intensity in their case series.

The exacerbation frequency was daily in about half and 5/7 days in another third, so the step-up to severe is frequent. Severe exacerbation length was from 30 min to 72 h for the most part.

Triggers for exacerbation turned out to be common and were similar to migraine, including stress or let down from stress, and alcohol, the latter also a trigger for CH. More than two-thirds of patients were agitated or restless with severe exacerbations, and more than one-fourth were described as aggressive (generally verbally, not physically). These symptoms are also similar to those found in CH.

Many patients with HC have other additional features or variable presentations. First, it is worth remembering that often patients with HC come in complaining about the exacerbations, not the daily headache. Asking about the presence or absence of headache-free time helps find patients with CDH, especially HC. This is a critical clinical point: Ask whether the patient has any truly headache-free days, that is, days without any residual or mild pain.

Additional features of HC include a foreign body sensation in the ipsilateral eye. This is variously described as like an eyelash or grit or sand. Sometimes, patients will complain that they can never get their contact lens comfortable on that side, and the sensation is also described as "itchy eye."

Ice-pick pains or primary stabbing headaches, also indomethacin responsive, frequently occur on the same side as the HC. Primary stabbing headaches are covered in Chap. 3, Other Primary Headaches. It is useful to ask a patient with HC-associated features about ice-pick pains, although they do occur in 40% of migraineurs as well.

The use of a daily nonsteroidal anti-inflammatory drug (NSAID) is frequently seen in patients with indomethacin-responsive syndromes. Thus, a patient coming in with side-locked daily headaches taking daily ibuprofen should raise suspicion for HC. Ibuprofen and other NSAIDs are close enough to indomethacin to provide some HC patients with partial relief, better than alternatives. The same behavior can be seen in patients with PH.

In ICHD-2, the severe exacerbations in HC were described as CH-like with autonomic features. However, HC exacerbations may mimic migraine, not cluster, in some patients, and the exacerbations may be triptan responsive, so in ICHD-3 the cranial autonomic symptoms are included in the criteria for HC diagnosis, but the exacerbations are described as "moderate or greater intensity" and not otherwise characterized.

Cittadini and Goadsby reported photophonophobia in around 75% of their HC patients, ipsilateral in about half. As previously noted, in case of unilateral photophonophobia a clinician should start thinking about a TAC, and if the pain is continuous and at least moderate, specifically about HC.

Many patients with HC reported by Cittadini and Goadsby had personal or family histories of migraine, often with histories of motion sickness.

However, if a patient with a history of migraine presents with chronic daily headache (CDH) which is side locked and is taking large daily quantities of NSAIDs, especially when mixed with caffeine, the diagnosis of medication overuse headache (MOH), chronic migraine, or transformed migraine with rebound becomes possible.

An indomethacin trial is often the only way to distinguish between chronic migraine with medication overuse and HC with migrainous exacerbations. Indometha-

Table 2.15 Clinical pearls on diagnosing HC

- Foreign body sensation in the ipsilateral eye or itchy eye
- Overuse of other NSAIDs
- Daily baseline headache can be mild, instead of moderate; average baseline headache intensity is 6/10
- Exacerbations can mimic migraine or cluster, and the exacerbations can be triptan responsive. Exacerbations occur frequently, often daily or near daily and are of moderate or greater intensity
- An indomethacin trial may be the only way to distinguish HC with migrainous exacerbations from chronic migraine with medication overuse
- Agitation and aggression during the exacerbations is common
- Dislike of light and noise can be ipsilateral and entirely unilateral
- The indomethacin trial should be to at least 225 mg/day
- Indomethacin responsiveness does not prove that a patient has primary HC, and an imaging study is necessary

cin will work completely in HC patients before they are weaned from the overused NSAIDs or other medications.

The required indomethacin dose is frequently high. In about one-third of the Cittadini and Goadsby series, 300 mg/day was necessary; one patient required 500 mg daily dosing. As noted, the ICHD-3 recommends at least a trial up to 225 mg/day. It is worth trying to lower the daily dose months after stability and headache suppression is achieved.

Indomethacin responsiveness is not diagnostic. Diagnostically, secondary headaches mimicking HC can be indomethacin responsive. Because HC is somewhat uncommon, a baseline MRI is necessary to exclude secondary causes, as in all of the TACs.

In ICHD-3, HC is subdivided into remitting and nonremitting subtypes. These subtypes correspond to chronic and episodic cluster and other TACs, but the criteria are a bit different. For cluster and other TACS, 1 month of no headaches per year is required for ECH, otherwise it is chronic. For HC, the remitting subtype manifests a pattern of pain that is not continuous but is interrupted by remission periods of ≥1 day without treatment. The HC unremitting subtype manifests a pattern of continuous pain without remission periods of ≥1 day for ≥1 year. The ICHD-3 notes that the majority of HC is the unremitting subtype.

Clinical pearls on diagnosing HC are summarized in Table 2.15.

Conclusions

There are four primary types of TACs: CH, PH, SUNHA, and HC. The first three are paroxysmal; HC is continuous. However, the first three paroxysmal TACs can have continuous lower-level headaches as well.

Two of the TACs are indomethacin responsive, PH and HC.

Table 2.16 Final clinical pearls on the TACs

- All TACs require careful imaging, specifically an MRI without and with contrast and a special look at the sella and posterior fossa
- Cluster, paroxysmal hemicrania, and SUNHA are primarily paroxysmal, although may have continuous lower-level headaches
- The continuous headache of HC is generally at least 6/10 in intensity
- The two TACs that are indomethacin responsive are PH and HC
- The two TACs that are associated with severe agitation are CH and HC
- The two forms of SUNHA are SUNCT and SUNA
- CH and PH are subdivided into episodic forms with remissions of at least a month a year and chronic forms with no remissions
- HC is subdivided into a remitting form with remissions of at least a day a year and a chronic form with no remissions
- SUNHA is subdivided into a form with both conjunctival tearing and injection, SUNCT, and a form with other autonomic features, SUNA

All of the TACs generally manifest autonomic features, usually parasympathetic activation, occasionally sympathetic paresis with a partial Horner's. Two of the TACs are associated with significant agitation, CH and HC.

All TACs require careful imaging before deciding that they are primary. This involves an MRI without and with contrast and a special look at the sella and posterior fossa.

CH and PH are subdivided into episodic forms with remissions of at least a month a year and chronic forms with no remissions. HC is subdivided into a remitting form with remissions of at least a day a year and a chronic form with no remissions. SUNHA is subdivided into a form with both conjunctival tearing and injection, SUNCT, and a form with other autonomic features, SUNA.

Suggested Reading

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Chapter 3
Diagnosis of Other Primary Headaches

Mark J. Stillman

Introduction: A Word to the Wise on the Other Primary Headaches

The Other Primary Headaches are a heterogeneous collection of generally short primary headaches without autonomic features, distinguishing them from the trigeminal autonomic cephalalgias (TACs). Workup for secondary causes is particularly important in these headaches, as many have frequent and serious secondary etiologies, such as aneurysm in thunderclap headache (TCH) or headache associated with sexual activity, and posterior fossa lesions or Chiari malformation in cough headache.

Some of the Other Primary Headaches can be indomethacin responsive, such as primary cough headache, primary stabbing headache, primary exercise headache, and headache associated with sexual activity. Several of the Other Primary Headaches are unique and orphan entities, a few with known treatments such as hypnic headache (HH), many with no known treatments such as nummular headache.

A chapter on Other Primary Headaches is generally a trip down a buffet table, with offerings that vary widely.

Because of the paucity of clinical and pathophysiological data, these primary headaches require special attention and clinical vigilance. It is always incumbent upon the treating clinician to assure these headaches are not secondary to some secondary treatable condition, and clinical complacency may not be so richly rewarded in that rare case where a serious lesion turns out to be the cause! This is particularly so with TCH, in which a primary diagnosis should be considered the exception, not the rule.

The International Classification of Headache Disorders, third edition, beta (ICHD-3) Other Primary Headaches are listed in Table 3.1.

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Table 3.1 Other Primary Headaches, ICHD-3

- Primary cough headache
- Primary exercise headache
- Primary headache associated with sexual activity
- Primary thunderclap headache
- Cold-stimulus headache
  - Headache attributed to external application of a cold stimulus
  - Headache attributed to ingestion or inhalation of a cold stimulus
- External-pressure headache
  - External-compression headache
  - External-traction headache
- Primary stabbing headache
- Nummular headache
- Hypnic headache
- New daily persistent headache (NDPH)

Table 3.2 Diagnostic criteria for primary cough headache, ICHD-3

A. At least two headaches with:
B. Sudden onset, lasting from 1 s to 120 min
C. Brought on by and occurring only with cough, sneeze, strain, and/or valsalva
D. Secondary causes excluded

Primary Cough Headache

Clinically, cough headache is a paroxysm, a quick upstroke of pain in less than a second, with a gradual resolution of generally less than 5 min. The sound "Puh" is associated with the explosive, almost instantaneous peak of pain with cough, sneeze, or valsalva. There are no associated features (Table 3.2).

Primary cough headache generally occurs over the age of 40. The younger the patient, the greater the concern for secondary causes. Cough headache usually responds to indomethacin, but indomethacin responsiveness can occur in both primary and secondary cough headache, so is not diagnostic.

Many patients coming in with indomethacin responsive headache such as primary cough headache will be taking other nonsteroidal anti-inflammatory drugs (NSAIDs). Thus, the use of a daily NSAID is frequently seen in patients with indomethacin-responsive syndromes.

Cough headaches should be assumed to be secondary until the clinician proves otherwise. While many primary headaches worsen with cough—for example, migraine headache—there are quite a few secondary headaches with cough exacerbation as a standout feature. Nearly half of all cough headaches are secondary to some condition (examples are listed in Table 3.3), generally Chiari malformation or other posterior fossa lesions (Table 3.4).

Table 3.3 Secondary causes of cough headache

- Arnold Chiari malformation with or without hydrocephalus
- Acute obstructive hydrocephalus
- Idiopathic intracranial hypertension
- Secondarily raised intracranial pressure (e.g., intracranial tumors, abscess, subdural hematoma)
- Meningeal irritation of any sort (e.g., subarachnoid blood, inflammatory cells, cancer, etc.)
- Low intracranial tension (spontaneous intracranial hypotension)
- Extracranial and intracranial arterial disease
- Aneurysms

Table 3.4 Clinical pearls on cough headache

- Primary cough headache occurs generally in older patients. The younger the patient with cough headache, the greater the concern for secondary causes
- Posterior fossa lesions are the most common secondary cause of cough headache, especially Chiari malformation
- Indomethacin responsiveness, while common in cough headache, is not diagnostic of a primary headache disorder, including cough headache

Table 3.5 Diagnostic criteria for primary exercise headache, ICHD-3

A. ≥ 2 headache attacks with both of the following:
   1. Precipitated by and occurring only during or after strenuous physical exertion
   2. Duration less than 48 h

B. Secondary causes excluded

Diagnostic imaging should include magnetic resonance imaging (MRI) with and without contrast combined with magnetic resonance angiography (MRA) of the intracranial and extracranial vasculature or computed tomography (CT) angiogram with venous imaging to look for cranial sinus disease.

Primary Exercise Headache

This throbbing headache is common and occurs with any type of exertion, such as weight lifting or running at high altitudes. When it is new in onset, subarachnoid hemorrhage or other bleed becomes a paramount concern. Other concerns include those listed for cough headache and TCHs (Tables 3.3 and 3.8).

Primary exercise headache is a disease of younger patients (Table 3.5). The older the patient, the greater the concern for secondary causes.

Table 3.6 Diagnostic criteria for primary headache associated with sexual activity, ICHD-3

A. ≧ 2 attacks with:
B. Headache and/or neck pain occurring during sex
C. Either or both of the following
1. Builds in intensity with increased sexual excitement
2. Abrupt explosive headache just before or accompanying orgasm
D. Duration of 1 min to 24 h with severe intensity and/or up to 72 h with mild intensity
E. Secondary causes excluded

Primary Headache Associated with Sexual Activity

The ICHD-3 no longer distinguishes between preorgasmic and orgasmic headaches in classifying primary headache associated with sexual activity; they are both subsumed in this diagnosis. Men are more likely to present clinically complaining of this disorder. They used to present to their physician with hat in hand, but nowadays men usually do not wear fedoras.

Primary sex headaches, as in exertional headaches, tend to occur in younger patients. The older the patient, the greater the concern for secondary causes.

Primary sex headache can be short lived or can last several hours, and in any fresh case, a workup is required. For many who present for the first time, it can present as an explosive headache that qualifies as a TCH or the worst headache in the patient's life. This is obviously a serious concern for the patient, the treating physician, and usually the patient's intimate partner.

Every effort should be made to determine if this is a subarachnoid bleed that the patient has luckily survived (i.e., a sentinel bleed). In such a situation, a good quality non-contrast CT of the brain will be able to demonstrate subarachnoid blood in over 95% of cases if done in the first 12 h post-ictus. For the small minority of cases in which the subarachnoid blood is too small to detect, or where the source of bleeding comes from the spinal cord or the posterior fossa and has not yet circulated over the cerebral convexities, a spinal tap with careful cell counts on serial tubes and testing with cerebrospinal fluid (CSF) spectrophotometry, when available, is necessary. Other secondary causes of sex headaches include CSF leaks, cervical spine lesions, extracranial arterial dissection, reversible cerebral vasospasm, and posterior fossa lesions.

Once secondary causes are excluded, pretreatment with indomethacin, or occasionally other NSAIDs, can sometimes be useful. Sex headaches occur sporadically and not generally with each sexual encounter, so knowing when to pretreat is problematic. And often, primary sex headaches remit over time (Table 3.6).

Primary Thunderclap Headache

Primary thunderclap headache (PTH) distinguishes itself by its rapid onset to peak pain; it reaches its apex generally within seconds to a minute. The ICHD-3 criteria list less than 1 min to peak with duration for 5 or more minutes. Patients often will

Table 3.7 Primary thunderclap headache, ICHD-3 diagnostic criteria

A. Severe head pain with:
B. Sudden onset, peaking in less than 1 min
C. Duration of at least 5 min
D. Secondary headache excluded

Table 3.8 Secondary causes of thunderclap headache

- Intracranial hemorrhage: subarachnoid hemorrhage or intracerebral hemorrhage
- Sentinel bleed
- Arterial dissection: carotid or vertebral
- Intracranial cerebral sinus thrombosis
- Acute stroke
- Cerebral vasculitis
- Spontaneous intracranial hypotension
- Pituitary apoplexy
- Reversible cerebral vasoconstriction syndrome (RCVS)
- Malignant hypertensive crisis
- Posterior reversible leukoencephalopathy syndrome (PRES)
- Third ventricular occlusion with ball valve mass (colloid cyst)
- Overwhelming intracranial infection
- Acute myocardial infarction (MI)

claim they were struck by lightning or hit on the head with a bat, unlike the normal less rapid trajectory of other severe headaches such as a migraine or cluster. Cough headache, neuralgias, and ice pick pains are the only equally fast-onset headaches.

The diagnostic criteria for PTH, also known as "crash headache," are listed in Table 3.7.

Most patients present to the emergency department with thunderclap, where the staff will work the patient up for a subarachnoid hemorrhage or intracranial bleed and will either consult the neurological service or send the patient to the consultant immediately after discharge. The differential diagnosis for this severe a headache is very large, and all of the entities in the differential should be systematically excluded before one is confident that this is a primary headache after all. Secondary causes of TCH are far more common than PTH.

Secondary headaches in the differential diagnosis of TCH are listed in Table 3.8.

Table 3.9 summarizes the evaluation and treatment of the secondary headaches in this large differential diagnosis.

Once the entities listed in Table 3.9 are excluded, the diagnosis of a primary TCH is made. In general, all patients should have a basic workup as well as a careful history and physical examination. This workup should include a CT (usually done in the emergency unit), an LP with a spinal fluid analysis including an opening pressure, and MRI with contrast. A study of the cerebral and extracerebral vasculature should be done, including an MR venogram, MR angiogram, or a CT angiogram (with a deliberate attempt to see the venous phase). Formal digital angiography can be done in place of CT or MR angiography.

Table 3.9 Evaluation and treatment of entities that present with thunderclap headaches

Entity	Cause	Evaluation	Comment
Intracranial hemorrhage	Subarachnoid hemorrhage (SAH), bleeding AVM, or intracerebral bleed (usually hypertensive)	Non-contrast CT of brain and LP; if bleed confirmed, angiogram (contrast digital or CT angiogram or MR angiogram)	SAH is the cause of ~25% of TCHs; 50% mortality from the bleed, a stroke, or medical complication
Sentinel bleed	Intracranial aneurysm that has rapidly dilated before rupture and/or bled into the vessel wall	Same as above	Precedes the SAH and is a warning of impending aneurysmal rupture
Arterial dissection (intracranial or extracranial)	Tear in the intima of the involved vessel from trauma, manipulation, or inflammation	Carotid/vertebral ultrasound; MR angiogram, CT angiogram, or formal digital angiogram; MRI of the neck with fat saturation views looking for vessel wall clot	May present with acute stroke from acute occlusion or distal artery to artery embolus; acute Horner's sign may be seen with headache +/− stroke-related deficits in the carotid distribution
Cerebral venous thrombosis	Hypercoagulability with or without infection, puerperium, surgery, oral contraception, or cancer	MR venogram and MRI brain, CT angiogram with venous phase, digital angiogram; hypercoagulability work-up	Presents with headache, raised intracranial pressure, and other CNS symptoms—mental status changes, seizures, stroke
Acute stroke	Thrombotic or embolic stroke	MRI brain with diffusion-weighted imaging	25–35% of strokes present with headache
Intracranial vasculitis	Primary or secondary to systemic disorders	General rheumatologic work-up; MR or CT angiography or preferably digital angiography	
Spontaneous intracranial hypotension	Spontaneous CSF leak; from trauma or seen in patients with connective tissue weakness/defects	MRI brain with contrast may show dural enhancement, posterior fossa descent and crowding; intracranial venous and pituitary dilation	LP done at the time of symptoms should show an opening pressure less than 65 mm water
Pituitary apoplexy	Infarction/hemorrhage of the pituitary gland; seen in pregnancy or with adenomas	CT and MRI of the pituitary gland; Endocrine workup; +/− LP	Present with TCH +/− Addisonian crisis. Must be supported with steroids/fluids acutely
Reversible Cerebral Vasoconstriction Syndrome (RCVS)	Puerperium, oral contraception, illicit or vasoactive drug use	CT of brain to exclude SAH and MR, CT, or formal angiography demonstrates segmental cerebrovascular constrictions which can resolve in 3 months	Presents with TCH +/− stroke. CSF is negative. Treated with calcium channel blockers +/− intravenous magnesium. Do not use steroids.

Table 3.9 (continued)

Entity	Cause	Evaluation	Comment
Malignant hypertension/ hypertensive encephalopathy	Poorly controlled hypertension; catecholsecreting tumor or drug reaction	Hypertension on exam, hematuria, renal dysfunction, papilledema, and hemorrhages in fundus; CT or MRI should show no acute bleed but may show stigmata of hypertension	May present a radiographic and clinical picture of RCVS
PRES (posterior reversible encephalopathy syndrome)	Acute reaction related to drugs, either prescribed or illicit	CT and MRI show areas of cerebral edema preferentially in the parieto-occipital lobes	Presents with TCH and seizures with mental status changes, MRI with T2 and FLAIR show the lesions. Associated with antirejection meds and illicit drugs
Acute hydrocephalus with ball valve phenomenon	Colloid or dermoid cyst in third ventricle	CT or MRI brain	
Intracranial infection	Bacterial or viral	CT (or MRI) and LP	Case reports in the literature
Myocardial infarction	Acute myocardial infarction	ECG, CT of brain	Case reports in the literature

AVM Arteriovenous malformation, *LP* lumbar puncture, *w/u* workup, *CNS* central nervous system, *FLAIR* fluid-attenuated inversion recovery, *ECG* electrocardiography

Table 3.10 Cold-stimulus headache, ICHD-3

A. ≥2 headaches with:
B. Precipitated by a cold external stimulus to the head
C. Resolved in less than 30 min after taking away the cold stimulus
D. Not due to something else

Table 3.11 Headache attributed to ingestion or inhalation of a cold stimulus, ICHD-3

A. ≥2 sudden-onset frontal or temporal headaches with:
B. Precipitated by a cold stimulus to the palate and/or posterior pharynx from a cold food or drink or breathing in cold air
C. Resolves in less than 10 min after stopping the cold stimulus
D. Not due to something else

Cold-Stimulus Headache

The cold-stimulus headache is a new addition to the category of Other Primary Headaches in ICHD-3 and is no longer relegated to the appendix. It is a common headache familiar to many patients who like to describe how their brain "freezes" when exposed to cold liquids (e.g., "ice cream headaches"). It merely describes a headache induced by either an externally applied cold stimulus or one that is ingested or inhaled. Table 3.10 lists the diagnostic criteria for an externally applied cold-stimulus headache, and Table 3.11 lists the criteria for cold-ingestion or -inhalation headache.

Note that these cold headaches are most commonly bifrontal or bitemporal but can be unilateral in those patients with a substrate of predominantly unilateral migraine.

For all of the Other Primary Headaches, a probable diagnosis can be given if the patient has had only one, and has not yet experienced a second such headache, or is missing one criterion. These probable subtypes are not listed in the tables for clarity. However, remember, that a probable diagnosis missing one criterion or a single attack should raise suspicion for a secondary cause.

External-Pressure Headache

This is yet another category of headache moved to a front burner in ICHD-3. This is a headache that arises when typically non-noxious stimuli are applied to the scalp and other pericranial tissues, that is, goggles, eyeglasses, helmet, or hat. A ponytail headache is a traction-induced variant of this headache. It is therefore not a post-traumatic headache in any sense of the word and is more a manifestation of central nociceptive hyperactivity, similar to migraine. The subtypes of this headache are depicted in Table 3.12.

Table 3.12 External pressure headache subtypes, ICHD-3

1. External-compression headache
a. ≥ 2 headaches with:
b. Induced within an hour of continuous external compression of the head (forehead or scalp)
c. The headache is the highest at the site of the compression
d. The headache goes away with an hour of stopping the external compression
e. Not due to something else
2. External-traction headache
a. ≥2 headaches with:
b. Induced by continuous external traction on the head or scalp
c. Maximal pain at the site of traction
d. Resolution of the headache within 1 h of relief of the external traction
e. Not due to something else

Table 3.13 Diagnostic criteria for primary stabbing headaches, ICHD-3

A. Single stab or volleys of stabs with:
B. Stabs that last no more than several seconds
C. Stabs that occur irregularly, from one to many/day, to irregular occurrences across time
D. No autonomic features, no photo/phonophobia, nausea, etc
E. Secondary causes excluded

Primary Stabbing Headaches

Primary stabbing headaches are also referred to as ice-pick pains or "jabs and jolts" and are actually quite common. They are brief, lasting 3 s or less, and can come in volleys or single jabs. Some patients have to stop short in their tracks and move the head from one side to another.

The stabs can move about the head and do not have to be restricted to the trigeminal distribution of the head. Primary stabbing headaches are commonly seen in migraineurs (up to 40 % of migraine patients) and cluster sufferers.

The onset of the stabs can herald the onset of an attack of migraine, TAC, or Other Primary Headache or occur during an attack. Sometimes, volleys of ice pick pains can be stopped with indomethacin. Table 3.13 lists the diagnostic criteria.

Nummular Headache

This unusual and inconsequential headache used to be called "coin headache," because it presents as a delimited coin-shaped headache area, usually in one or the other parietal region. It tends not to move around or to change much. It has not attracted much research interest for good reasons; it is not very inspiring. It is both benign and refractory to most treatments.

Table 3.14 Diagnostic criteria for nummular headaches, ICHD-3

1. Continuous or intermittent headache
2. Felt in an area of the scalp with:
   a. A sharp border around the entire area of head pain
   b. The area of head pain is fixed and not variable
   c. The area of head pain is round or oval
   d. The diameter of the circumscribed head pain is 1–6 cm
3. Not secondary

The literature has numerous single case reports of a single patient who responded to a single treatment here and there, never the same treatment. As with primary stabbing headaches, the best approach is reassurance. The diagnostic criteria are listed in Table 3.14.

Hypnic Headache

Hypnic Headache (HH) is a rare primary headache and, as with cluster, is known as an alarm clock headache, because it occurs at the same time of the night in patients, suggesting it is somehow related to the same pacemaker in the hypothalamus that is responsible for cluster headache (CH). The headache, which lasts 15–180 min and can also occur during the day if a patient takes a nap, may be associated with rapid eye movement (REM) sleep.

HH is a mild to moderate, dull, aching headache, which is bilateral and frontal in location. Occasionally, the headaches can be unilateral. Unlike the TACs, it is not associated with parasympathetic discharge or other autonomic features.

Workup for HH includes an MRI without and with contrast. Tumor and CSF leak have both been reported to cause secondary HH. As always, a sedimentation rate should be obtained if this is the new onset of headache in an elderly patient, because of the variable presentations of giant cell arteritis.

HH tends to be a geriatric headache disorder, mostly in people over the age of 50. Women are affected more than men; 65 % of patients are female. Patients seem to respond to caffeine, lithium, melatonin, or indomethacin.

Duration of the attacks, as noted, is generally 1–2 h. Frequency should be high. Attacks should occur at least 10 nights per month. Table 3.15 lists the diagnostic criteria.

Table 3.15 Diagnostic criteria for hypnic headache, ICHD-3

A. All of the following:
B. Develops only during sleep and awakens patient
C. Occurs at least 10 days/month for at least 3 months
D. Duration from at least 15 min to no more than 4 h after awakening
E. No cranial autonomic symptoms or agitation
F. Secondary causes excluded

Table 3.16 New daily persistent headache, ICHD-3

A. Continuous headache with:
B. The patient clearly remembers the onset on a particular day, with continuous pain (no remissions) within 24 h
C. The headache has been continuous for at least 3 months
D. Not secondary, this is an abrupt-onset primary chronic daily headache with any phenotype

New Daily Persistent Headache

New daily persistent headache (NDPH), an all too common primary headache, is discussed in Chap. 4, Diagnosis of Primary Chronic Daily Headaches, but is included in the ICHD-3 under Other Primary Headaches. NDPH starts abruptly, and the patient can remember the brief period of time when the daily headache started. The headache is continuous and persistent from onset and can have either tension-type or migraine features or both. Most of the time the headache is bilateral. NDPH tends to be resistant to treatment, and it is important that a complete workup for structural causes of head pain is completed before assigning this diagnosis.

Potential causes of abrupt onset of daily headaches are CSF leak or other CSF abnormalities, infectious (Lyme, HIV), neoplastic, and multiple vascular causes. These can include dissection, vasculitis, bleed, and cortical vein thrombosis. The closer the patient is to the onset of the daily headache in time, the greater the concern for secondary causes. The requirement for at least 3 months of continuous headache makes the primary diagnosis more secure.

Thus, NDPH is the abrupt and remembered onset of a primary chronic daily headache of any phenotype. In almost half of patients, there is an antecedent upper respiratory or viral infection. Other patients recall a stressful life event immediately preceding the onset of the daily headache.

Table 3.16 gives the diagnostic criteria for NDPH. Note that there is a chronic persisting subform of this headache (more common) and a self-limiting subform. There have also been descriptions of relapsing and remitting NDPH.

Prognosis does not seem to matter whether there is a remembered preceding event or whether the headache has tension-type or migrainous features. In one case series by Robbins and colleagues, about three-quarters of patients had the chronic persisting subform.

Conclusions and Final Clinical Pearls on Other Primary Headaches

- All TACs and Other Primary Headaches require a baseline MRI looking for secondary headache causes
- Some of the Other Primary Headaches are particularly likely to be secondary and not primary at all, including TCH, cough headache, and headache associated with sexual activity
- The younger the patient, the more likely the cough headache is secondary to Chiari or a posterior fossa lesion
- The older the patient, the more likely exercise or sex headaches is secondary, especially due to aneurysmal bleed
- HH tends to be a geriatric disorder; the younger the patient, the more likely a secondary cause
- The more recent the onset of NDPH, the more likely a secondary cause
- Nummular headache is almost always benign and frequently untreatable
- Primary stabbing headache, primary cough headache, and primary headache associated with sexual activity tend to be indomethacin responsive

Suggested Reading

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Part II
Diagnosis of Chronic Headaches

Chapter 4
Diagnosis of Primary Chronic Daily Headaches

Stewart J. Tepper and Deborah E. Tepper

Introduction

Chronic daily headache (CDH) is a term of art, rather than an International Classification of Headache Disorders, 3rd edition, beta version (ICHD-3) diagnosis. It is defined as headaches present at least 15 days per month for at least 3 months for at least 4 h per day treated or untreated. Elimination of secondary causes, for example space-occupying lesions, infections, or metabolic causes such as hypothyroidism, is always the first step when a patient with CDH presents in the office of the physician. Once these are eliminated, there are only four primary CDH types. However, by convention, medication overuse headache (MOH, rebound) is often included in CDH, even though it is a secondary headache (see Table 4.1). ICHD-3 states that both chronic migraine (CM) and MOH can be diagnosed at the same time.

Short daily headaches, 3 h or less per day, are generally placed into the trigeminal autonomic cephalalgias (TACs), covered in Chapter 2.

The Four Primary Chronic Daily Headaches

The four CDHs are: Chronic Tension-Type Headache (CTTH), Hemicrania Continua (HC), New Daily Persistent Headache (NDPH), and Chronic Migraine (CM) (see Table 4.2). There are controversies about the diagnosis, and inclusion and exclusion criteria for each of the long daily headaches.

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Table 4.1 The definition of chronic daily headache

1. Headaches present at least 15 days per month
2. Headaches last at least 4 h per day treated or untreated
3. Daily or near-daily headaches have been present at least 3 months in a row
4. CDH is generally primary, but many clinicians include medication overuse headache (MOH) in the term
5. CDH is not an ICHD-3 diagnosis

Table 4.2 The four primary Chronic Daily Headaches (CHD)

1. Chronic Tension-Type Headache (CTTH)
2. Hemicrania Continua (HC)
3. New Daily Persistent Headache (NDPH)
4. Chronic Migraine (CM)

Table 4.3 Chronic Tension-Type Headache (CTTH), ICHD-3 criteria

A. Headache occurring on ≥15 days/month on average for >3 months (≥180 days per year)
B. Headache lasts hours or is continuous
C. Headache has ≥2/4 of the following:
1. Not unilateral (bilateral location)
2. Not throbbing (pressing/tightening, non-throbbing)
3. Not severe (mild or moderate)
4. Not aggravated by routine physical activity (e.g., walking or climbing stairs)
D. Both of the following:
1. No more than one of photophobia, phonophobia, or mild nausea (can have none of these)
2. Neither moderate or severe nausea nor vomiting
E. Not secondary

Chronic Tension-Type Headache

Clinically, CTTH is a featureless, low-level headache that is never severe and generally lacks migrainous features. The ICHD-3 criteria do not call for neck pain as a criterion, a frequently mistaken quality ascribed to this diagnosis. Location does not define tension-type headache (TTH), although bilaterality is one of four listed criteria, the others being a pressing or tightening quality, mild to moderate intensity, and not aggravated by usual activities. Two of these criteria must be met for TTH.

In keeping with the "not migraine" approach described in Chapter 1, CTTH is not throbbing, not severe, not unilateral, not worsened by activity, and generally has no nausea or photophonophobia. The ICHD-3 criteria have some unexpected diagnostic rules for CTTH. Patients are allowed no more than one of photophobia, phonophobia, or mild nausea, or none of these. Patients with CTTH are not allowed to have moderate or severe nausea or vomiting (see Table 4.3).

Table 4.4 Clinical pearls on diagnosing Chronic Tension-Type Headache (CTTH)

- No migrainous features: a continuous, low-level CDH
- Minimal impact from the headaches
- Gradual onset

It is far more clinically frugal and apt to simply require no migrainous features for the diagnosis of TTH. CTTH, besides being featureless, is also usually without impact or disability.

No requirement is made for a previous history of Episodic Tension-Type Headache (ETTH) in order for a patient to be diagnosed with CTTH. Clearly, by ICHD-3 criteria, CTTH and migraine can coexist, with migraine occurring on days that do not meet CTTH criteria. This is the Danish view of CDH, that migraine and TTH can always be distinguished, that it is worth doing so, and that there are therapeutic and pathophysiologic bases for separating them.

The American view, for the most part, is that migraine can turn into CDH, but the transformed headache remains a migraine disorder. Thus, patients with transformed migraine have a primarily migrainous disorder, with bad and not-so-bad days.

There are patients who have "pure" CTTH who never have any migrainous symptoms. These patients are rare.

No mention is made in the ICHD-3 criteria of the manner of presentation of CTTH. However, since NDPH is defined as the abrupt onset of CDH, it follows that to truly diagnose CTTH or CM, patients should have a gradual onset.

So, remember the three pearls on diagnosis of CTTH: no migrainous features, generally no individual impact, and gradual onset. These are included in Table 4.4.

Hemicrania Continua (HC)

Hemicrania Continua (HC) is characterized as a TAC in ICHD-3 and is a primary, continuous, strictly one-sided, moderate to severe headache with cranial autonomic symptoms and periodic moderate or greater intensity exacerbations. By definition, this headache is exquisitely indomethacin-responsive.

Because of the autonomic features, it overlaps more with TACs than CTTH or CM. For these reasons, the main section on HC is now included in Chapter 2 on the TACs. However, for completeness, the ICHD-3 criteria for HC are also in Table 4.5.

Differential Diagnosis on Hemicrania Continua

A few clinical pearls are noted below on differential diagnosis for HC. If you have not read the section in Chapter 2, do so now before reading on.

Table 4.5 Hemicrania continua (HC), ICHD-3 criteria

A. Unilateral continuous CDH for > 3 months with moderate to severe exacerbations
B. At least one of the following, ipsilateral to the side of pain:
   1. Conjunctival injection
   2. Lacrimation
   3. Nasal congestion
   4. Rhinorrhea
   5. Ptosis
   6. Miosis
   7. Eyelid edema
   8. Forehead or facial sweating or flushing
   9. Sense of fullness in the ear
   10. Restlessness or agitation or worsening of pain with movement
C. Complete response to therapeutic doses of indomethacin, with a trial up to at least 225 mg/day
D. Not secondary

- *Remitting subtype:* Interruptions of pain for ≥ 1 day without treatment
- *Unremitting subtype:* Continuous pain with no remission periods of pain for ≥ 1 day for ≥ 1 year

In a patient with continuous side-locked daily headache, the first step is to exclude secondary causes. Side-locked headaches in and of themselves merit a work-up. Switching sides is reassuring for primary or benign diagnosis.

The differential on a continuous *primary* side-locked headache includes HC, cervicogenic headache, CM with or without MOH, and other TACs which can have interictal continuous headache such as Cluster Headache (CH) and Paroxysmal Hemicrania (PH).

The late Dr. John Edmeads of Toronto listed many of his criteria for cervicogenic headache, and although not part of ICHD-3, they are worth repeating here: (1) the headache should be unilateral and the pain should move from the neck forward, (2) the patient should note the neck is a significant component of the pain, (3) the headache should not meet ICHD criteria for a different definable headache disorder, and (4) the headache should respond to differential or placebo-controlled upper cervical, medial branch, or facet blocks. Since HC generally has autonomic features, would not respond to the blocks, and is indomethacin-responsive, these disorders can be distinguished with an indomethacin trial.

Remember, the indomethacin should be 100 % effective, like a key in the lock, for HC. In degenerative conditions such as cervicogenic headache, the anti-inflammatory properties of indomethacin can provide partial relief. Invasive upper cervical blocks do not help HC, although partial relief can occur with occipital nerve blocks in HC.

CM with or without medication overuse will not be 100 % responsive to indomethacin and is treatable with onabotulinumtoxinA (onabot). There is no prospective controlled evidence that onabot works for HC.

Also, the remarkable response to indomethacin in HC occurs with or without a wean of overused medications. Once the indomethacin is working, the wean of inef-

Table 4.6 Clinical pearls on the differential diagnosis of Hemicrania Continus (HC)

- Foreign body sensation in the ipsilateral eye or itchy eye—this generally does not occur in CM with or without MOH, in cervicogenic headache, or in the other TACs
- Overuse of other NSAIDs—this can occur in PH, cervicogenic headache, or MOH, but does raise the question of HC
- Average baseline headache intensity is 6/10, which often helps distinguish HC from the "ghost headache," the mild interictal continuous pain of CH or PH
- Exacerbations can mimic migraine instead of cluster, and the exacerbations can be triptan-responsive. Exacerbations occur frequently, often daily or near daily. This can make distinguishing HC from CM or the other TACs more difficult
- An indomethacin trial may be the only way to distinguish HC with migrainous exacerbations from CM with MOH or even cluster
- Agitation and aggression during the exacerbations is common, as in cluster, but not PH, cervicogenic headache, or CM
- Dislike of light and noise can be ipsilateral and entirely unilateral in all of the TACs, but unilaterality of photophonophobia is very rare in CM and nonexistent in cervicogenic headache
- The indomethacin trial should be to at least 225 mg/day. 1/3 of patients in the Cittadini and Goadsby case series required at least 300 mg/day
- Indomethacin responsiveness does not prove that a patient has primary HC, and an imaging study is necessary

fective overused medications in HC patients can be done easily, generally with great patient cooperation and enthusiasm, unlike the more challenging MOH situation.

The exacerbations of severe headache in HC can be more migrainous than cluster-like, sometimes adding to the diagnostic dilemma. These exacerbations can even be triptan-responsive. When in doubt, an indomethacin trial is in order.

As noted in Chapter 2, CH and PH can manifest continuous interictal pain in as many as 1/3 of patients. This continuous pain in the other TACs is generally of lower intensity compared with the 6/10 average intensity of the continuous unilateral pain of HC.

However, overlap can occur. The attacks in CH and PH can look just like the severe exacerbations in HC, and the continuous one-sided headache can be of intermediate pain levels in any of the three disorders. If the exacerbations are short, as in PH, since PH and HC are both indomethacin-responsive, it can be impossible to distinguish them clinically. This is rare, however. Generally, the short, frequent exacerbations in PH and the higher intensity continuous pain and longer exacerbations of HC tell the clinician which is which (see Table 4.6).

New Daily Persistent Headache

The ICHD-3 criteria for NDPH are the abrupt onset of a primary CDH with no specified features at a specific time remembered by the patient. The requirement is that the onset of CDH occurs within 24 h (see Table 4.7). The diagnosis should be made on the basis of the sudden onset of CDH of any phenotype with no secondary cause.

Table 4.7 New Daily Persistent Headache (NDPH), ICHD-3 criteria

A.	Abrupt onset, a clear and remembered beginning within 24 h, of continuous chronic daily headache and no remissions, no pain-free periods
B.	Headache is continuous for > 3 months
C.	Not secondary

NDPH was covered in Chapter 3, Diagnosis of Other Primary Headaches, because that is where it is placed in the ICHD-3. However, as it overlaps with CM and CTTH and is so problematic, it is discussed again here.

A case series in 2010 by Robbins and colleagues of 71 patients with abrupt onset of CDH found that more than half of them had migrainous features. Two groups of NDPH, those with abrupt onset resembling CTTH and those resembling CM, did not differentiate prognostically or therapeutically.

The key to the diagnosis lies more with the patient's recollection of abrupt onset, and not with the character of the daily headaches. Robbins and colleagues noted three temporal profiles: continuous headache from onset and not remitting, complete remission or with residual headache < 5 days/month for ≥ 3 months, and a relapsing/remitting form, with runs of daily headache and periods of headache freedom.

Additional features that could be useful diagnostically include that almost half of the patients with abrupt-onset CDH had family histories of frequent headaches. Also, almost half remembered a specific trigger such as an antecedent respiratory illness or a stressful life event.

Clinically, one of the key points in diagnosing patients with daily headache is to ask if they had a period of transformation, of gradually increasing frequency of headache days, or if they had a sudden and precipitous onset. Unless explicitly asked, clinicians run the risk of missing the diagnosis of NDPH, a diagnosis necessary to make because of its difficulty in treatment.

The more recent the onset of NDPH, the more concern there should be for a secondary cause. The ICHD-3 requires at least 3 months of continuous headache, and a primary NDPH is obviously more likely in those patients who have had years of continuous daily headache and who had the required abrupt onset.

Potential secondary causes of NDPH include infection (such as HIV or Lyme), cerebrospinal fluid (CSF) leak, vascular causes, metabolic causes, and neoplasm (see Table 4.8).

A clinical history of positional headache (better lying down), tinnitus, photophobia, neck pain, and hyperacusis suggests CSF leak, even without antecedent trauma. MRI without and with contrast, to look for the pachymeningeal enhancement or brain sag associated with CSF leak, is necessary before diagnosing relatively recent-onset NDPH.

Vascular causes, when the NDPH duration is on the short side, that is, months' not years' duration, include dissection, vasculitis, pituitary apoplexy, arterial bleed from aneurysm or arteriovenous malformation (AVM), or cortical vein thrombosis. These vascular causes of abrupt-onset daily headache are often associated with

Table 4.8 Potential secondary causes of abrupt onset of daily headache

• CSF leak should be suggested by positional headache, tinnitus, photophobia, hyperacusis, and neck pain. Diagnosis can be established with an MRI without and with contrast showing pachymeningeal enhancement and/or brain sag
• Infection can present abruptly, so remember HIV and Lyme and other subacute meningo-encephalitides
• Vascular causes can include dissection, pituitary apoplexy, vasculitis, arterial bleed from aneurysm or AVM, or cortical vein thrombosis, so MRA/MRV may be necessary, depending on how close the patient is to the onset of the daily headache
• In the elderly, think subdural hematoma

Table 4.9 Clinical pearls in diagnosing New Daily Persistent Headache (NDPH)

• Patient should remember the approximate date of onset
• Any phenotype
• Some NDPH remits or is relapsing/remitting
• Almost half of NDPH patients remember a trigger such as a preceding respiratory illness or stressful life event
• Almost half of NDPH patients have family histories of frequent headaches

thunderclap onset. Magnetic resonance angiography (MRA) and magnetic resonance venography (MRV) may be necessary, depending on how close the patient is to the onset of the daily headache.

Metabolic causes for daily headache, such as thyroid disease, rarely can have abrupt onset. In the elderly, consideration for a subdural hematoma, even in the absence of trauma should always be given.

Some clinical pearls for diagnosing NDPH are included in Table 4.9.

Chronic Migraine

Unlike the other three CDHs, CM is a controversial diagnosis, with multiple suggestions and positions on diagnostic criteria vying for position. The history of the terms used in diagnosis helps the clinician attempting to accurately diagnose this group of patients.

CM is often used to mean CDH. Thus, many clinicians include both *primary* CDH and *secondary* CDH (MOH, analgesic rebound) in the definition of CM. This was done historically and is based on the similarity of presentation in patients with CDH. Rebound headache has often been telescoped into CM, so diagnosis of MOH is also briefly covered here.

Silberstein, Mathew, Lipton, and colleagues, in 1994, suggested that since episodic migraine transforms into CDH, the term for the daily headache patient should be transformed migraine, with or without medication overuse. The term transformed migraine is still in widespread use and simply means a patient with

Table 4.10 Criteria for transformed migraine. (Silberstein–Lipton, 1994)

1. The headache is not a CDH that develops de novo in a previously headache-free subject, that is, it is not NDPH
2. One of the following three exists:
   a. A prior history of ICHD-defined migraine
   b. A period of escalating headache frequency
   c. Concurrent superimposed attacks of migraine that fulfill ICHD criteria for episodic migraine
3. The patient has CDH, that is, headache > 4 h/day untreated for at least 15 days/month for > 3 months in a row
4. TM can occur with or without medication overuse

Table 4.11 ICHD-3 criteria for chronic migraine

A. Headache (tension-type and/or migraine) on ≥ 15 days per month for > 3 months
B. Occurring in a patient who has a preexisting diagnosis of migraine
C. On ≥ 8 days per month for > 3 months headache at least with one of the following:
   1. Criteria for migraine
   2. The patient feels it is migraine
   3. Successfully treated by triptan(s) or ergot
D. No other cause
E. If medication overuse is present, the ICHD-3 states, "patients meeting criteria for both chronic migraine and for medication-overuse headache should be given both diagnoses. After drug withdrawal, migraine will either revert to the episodic subtype or remain chronic, and be re-diagnosed accordingly"

Table 4.12 ICHD-3 criteria for medication overuse headache

1. Headache on ≥ 15 days/month in a patient with a previously established headache disorder
2. Regular overuse for > 3 months of ≥ 1 acute headache drugs

preexisting episodic migraine has gradually transformed to primary or secondary CDH (see Table 4.10).

The ICHD-2 declared that since MOH is a secondary headache, the term CM should be reserved for primary transformation to daily headache. In what turned out to be an ill-fated and short-lived mistake, the official ICHD-2 criteria required the patient to have headache meeting criteria for migraine at least 15 days/month, that is, reaching a migraine level almost daily without medication overuse.

The ICHD-3 criteria for CM require the patient with CDH to reach migraine level or respond to migraine-specific treatment at least 8 days per month out of their daily headaches. Once again, rebound patients are excluded, as they have secondary CDH (see Tables 4.11 and 4.12).

The ICHD-3 criteria for MOH are CDH with enough acute medication intake to propagate the rebound. Criteria are simply taking enough acute medication for more than 3 months to be associated with CDH (see Table 4.12).

The ICHD-3 continues to separate the number of days of intake necessary to generate MOH for different medications. While it turns out there is a hierarchy of

Table 4.13 Clinical pearl on medication overuse headache

• Patients with MOH develop a new headache or a marked worsening of their preexisting headache with their medication overuse

susceptibility to acute medications in terms of likelihood for initiating rebound, it is not the same as listed in ICHD-3. This discussion of rebound will be covered more extensively in Chapter 13.

A good rule of thumb is that if a patient has CDH and is taking acute medications at least 10 days per month, that patient likely has MOH. Fewer days of butalbital (5 days or use or more per month) or opioids (8 days of use or more per month) can also cause MOH (see Table 4.13).

The discussion section under MOH in the ICHD-3 states that these patients "develop a new headache or a marked worsening of their pre-existing headache" with their medication overuse. While not part of the ICHD-3 criteria, this finding is extremely helpful diagnostically in diagnosing MOH.

The ICHD-3 diagnostic issue is how to proceed in a patient with CDH and medication overuse. The patient could have primary CM, and the medication overuse is not playing a role. Or the patient could have MOH, and with a wean reverts to episodic migraine.

The way the ICHD-3 works is seen in the following two diagnostic scenarios:

Scenario 1. You have a patient with episodic migraine who overuses combination analgesics and starts to rebound and develops daily headache. Per ICHD-3, you diagnose both CM and MOH at that first visit.

You take the patient off the analgesics, and the patient goes back from daily headache to discrete episodes of migraine with no headache at all in between. Now you know, the patient initially had MOH and currently has episodic migraine without aura, so you change your diagnosis once this pattern has established itself.

Scenario 2. You have a patient with episodic migraine who overuses combination analgesics and develops daily headache. Per ICHD-3 you diagnose both CM and MOH at that first visit.

You take the patient off the analgesics and the patient continues to have daily headache 6 months later, but is taking no acute medications. Now you know, the patient actually has primary CM and has daily headache without rebound acute medications provoking and continuing the daily headache. You can remove the diagnosis of MOH; this patient has just CM.

In 2010, regulatory randomized controlled studies on the use of onabotulinumtoxinA (onabot, BOTOX) were published in which onabot or vehicle was given subcutaneously for CDH. In those studies, a mixture of patient diagnostic criteria was used for inclusion, including primary CM and MOH for the most part excluding opioid and butalbital rebound. Patients were required to have headache-free periods each month (not a requirement for any CDH diagnosis), and NDPH patients were also excluded. The reason given for studying the treatment of this mixture of primary and secondary headaches was that the phenotype of these patients is similar.

Table 4.14 Criteria for CDH/"chronic migraine" as studied in the onabotulinumtoxinA prevention studies

1. CDH
2. Must have ≥ 4 distinct headache episodes, each lasting ≥4 hours. (cannot be continuous 24/7 headache)
3. MOH allowed but not overuse of butalbital or opioids
4. NDPH excluded

The investigators of onabot lumped all of the subjects into what they called "chronic migraine." This was not CM by ICHD-3 criteria, as it included both secondary CDH (MOH) and primary CM, and also required times of clearing of headache per month, not in the ICHD-3 criteria for CM. These studies served as the regulatory submission for onabot for CDH, but the request was approval for onabot for CM.

Onabot was approved for CM in the USA in October of 2010. The US prescribing information approved by the Food and Drug Administration (FDA) defines CM as headache present for at least 15 days per month for at least 4 h per day, which is CDH.

The reason for belaboring this point is diagnostic: The "chronic migraine" studied in the onabot studies does not correlate with true primary CM by strict ICHD-3 criteria. It also does not include all MOH by ICHD-3 criteria. The "chronic migraine" of the onabot studies is actually a blend of diagnoses and requirements not fitting any one of the established and validated ICHD diagnoses of either primary or secondary CDH (see Table 4.14). The FDA-approved onabot prescribing information definition of "chronic migraine" is just CDH with or without medication overuse, which may be liberating, in terms of diagnosing and treating the phenotype of CDH (see Table 4.15).

Conclusions on Diagnosis of Chronic Daily Headache

There are 4 primary types of CDH, and they are HC, CTTH, NDPH, and CM. There is not much controversy over diagnosing the first two. The diagnosis of NDPH is made on the basis of abrupt onset (within 24 h) of primary CDH of any phenotype, continuous from onset (see Table 4.16).

When diagnosing CM, it is important to make clear whether the clinician is diagnosing the primary CM of the ICHD-3, that is, transformed migraine without medication overuse, or whether one is diagnosing a phenotype of CDH including MOH. Technically, the ICHD-3 diagnosis of CM should not include secondary causes of CDH, but it is allowed to diagnose both CM and MOH prior to weaning overused medication in the setting of CDH.

It is also important to note that some therapy trials, such as that for onabotulinumtoxinA, used hybridized inclusion criteria, involving some features of the

Table 4.15 FDA-approved definition of chronic migraine in onabot prescribing information

• Chronic migraine is headache ≥ 15 days/month for ≥ 4 h/day (= chronic daily headache with or without medication overuse)

Table 4.16 Concluding pearls on diagnosis of primary chronic daily headache

• There are only 4 validated forms of primary CDH according to the ICHD-3: CTTH, HC, NDPH, and CM
• CTTH is a low-level featureless headache, with minimal impact
• HC is a unilateral moderate headache with periodic severe exacerbations, accompanied by autonomic signs. HC is defined by its indomethacin responsiveness
• NDPH is diagnosed as abrupt-onset primary CDH of any phenotype
• Pure ICHD-3 CM is a primary CDH in which a patient transforms from episodic migraine to CDH without secondary causes, including MOH
• MOH is not a primary CDH; it is characterized by overuse of enough acute medication to transform a patient to secondary CDH
• The term "Chronic Daily Headache" (CDH) is not an ICHD-3 term and generally refers to the phenotype of CM + MOH
• The FDA-approved definition of "chronic migraine" is CDH, both primary and secondary, with any phenotype of CDH

ICHD criteria for CM and some secondary MOH criteria. The diagnostic description of CM in the prescribing information for onabotulinumtoxinA for "chronic migraine" is that it is just CDH, primary or secondary. When evaluating a patient, it may be useful to use pure diagnostic criteria to plan treatment. On the other hand, there is a liberating aspect to just using these FDA-approved criteria in lumping all patients with CDH into CM (see Table 4.15). Treatment of MOH will be covered in Chapter 13; treatment of CM is covered in Chapters 14 and 15.

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Part III
Diagnosis of Addiction, Substance Use, and Headache

Chapter 5
Diagnosis of Addiction, Substance Use, and Headache

Mark J. Stillman, Jennifer S. Kriegler, Edward C. Covington, and Steven J. Krause

Introduction

This chapter is divided into two sections. In Part 1, we discuss definitions related to substance use disorder. Part 2 describes aberrant drug behavior as it relates to management of headache.

Part 1: Definitions Related to Substance Use Disorder

The task of assessing substance use disorders in clinical populations represents a significant challenge to the practicing headache clinician, indeed for all health-care providers. The use of potentially psychoactive medications is highly stigmatized in mainstream American society, and frequently subject to legal, social, and employment sanctions.

As a consequence, patients frequently hide, minimize, and distort their histories regarding the use of these substances. Health-care providers may thus find themselves attempting to help patients without a complete and reliable understanding of the patient's use of both prescribed and nonprescribed medications. Additionally, the task of differentiating appropriate from inappropriate medication use becomes particularly problematic in the context of headache and other chronically painful conditions, as opioids, benzodiazepines, and sedative/hypnotics are frequently prescribed to treat these conditions and their common comorbidities.

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Table 5.1 Definitions related to substance use

- Dependence
  - The development of a stereotypical withdrawal syndrome if the drug is abruptly discontinued or if an antagonist to the drug is administered
  - Dependence is a manifestation of receptor physiology and will occur in any individual who is exposed chronically to a drug that binds to receptors, whether or not the individual has addictive tendencies
- Tolerance
  - Diminishing effect of a substance resulting from ongoing use
  - Tolerance is defined by a requirement to increase doses in order to maintain a stable therapeutic benefit or diminishing medication effectiveness in the context of a stable dose
  - Tolerance is common with opioids and some other substances, but is not sufficient to diagnose addiction
- Addiction
  - A neurobiological disease with genetic, psychosocial, and environmental factors which manifests as maladaptive drug use pattern characterized by impairment of functioning following initiation of a substance, loss of control over substance use, and preoccupation with use of the substance
  - Addiction needs to be carefully differentiated from the loss of functioning resulting from the headaches themselves
  - Addiction is *not synonymous* with physical dependence, which results from the chronic use of opioid analgesics
- Substance use disorder
  - DSM-5 has abandoned the prior terms *abuse* and *dependence* in favor of *substance use disorder,* conceptualized as a continuum of *substance-related impairment from mild to severe*
  - Dependence and tolerance, when they occur in the context of medications taken as prescribed and under medical supervision, are no longer considered evidence of a substance use disorder
- Drug misuse
  - The use of any medication for nonmedical purposes or for an unintentional purpose
  - Drug misuse may or may not be deliberate, and the drug misuse is *not* intended for the induction of a euphoric sensation in this definition
- Drug diversion
  - The transfer or movement of controlled substances to illegal channels
  - Drug diversion can be perpetrated by the patient or health provider (or both)
- Aberrant drug-related behavior (ADRB)
  - Behavior outside the boundaries of an agreed-upon treatment plan

Addiction has Frequently been Summarized as "Use Despite Harm"

The *Diagnostic and Statistical Manual of Mental Disorders,* fourth edition (DSM-4) defined substance dependence as "a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues use of the substance despite significant substance-related problems." The *Diagnostic and Statistical Manual of Mental Disorders,* fifth edition (DSM-5) refers to a "maladaptive pattern of substance use leading to clinically significant impairment or distress."

Table 5.2 Pearls on addiction, dependence, and tolerance

- Addiction manifests as a maladaptive drug use pattern characterized by impairment of functioning following initiation of a substance, loss of control over substance use, and preoccupation with use of the substance
- Dependence and tolerance, in the context of prescribed medications used properly under medical supervision, are no longer considered evidence of a substance use disorder
- Even with a clear understanding of the criteria for diagnosing a substance use disorder, clinical assessment remains difficult, particularly when both positive and negative medication effects are present

Both definitions require the clinician to judge the particular antecedents of an individual patient's disability, and these may be quite uncertain (Table 5.1). For example, one frequently encounters patients taking opioids under prescription for headaches who nonetheless complain of severe and unremitting pain, endorse symptoms of depression, and spend much of the day in a dark bedroom to the neglect of their usual activities. Are such patients demonstrating the debilitating consequences of chronic headaches, are they suffering from a substance use disorder, or are they caught in a medication overuse headache (MOH) cycle without disordered substance use?

"Use despite harm" implies that the harm results from the use, but the actual causal sequence is rarely so clear (Table 5.2).

Factors Complicating Assessment of Substance Use Disorders in Headache Patients

Psychoactive substance use and functional impairment frequently coexist with headaches, and clinicians should not prejudge whether observed impairments represent a consequence of headache, substance use, both, or some other factors. Careful attention to the history with clinical acumen must be combined to differentiate these possibilities.

Patients frequently underestimate their use of psychoactive substances, due to deliberate deception, embarrassment, or simple inattention. In the past, traditional criteria for diagnosing substance use disorders emphasized tolerance and dependence. While these criteria had value as evidence of ongoing substance use, the previous focus on them considered all use of habit-forming medications as illicit, even if taken under appropriate medical supervision and within the bounds of prescribed doses.

Medications taken for headache may have both substantial benefits and side effects, rendering assessment of their value ambiguous. Patients and providers may disagree on the relative importance of each (Table 5.3).

The evaluation of substance use disorders should be completed as part of the initial assessment of headache. If the patient shows no evidence of current controlled substance use, then inquiry regarding prior disordered substance use should be completed in the context of a general medical history. Research has suggested

Table 5.3 Factors complicating assessment of substance use disorders in headache patients

- Use of psychoactive substances and functional impairment frequently coexist with headaches
- Health-care providers should not prejudge whether observed impairments represent a consequence of headache, substance use, both, or something else. Careful attention to the history is required to differentiate these possibilities
- Patients frequently underestimate their use of psychoactive substances, whether due to deliberate deception, embarrassment, or simple inattention
- In the context of prescribed medications used properly under medical supervision, dependence and tolerance are no longer considered evidence of a substance use disorder
- Medications taken for headache may have both substantial benefits and side effects, rendering assessment of their value ambiguous, and patients and providers may disagree on the relative importance of each

Table 5.4 Pearl on assessing for addiction

- The single question "Has anybody close to you expressed concern about your substance use?" is highly predictive of substance use disorders, and can be used to screen patients requiring further evaluation

Table 5.5 General guidelines for substance use assessment in the context of headache care

- When taking a medical history, pay careful attention to the chronology of medical symptoms, medication use, and functional activity, which frequently reveals whether a substance use disorder predated headache care, and can often prevent erroneous causal inferences
- Ask questions regarding past and present substance use of all new patients, and reassess periodically with established patients. If delivered in the same "matter-of-fact" tone as other medical history inquiries, these questions seldom offend patients
- Whenever possible, obtain medical records from previous providers and review the state's prescription monitoring program, as patients' self-reports may or may not be reliable
- Whenever possible, include a collateral interview with spouses, parents, children, or other intimates as appropriate. Openly inquire whether they have any concerns about the patients' use of prescribed or nonprescribed medications
- Evaluate functioning, disability, or headache impact at each patient visit, using a brief instrument such as the Headache Impact Test (HIT-6) or the Migraine Disability Assessment Scale (MIDAS). These tools provide an additional check on whether the use of particular medications have led to improvements, deterioration, or no change
- A patient's stated concern with the availability of pain medications may not necessarily indicate substance misuse, but an understandable concern with analgesia. However, patients who insist on continuing controlled substances even in the absence of demonstrated efficacy or after being informed that such substances contribute to exacerbation of their headaches are of greater concern
- As noted above, and worth restating, obtain records of controlled substance prescriptions from state databases or prescription monitoring programs when available

that the single question "Has anybody close to you expressed concern about your substance use?" is highly predictive of substance use disorders, and can be used to screen patients requiring further evaluation (Tables 5.4, 5.5, and 5.6).

Part II of this chapter elaborates further on aberrant drug behavior by patients. However, the health-care provider's attitude and manner in making a referral for further substance use evaluation make a considerable difference in whether patients

Table 5.6 Findings that deserve further inquiry in evaluating for substance use disorders

• Renewal of prescriptions prior to their scheduled completion
• Multiple prescribers of controlled substances, particularly if they come from different practice groups, or if prescription periods overlap
• Multiple pharmacies filling prescriptions

Table 5.7 Guidelines for referring a patient for substance use evaluation

• State openly that your concern about the patient's use of controlled substances is directly related to the risk that this use will result in exacerbation of their headaches
• Make clear that you recommend all patients taper and discontinue their use of opioids, sedative/hypnotics, and benzodiazepines
• Substance use evaluation is indicated only when the provider has concerns that the patient's ability to accomplish this taper needs appropriate supervision
• Neither state nor imply any moral judgment about the patient's behavior. Your role as an advisor and advocate is to promote a patient's health, and all recommendations should be discussed in this context
• Remind the patient that discontinuation of controlled substance treatment is not the end of all treatment, and that you remain eager to work with them on continued management of their headaches using any treatments that are available, safe, and consistently effective

will perceive the referral as one motivated by genuine concern, or merely as an effort to deflect care to another provider (Table 5.7).

Part II: Aberrant Drug Behaviors and Chronic Headache Disorders

For more than three decades, data have been accumulated suggesting that certain medications, used at known frequencies, such as opioid analgesics, barbiturates, and other sedative hypnotics, as well as more common analgesics, can transform episodic migraine and tension-type headaches into refractory, generally daily or near-daily headaches. Headache experts and specialty clinics are often confronted with patients suffering from chronic daily headaches due to inappropriate use, or overuse, of analgesics. In cases in which the offending drug is easily obtained, such as over-the-counter analgesic medications, the treatment involves simple detoxification and institution of appropriate acute and preventive therapies. Specific methods for wean or detoxification are discussed in greater detail in Chapters 13 and 16.

Use of stronger analgesics and other controlled substances occurs commonly in the treatment of severe pain and suffering in the community and in emergency rooms. These agents include opioid analgesics, sedative hypnotics, such as barbiturates and benzodiazepines, sleep-inducing agents, and centrally acting muscle relaxants such as carisoprodol and cyclobenzaprine.

Table 5.8 Opioids in chronic noncancer pain: not a good idea

- In patients with noncancer pain, opioids may actually exhibit a ceiling effect and lead to rapidly developing tolerance and hyperalgesia
- Dose escalations of opioid analgesics, in an attempt to offset escalating pain in a noncancer patient already on large doses, is a questionable practice
- The granting of prescriptive privileges for opioids and controlled substances to poorly educated or inexperienced practitioners has led to rising incidence in accidental drug overdoses, deaths, and drug diversion

No one questions their use in symptom relief of patients who are postoperative or suffering from cancer-related pain or some other terminal illness. Opioid analgesics remain the most versatile and effective class of pain relievers in medicine.

However, there are some pain researchers and clinicians in the US and Europe who feel that consumption of *any* opioid or sedative hypnotic undermines *any* effort to prevent migraine headaches and adversely affects the body's integral antinociceptive system. A single dose of opioid was noted to increase the risk of transformation to daily headache in the population in the American Migraine Prevalence and Prevention (AMPP) study.

There is similar concern for the use of opioid analgesics resulting in adverse outcomes in the treatment of chronic noncancer-related pain, similar to the risk in their use in primary headaches. The Patient Safety Subcommittee of the American Academy of Neurology requested a review of the science and policy issues concerning the burgeoning epidemic of prescription opioid abuse, drug diversion, and morbidity and mortality from opioid overdoses. The author, Professor Gary M. Franklin, who has extensive experience in health-care policy, makes an argument that disagrees with accepted pain practices since the late 1980s. This argument is summarized as follows: (1) Opioids may exhibit a ceiling effect and lead to rapidly developing tolerance and hyperalgesia when used in patients with noncancer pain, (2) dose escalations of opioids, attempting to offset accelerating pain in a noncancer patient already on large doses, is a questionable practice, and (3) allowing poorly educated or inexperienced health-care providers to prescribe opioids and controlled substances without additional training or supervision has led to the rise in accidental drug overdoses, deaths, and drug diversion (Table 5.8).

Why, then, do so many patients appear in specialty clinics with chronic headache disorders related to drugs or drug withdrawal? There are numerous reasons why patients with migraine and tension-type headaches continue to be managed with medications now known to promote headache chronification. In spite of attempts to educate the medical community for more than 20 years, many primary-care physicians remain unaware of or unconcerned about the deleterious effects of overuse of acute analgesics in migraineurs and other headache sufferers (Table 5.9).

For some patients, a comorbid painful condition requires the use of opioids and sedative hypnotics, and these agents are prescribed in spite of a coexistent headache problem. For other patients, the specific migraine abortive agents are either too expensive or limited by payers to amounts that underestimate need.

Table 5.9 International Classification of Headache Disorders, third edition, beta version (ICHD-3) list of disorders associated with medication overuse

Name	ICHD-3 code
Headache attributed to a substance or its withdrawal	8
Headache attributed to use of or exposure to a substance	8.1
Cocaine-induced headache	8.1.6
Medication overuse headaches	8.2
Simple analgesic overuse headache	8.2.3
Opioid overuse headache	8.2.4
Combination analgesic overuse headache	8.2.5
Medication overuse headache attributed to multiple drug classes not individually overused	8.2.6
Medication overuse headache attributed to unverified overuse of multiple drug classes	8.2.7
Headache attributed to substance withdrawal	8.3
Caffeine-withdrawal headache	8.3.1
Opioid-withdrawal headache	8.3.2
Headache attributed to withdrawal from chronic use of other substance	8.3.4

While some insurance companies place onerous quantity limits without an evidence base for triptans, combination tablets containing butalbital with or without codeine are cheap, generic, and can be ordered with refills. To a busy clinician, reverting to generic, acute analgesics that have been used for generations is easier than writing one more letter of medical necessity to a tight-fisted insurance provider. And in an unfortunately all-too-common situation, some health-care providers find it much less noxious to write for a "reasonable" number of mild opioid or combination analgesics (with refills sufficiently generous to keep the patient at bay for up to a year) than to confront a hostile, aggressive patient in the middle of a busy clinic schedule!

A small percentage of patients gets no relief with any medication other than opioids. The size of this population is not known, but when a potentially more beneficial therapy, such as an interdisciplinary pain program, is either not available or not feasible, in this population, chronic opioid therapy *might* represent a reasonable alternative approach. Guidelines for the institution of chronic opioid therapy in cases of refractory primary headache disorders have been published by Dr. Joel Saper and colleagues in 2010, and this reference is in the suggested reading at the end of this chapter.

For the practitioner with no other option but to travel this path, it cannot be emphasized enough that he/she must be very familiar with the use of such agents in this patient population. The alternative is to refer the patient to a specialty practice knowledgeable in the use of opioids and other controlled substances and cognizant of their attendant risks. The discussion that follows is meant to introduce the problems and risks that accompany the use of opioids and other controlled drugs in the chronic headache and chronic noncancer patient population.

Table 5.10 Evaluating the patient for potential aberrant drug-related behavior

- Risk stratification (if the patient is to continue to take any scheduled drugs)
- Ongoing monitoring if the patient has been detoxified, is being detoxified, or if it is determined he should be maintained on controlled medications
  - Point–of-care drug testing
  - Prescription monitoring programs

Assessing the Patient: Screening a Patient for Potential Aberrant Drug-Related Behavior

The headache consultant, confronted with a new chronic headache patient who is either self-referred or referred from another practice, must anticipate any and all possibilities. The practitioner must recognize and uncover any evidence of use of opioids and sedative hypnotics (overt or covert), as patients may or may not admit to using them. With regard to potential aberrant drug-related behavior (ADRB), a proper evaluation should include risk stratification, monitoring, and point-of-care testing (Table 5.10)

A significant body of literature now exists on the assessment of those patient characteristics predictive of ADRB. In an early retrospective study of two small populations of chronic noncancer (and nonheadache) pain patients managed with opioids in a tertiary-care teaching hospital, Dunbar and Katz segregated the two populations into opioid abusers and opioid nonabusers on the basis of clinically observed follow-up.

From their clinic records, they were able to cull six features that distinguished the opioid abuser group from the opioid nonabuser group. They noted that the patients that seemed to do well had social support systems, including being in a 12-step program.

More importantly and contrary to common belief, opioid pain treatment agreements did not predict success in those patients who exhibited prognostic signs of failure. The predictors for poor outcomes were: (1) unauthorized dose escalations, (2) more than two telephone calls to the office per month, (3) multisourcing, (4) lost or "stolen" prescriptions, (5) more than three unscheduled office visits, and (6) attempts to switch opioids or requests for a specific opioid (Table 5.11).

On the basis of similar experiences, others have itemized risk factors that should be assessed during the patient intake session. Webster and Webster listed the following historical items as risk factors for current or future ADRB: (1) Genetic predisposition, especially among males, based on evidence that genetic influence in abuse of marijuana, stimulants, and sedatives is shared across drug classes; (2) alcohol abuse, in accordance with evidence of polysubstance abuse among alcoholics; (3) illegal drug abuse, both current or historical; (4) psychological disorders (attention deficit hyperactivity disorder (ADHD), schizophrenia, bipolar disorder, obsessive–compulsive disorder (OCD)); and (4) preadolescent sexual abuse giving rise to posttraumatic stress disorder (PTSD) (see Tables 5.12 and 5.13).

Table 5.11 Clinical pearls: The six observed behaviors used to distinguish a population of opioid-abusing chronic pain patients from a population of nonabusers. (Adapted from Dunbar and Katz 1996)

1. Unauthorized dose escalations in a 3-month period
2. Frequent telephone calls to the clinic (>2 calls/month)
3. Multi-sourcing or doctor shopping to obtain additional prescriptions of controlled substances (without their doctor's knowledge)
4. Losing or reporting "stolen" opioid prescription
5. Greater than three unauthorized visits to the clinic without appointment during the year
6. Multiple attempts to change the opioid to another (i.e., "drug allergies") or specifically asking for a certain opioid

Table 5.12 Historical risk factors for addiction concerns

• Family history or genetic predisposition, especially in males
• Alcohol abuse
• Illegal drug abuse, current or historical
• Comorbid psychiatric disorders (ADHD, schizophrenia, bipolar, OCD, etc.)
• History of preadolescent sexual abuse
• PTSD

Several validated screening tools are available to use before initiating chronic opioid therapy in the chronic noncancer patient. While none has been formally studied in the chronic headache patient, and chronic opioid therapy is generally not recommended for primary headache sufferers, any one of these tools can be used to screen patients for the potential of current or future management difficulties. The Opioid Risk Tool (ORT), a five question self-administered questionnaire has been recommended for its high sensitivity and specificity in detecting increased risk for opioid abuse, misuse, and diversion (see Table 5.13).

Assessing the Patient: Confirming Misuse, Abuse or Diversion

As important as a good history is in the field of pain management, history taking is only as good as its source, and many patients will choose to withhold certain facts. In cases where interviewing the patient's family or significant other is not revealing, there are other methods available. Urine drug testing (UDT) and State Prescription Monitoring Programs (PMPs) provide means of confirming or refuting facts obtained from the patient and/or family.

UDT provides a low-cost, point-of-contact screening tool capable of detecting illicit and prescribed drugs 1–3 days after exposure. The test most commonly utilized in workplaces and emergency rooms tests for five mandated drugs of abuse: amphetamines, cannabinoids, cocaine, opioids, and phencyclidine. Emergency room laboratories may test for more than this, including alcohol, barbiturates, and

Table 5.13 Opioid risk tool (ORT). (Adapted from Webster and Webster 2005)

	Yes/no	Item score	Item score
Family history (parents and siblings)		If female	If male
Alcohol abuse	----	1	3
Illegal drug use	----	2	3
Prescription drug abuse	----	4	4
Personal history			
Alcohol abuse	----	3	3
Illegal drug use	----	4	4
Prescription drug abuse	----	5	5
Mental health			
Diagnosis of ADD, OCD, bipolar, schizophrenia	----	2	2
Diagnosis of depression	----	1	1
Other			
Age 16–45 years	----	1	1
History of pre-adolescent sexual abuse	----	3	0
Total			
Scoring			
0-3 low risk: 6% chance of developing problematic behaviors			
4-7 moderate risk: 28% chance of developing problematic behaviors			
>8 high risk: >90% chance of developing problematic behaviors			

Table 5.14 Urinary drug testing (UDT)

- Low-cost, point-of-contact, screening tool capable of detecting illicit and prescribed drug use 1–3 days after exposure
- Used in workplace and emergency room to detect the following:
  1. Amphetamines
  2. Cannabinoids
  3. Cocaine
  4. Opioid analgesics
  5. Phencyclidine
- If requested, laboratories can add other tests such as alcohol, benzodiazepines, barbiturates. It is wise to check what the laboratory screens beforehand and add those tests felt to be necessary
- Methadone is not routinely screened
- Cannabinoids can be detected for a week or more after use

benzodiazepines, but certain drugs, such as methadone, are not routinely part of the screen (see Table 5.14).

UDT objectively tests for compliance in patients who are being maintained on controlled substances and can also expose evidence of drug abuse, misuse, and diversion in the patient who denies them. UDT is able to detect cannabinoids for weeks after exposure and thereby serves as a clue to potential drug abuse in the future.

There are false positive tests of which the clinician should be aware. Phentermine and pseudoephedrine, the latter a common ingredient in over-the-counter sinus remedies, the former an ingredient, along with topiramate, in the prescription

Table 5.15 Pearls on false positives and false negatives in urine tox screens

- Pseudoephedrine, contained in some sinus medications, and sold under the brand name Sudafed, can cause a false positive urine tox screen for amphetamine
- Phentermine, by prescription alone, or contained along with topiramate in the prescription combination weight-loss medication sold under the brand name Qsymia, can cause a false positive urine tox screen for amphetamine
- Conventional urine tox screens generally do not pick up methadone (false negative)

Table 5.16 Prescription monitoring programs (PMPs) and what they provide

- Require all pharmacies to provide prescription information for Schedule II, III, and IV drugs (as mandated by the National All Schedules Prescription Reporting Act of 2005)
- Require sharing this information among all the states (not yet realized)
- Provides the following information to registered users:
  - The prescriber's name, title and address
  - The medication
  - When the prescription was written
  - The number of units prescribed and dispensed
  - The date and place (pharmacy) of dispensation
  - Dates of dispensation for the past year
- To find a given state's PMP, go to http://www.attcnetwork.org/topics/rxabuse/pdmpmap.htm

combination weight-loss medication Qsymia, can test positive on the amphetamine urine screen. Keep in mind that pseudoephedrine may be responsible for promoting chronification of episodic headache in the population of chronic daily headache sufferers (Table 5.15).

If there are any specific concerns, or if important clinical determinations are to be based on the presence of either a positive or negative test, confirmatory testing should be run on the urine with mass spectroscopy or gas chromatography (call the laboratory to order this), or a blood test should be ordered using these same techniques. This is particularly true for methadone, which is not detected routinely by enzyme-linked immunosorbent assay (ELISA) methods. The results will arrive after several days' delay and at a greater expense.

Another powerful tool that has recently emerged is the state PMP. The National All Schedules Prescription Electronic Reporting Act (NASPER) was enacted in 2005 by Congress and requires all pharmacies to report the prescription information for Schedule II, III, and IV medications. It also mandated the sharing of this information among the states, and the result has been the establishment, at the state level, of clinician-friendly access to this information. The available data include who wrote the prescription, the number of units prescribed, and when the prescriptions were written. In addition, also included are the pharmacy which dispensed the drugs and when they were dispensed. Other information provided may include how the prescription was paid for (Table 5.16).

It is recommended that this information be shared across state borders, and there are systems in which multiple states collaborate. Unfortunately, not all states have PMPs that are active, not all states have elected to collaborate, some medications

are only irregularly included (e.g., butalbital or tramadol), and some states only release prescription information to health-care providers within that state, a situation which allows for patient migration across state borders to obtain more scheduled medications, increasing risk.

For example, in the state of Ohio, the State Medical Board of Ohio and the Ohio State Board of Pharmacy have jointly sponsored the website known as the Ohio Automated Rx Reporting System (OARRS) since 2006 in an attempt to both assist health-care professionals in providing better treatment for patients and quickly identify drug-seeking behavior and drug diversion. The website resides at https://www.ohiopmp.gov/portal/contact.aspx and is available to the following individuals: "Prescribers, pharmacists and officers of law enforcement agencies whose primary mission involves enforcing prescription drug laws can register for an OARRS account. Registered prescribers may also permit delegates to register for an OARRS account in order to request Prescription History Reports on the prescriber's behalf."

Once registered as a state-licensed provider, one must provide a password and patient information, including first and last names, date of birth, gender, and home zip code in order to access the past year's profile of pharmacy-controlled substance purchases. For Ohio, access is currently available for the pharmacy dispensary records from additional states, including Arizona, Kansas, Minnesota Michigan, South Dakota, Connecticut, Kentucky, South Carolina, Virginia, and Indiana, a total of ten states, and the list has been growing.

The Illinois PMP allows out-of-state physicians to register after providing proof of licensure and completion of a phone interview. The Illinois site connects not only to Michigan, Kentucky, Connecticut, Arizona, South Dakota, Virginia, and Indiana but also to North Dakota, New Mexico, Colorado, and Iowa.

The Kentucky PMP, Kentucky All Schedule Prescription Electronic Reporting (KASPER), allows out-of-state physicians to register after providing notarized documentation of licensure. KASPER connects not only to Indiana, Ohio, Michigan, South Carolina but also to Alabama. And so, enterprising health-care providers can expand the access network for evaluating patient prescriptions.

However, many states illogically and foolishly do not allow out-of-state health-care providers to access the network, such as New York's Internet System for Tracking Over-Prescribing–Prescription Monitoring Program (I-STOP/PMP). This actually encourages addicted patients in states adjacent to New York to go into New York to access scheduled medications so that their own health-care providers cannot follow them!

In addition, the US Veterans Administration (US VA) health-care system does not contribute information about veterans' scheduled prescriptions to the states' PMPs. Once again, patients can cross in and out of the US VA system to avoid revealing their filling of prescription scheduled medications.

It should be obvious that the information gleaned will not include drugs obtained illegally by patients, but the information available from PMPs will help clinicians detect multi-sourcing and other ADRBs by patients. It will also highlight attempts at drug diversion by both prescribers and patients. This level of scrutiny by the State and the

Federal governments initially created fear among providers who were heavy prescribers of opioids (e.g., cancer pain specialists), but that fear has generally been unfounded.

The following website will allow a state-by-state search for signing up for available PMPs: http://www.pmpalliance.org. The best way forward for PMPs would be to pass a national PMP allowing all licensed health-care providers to access all scheduled prescriptions, regardless of state.

Conclusions on Aberrant Drug Behaviors and Chronic Headache Disorders

Specialists in headache medicine now recognize that the overuse of common analgesics, as well as the use of even small amounts of scheduled opioid analgesics or sedative hypnotics, can lead to the development of chronic headaches. Despite the best efforts to educate the medical community about more prudent prescribing practices, many patients continue to be referred to headache centers with refractory chronic headaches. The responsibility for the perpetuation of this problem does not rest solely on the practitioners' shoulders; there are patients in all communities who exhibit ADRBs. It should be the individual clinician's goal to detect and isolate this harmful trend so that patients can be offered more beneficial treatment. Tools are currently available to meet that challenge.

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Part IV
Diagnosis of Secondary Headaches

Chapter 6
Diagnosis of Major Secondary Headaches 1, the Basics, Head and Neck Trauma, and Vascular Disorders

MaryAnn Mays

Introduction

Headaches attributable to another disorder are classified as secondary headaches.

If during the investigation, no underlying disorder or disease process can be identified, the headache is then considered a primary headache.

The most common primary headache disorders include migraine, tension-type headache, and cluster headache. Although primary headaches are what are most often encountered in clinical practice, concern for secondary causes often requires that the clinician initiate an appropriate investigation with laboratory and neuroimaging studies.

There are numerous causes of secondary headaches, classified into eight groups by the International Classification of Headache Disorders, 3rd edition, beta version (ICHD-3); see Table 6.1). In order to cover the investigation and treatment of secondary headaches, two chapters have been set aside. Chapter 6 covers the basics of when to work up the possibility of secondary headaches, and also examines headaches stemming from head and neck trauma and vascular disorders. Chapter 7 covers secondary headaches caused by nonvascular disorders. Chapter 7 will also review those headaches not considered to be a primary headache disorder which are classified under painful cranial neuropathies, other facial pains, and other headaches.

Diagnostic Criteria for Secondary Headaches

By definition, either a secondary headache must be in close temporal relation to another disorder or there is evidence of a causal relationship (Table 6.2). Patients may present to the emergency department when a new headache is acute in onset or seek outpatient evaluation when the headache is subacute or chronic.

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Table 6.1 Secondary headaches and cranial neuralgias as classified by ICHD-3

- Headache attributed to trauma or injury to the head and/or neck
- Headache attributed to cranial or cervical vascular disorder
- Headache attributed to nonvascular intracranial disorder
- Headache attributed to a substance or its withdrawal
- Headache attributed to infection
- Headache attributed to disorder of homeostasis
- Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cervical structure
- Headache attributed to psychiatric disorder
- Painful cranial neuropathies and other facial pains
- Other headache disorders

Table 6.2 Diagnostic criteria for secondary headaches

A patient with secondary headache must have:

1. A disorder known to cause headaches
2. Two of the following in support of causation
   A. Headache onset temporally related to the onset of the presumed causative disorder
   B. Headache that improves or worsens in parallel with the improvement or worsening of causative disorder
   C. Characteristics of headache that are typical for the causative disorder
   D. Other evidence of causation is present, not specified
3. Headache cannot be attributed to another ICHD-3 diagnosis

It is easier to establish causation in acute onset headaches, but less so in those that are in a chronic pattern. Secondary headaches often lack defining features or may have characteristics that overlap with primary headaches. Causative disorders may also change the frequency or pattern of headache in an individual known to have a primary headache disorder. This can make the diagnosis of secondary headache challenging. Previously, the ICHD-2 criteria specified that the diagnosis of a secondary headache could be made only if the headache improved or remitted within 3 months of treatment of the causative factor. This stipulation is no longer required for diagnosis with the ICHD-3.

Clinical History of Secondary Headaches

Some patients with secondary headache have a preexisting history of primary headaches. Therefore, clinicians must be vigilant for any change in pattern, character, or overall worsening of the patient's headaches, as this may suggest a new secondary etiology.

Obtaining a detailed headache history is essential in the evaluation of secondary headaches. It is important to know whether the onset was preceded by an unusual event or provocation, whether there is a trend in pain intensity since onset, duration,

Table 6.3 The SNOOP mnemonic for red flags for secondary headache. (Adapted from Dodick 2003)

S ystemic symptoms (fever, weight loss) or
S econdary risk factors underlying disease (HIV, cancer, autoimmune disease)
N eurologic symptoms or abnormal signs (confusion, impaired alertness or consciousness, focal exam)
O nset: sudden, abrupt, or split-second (first, worst)
O lder age onset: new onset and progressive headache, especially in age > 50 (giant cell arteritis, cancer)
P attern change: first headache or different, change from
P revious headache history: attack frequency, severity or clinical features

associated symptoms, and particularly any reported focal neurological deficits. A workup is warranted in patients whose clinical history raises red flags or is atypical. As previously mentioned in Chap. 1, a useful mnemonic created by Dr. David Dodick for identifying red flags is "SNOOP" (Table 6.3).

Diagnostic Testing

Many patients, particularly those presenting with an episodic occurrence of a typical primary headache, do not warrant further investigation if their physical and neurological examinations are normal and no red flags are elicited in the history. Fortunately, less than 5 % of the patients presenting to the emergency department or physician's office with headache will be found to have significant underlying causative pathology. The majority of those pathological diagnoses are found in older individuals. In the pediatric population, it is even more unlikely to find an intracranial tumor as a cause of headache in the absence of any focal neurological signs or symptoms. Only a small percent of chronic headache suffers, ~ 1 %, will have significant findings on neuroimaging. Despite the relatively low odds of finding such pathology, clinicians still have to determine which patients, presenting with de novo or persistent headache, warrant investigation to uncover potentially treatable headache etiologies.

Some patients are so disabled by fear that a serious cause underlies their headache that investigation is appropriate to relieve their concerns. There are various medicolegal and managed care constraints that also influence ordering of diagnostic tests. Patients reporting typical common headache characteristics along with demonstration of a normal neurological examination may simply be reassured that the likelihood of finding an intracranial abnormality of significance, with imaging testing, is similar to the general population. The American Academy of Neurology (AAN) has published practice parameter guidelines for nonacute headache neuroimaging (Table 6.4) and the American College of Emergency Physicians (ACEP) has published recommendations for acute headache imaging (Table 6.5). These guidelines along with the clinician's clinical judgment can be helpful in deciding which patients warrant further testing.

Table 6.4 American Academy of Neurology (AAN) Guidelines: Neuroimaging recommendations for nonacute headache

Neuroimaging should be considered when:
• There are unexplained abnormal findings on the neurological examination
• Patients present with atypical headache features or headaches not meeting strict criteria for migraine or other primary headache disorders
• Patients have additional risk factors for secondary headache such as immunodeficiency, infection, neoplasm, or autoimmune disease
Neuroimaging is usually not warranted in patients with migraine and a normal neurologic examination
No evidence-based recommendations are established for the following:
• Presence or absence of neurologic symptoms alone
The following symptoms may indicate a higher likelihood of significant abnormality on neuroimaging, but absence did not lower the odds of this:
• Headache worsened by Valsalva maneuver
• Rapidly increasing headache frequency
• History of dizziness or lack of coordination
• History of subjective numbness or tingling
• History of headache causing awakening from sleep

Table 6.5 American College of Emergency Physicians (ACEP): Neuroimaging recommendations for acute headache

• Patients presenting to emergency rooms (ERs) with headache and new abnormal neurological signs (e.g., focal deficit, altered mental status, altered cognitive function) should undergo emergent[a] noncontrast head computed tomography (CT)
• Patients presenting with new sudden-onset severe headache should undergo emergent[a] head CT
• HIV-positive patients with a new type of headache should be considered for an emergent[a] neuroimaging study
• Patients who are older than 50 years and presenting with a new type of headache but with a normal neurologic examination should be considered for an urgent[b] neuroimaging study

[a] Emergent studies are those essential for a timely decision regarding potentially life threatening or severely disabling entities

[b] Urgent studies are those that are arranged prior to discharge from the emergency department

Diagnostic tests generally include imaging such as computed tomography (CT) or magnetic resonance imaging (MRI), and/or lumbar puncture (LP), and laboratory studies. Although routine blood tests are generally not useful in headache diagnosis, many clinicians order a baseline complete blood count (CBC) and chemistry profile (CMP) to include renal and liver function tests, along with a thyroid-stimulating hormone (TSH). Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are useful to exclude the diagnosis of giant cell arteritis (GCA) in patients aged 50 years and above. Other laboratory tests which may be helpful depending on the clinical situation are listed in Table 6.6.

MRI is the imaging study of choice in most instances because of its increased sensitivity in detecting pathology, as well as its higher resolution for normal structures. MRI with gadolinium is advised when there is concern for an inflammatory or infectious process, brain tumor, demyelinating disease, or low cerebral spinal fluid

Table 6.6 Useful diagnostic tests in diagnosis secondary headaches

Test	Indication
CBC, CMP, TSH	• Baseline studies • Hypothyroidism/hyperthyroidism
ESR, CRP, antinuclear antibodies (ANA), rheumatoid factor (RF)	• Giant cell arteritis • Systemic lupus erythematosus • Rheumatologic conditions
Hypercoagulable panel, lupus anticoagulant, anticardiolipin antibodies	• Stroke • Cerebral venous thrombosis • Vasculitis • Extensive white matter abnormalities
HIV antibody, Lyme antibody	• Infectious disease
Toxicology screen	• Opioid abuse • Medication compliance • Vasculitis secondary to illicit substances
Carboxyhemoglobin level	• Carbon monoxide intoxication
Genetic testing	• NOTCH 3 gene (cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy, CADASIL) • Mitochondrial DNA (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes, MELAS)
MRI with or without gadolinium (MRI generally preferred over CT)/ CT with or without contrast	• Tumor • Stroke • Hemorrhage: subarachnoid or intracranial • Hematoma: subdural or epidural • Chiari malformation • Vasculitis • Infection: encephalitis or meningitis
Magnetic resonance angiography (MRA)	• Aneurysm • Vascular dissection • Vascular malformation
Magnetic resonance venography (MRV)	• Cerebral venous thrombosis
Computer tomography angiography (CTA)	• Aneurysm, vascular dissection (higher sensitivity than MRA)
Computer tomography venography (CTV)	• Cerebral venous thrombosis
Conventional angiography	• Aneurysm • Vasculitis • Vascular dissection • Vascular malformation
Lumbar puncture	• Infection: meningitis or encephalitis • Carcinomatosis • Subarachnoid hemorrhage • Vasculitis • Idiopathic intracranial hypertension • Low CSF pressure headache
EEG	• Only indicated if concern for underlying seizure disorder associated with headache

headache. However, in the acute/emergency setting, or if contraindications to MRI exist, CT is still useful and will detect most abnormalities that cause headache.

Conventional cerebral angiography remains the best diagnostic tool for central nervous system vasculitis or for patients with subarachnoid hemorrhage (SAH). MR angiography/venography (MRA/MRV) and CT angiography/venography (CTA/CTV) are useful for detecting vascular lesions such as arterial stenosis, dissection, thrombosis, reversible cerebral vasoconstriction syndrome (RCVS), and aneurysm. CTA has a higher sensitivity than MRA in detecting cerebral aneurysms. When lesions are identified that require serial monitoring with repeat imaging, MRI is the preferred method due to risk of repeated radiation exposure with CT.

Electroencephalography (EEG) is only recommended in patients with headache who also report symptoms that may be suggestive of a seizure. EEG is no longer indicated in the routine evaluation of headache as a means to exclude a structural lesion.

In patients presenting to the ER with sudden-onset, severe headache and a negative noncontrast head CT scan result, LP should be performed to rule out SAH. The timing of the LP is important when interpreting results, as results may be falsely negative when performed within 12 h of onset of bleeding. Patients with signs of meningeal irritation should undergo an LP to exclude meningitis/encephalitis. As a general rule, cerebrospinal fluid (CSF) white blood cells (WBCs) should be less than 5, with 1 additional WBC allowed for each 700 red blood cells (RBCs) in the case of a traumatic tap. CSF protein is also elevated in the presence of RBCs, with an increase of 1 mg/dL for every 750 RBCs. CSF glucose should be two-thirds of serum glucose level.

Headache Attributed to Trauma or Injury to the Head and/or Neck

Following trauma to the head or neck, it is not uncommon for patients to report the onset of new headache. Headache attributed to trauma or injury to the head and/or neck may be associated with mild, moderate, or severe head injury, whiplash-type injuries, as well as following craniotomy. Traumas may worsen preexisting headache conditions. Post-traumatic headache (PTHA) is frequently associated with other somatic, psychological, and cognitive symptoms which are referred to as post-concussion syndrome or post-traumatic syndrome in those who did not suffer a concussion (Table 6.7). PTHA and concussion are covered more extensively in Chap. 24, but will be discussed briefly here.

The risk for developing PTHA and post-concussion syndrome seems to be inversely related to the severity of head injury. Other risk factors include female gender, prior known headache disorder, as well as history of psychiatric disease. The mechanism and pathophysiology behind PTHA and this post-concussion syndrome is not well understood. It is likely that axonal injury along with changes in brain metabolism and blood flow can contribute to PTHA, particularly in individuals with

Table 6.7 Features of post-concussion/post-traumatic syndrome

- Headache: tension-type, migraine, cluster, cervicogenic, occipital neuralgia
- Dizziness/vertigo
- Nausea/vomiting
- Tinnitus/hearing loss
- Blurred vision
- Anosmia
- Photophobia and/or phonophobia
- Orthostatic intolerance/dysautonomia
- Fatigue
- Disturbed sleep: insomnia, nonrestorative sleep, and hypersomnolence
- Memory loss/poor concentration
- Impaired libido
- Personality changes: apathy, anger, irritability
- Depression/anxiety

a genetic predisposition or premorbid conditions. Recent scientific evidence with more sophisticated imaging has demonstrated structural abnormalities to the brain even with minor head injuries.

Acute headache attributed to trauma or injury to the head and/or neck by ICHD-3 beta definition occurs within 7 days of the head or neck trauma (or within 7 days of when the patient regains consciousness or is able to feel pain and report it), and resolves within 3 months. Persistent headache attributed to trauma or injury to the head and/or neck is diagnosed when the headache following injury fails to resolve after 3 months' time. This was previously referred to as chronic PTHA. The post-traumatic headaches are also classified according to the severity of injury, mild, moderate, or severe. Cases in which headache onset is delayed greater than 7 days following injury should be noted as such by the clinician.

Clinical features of PTHA are not specified by the ICHD-3 beta, and are similar to the primary headache disorders, most frequently tension-type headache. Patterns similar to migraine, cluster headache, cervicogenic headache, and a variety of other headache types have been noted as well. These patients are at risk of medication-overuse headache (MOH), and development of this secondary etiology should be considered in persistent cases. The role that litigation or malingering plays in persistence of symptoms is still undetermined.

Headaches Associated with Vascular Disease

Headache is a relatively common symptom in a variety of underlying cerebrovascular diseases (Table 6.8). Intracranial hemorrhages are most often associated with an abrupt onset of severe headache, termed "thunderclap" headache. Thunderclap headache is defined as a severe headache reaching maximal intensity within seconds

Table 6.8 Vascular diseases associated with headache

Vascular pathology	Vascular diagnosis
Ischemic	• Ischemic stroke
	• Transient ischemic attack
Intracranial hemorrhage	• Intracerebral hemorrhage
	• Subarachnoid hemorrhage
Unruptured vascular malformation	• Saccular aneurysm
	• Arteriovenous malformation
	• Arteriovenous fistula
	• Cavernous angioma
Arteritis	• Giant cell arteritis
	• Primary central nervous system angiitis
Carotid or vertebral artery pain	• Cervical arterial dissection
	• Post-carotid endarterectomy headache
	• Post-angioplasty headache
	• Post-stenting headache
	• Post-coiling/clipping headache
Venous thrombosis	• Cerebral venous thrombosis
Other vascular disorders	• CADASIL
	• MELAS
	• Reversible cerebral vasoconstriction syndrome (RCVS)

to a minute. Headaches may be a consequence of stroke, particularly hemorrhagic infarction. Migraine is also a known risk factor for stroke or vascular dissection.

Headache-Attributed Stroke and Transient Ischemic Attacks

Headache may be reported in 10–30 % of patients presenting with an acute ischemic stroke and less commonly in transient ischemic attacks (TIAs). Distinguishing the focal neurologic deficit of a TIA from a migraine aura can be challenging. Deficits associated with a TIA are sudden in onset versus those related to a migraine aura, which tend to develop over 15–20 min. Headaches can also occur in association with strokes related to large-vessel atherothrombotic disease, cardioembolism, and to a lesser extent small-vessel atherothrombotic disease resulting in lacunar infarcts (Table 6.9).

The symptoms of TIA-related headache may develop just prior to or concurrent with the development of focal neurologic deficits. There are no defining characteristics of the headache associated with ischemia, but they tend to be of moderate intensity.

Ischemia in the distribution of the posterior circulation is more likely to produce headaches than ischemia involving the anterior circulation. The headache pain is often unilateral, occurring on the same side of the stroke. A stroke patient who develops progression of neurologic deficits along with new-onset headache must be reevaluated for hemorrhagic transformation of the area of ischemia (Table 6.10).

Table 6.9 Clinical pearls on distinguishing TIAs versus migrainous aura

- Onset of symptoms in a TIA is usually sudden; aura is usually gradual over 15–20 min
- Duration of TIAs is brief, usually lasting from seconds to minutes; average duration of aura is 20–30 min up to an hour
- TIAs usually present with negative symptoms (curtain coming down); auras with positive or mixed symptoms (zigzags, scintillating scotoma)

Table 6.10 Clinical pearls on headache and stroke

- Ischemia in the distribution of the posterior circulation is more likely to produce headaches than ischemia involving the anterior circulation
- Headache pain is often ipsilateral to the side of the stroke
- A stroke patient who develops progression of neurologic deficits along with new-onset headache must be reevaluated for hemorrhagic transformation of the area of ischemia

Headache Attributed to Intracranial Hemorrhage

For patients presenting with acute focal neurologic deficits consistent with a stroke pattern, the concurrent report of sudden headache raises great concern for the presence of an intracranial hemorrhage (ICH). Indeed, headache is reported in up to 70 % of patients diagnosed with ICH. The headache is most severe on the day of onset, localized to the side of hemorrhage, and tends to resolve with clinical improvement. Hemiparesis and decreased consciousness are associated clinical findings. Hypertension and advanced age are the two most significant risk factors for ICH. Headaches associated with ICH are more severe in nature than those associated with ischemic stroke.

Headache Attributed to Subarachnoid Hemorrhage (SAH)

Patients with subarachnoid hemorrhage (SAH) usually present with the sudden onset of "the worst headache of my life" or thunderclap headache. Thunderclap headache was covered in Chap. 3, but because of its importance and the frequency with which it is a secondary and not a primary headache, it is reviewed again here. The headache may be associated with alteration of consciousness, vomiting, photophobia, drowsiness, agitation, or neck stiffness. In 50 % of patients, an unruptured aneurysm may produce a warning headache referred to as a sentinel headache. Sentinel headaches occur in the days to weeks prior to aneurysm rupture.

Although thunderclap headache is the classic presentation of rupture of a saccular aneurysm resulting in SAH, many other diagnoses can have an abrupt presentation as well (Table 6.11). Diagnosis is confirmed by an emergent CT and/or lumbar puncture. Cerebral angiography is usually needed to identify the source of the hemorrhage (Table 6.12).

Spontaneous SAH occurs when aneurysms reach 7–10 mm in size. Aneurysmal rupture increases in risk with age, with a mean incidence of 50 years, and rarely

Table 6.11 Differential diagnosis of thunderclap headache

Secondary headaches	Primary headaches
– SAH	– Primary thunderclap headache
– Sentinel leak	– Primary exertional headache
– Unruptured cerebral aneurysm	– Primary cough headache
– Intracranial hemorrhage	– Primary sexual headache
– Cerebral venous thrombosis	
– Cervical artery dissection	
– Acute hypertensive crisis	
– Posterior reversible leukoencephalopathy syndrome (PRES)	
– Reversible cerebral vasoconstriction syndrome (RCVS)	
– Primary Angiitis of the Central Nervous System (PACNS)	
– Pituitary apoplexy	
– Spontaneous intracranial hypotension	
– Infection: meningitis, sinusitis	

Table 6.12 Clinical pearls in diagnostic evaluation of subarachnoid hemorrhage (SAH)

- Sensitivity of noncontrast CT scan in the diagnosis of SAH
  - < 12 h: 98 %
  - 24 h: 93 %
  - 7 days: 50 %
- Spectrophotometry is able to detect xanthochromia in CSF in 100 % of cases when collected between 12 h and 2 weeks after symptom onset

occurs before 20 years of age. SAH is considered a neurosurgical emergency with a high morbidity and mortality rate. A high index of suspicion is required to avoid misdiagnosis, which has been reported to occur in as much as 25–50 % of patients.

Giant Cell Arteritis (GCA)

Giant cell arteritis (GCA), formerly known as temporal arteritis, is a vasculitis of large- and medium-sized arteries that affects the elderly. The inflammation predominantly involves extracranial branches of the carotid artery, especially the temporal artery.

GCA exclusively occurs in individuals over the age of 50 years, and the incidence increases with age. Women are more likely to be affected than men. It is rare in African-Americans.

Classical symptoms of GCA include headache, scalp tenderness, jaw claudication, and visual loss if untreated. An elevated ESR (> 50 mm/h) is suggestive of the diagnosis, and the ESR is rarely normal, most often early in the disease (Table 6.13). Transcranial Doppler ultrasonography may be useful in confirming the diagnosis, but temporal artery biopsy remains the gold standard for diagnosis.

Table 6.13 American College of Rheumatology's diagnostic criteria for giant cell arteritis

- Age 50 years or older
- Newly onset localized headache
- Temporal artery tenderness or decreased temporal artery pulse, unrelated to arteriosclerosis of the arteries
- ESR > 50 mm/h
- Abnormal artery biopsy specimen characterized by mononuclear infiltration or granulomatous inflammation, usually with multinucleated giant cells

Some patients with GCA have myalgias consistent with the related inflammatory disorder, polymyalgia rheumatica. Prompt treatment with corticosteroids for GCA can prevent permanent visual loss which is the result of anterior ischemic optic neuropathy. The headache associated with GCA will dramatically improve or resolve within 3 days of high-dose steroid treatment.

Primary Angiitis of the Central Nervous System (PACNS) and Reversible Cerebral Vasoconstriction Syndrome (RCVS)

Primary angiitis of the central nervous system (PACNS) is a rare form of central nervous system (CNS) vasculitis. Common presenting symptoms include headache along with altered mental status. It is not uncommon for patients to go undiagnosed for 6 months or more due to the fact that other focal neurologic signs are less common at onset. Situations that should trigger consideration and possible investigation for possible PACNS would include multiple infarcts in different vascular territories, headache associated with cognitive changes, and chronic aseptic meningitis (Table 6.14).

This condition typically affects males over the age of 50 years. In contrast to other primary systemic vasculitides, serologic markers of inflammation are typically normal. MRI of the brain may demonstrate nonspecific white matter changes. CSF studies may also be nonspecific, revealing a modest elevation in total protein as well as a modest lymphocytic pleocytosis. Conventional angiography may be useful in diagnosing by demonstrating "beading" as evidence of segmental arterial narrowing, but confirmatory diagnosis with leptomeningeal and brain biopsy is often necessary. Once diagnosis is confirmed, immunosuppressive treatment is initiated with either corticosteroids and/or cyclophosphamide.

Reversible cerebral vasoconstriction syndrome (RCVS) is a syndrome that can be difficult to distinguish from primary CNS angiitis, because presenting signs and symptoms are similar. Angiography in both disorders demonstrates segmental narrowing but in RCVS this is related to vasospasm. Imaging of brain parenchyma can be normal in RCVS, but when infarcts occur, they are typically larger than those as a result of PACNS. Intracranial hemorrhage can be associated with RCVS but is not typical of PACNS. The correct diagnosis is critical, because RCVS patients are treated with calcium channel blockers, and CNS angiitis is often treated with cytotoxic therapy. The outcome is more favorable for RCVS (Table 6.15).

Table 6.14 Differential diagnosis of primary angiitis of the central nervous system (PACNS). (Adapted from Ju 2010 and Hajj-Ali 2013)

Noninflammatory vasculopathies
- Cerebrovascular atherosclerotic disease
- RCVS
- Fibromuscular dysplasia (FMD)
- Moyamoya
- CADASIL
- MELAS
- Hypercoagulable state

Infections
- Emboli from subacute bacterial endocarditis (SBE)
- Basilar meningitis caused by tuberculosis (TB) or fungal infection (aspergillosis, nocardiosis, cryptococcus, histoplasmosis)
- Bacterial or viral meningoencephalitis (syphilis, Lyme, HSZ, HIV)

Demyelinating syndromes
- Multiple sclerosis (MS)
- Acute disseminated encephalomyelitis (ADEM)

CNS vasculitis, secondarily affected as part of a primary vasculitis
- Large-vessel vasculitis (e.g., GCA, Takayasu arteritis)
- Medium-vessel vasculitis (e.g., polyarteritis nodosa, Kawasaki disease)

Small-vessel vasculitis
- Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (e.g., Wegener's granulomatosis)
- Churg–Strauss syndrome, microscopic polyangiitis
- Immune complex deposition (e.g., Henoch–Schönlein purpura, cryoglobulinemia)

Other systemic inflammatory conditions
- Neuro-Behcet's disease
- Systemic lupus erythematosus
- Scleroderma
- Sjogren's syndrome
- Crohn's disease
- Cogan's syndrome
- Sarcoid granulomatosis and angiitis
- Susac's syndrome

Neoplasms
- Primary CNS lymphoma
- Lymphomatoid granulomatosis
- Meningeal carcinomatosis
- Gliomatosis cerebri

Cerebral Venous Thrombosis

Thrombosis within the cerebral venous system most often is associated with a headache that is acute to subacute in onset. The headache pain is generally described as severe, diffuse, and constant in nature, but has occasionally been described as thunderclap in onset. The headache is worsened by recumbency or Valsalva-type maneuvers such as coughing or sneezing.

Table 6.15 Clinical features of primary angiitis of the central nervous system (PACNS) and reversible cerebral vasoconstriction syndrome (RCVS)

Characteristics	PACNS	RCVS
Demographics		
• Age range	40–60	20–40
• Sex	Males	Females
Clinical symptoms		
• Headache	Insidious, progressive	Acute, thunderclap
• Focal neurological symptoms	Yes, later in disease course	Yes, at onset
Provocative factors (migraine, pregnancy, medicines)	No	Yes
MRI	Nonspecific white matter changes	Normal
	Infarct	Infarct
	Mass lesion	Hemorrhage: ICH, SAH
	Hemorrhage: ICH, SAH	Posterior reversible encephalopathy syndrome (PRES)
	Gadolinium enhancement	
Angiogram	Beading, irregularity, often irreversible	Reversible vasospasm
Treatment	Corticosteroids	Calcium channel blockers
	Cyclophosphamide	

This disorder typically affects children or young adults, and women much more frequently than men (Table 6.16). Obstruction of the venous sinuses results in intracranial hypertension and thrombosis. This may eventually lead to venous infarctions which tend to undergo hemorrhagic transformation. Focal neurologic signs, encephalopathy, or seizures commonly accompany the onset of headache.

Patients with cortical vein thrombosis may present very similarly to idiopathic intracranial hypertension (pseudotumor cerebri, IIH) with signs and symptoms of dizziness, tinnitus, diplopia, and visual obscurations. Papilledema may be found on examination.

Risk factors for cortical vein thrombosis include hypercoagulable states, pregnancy, use of oral contraceptives and dehydration. Venous thrombosis may be diagnosed through MRV or CTV. The recommended duration of treatment with anticoagulation for cerebral venous thrombosis is 6 months. However, the headache generally resolves within 1 month of the initiation of treatment.

Headache Attributed to Carotid or Vertebral Artery Pain

Spontaneous dissection of the vertebral or carotid artery may produce head pain. The diagnosis should be considered in individuals reporting new onset of head pain along with neck pain. Clinical suspicion should be raised if the patient endorses a recent history of known provocative factors such as chiropractic adjustment, severe vomiting, and neck trauma including whiplash-type injuries. Patients with colla-

Table 6.16 Clinical pearls on cerebral venous thrombosis

Characteristics	Findings
Demographics	
• Sex	Women > Men
• Age	Children, young adults
Headache	
• Onset	Acute to subacute
• Description	Throbbing, band like, thunderclap
	Worsened by Valsalva
Clinical symptoms	Seizures
	Encephalopathy
	Nausea and vomiting
	Papilledema
	Cranial nerve palsy
	Diplopia, visual obscurations
	Tinnitus
	Focal findings related to stroke
Complications	Venous infarction
	Hemorrhagic transformation (Parenchymal > subarachnoid, subdural)
Risk factors	Hypercoagulable state
	Oral contraceptives
	Pregnancy
	Dehydration
	Infection: sinusitis, mastoiditis, otitis
	Trauma
	Inflammatory/rheumatologic disease
Evaluation	CBC
	Hypercoagulable profile
	Antiphospholipid/anticardiolipin antibodies
	ESR, CRP, ANA
	MRV/CTV
	EEG
Treatment	Anticoagulation
	Interventional angiography: thromobolytic therapy in severe cases

gen vascular disease or fibromuscular dysplasia are at particular risk. The headache tends to be ipsilateral to the side of dissection (Table 6.17).

Location of pain is frontal for carotid dissections and more occipital for vertebral dissections. Carotid artery dissection may manifest clinically with a Horner's syndrome or amaurosis fugax. Vertebral artery dissection may produce vertebrobasilar symptoms, especially a Wallenberg syndrome (difficulty with swallowing, hoarseness, dizziness, nausea, nystagmus, gait and balance abnormalities, and sensory and motor deficits, sometimes on opposite sides). Patients should undergo diagnostic evaluation with an MRI/MRA with a fat-saturation protocol, CT angiogram, or conventional angiography, which will also help identify secondary complications such as stroke or pseudoaneurysm formation.

Headache has been reported following carotid endarterectomy, carotid clipping, and other endovascular procedures including angioplasty, coiling, embolization,

Table 6.17 Clinical pearls on headache and dissection

Characteristics	Findings
Headache	
• Onset	Acute to subacute
• Description	With neck pain
	Headache is ipsilateral to side of dissection
	Frontal pain for carotid dissection
	Occipital pain for vertebral dissection
Clinical symptoms	Horner's syndrome for carotid dissection
	Amaurosis fugax/transient monocular blindness for carotid dissection
	Vertebrobasilar symptoms, especially a Wallenberg syndrome for vertebral dissection
Risk factors	Chiropractic adjustment
	Severe vomiting
	Neck trauma including whiplash-type injuries
	Collagen vascular disease or fibromuscular dysplasia
Evaluation	MRI/MRA with a fat-saturation protocol, CT angiogram, or conventional angiography (also helps identify secondary complications such as stroke or pseudoaneurysm formation)
Treatment	Anticoagulation

and stenting. The headache begins in the first few days after surgery but often resolves within the month of onset.

Post-carotid endarterectomy headache follows three pain patterns unilateral and ipsilateral to the side of surgery:

1. Diffuse mild pain
2. Cluster headache-like pain
3. Severe and pulsating pain

Preexisting headache conditions may be a risk factor for these post-procedural headaches. The mechanism can be related to a hyperperfusion syndrome following improved blood flow or manipulation of intracranial vessel resulting in activation of the trigeminovascular system.

Pituitary Apoplexy

Pituitary apoplexy is an important syndrome to recognize, as it can be a life-threatening emergency. It is the result of hemorrhage or infarction of the pituitary gland, most often in patients with a pituitary adenoma. Patients report the abrupt onset of a severe headache along with symptoms of vision loss, ophthalmoplegia, and mental status change. Serious complications include adrenal crisis, coma, and even death. MRI is the most sensitive imaging study for detection of pituitary apoplexy (Table 6.18).

Table 6.18 Clinical pearls on pituitary apoplexy

- Severe acute retro-orbital, frontal, or diffuse headache accompanied by at least one of the following symptoms:
  - Nausea and vomiting
  - Fever
  - Altered level of consciousness
  - Hypopituitarism
  - Hypotension
  - Ophthalmoplegia or impaired visual acuity
- Evidence of acute hemorrhagic pituitary infarction
- Symptom resolution within 1 month

Conclusions on Diagnosis of Secondary Headaches

- Use the SNOOP mnemonic (Table 6.3) to decide when to workup patients with headache for secondary causes
- MRI is generally superior to CT in working up secondary headaches
- Post-traumatic headaches begin within 1 week of the injury, according to the ICHD-3 beta, and have no required clinical features
- Headaches associated with TIA, stroke, and dissection are usually ipsilateral to the event
- TIAs can usually be distinguished from migrainous aura by sudden onset, negative features, and briefer duration
- Always work up headache in the elderly with a sedimentation rate and CRP for GCA

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Chapter 7
Diagnosis of Major Secondary Headaches, Nonvascular Disorders

MaryAnn Mays, Deborah E. Tepper, and Stewart J. Tepper

Introduction

The second chapter on diagnosis of secondary headaches includes nonvascular disorders.

The organization of the chapter is by unrelated secondary disorders, linked by their propensity to cause headache, and their ICHD-3 classification are listed in Table 7.1.

Secondary Idiopathic Intracranial Hypertension (Pseudotumor Cerebri)

Normal cerebrospinal fluid (CSF) pressure ranges from 70 to 250 mm of H_2O. Elevated intracranial hypertension may be idiopathic or due to secondary causes. Secondary causes for increased intracranial pressure (ICP) are listed in Table 7.2.

Once secondary causes of raised ICP are excluded, the diagnosis of idiopathic intracranial hypertension (IIH, pseudotumor cerebri) can be made on the basis of headache, documented raised ICP, and headache either developing along with the increased pressure and/or reported improvement of headache with lowering of ICP following removal CSF with lumbar puncture (LP). Although once considered the hallmark of IIH, evidence of papilledema is no longer a necessary criterion, given

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Table 7.1 ICHD-3 organization of secondary nonvascular headache disorders

1. Increased CSF pressure (idiopathic intracranial hypertension, IIH)
2. Low CSF pressure
3. Brain tumor
4. Infections such as HIV
5. Chiari malformation type 1
6. Homeostasis disorders
7. Toxic substances
8. Cervicogenic
9. Temporomandibular disorder
10. Trigeminal neuralgia and painful trigeminal neuropathies
11. Other cranial neuralgias

Table 7.2 Secondary causes of intracranial hypertension

- Venous sinus thrombosis
- Mass lesion/cerebral edema
- Meningitis
- Radical neck dissection
- Hypothyroidism/hypoparathyroidism
- Vitamin A intoxication/deficiency
- Renal disease
- Obesity
- Anemia from iron deficiency
- Drugs (tetracycline, minocycline, tretinoins, human growth hormone, corticosteroid withdrawal, oral contraceptives, lithium)

Table 7.3 Idiopathic intracranial hypertension (IIH, pseudotumor cerebri), ICHD-3 criteria

1. Diagnosed by CSF pressure greater than 250 mm CSF with LP in a lateral decubitus position without sedation, or by monitoring
2. ≥2 of:
   a. Headache developed with IIH
   b. Headache is relieved by decreasing intracranial CSF pressure
   c. Headache is worse with increased CSF pressure

the fact that cases of IHH without papilledema does infrequently occur. The finding of papilledema on examination still remains strong supporting evidence for the diagnosis.

As noted above, IIH was previously referred to as benign intracranial hypertension as well as pseudotumor cerebri. Diagnostic criteria by the ICHD-3 for IIH are listed in Table 7.3.

The disorder tends to affect obese females (body mass index >30). Patients most often report a constant, daily, pressure-like headache pain that may be frontal, retro-orbital or diffuse in location, and at least moderate in severity. The headache is aggravated by Valsalva-type maneuvers. Other signs and symptoms include papilledema as well as cranial nerve dysfunction. It is not uncommon for the patient

Table 7.4 MRI findings suggestive of idiopathic intracranial hypertension (IIH, pseudotumor cerebri)

- Empty sella turcica or flattening of pituitary gland
- Distension of the optic nerve sheaths
- Vertical tortuosity of the optic nerves
- Flattening of posterior globes
- Protrusion of the optic nerve heads
- Transverse cerebral venous sinus stenosis

Table 7.5 Clinical pearls for diagnosing idiopathic intracranial hypertension (IIH, pseudotumor cerebri)

- Obese women, age 20–50
- Dull, constant, daily, nonthrobbing headache
- Papilledema
- Diplopia
- Transient visual obscurations (TVOs)
- Tinnitus
- Neck or back pain
- Enlarged blind spot
- Shoulder and arm pain
- Unusual noises in the head can be heard by patient; sometimes bruits by examiner
- Empty sella or normal MRI

The clinical pearl for IIH diagnosis:

- *The diagnosis of IIH cannot be made without an LP done in the lateral decubitus position*!

to report visual changes such as blurring or transient visual obscurations (TVOs). Diplopia related to cranial nerve VI palsy and pulsatile tinnitus are additional common complaints. Persistently elevated CSF pressures can lead to permanent visual loss.

The patient should be evaluated with magnetic resonance imaging (MRI) and magnetic resonance venography (MRV) to rule out venous thrombosis, which as noted, is the most common secondary cause other than obesity. Other findings suggestive of IIH can be seen on MRI as listed in Table 7.4. A neuro-ophthalmologic examination, including visual field testing, is required to monitor visual acuity. An LP is necessary to document raised ICP. *The diagnosis of IIH cannot be made without an LP performed in the lateral decubitus position*! (Table 7.5).

An opening pressure of greater than 250 mm H_2O in adults, and greater than 280 mm H_2O in children is confirmatory of the diagnosis. The previous ICHD-2 classification allowed for the diagnosis of IIH if the opening pressure was greater than 200 mm H_2O in nonobese individuals, but this criterion has been changed in the ICHD-3 criteria of 2013. Patients respond favorably after the withdrawal of CSF, but unfortunately the response is short lasting, and further treatment will be described in Chap. 17.

Table 7.6 Common clinical manifestations of intracranial hypotension

- Headache that worsens immediately after assuming the upright position and improves within a minute of lying down; delayed responses to postural changes are also possible
- Headache is bilateral, throbbing, located frontally, or occipitally
- Tinnitus
- Impairment in hearing (muffled, echoed, ear fullness)
- Photophobia
- Nausea, vomiting
- Vertigo, dizziness
- Pain and stiffness in the neck, interscapular region, arm
- Cranial nerve dysfunction (commonly horizontal diplopia from impaired function of CN VI, III, or the MLF)
- Gait imbalance
- Anorexia
- Blurry vision
- Phonophobia, hyperacusis, change in hearing
- Facial numbness
- Galactorrhea
- General malaise

CN cranial nerve, *MLF* medial longitudinal fasciculus

Low Cerebrospinal Fluid Pressure Headache

Headache caused by low CSF pressure is either the result of a previous LP, a CSF fistula, or idiopathic in etiology. The clinical manifestations are similar despite the etiology of the intracranial hypotension (Table 7.6).

Classically, patients report a headache in the upright position with relief of symptoms when recumbent. CSF opening pressure is measured at below 60 mmHg H_2O. Studies of the CSF may reveal a normal to slightly elevated protein level and even a mild lymphocytic pleocytosis.

Approximately a third of patients will develop headache following LP. The postdural puncture headache (previously termed postlumbar puncture headache) generally occurs within 5 days after the dural puncture. Spontaneous improvement typically occurs within 2 weeks of the onset of symptoms. In cases without spontaneous improvement, an epidural lumbar blood patch can provide prompt relief.

The symptoms are most likely related to a persistent dural tear caused by the LP needle, resulting in fistula formation. Female gender, younger age (31–50 years), and prior history of postdural puncture headache are risk factors.

Methods to try to reduce the risk of postdural puncture headache include inserting the LP needle bevel parallel to the longitudinal axis of the dural fibers, using a smaller needle size, replacement of the stylet before the needle is withdrawn, and using noncutting needles such as the Sprotte needle. The duration of recumbency following an LP or the recommendation to increase fluids does not seem to influence the occurrence of postdural puncture headache.

Idiopathic low CSF pressure headache or CSF fistula headache also produces symptoms of low-pressure headache, although the response to positional changes

Table 7.7 Neuroimaging findings and low CSF pressure headache

Computed tomography
• Subdural hematomas, hygromas
Radioisotope cisternography
• No evidence of radioactivity beyond the basal cisterns with a paucity or absence over the cerebral convexities
• Parathecal radioactivity episode of CSF leak
• Early (<4 hours) appearance of radioactivity in the kidneys and bladder
MRI brain
• Diffuse pachymeningeal enhancement
• Descent or "sagging" of the brain (cerebellar tonsils herniation, crowding of the posterior fossa, obliteration of the prepontine or perichiasmatic cisterns)
• Flattening of the optic chiasm
• Enlargement of the pituitary
• Subdural hematomas or hygromas
• Ventricular collapse
• Engorgement of cerebral venous sinuses
MRI spine/MR myelography/CT myelography
• Extra-arachnoid fluid collection
• Extradural extravasation of fluid/contrast
• Spinal pachymeningitis/paraspinal enhancement
• Engorgement of the spinal venous plexus
• Meningeal diverticula/dilated nerve root sleeves
• Contrast extravasation of a single nerve root

is less impressive than with postdural puncture headache. If the headache develops into a chronic condition, the classical features of orthostatic headache often diminish and may even be present in the lying position.

In the case of a CSF fistula, there is sometimes a known trauma or iatrogenic cause such as a neurosurgical procedure. More commonly, fistulas may occur spontaneously without a known precipitating event, as in the case of idiopathic low CSF pressure headache. Spontaneous CSF leaks are most commonly identified in the cervical or thoracic region.

An MRI of the brain with and without gadolinium is often diagnostic of low CSF pressure headache, demonstrating evidence of brain sag and diffuse pachymeningeal enhancement without evidence of leptomeningeal involvement. Other imaging findings are listed in Table 7.7.

Unfortunately, despite the number of diagnostic imaging studies which can be utilized, finding the actual site of the leak is often quite difficult and in some cases impossible. Radioisotope cisternography is no longer recommended given poor sensitivity and more useful modalities such as MRI with fat suppression and computed tomography (CT) myelography. CT myelography may be the most reliable diagnostic approach to utilize.

Headache Attributed to Intracranial Neoplasm

Headache may be the initial presentation in approximately 20% of patients with brain tumors. The incidence of headache increases to 50–70% of patients later in the course of their illness.

Most individuals with an underlying brain tumor who present with headache will also have other focal neurologic symptoms such as seizures, confusion, or hemiparesis. Brain tumor headache is characterized as progressive, diffuse, nonpulsating, and associated with nausea and/or vomiting. The headache may be constant or intermittent. The headache worsens with physical activity, Valsalva-type maneuvers, and tends to be most severe in the morning and after napping.

Both mass effect of the tumor and hydrocephalus contribute to the headache, causing local pressure and/or traction on pain-sensitive structures of the brain. Headache is more frequent with infratentorial tumors than supratentorial tumors. Finally, patients with primary headache disorders before developing a brain tumor will often have some features of their preexisting headaches with their brain tumor headache.

Headache Attributed to Infectious Diseases

Any underlying infection may produce a headache or worsen a preexisting primary headache condition. The infection may be systemic or intracranial. Patients with headache related to systemic infection generally have fever, malaise, and diffuse myalgias.

Headache is common in HIV-infected patients at any stage of the illness and has been noted to occur with HIV seroconversion related to primary infection. Later in HIV illness, any presentation of headache or change in pattern of headache should be assumed to be secondary (Table 7.8).

Intracranial infections are most often bacterial or viral, but various opportunistic infections may occur, particularly in immunosuppressed patients. In general, the greatest risk for opportunistic infections is in HIV patients with CD4 counts below 200 cells/mm^3, and those with CD4 counts greater than 500 cells/mm^3 are not considered to be at risk. Evaluation for intracranial infections should be performed in individuals presenting with new-onset or worsening headache associated with fever, meningismus, altered mentation, or focal neurologic deficits.

Headaches associated with infection can be caused by meningitis, encephalitis, brain abscess, or subdural empyema. Antibiotic therapy should be initiated immediately if there is concern for intracranial infection, after which the clinician can proceed with diagnostic testing with urgent CT, LP, and MRI.

The headache attributed to infection should resolve within 3 months of successful treatment. A *persistent* headache pattern may develop in up to 1/3 of patients following a past episode of meningitis despite adequate treatment. Another subset,

Table 7.8 The clinical pearl on HIV headache

• *Any presentation of headache or change in pattern of headache in HIV-positive patients should be assumed to be secondary*

chronic headache attributed to infection, refers to headaches lasting for more than 3 months when the underlying infection remains active.

Headache Attributed to Chiari Malformation Type I

Chiari malformation type 1 (CM1) is most often congenital although acquired cases may occur, most commonly as a result of intracranial hypotension, excessive CSF drainage or injury. CM1 is diagnosed on MRI if there is greater than a 5-mm inferior displacement of the cerebellar tonsils below the foramen magnum; only 3 mm is required if there is associated crowding of the subarachnoid space at the craniocervical junction as evidenced by obstruction of CSF flow seen on MRI CINE flow studies.

Patients with CM1 commonly report headache along with a number of other symptoms related to compression of the cerebellum, brainstem, and cervical cord (Tables 7.9 and 7.10). It is important to remember that not all patients with evidence of CM1 on imaging are symptomatic.

Commonly associated with this condition are tethered cord, IIH, syringomyelia, and scoliosis. The headache is located occipitally and is brief in duration, lasting less than 5 min. It is often triggered by Valsalva-type maneuvers. This secondary cough headache is further discussed with primary cough headache in Chapter 3. Although a patient's symptoms can be effectively treated with various medications, especially indomethacin, suboccipital decompression surgery may be indicated for those with headache with significant neurological signs and symptoms.

Headaches Associated with Disorders of Homeostasis

There are a number of systemic disorders and metabolic conditions frequently associated with headache (Table 7.11). The patient will exhibit signs and symptoms related to the underlying condition in addition to the headache. Diagnostic testing is required to confirm the diagnosis. Upon treatment of the underlying condition, the headache will resolve.

Table 7.9 Headache attributed to Chiari malformation type 1, ICHD-3 criteria

A. Diagnosis of Chiari malformation type 1 by imaging
B. ≥2 of:
a. History consistent with >1 of:
i. Headache started with CM1
ii. Headache stopped within 3 months after successful treatment of CM1
b. Headache has ≥1 of:
i. Triggered by Valsalva, such as cough
ii. Posterior location
iii. Duration less than 5 min
C. Headache occurs along with other symptoms or signs of posterior fossa or cervical spinal cord dysfunction

Table 7.10 Commonly reported symptoms in patients with Chiari malformation type I

• Occipital or suboccipital headache induced by cough or Valsalva maneuver (secondary cough headache)
• Dizziness, vertigo, disequilibrium, impaired coordination
• Ears: pressure, loss of hearing, hyperacusis, tinnitus
• Eyes: nystagmus, oscillopsia, photopsia, visual blurring, visual field deficits, diplopia
• Dysphagia, hoarseness
• Nausea and vomiting
• Neck pain
• Muscle weakness
• Numbness and paresthesias of extremities
• Insomnia, sleep apnea
• Depression

Toxic Headaches

A number of substances may produce headache either due to exposure or withdrawal (Table 7.12). Typically, once the exposure ends, the headache resolves. Headache is a commonly listed adverse effect of multiple medications. Therefore, a review of the patient's list of medications noting their start date can be helpful in pinpointing any correlation with the headache.

Cervicogenic Headache

Headache may be a referred pain originating from the neck. This type of headache must be distinguished clinically from those patients with neck pain as an associated symptom of a primary headache disorder.

Patients at risk for cervicogenic headache include those with a history of arthritis with known cervical spondylosis and degenerative disc disease, or those with a history of neck trauma, particularly whiplash-type injuries. An examination may

Table 7.11 Headaches related to disorders of homeostasis, ICHD-3

- Headache secondary to hypoxia/hypercapnia
  - High altitude headache
  - Headache attributed to airplane travel
  - Diving headache
  - Sleep apnea headache
- Dialysis headache
- Headache secondary to arterial hypertension
  - Headache associated to pheochromocytoma
  - Headache attributed to hypertensive crisis without hypertensive encephalopathy
  - Headache attributed to hypertensive encephalopathy
  - Headache attributed to preeclampsia oreclampsia
  - Headache attributed to autonomic dysreflexia
- Headache associated with hypothyroidism
- Fasting headache
- Cardiac cephalgia

Table 7.12 Some of the substances known to provoke headache

- Nitric oxide donor (nitroglycerin, nitrates, and nitrites of cured meats)
- Phosphodiesterase inhibitor (e. g., sildenafil, vardenafil for erectile dysfunction)
- Carbon monoxide
- Alcohol
- Food components and additives (MSG, aspartame, tyramine)
- Cocaine
- Cannabis
- Histamine induced
- Calcitonin gene-related peptide (CGRP)
- Medications including herbal remedies

MSG monosodium glutamate

reveal tenderness, muscle spasm of the cervical paraspinal and neck muscles, and limitations in cervical range of motion.

Cervical myofascial pain alone without evidence of degenerative changes in the cervical spine should be diagnosed as tension-type headache. Degenerative change in the spine is a very common finding in individuals without symptoms of headache and neck pain, and therefore this finding in isolation cannot be used for definitive diagnosis of cervicogenic headache.

The pain is most often unilateral, typically starts in the occipital region, and radiates frontally. The unilaterality must be stressed as a key clinical symptom, along with the primary neck pain complaint, and the report that neck movement precipitates or aggravates the pain. Even when pain is reported bilaterally, there tends to be a one-sided predominance.

Relief after cervical anesthetic blockade can confirm the diagnosis. The head pain likely originates from stimulation of the upper cervical roots leading to the

Table 7.13 Cervicogenic headache, ICHD-3 criteria

A. Clinical, lab, or imaging evidence for a lesion of the cervical spine or cervical neck tissues known to cause headache
B. Proof of causation with ≥2 of:
a. Headache developed with the onset of the neck lesion
b. Headache improved with treatment of the neck lesion
c. Headache is made worse by provocative neck maneuvers, and neck range of motion is reduced
d. Headache is abolished by diagnostic cervical blocks

Table 7.14 Clinical pearls on cervicogenic headache

• *Symptoms*: must have neck pain as a key complaint and must not fit ICHD-3 beta criteria for migraine or hemicrania continua. There should be no autonomic features, and usually no migrainous features of photophobia, phonophobia, or nausea
• *Risk factors*: arthritis, trauma to neck, whiplash injury
• *Pain*: unilateral (key!), occipital, frontal
• *Triggers*: movement of neck (key!), coughing, sneezing, pressure on upper cervical or occipital region, prolonged upright position
• *Exam*: cervical range of motion limitations, awkward head position
• Imaging evidence of a disorder or lesion within the spine or muscles of the neck
• Abolished by diagnostic cervical blockade

activation of the trigeminal nucleus caudalis located within the upper segment of the cervical spinal cord.

The ICHD-3 criteria for cervicogenic headache are somewhat limited in utility. They are included in Table 7.13, but clinically useful pearls follow in Table 7.14.

Temporomandibular Disorder

Temporomandibular joint (TMJ) dysfunction is a fairly common problem. Patients may present with headache which is localized to the preauricular region, mandible, masseter, and temporal region. In addition to frontotemporal headache, patients often complain of otalgia, tinnitus, and dizziness. Clinical history may elicit symptoms of bruxism during sleep and reported jaw locking or popping. Limited jaw opening and tenderness of the masticatory muscles may be noted during examination. TMJ dysfunction leads to myofascial pain contributing to the symptoms of headache. Symptoms are often self-limited, but in persistent cases, referral to a TMJ specialist may help to correct the problem.

Headache attributed to TMJ disorder should have pain in conjunction with the development of the disorder and should remit as the problem is treated. If this is still uncertain, provocative maneuvers including active or passive movement of the jaw should be able to provoke the headache. ICHD-3 beta points out that there is an overlap between this disorder and tension-type headache, and when there is uncertainty about TMJ dysfunction as a cause, coding should lean toward the diagnosis of tension-type headache.

Table 7.15 Trigeminal neuralgia/trigeminal neuropathy, ICHD-3 classification system

I. Classical trigeminal neuralgia
a. Classical trigeminal neuralgia, purely paroxysmal
b. Classical trigeminal neuralgia, with concomitant persistent facial pain
II. Painful trigeminal neuropathy
a. Painful trigeminal neuropathy attributed to acute herpes zoster
b. Postherpetic trigeminal neuropathy
c. Painful posttraumatic trigeminal neuropathy
d. Painful trigeminal neuropathy attributed to multiple sclerosis (MS) plaque
e. Painful trigeminal neuropathy attributed to space-occupying lesion, e.g., neoplasm
f. Painful trigeminal neuropathy attributed to some other disorder

Trigeminal Neuralgia

Trigeminal neuralgia (TN) is a disorder involving one or more of the sensory divisions of the trigeminal nerve that often produces brief but severe lancinating pain. The disorder was previously referred to tic douloureux and typically affects older individuals in its classical form.

TN used to be divided into classical or symptomatic subtypes. The 2013 ICHD-3 beta dropped the symptomatic form, and TN is divided into two broad categories, classical TN and what is really not TN and is now called painful trigeminal *neuropathy* (PTN; see Table 7.15).

Classical TN is further subdivided into a purely paroxysmal form, with lightning-like, electric shock-like pains lasting seconds, and a form with concomitant persistent facial pain of moderate intensity in the same affected area, usually the second and third division of the trigeminal nerve (V2, 3). Classical TN is often related to neurovascular compression of the trigeminal nerve root near the dorsal root entry zone, usually by the superior cerebellar artery.

PTN encompasses the trigeminal neuropathic pain syndromes caused by other disorders such as multiple sclerosis, postherpetic neuralgia, trauma, and that caused by a tumor or lesion. Thus, all TN is really secondary.

Diagnosis of Classical Trigeminal Neuralgia

The diagnosis of TN requires recognition of the well-described, excruciating lightning-like paroxysms of pain in one or more of the divisions of the trigeminal nerve, with triggers, without radiation, without autonomic features, and with latency periods. Pain is brief but tends to have successive recurrences, with refractory periods.

The location of TN is in V2 and V3; < 5 % of TN is located in V1. Bilateral cases are rare, except for PTN related to multiple sclerosis.

Chewing, talking, or touching the face may trigger pain, although paroxysms can occur spontaneously as well. The triggers are characteristically described as innocuous, often occurring in a stereotypical location, and are sometimes so severe

Table 7.16 Classical trigeminal neuralgia, ICHD-3 overall diagnostic criteria

I.	Pain is strictly located in ≥one branch of V, with no additional radiation
II.	≥3 of:
	a. Paroxysms of pain lasting from less than 1 sec to 2 min
	b. Severe
	c. Quality is electric shock-like, shooting, stabbing, sharp
	d. Provoked by triggers of innocuous stimuli to the ipsilateral face

Table 7.17 Clinical features of classical trigeminal neuralgia

- Unilateral facial pain limited to the distribution of the trigeminal nerve (mandibular (V3) or maxillary (V2) divisions > ophthalmic (V1) division
- Affects older patients, > age 50 years
- Women > men
- Attacks are of brief, less than a second to 2 min in duration
- Pain often provoked by triggers, but after repeated triggers, there is often a refractory period
- Constant, dull pain can develop between bouts of acute pain
- Rarely occurs during sleep
- Attacks become more common over time
- Remissions are possible
- Neurologic examination is normal except in cases in which there is an underlying lesion
- No autonomic features

that patients stop eating and lose weight. After repeated triggering, there is often a refractory period of relief in TN.

The ICHD-3 criteria for the diagnosis of TN overall are listed in Table 7.16.

From a diagnostic standpoint, the differential will be between TN and primary stabbing headaches, as well as the shorter trigeminal autonomic cephalalgias (TACs), such as paroxysmal hemicrania (PH) and short-lasting unilateral neuralgiform headache attacks (SUNHAs). Table 7.17 lists the major clinical features of TN and Table 7.18 some pearls on distinguishing TN from the short-lasting TACs and primary stabbing headaches. Rarely, the short-lasting TACs and TN can occur in the same individual, requiring separate concomitant treatments.

As noted, classical TN comes in two forms, a purely paroxysmal form and a form with the shock-like paroxysms, but a persistent moderate facial pain in between the stabs. The ICHD-3 criteria for these two forms, simply distinguished by the absence or presence of the continuous facial pain, are listed in Table 7.19.

PTN, formerly called symptomatic TN, is the result of an underlying structural lesion (Table 7.20). Common secondary causes include herpes zoster, multiple sclerosis, aneurysms, syringomyelia, post medullary infarction, sarcoidosis, and various tumors including meningiomas, schwannomas/acoustic neuromas, cholesteatomas, epidermoids, and metastases. PTN can also be posttraumatic. The ICHD-3 types of PTN are listed in Table 7.21.

Clinical features of PTN are listed in Table 7.22 and clinical pearls on diagnosing classical TN versus PTN are listed in Table 7.23. Patients should undergo an MRI/MRA of the brain with and without gadolinium to determine if they have a lesion where repair or treatment could lead to cure.

Table 7.18 Clinical pearls on distinguishing trigeminal neuralgia (TN) from short-lasting TACs, such as paroxysmal hemicrania or SUNHA, and primary stabbing headaches

- Location:
  - TN is in V2–V3
  - Paroxysmal hemicrania (PH) attacks are in V1, with some ear symptoms
  - SUNHAs are in V1, with some ear symptoms
  - Primary stabbing headaches can occur anywhere on the head, including out of a trigeminal distribution and tend to vary and migrate
- Duration:
  - TN attacks are less than a second to 2 min
  - PH attacks have a mean duration of 14 min and do not overlap with TN
  - SUNHA lasts from 1 to 600 s and can overlap with TN
  - Primary stabbing headaches last for a few seconds and can overlap with TN
- Autonomic features
  - TN has no autonomic features
  - PH and SUNHA have autonomic features, and both have, as diagnostic features, a "sensation of fullness in the ear"
  - Primary stabbing headaches have no autonomic features
- Triggers
  - TN has triggers and trigger zones
  - PH and SUNHA also can have triggers, but without a refractory period. The triggers can overlap or coexist with TN
  - Primary stabbing headaches do not have triggers
- Treatment
  - TN responds to antiepilepsy drugs (AEDs), carbamazepine, oxcarbazepine, lamotigine, gabapentin, and baclofen
  - PH is an indomethacin-responsive syndrome
  - SUNHA responds to AEDs such as gabapentin, and lamotrigine, and so can overlap with TN
  - Primary stabbing headaches, when they occur in volleys, are often indomethacin responsive
- Primary stabbing headaches:
  - These ice-pick pains tend to occur in single jabs, occur irregularly across time, can occur outside a trigeminal distribution, and do not have triggers
  - They occur in 40 % of migraineurs
  - They can herald attacks of migraine
  - Volleys of ice-pick pains are indomethacin responsive
- SUNHA:
  - The autonomic features are key, as is the V1 location
  - SUNHA occurs as single stabs, series of stabs, or in a sawtooth pattern. The latter would distinguish from TN. The single stab can herald a longer attack with autonomic features, which would distinguish from TN
  - SUNHA and PH have, as a diagnostic feature, a "sensation of fullness in the ear." TN does not
- Hemicrania continua:
  - The exacerbations in HC tend to be long, not lightning-like, so the differential from TN with concomitant persistent facial pain is straightforward, especially because HC is indomethacin responsive and TN is not

Table 7.19 The two forms of classical trigeminal neuralgia, ICHD-3 criteria

I.	Classical trigeminal neuralgia, purely paroxysmal
	a. Meets criteria for classical TN
	b. No interictal persistent facial pain
II.	Classical trigeminal neuralgia with concomitant persistent facial pain
	a. Meets criteria for classical TN
	b. Persistent moderate intensity facial pain in the affected area interictally

Table 7.20 Summary of the differences between trigeminal neuralgia (TN) and the pain trigeminal neuropathies (PTN)

- Classical TN: typically caused by a neurovascular anomaly resulting in compression of the trigeminal nerve
- Painful trigeminal neuropathies (PTN, formerly called symptomatic TN): caused by an underlying structural lesion (e.g., herpes, trauma, MS, or space-occupying lesion such as neoplasm)
- Both have a clinical response to carbamazepine/oxcarbazepine. Response to medication does not determine diagnosis

Table 7.21 Painful trigeminal neuropathies (PTN), ICHD-3 criteria

I.	Painful trigeminal neuropathy attributed to acute herpes zoster
II.	Postherpetic trigeminal neuropathy
III.	Painful trigeminal neuropathy attributed to multiple sclerosis (MS) plaque
IV.	Painful trigeminal neuropathy attributed to space-occupying lesion
V.	Painful trigeminal neuropathy attributed to another disorder

Table 7.22 Clinical findings suggestive of painful trigeminal neuropathy (PTN), ICHD-3 criteria (formerly known as symptomatic trigeminal neuralgia)

- Bilateral pain
- Neurologic abnormalities: sensory loss, masticatory weakness
- Pain in the ophthalmic division (V1)
- Onset below the age of 50 years
- Unresponsiveness to medical treatment
- Abnormal trigeminal reflex testing

Table 7.23 Clinical pearls on diagnosing classical trigeminal neuralgia (TN) versus painful trigeminal neuropathy (PTN)

- In young patients, PTN is far more common, and MS should be considered in the differential diagnosis
- In older patients, classical TN is more likely and is usually related to neurovascular compression, typically from the superior cerebellar artery overlying a trigeminal root
- If a patient has pain in V1, it is probably not TN
- If a patient does not have triggers, it is probably not TN
- If a patient does not have refractory periods, it is probably not TN
- If a patient has autonomic features, first consider one of the trigeminal autonomic cephalalgias
- If a patient has continuous pain without lancinating paroxysms, it is not TN

Table 7.24 Other facial neuralgias

Classification	Clinical features
Persistent idiopathic facial pain (atypical facial pain)	Pain: bilateral, > 2 hrs/day or constant dull ache or nagging pain Location: may involve entire face May be seen as part of a more diffuse chronic pain syndrome Triggers: stress or chronic pain syndrome Age: < 50
Glossopharyngeal neuralgia	Pain: paroxysmal, unilateral, jabbing Location: angle of jaw, base of tongue, tonsillar fossa, or ear Triggers: swallowing, talking, coughing Age: tends to be younger than classic TN Bilateral cases do occur May have TN as well Syncope, bradycardia, and asystole (especially with glossopharyngeal–vagal neuralgia) Pathology: vascular compression
Nervus intermedius neuralgia	Pain: a brief stabbing pain or long duration Location: deep within the internal auditory canal Trigger point: located within posterior wall of auditory canal
Postherpetic trigeminal neuropathy	Known herpetic eruption or CSF varicella zoster virus detected Pain: constant, severe, burning Associated hyperpathia Location: follows dermatomal distribution of prior skin eruption V1 most common trigeminal distribution

Other Facial Neuralgias

There are a number of other facial pain syndromes and neuralgias which are listed in Table 7.24. Many of these neuralgias have very specific diagnostic features, such as the swallowing trigger of glossopharyngeal neuralgia and the deep ear pain location for nervus intermedius neuralgia. A careful imaging workup for these rare neuralgias looking for secondary causes such as neoplasm is always mandatory.

Patients who do not fit a typical pattern of TN and for whom no secondary causes could be found were previously referred to as having atypical facial pain and are now said to have *persistent idiopathic facial pain*. They tend to describe the pain as being more diffuse, often bilateral, and more constant in nature.

These individuals tend to be younger in age and often were believed to have underlying psychiatric illness due to the fact that stress can exacerbate the condition. Atypical facial pain may also be part of a more diffuse chronic pain syndrome that involves other parts of the body.

Conclusions on Secondary Nonvascular Headaches

- IIH is often a disease of obese women, aged 20–50
- The diagnosis of IIH cannot be made without an LP
- Any presentation of headache or change in pattern of headache in HIV-positive patients should be assumed to be secondary
- Low CSF pressure headache is confirmed with an MRI without and with contrast that shows pachymeningeal enhancement, sometimes with brain sag
- Classic TN is a disease of the elderly and generally due to a vascular anomaly; PTN is a disease of younger patients and often due to MS

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Part V
Diagnosis of Pediatric Headaches

Chapter 8
Diagnosis of Headache in Children and Adolescents

Catalina Cleves-Bayon and A. David Rothner

Introduction

Pediatric headache is one of the most common reasons for referral to neurology practices. Headache in children is most frequently due to a benign process such as an acute viral illness or a primary headache disorder such as migraine. It often results in significant distress for patients and their family, as the fear of serious intracranial pathology such as a brain tumor is often present.

A careful evaluation is necessary in order to exclude serious intracranial pathology, reach the most reasonable clinical diagnosis, formulate a treatment plan, and, most importantly, provide confident reassurance to patients and families.

This chapter reviews the evaluation and diagnosis of children and adolescents who present with headache, as well as episodic migraine and its subtypes. Chapter 9 will cover episodic syndromes that may be associated with migraine (formerly called childhood periodic syndromes), tension-type headache, and daily headache, as well as other common primary headache disorders encountered in children.

Evaluation of Headache in Children and Adolescents

Headache in the pediatric population is one of the most common conditions in primary care settings and accounts for 30 % of neurologic referrals. It is a frequent cause for concern among both health practitioners and parents, as headache in children may be the initial symptom of serious intracranial pathology (brain tumor),

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leading in many instances to unnecessary testing. Thorough history taking and physical and neurological examinations will help the health-care provider determine the likelihood of a secondary cause and whether further diagnostic testing is needed.

Two major categories of headache occur in children: primary headache disorders (e.g., migraine, tension-type) and secondary headache due to infection, fever, trauma, or serious intracranial pathology (brain tumor, hydrocephalus). The most frequent cause of recurrent headache seen by the pediatric neurologist is a primary headache disorder such as migraine or episodic syndromes that may be associated with migraine, tension-type headache, and chronic daily headache (CDH). New daily persistent headache (NDPH) is being recognized with increased frequency as well. In the secondary headache category, trauma (in particular concussions), an infectious process, medication overuse, and idiopathic intracranial hypertension (IIH, previously known as pseudotumor cerebri) are frequently encountered.

Note: There is no laboratory or ancillary test that establishes the diagnosis of a primary headache disorder. Diagnosis is based upon an accurate history and clinical criteria established by the International Headache Society (IHS). Most patients have a normal neurological examination.

It is important to ask parents what they think might be causing their child's headache. Parental insight into the situation may help identify risk factors (stress, injury, etc.) and also provides parents with an opportunity to express their own concerns.

Adult neurologists are often anxious when confronted with children with headache. However, the key components of the evaluation for the child include, as in any neurological problem, clinical history, physical and neurological exam, including vital signs, and ancillary testing if indicated.

Clinical History

A thorough clinical history will establish the diagnosis or help narrow the differential diagnosis. Its key components, which do not vary from adults, are temporal pattern, frequency, severity, degree of disability, headache characteristics, and family history. From these, a differential diagnosis can be determined (see Tables 8.1–8.4) and is discussed below.

Family History

Note: Most children with primary headache disorders such as migraine have a positive family history of headache, most often maternal.

Table 8.1 Temporal patterns of secondary or symptomatic pediatric headache

- Most secondary causes of headache evolve over a few weeks to 3–4 months
- Secondary causes will be less likely in patients who have experienced headache for several years
- Even patients with a primary headache disorder such as migraine may develop a secondary headache later on (brain tumor, increased intracranial pressure, etc.)
- Patients with a long-standing history of headache with *any* recent change in headache pattern must be reevaluated

Table 8.2 Common temporal headache patterns encountered in children

Temporal pattern	Examples
Acute single episode	Infectious (meningitis, systemic viral/bacterial illness), vascular (stroke, intracranial hemorrhage), trauma
Acute recurrent	Episodic migraine, tension-type headache, trigeminal autonomic cephalalgias (TACs)
Chronic nonprogressive	Chronic migraine, chronic tension-type headache
Chronic/subacute progressive	Space-occupying lesions (tumor, abscess), hydrocephalus, idiopathic intracranial hypertension (IIH), Chiari malformations
Acute/Chronic	Primary headache disorder such as chronic migraine with superimposed secondary cause

Table 8.3 Frequency of symptoms and degree of disability

- Migraine attacks are characterized by significant disability, whereas tension-type headache typically are not
- Inquire about participation in daily activities and school absenteeism as a measure of disability
- Episodic migraine frequency is < 15 days/month

Table 8.4 Pediatric headache characteristics

Feature	Example
Location	Bifrontal, bitemporal → migraine Occipital → posterior fossa disease
Quality	Throbbing, pounding → migraine Pressure-like → tension-type headache (TTH)
Duration	2–4 h → migraine Seconds to minutes → trigeminal autonomic cephalalgias (TACs)
Associated symptoms	Photophobia and phonophobia → migraine Unilateral tearing, nasal congestion → TACs
Aggravating factors	Activity → migraine Valsalva maneuvers, straining → increased intracranial pressure
Alleviating factors	Sleep → migraine
Prodrome	Migraine
Aura	Migraine Occipital lobe epilepsy may also present with visual phenomena and ictal emesis

Possible Headache Causes

It is important to ask the patient and parents what they believe might be causing the headache. Their answer might shed light into overlooked factors such as head trauma. It also allows the parents to express their concerns and discuss the child's symptoms. This will allow the practitioner to address these concerns and provide confident reassurance once the evaluation has been completed.

Pediatric Neurological Physical Examination

A thorough physical and neurological examination must be performed in all children with headache. Features that must be specifically looked for are summarized in Table 8.5.

Ancillary Testing

The American Academy of Neurology (AAN) first published practice parameters for the evaluation of children and adolescents with recurrent headaches in 2002. Their key recommendations are summarized in Table 8.6.

Variables that predict the presence of intracranial pathology in pediatric patients with headache are summarized in Table 8.7.

The most important factors in the accurate evaluation and correct diagnosis of children and adolescents presenting with headache are a thorough clinical history, as well as physical and neurological examinations. Table 8.8 summarizes those features that, when present, should raise concern for secondary causes and prompt further evaluation.

International Classification of Headache Disorders as it Applies to Children

In 1988, the IHS published the first system for diagnosis and classification of headache disorders. Although diagnostic criteria for children were also included, these were derived, for the most part, from adult criteria. In 2013, a revised third edition in beta was published, and the changes in this most recent edition of ICHD-3 beta are noted throughout this chapter. What used to be called "migraine precursors, childhood periodic syndromes, or migraine variants" are now grouped under "episodic syndromes that may be associated with migraine." These disorders will be addressed in Chapter 9.

The following section reviews the most common primary headache syndromes in children and adolescents as established by the IHS, in the ICHD-3 beta.

Table 8.5 Pediatric neurological exam

Features	Worrisome signs
Vital signs	Fever, hypertension, tachycardia, growth failure
Neck	Nuchal rigidity and meningeal signs
Head, nose, and throat	Head circumference Signs of upper respiratory disease: Headache frequently accompanies viral illness and sinusitis
Neurocutaneous stigmata	Café-au-lait macules, hypopigmented lesions
Fundoscopic exam	Absent venous pulsations, papilledema, optic atrophy, hemorrhages
Neurological exam	Cranial nerve abnormalities, motor or sensory deficits, and cerebellar signs
Back	Scoliosis

Table 8.6 AAN guidelines for evaluation of recurrent headache in children and adolescents

- Routine laboratory testing and lumbar puncture are not recommended
- EEG: Routine EEG is not recommended and is not helpful in distinguishing primary vs. secondary headache or between migraine and other primary headache disorders
- Neuroimaging: Incidental abnormalities, that is, unrelated to headache symptoms, have been reported in approximately 16% of patients undergoing routine neuroimaging. Some of these abnormalities include: arachnoid cysts, pineal cysts, Chiari malformations, developmental venous anomalies, paranasal sinus disease, and nonspecific white matter abnormalities, among others. Routine neuroimaging is not recommended in the evaluation of headache in children

Table 8.7 Variables predicting pediatric intracranial pathology with headache

- Headache of less than 1 month duration
- Absence of family history of headache
- Abnormal neurological examination
- Gait abnormalities
- Seizures

Key concept: All children with headache due to intracranial pathology necessitating medical or surgical intervention had additional worrisome neurological symptoms and abnormal findings on neurological examination

Table 8.8 Features raising concern for secondary causes and the need for further workup

- New-onset progressive headache in a patient without prior history of headache
- Headache that awakens the child from sleep, is worse upon awakening, or is associated with early morning emesis
- Headache that worsens with straining or Valsalva maneuvers
- Toddlers (pediatric brain tumors frequently manifest in this population)
- Associated symptoms such as projectile emesis, visual changes, neurological deficits, endocrine abnormalities
- Physical exam features: neurocutaneous stigmata (disorders such as neurofibromatosis, tuberous sclerosis, and Sturge–Weber syndrome are associated with increased risk of intracranial pathology)

Key concept: An abnormal neurological examination is the highest predictor of intracranial pathology in children and adolescents

Table 8.9 Pediatric migraine incidence by gender

	Male		Female	
	Incidence (%)	Peak (yrs)	Incidence (%)	Peak (yrs)
Migraine with aura	6.6	5	14.1	12–13 (14.1)
Migraine without aura	10	10–11	18.9	14–17 (18.9)

Table 8.10 Pediatric migraine prevalence according to age

Age	Prevalence (%)	
	Male	Female
5–11 years	3.8	3.6
7–11 years	4–11	4–11
Teens	4.1	17%

Table 8.11 Key epidemiological features of pediatric migraine

- Begins earlier in boys
- Incidence peaks earlier in boys than in girls
- Prevalence is slightly higher in boys compared to girls before puberty
- Prevalence remains stable in boys but steadily increases in girls after puberty into adulthood

Migraine and Related Disorders

Migraine headache is the most common primary headache disorder. According to epidemiologic studies by Stewart, migraine begins earlier in males; its incidence peaks at 5 years of age (6.6/1,000 person-years), while in females it peaks between 10 and 14 years (18.9/1,000 person-years). Migraine incidence and prevalence are illustrated in Tables 8.9 and 8.10, respectively.

The American Migraine Prevalence and Prevention Study (AMPP) is, to date, the largest epidemiological study on migraine. It included data from adolescents between 12 and 19 years of age. The prevalence of migraine among males remained relatively stable throughout the teen years (2.9–4.1 %), while in females, it continued to increase and reached 6.3 % by 19 years of age.

Before puberty, the prevalence of migraine is higher in boys than in girls. With the onset of puberty, migraine increases more rapidly in girls and continues to do so until the fourth decade of life. Key pediatric epidemiological features of migraine are summarized in Table 8.11.

Migraine Without Aura

Migraine without aura is the most frequent type of headache encountered in the pediatric population, comprising 60–85 % of migraine cases. Clinical characteristics of migraine without aura are summarized in the ICHD-3 diagnostic criteria listed in Table 8.12.

Table 8.12 Pediatric migraine without aura, ICHD-3 criteria

A. ≥5 attacks fulfilling criteria B–D
B. Headache duration 2–72 h
C. Headache with at least two of the following features:
1. Unilateral, but can be bilateral or frontotemporal
2. Pulsatile
3. Moderate or severe intensity
4. Worse with routine physical activity
D. ≥1 of the following associated symptoms:
1. Nausea and/or vomiting
2. Photophobia and phonophobia
E. Not attributed to another ICHD-3 diagnosis

Table 8.13 Special features of pediatric migraine without aura

• Headache may be as short as 2 h (untreated)
• Often frontotemporal, bilateral
• Onset more frequent in the afternoon in younger children
• Pain is severe enough to interfere with activity
• Associated symptoms such as nausea, photophobia, and phonophobia may be inferred from the child's behavior

Special considerations must be taken into account when diagnosing pediatric migraine (see Table 8.13). Migraine tends to be shorter in children; although 2–72 h is described, most attacks last 2–4 h. This is important to keep in mind when treatment options are considered. Ideally, medications should have a rapid onset of action with minimal side effects and relatively short half-life to prevent lingering side effects once the headache has resolved.

Onset of pediatric migraine is often abrupt, with a much more rapid time to peak than the usual adult migraine. Pediatric migraine attacks are frequently terminated by vomiting or napping, neither of which are very reliable techniques for stopping migraine in adults.

Children may have difficulty describing the location of the pain and should be asked to "point" to its location. It is also important to note that although unilaterality is part of the diagnostic criteria for migraine in adults, in children the pain is often bifrontal or bitemporal. As they reach adulthood, the location of the headache may become predominantly unilateral.

Associated features such as nausea, photophobia, and phonophobia may be difficult to describe for a young child but can be easily inferred from their behavior. For example, children will prefer to lie down in a quiet, dark room during the attack. Some children may develop a dark discoloration around their eyes and pallor also known as the pediatric "migraine facies."

Timing of headache onset is also different in children, who usually become ill in the afternoon hours. As they grow older, the headache tends to occur earlier during the morning hours similar to the adult population.

Table 8.14 Pediatric migraine with aura, ICHD-3 criteria

A. ≥2 fulfilling criteria B and C
B. One or more of the following fully reversible aura symptoms:
1. Visual
2. Sensory
3. Speech or language
4. Motor
5. Brainstem
6. Retinal
C. ≥2 of:
1. ≥1 symptom develops over ≥5 min and/or two or more symptoms occur successively
2. Each aura symptom lasts 5–60 min
3. At least one aura symptom is unilateral
4. Aura is accompanied, or followed within 60 min by headache
D. No secondary cause

Migraine with Aura

Migraine with aura refers to attacks of headache usually with migrainous features, preceded by transient, fully reversible neurological symptoms, usually visual. In the ICHD-3 classification, migraine with aura has been subdivided into several categories:

- Migraine with typical aura
  - Typical aura with headache
  - Typical aura without headache
- Migraine with brainstem aura (previously known as basilar-type migraine, BTM)
- Hemiplegic migraine
- Retinal migraine

Of these, migraine with typical aura is encountered in 15–30 % of children and often coexists with migraine without aura. The ICHD-3 pediatric criteria for migraine with aura are identical to those for adults.

Migraine with aura manifests earlier in life. It occurs exclusively in 15 % of patients with migraine, while 13 % of patients may have a mixture of both migraine with and without aura. Migraine aura without headache is rarely seen in children and adolescents.

Visual phenomena are the most frequent type of aura. These may manifest as fortification spectra, bright dots, flashes of color, binocular vision, and scotomas. Visual distortions such as macropsia and micropsia may rarely be seen as part of the "Alice in Wonderland" syndrome in which objects appear either much smaller or much larger than they really are. When evaluating children, it is useful to ask the patient to draw the aura for a better understanding of what the child actually "sees."

Positive symptoms such as phosphenes are more common than negative symptoms such as amaurosis fugax in migraine aura. Negative symptoms should always raise the concern of an ischemic event.

Table 8.15 Clinical pearls in pediatric migraine with aura

• Positive symptoms such as phosphenes are more common than negative symptoms such as amaurosis fugax in migraine aura. Negative symptoms should always raise the concern of an ischemic event
• In a child or adolescent presenting with visual phenomena, occipital lobe epilepsy must be considered in the differential diagnosis and may also manifest with visual distortions and/or hallucinations.

In a child or adolescent presenting with visual phenomena, occipital lobe epilepsy must be considered in the differential diagnosis and may also manifest with visual distortions and/or hallucinations.

Sensory and aphasic auras may rarely occur. As stated in the diagnostic criteria above, symptoms can occur in succession, starting with visual aura, followed by sensory and speech disturbances.

The pediatric aura has a gradual onset, lasts minutes, and resolves spontaneously without residual deficit. In most patients, the aura phase of the migraine attack lasts 60 min or less, except for hemiplegic migraine (see Table 8.15). In some patients, the headache following the aura phase may not necessarily fulfill criteria for migraine. Aura and headache may overlap in time.

Hemiplegic Migraine

Hemiplegic migraine is characterized by motor weakness during the aura. The onset of weakness is gradual, sometimes followed or accompanied by other aura symptoms.

A headache with migrainous characteristics develops that may be either ipsilateral or contralateral to the side of weakness. Motor weakness may outlast the headache, sometimes lasting up to 72 h.

Hemiplegic migraine may be familial (FHM, autosomal dominant), or sporadic. Three different channelopathies resulting in abnormal electrolyte transport and cell membrane depolarization are known to cause FHM, and the different mutations may be characterized by different symptom complexes and are summarized in Table 8.16.

Several phenotypes have been described, and attempts have been made to further determine phenotype–genotype correlation. For example, fever, altered mental status, and even coma following minor head trauma have been associated with S218L mutations in the CACNA1A gene.

Transient vasospasm on magnetic resonance angiography (MRA) has been reported in some children with hemiplegic migraine during the acute phase.

Hemiplegic migraine is a diagnosis of exclusion unless the genetic testing is positive for one of the known mutations. Patients need to be evaluated urgently during the acute attack to exclude more sinister causes of hemiparesis such as ischemic vascular events or other acute intracranial processes.

Table 8.16 Clinical presentations of pediatric familial hemiplegic migraine by mutation

- FHM1: CACNA1A mutations, also associated with Episodic Ataxia type 2 (EA2), Spinocerebellar ataxia type 6 (SCA6), and absence epilepsy
- FHM2: ATP1A2 mutations, associated with periodic paralysis and some forms of episodic ataxia
- FHM3: SCN1A mutations, also associated with epilepsy

Table 8.17 Pediatric ICHD-3 migraine with brainstem aura

A. At least two attacks fulfilling criteria B–D:
B. Aura consistent with visual, sensory, speech/language symptoms, but no motor or retinal symptoms
C. At least two of the following brainstem symptoms: dysarthria, vertigo, tinnitus, hypacusis, diplopia, ataxia, decreased level of consciousness
D. At least two of the following characteristics:
   1. ≥1 symptom of the aura develops over ≥5 min and/or two or more symptoms occur in succession
   2. Each aura symptom lasts 5–60 min
   3. At least one aura symptom is unilateral
   4. The aura is accompanied or followed within 60 min by headache
E. No secondary cause

Migraine with Brainstem Aura

Previously known as basilar-type migraine (BTM), migraine with brainstem aura is characterized by symptoms of brainstem and cerebellar dysfunction, including vertigo and bulbar dysfunction (see Table 8.17). Although considered to be a frequent pediatric entity, its true prevalence is uncertain, since a diagnosis of BTM is sometimes made when patients complain of dizziness associated with the migraine attack. The estimated prevalence is 3–19% depending on the study and definitions used.

As with hemiplegic migraine, the diagnosis of migraine with brainstem aura requires at least two brainstem symptoms during the aura, as well as the presence of a typical aura.

Migraine with brainstem aura begins early in childhood, around 5–7 years of age. Some authors have questioned whether *benign paroxysmal vertigo of childhood,* characterized by episodes of pallor, vertigo, and vomiting (see Chapter 9 under Episodic Syndromes that may be associated with migraine), is an early manifestation of migraine with brainstem aura in children.

With migraine with brainstem aura, patients present with nausea, vomiting, vertigo, visual phenomena, and bilateral paresthesias, although the latter are no longer part of the diagnostic criteria. Dysarthria may also occur. Symptoms are associated with headache with migrainous features typically *occipital* in location.

In the past, the term "confusional migraine" was used to describe those patients who presented with symptoms consistent with migraine with or without aura in addition to mental status changes for whom no other etiology was identified. Of note,

Table 8.18 Concluding clinical pearls on pediatric headache

- Pediatric migraine can be shorter than its adult counterpart. Onset is often abrupt, and the attack is frequently terminated by vomiting or napping
- Positive symptoms are more common than negative symptoms in pediatric migraine aura. Negative symptoms should always raise the concern of an ischemic event
- In a child or adolescent presenting with visual aura, occipital lobe epilepsy must be considered
- Hemiplegic migraine and migraine with brainstem aura are diagnoses of exclusion after careful workup has been completed

the new diagnostic criteria for migraine with brainstem aura include decreased level of consciousness as part of the clinical manifestations of this entity. Therefore, it is possible that those patients previously labeled as having "confusional migraine" were actually experiencing migraine with brainstem aura.

As noted above, the same calcium channelopathy CACNA1A mutations known to cause hemiplegic migraine has been diagnosed in patients presenting with altered mental status, raising the question of whether migraine with brainstem aura and hemiplegic migraine, when associated with these channelopathies, are actually the same entity with varying manifestations.

Migraine with brainstem aura is a diagnosis of exclusion. Pediatric patients may present with similar symptoms of posterior fossa involvement due to brainstem and cerebellar tumors, vascular disorders, and other posterior fossa disorders.

Conclusions

Pediatric headache is one of the most common reasons for referral to neurologists. A thorough history with physical and neurological examination combined is the most important factor in determining the likelihood of underlying serious intracranial pathology and the need for further diagnostic evaluation (Table 8.18).

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Chapter 9
Episodic Syndromes that May Be Associated with Migraine, Pediatric Tension-type Headache, Chronic Daily Headache Syndromes in Children and Pediatric Idiopathic Intracranial Hypertension

Catalina Cleves-Bayon and A. David Rothner

Introduction

This chapter is divided into four sections on pediatric headache and includes episodic syndromes that may be associated with migraine, tension-type headache (TTH), and chronic daily headache (CDH) syndromes. A brief overview on idiopathic intracranial hypertension (IIH) is also included, as this represents one of the most common secondary headaches in children and adolescents. The trigeminal autonomic cephalalgias (TACs) are mentioned briefly, as these are covered in more detail in other chapters of this book.

Episodic Syndromes that may be Associated with Migraine

The term "childhood periodic syndromes" was first introduced by Wyllie and Schlesinger in 1933 to describe stereotypical, recurrent episodes of vomiting, headache, and/or abdominal pain, separated by symptom-free intervals. Several years later, Dr. Charles Barlow described how these periodic syndromes were common precursors of migraine.

The International Classification of Headache Disorders, third edition, beta version (ICHD-3) includes the category *Episodic syndromes that may be associated with migraine (1.6)*. Within this grouping are benign paroxysmal vertigo (BPV), benign paroxysmal torticollis (BPT), as well as a new subcategory, *Recurrent gas-*

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S. J. Tepper, D. E. Tepper (eds.), *The Cleveland Clinic Manual of Headache Therapy, Second Edition,* DOI 10.1007/978-3-319-04072-1_9,

Table 9.1 Secondary causes to be considered in childhood periodic syndromes

• *Central nervous system*
Increased intracranial pressure
Posterior fossa mass
Epilepsy
Infection (meningitis, encephalitis)
• *Inborn errors of metabolism*
Organic acidemias
Urea cycle defects
• *Mitochondrial disorders*
• *Acute intra-abdominal disease*
Bowel obstruction
Ureteropelvic junction obstruction
Hepatitis
Pancreatitis

trointestinal disturbance, covering cyclical vomiting syndrome (CVS) and abdominal migraine (AM).

Although more frequently encountered in the pediatric population, these disorders may also occur in adults. They are considered diagnoses of exclusion (see Table 9.1). Inborn errors of metabolism such as organic acidemias, urea cycle defects, mitochondrial disorders, increased intracranial pressure (ICP), posterior fossa tumors, and acute intrabdominal pathology may present in a similar fashion. Therefore, a thorough evaluation for these disorders is necessary in order to avoid missing causes that untreated could result in significant morbidity and mortality.

Recurrent Gastrointestinal Disturbance

Previously known as functional abdominal pain, chronic abdominal pain, functional dyspepsia, and irritable bowel syndrome, recurrent gastrointestinal disturbance is characterized by recurrent attacks of abdominal pain that may be associated with nausea and/or vomiting, and may occur intermittently with a predictable pattern or in a more chronic fashion. Attacks may be associated with migraine headache as well. The diagnostic criteria for this disorder are summarized in Table 9.2.

Cyclical Vomiting Syndrome

First described by Heberden in 1806, cyclical vomiting syndrome (CVS) is characterized by recurrent episodes of nausea, vomiting, and lethargy separated by symptom-free intervals. Its estimated prevalence is 0.4–1.9%, with girls more affected than boys (see Table 9.3 for diagnostic criteria). Patients of northern European ancestry are more frequently affected.

Table 9.2 Recurrent gastrointestinal disturbance, ICHD-3 diagnostic criteria

A. At least five attacks characterized by abdominal pain and/or discomfort, nausea, and/or vomiting
B. Normal gastrointestinal examination and evaluation
C. Not secondary

Table 9.3 Cyclical vomiting syndrome, ICHD-3 diagnostic criteria

A. ≥5 attacks fulfilling criteria B and C
B. Stereotypical attacks for each patient, with predictable recurrence
C. All of the following:
1. Nausea and vomiting occurring at least four times per hour
2. Attacks lasting 1 h–10 days
3. Attacks occur at least 1 week apart
4. No interictal symptoms
5. Not secondary

Attacks are more common in the early morning hours or soon after waking up. Patients develop multiple episodes of emesis per hour, associated with nausea, retching, pallor, and in some cases, dysautonomia. Symptoms peak between 1 and 2 h after onset, but an individual attack may last from 6 to 48 h. Following the ictal phase, children often fall asleep for several hours, to wake up later back to baseline.

CVS is more frequent in young children between 4 and 5 years old, but is increasingly recognized in adults. Eighty-seven percent of patients have a positive family history of migraine. Episodes tend to subside by 10 years of age, but approximately 75 % of affected patients develop migraine later on. As noted, in some patients, symptoms persist into adulthood.

Although episodes may occur infrequently in some patients, they are very disabling for the child, leading to frequent hospitalizations, emergency room visits, and school absences. Therefore, preventive therapy should be strongly considered for these patients, even if the episodes are infrequent.

Over the last decade, CVS has also been recognized as an important clinical manifestation of other disorders, such as neurometabolic and mitochondrial disease. Some authors have referred to this form as *CVS Plus* (CVS+), in which patients not only manifest stereotypical cyclical vomiting, but may also have additional symptoms such as neuromuscular disease, cognitive delay, or seizures. Patients with CVS+ may develop clinical manifestations earlier in life compared to patients with the migraine-related CVS form and should be thoroughly evaluated to rule out underlying neurometabolic disease (Table 9.4).

In 2008, the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition published a consensus statement for the diagnosis and management of CVS. This publication highlights symptoms and patient characteristics that may increase the risk of a serious underlying disorder as opposed to idiopathic CVS and are summarized in Table 9.5.

Table 9.4 Evaluation of patients presenting with cyclical vomiting syndrome

Serum electrolytes, glucose
Upper GI series
Abdominal US
Long chain fatty acids analysis

GI gastrointestinal, *US* ultrasound

Table 9.5 When to consider underlying organic disease manifesting as cyclical vomiting syndrome

- Patients less than 2 years old are more likely to have surgical or metabolic disease
- Bilious vomiting
- Severe abdominal pain or tenderness
- Attacks precipitated by intercurrent illness, fasting, and/or high-protein meal
- Abnormal neurological evaluation
- Progressively worsening attacks and or conversion into a continuous pattern without symptom-free interval

Abdominal Migraine

Abdominal migraine (AM) was first described by Buchanan in 1921 as recurrent attacks of abdominal pain without headache. Episodes are characterized by disabling abdominal pain, dull in quality, with a location that is either periumbilical or diffuse. Children may also exhibit other symptoms classically associated with migraine such as pallor, flushing, dark circles around the eyes, and anorexia (Table 9.6). Of note, according to the most recent ICHD-3 criteria, episodes must last a minimum of 2 h (treated or unsuccessfully treated). Vomiting may be present, but it is less severe than in CVS. Visual aura may also occur. Headache does not occur during these attacks. Patients are symptom-free between attacks.

Table 9.6 Abdominal migraine, ICHD-3 diagnostic criteria

A. ≥5 attacks of abdominal pain, fulfilling criteria B–D
B. Pain has at least two of the following features:
   1. Midline location, periumbilical, or poorly localized
   2. Dull or described as “sore” in quality
   3. Moderate to severe in intensity
C. At least two of the following during attacks:
   1. Anorexia
   2. Nausea
   3. Vomiting
   4. Pallor
D. Spells last 2–72 h whether treated, or unsuccessfully treated
E. Symptom-free intervals
F. Not secondary

Frequent triggers include psychological (excitement) and physical stress (illness). Motion sickness is frequently reported.

AM is more common in girls. The age of onset is between 3 and 10 (mean 7 years) with an estimated prevalence of 2.4–4.1%. A family history of migraine is common.

Benign Paroxysmal Vertigo

Benign paroxysmal vertigo (BPV) was first described by Basser in 1964; it is characterized by abrupt loss of balance, vertigo, and even falls. The prevalence is 2–2.6%, with equal distribution between boys and girls.

At the beginning of the episode, children may appear frightened, while trying to hold on to furniture or to another person to avoid falling. They refuse to walk and want to lie still. Older children may describe dizziness and nausea.

Associated symptoms include nystagmus, pallor, nausea, diaphoresis, phonophobia, and photophobia. Severe vomiting may also occur. There is no loss of consciousness.

Attacks are typically brief, lasting less than 5 min in most cases, although episodes up to 48 h have been described. They occur once every 1–3 months, with decreasing frequency with advanced age. Movements that stimulate the labyrinth such as swings and roundabouts may trigger the episodes.

Onset is between 2 and 4 years, and BPV symptoms of childhood resolve in most cases by 5 years. A positive family history of migraine is common; Abu-Arafeh and Russell also described a higher prevalence of migraine in children with BPV. It has also been suggested that BPV constitutes a precursor of migraine with brainstem aura. The diagnostic criteria for BPV are summarized in Table 9.7.

BPV is a diagnosis of exclusion; differential diagnosis includes posterior fossa pathology and episodic ataxia, among others. It must also be differentiated from migraine-associated vertigo, which occurs in older children. Later in life, children

Table 9.7 Benign paroxysmal vertigo, ICHD-3 diagnostic criteria

A.	≥5 of attacks fulfilling criteria B–C
B.	No aura or prodrome, precipitous onset vertigo, peak at onset, resolving in minutes to hours without loss of consciousness
C.	At least one of the following:
	1. Nystagmus
	2. Ataxia
	3. Vomiting
	4. Pallor
	5. Fearfulness
D.	Normal interictal audiometry, vestibular testing, and exam between attacks
E.	Not secondary

may develop CVS or migraine. Of note, a normal EEG is no longer required as part of the diagnostic criteria.

Benign Paroxysmal Torticollis

First described by Snyder in 1969, Benign Paroxysmal Torticollis (BPT) is characterized by sudden onset, recurrent dyskinesias involving the neck. During the attack, there is an abnormal rotation of the head and neck toward the affected side, which may be accompanied by vomiting and ataxia. Other symptoms frequently encountered in migraine such as pallor, drowsiness, photophobia, and epiphora may occur.

Each episode may last hours to days and resolves spontaneously without sequelae. Patients develop symptoms between 2 and 8 months of age that resolve by age 3–5 years. The frequency and severity of attacks decrease as children get older. It is more frequently encountered in girls, and a family history of motion sickness and migraine is common.

BPT shares several features with migraine, including its paroxysmal nature, female preponderance, and associated migrainous features. Over the last decade, families with clustering of migraine, other episodic disorders that may be associated with migraine, BPT, and underlying calcium channelopathy CACNA1A mutations have been described, providing evidence that BPT may represent a migraine precursor. BPT is now included in the ICHD-3 as part of the episodic syndromes that may be associated with migraine. Diagnostic criteria for BPT can be found in Table 9.8.

Summary of Childhood Periodic Syndromes

Tables 9.9 and 9.10 provide summaries of the differences and similarities between the different periodic syndromes.

Table 9.8 Benign paroxysmal torticollis, ICHD-3 diagnostic criteria

A.	Recurrent attacks in a young child fulfilling:
B.	Head tilt to one side (variable side), sometimes with slight rotation, remitting spontaneously after minutes to days
C.	At least one of the following associated symptoms or signs:
	1. Pallor
	2. Irritability
	3. Malaise
	4. Vomiting
	5. Ataxia
D.	Interictal normal exam
E.	No secondary cause

Table 9.9 Summary of episodic syndromes that may be associated with migraine

Disease	Age of onset	Prevalence (%)	Predominant symptoms	Duration	Age of resolution (years)	% of patients who develop migraine
CVS	4–5 years	0.4–1.9	Multiple episodes of emesis/hour	1–6 h	10	75
BPV	2–4 years	2–2.6	Vertigo, imbalance	5 min	5	75
AM	3–10 years	2.4–4.1	Epigastric/diffuse abdominal pain	1–72 h	10	70
BPT	2–8 months		Torticollis	Hours–days	3–5	To be determined

CVS cyclical vomiting syndrome, *BPV* benign paroxysmal vertigo, *AM* abdominal migraine, *BPT* benign paroxysmal torticollois

Table 9.10 Episodic syndromes that may be associated with migraine (childhood periodic syndromes): Clinical Pearls

- Female predominance
- Strong family history of migraine and motion sickness
- Sudden onset and spontaneous resolution without sequelae
- Symptoms associated with migraine may be seen (pallor, flushing, nausea, vomiting, photophobia)
- Normal physical and neurological evaluation
- 70–75% of patients develop migraine later in life

Pediatric Tension-Type Headaches

Episodic Tension-Type Headache

Tension-Type Headache (TTH) is considered to be the most frequent headache type encountered in adult series. It is also estimated, based on population studies, to occur in 10–72% of school-age children, although clinic-based studies have reported an incidence of approximately 30%.

Its true prevalence may be underestimated, as many patients with TTH may not need to seek medical attention and, since most studies are done in school-age children, the very young patients (below 7–8 years of age) are not accounted for. Episodic TTH (ETTH) is equally prevalent in boys and girls before puberty, but becomes more prevalent in young women later on.

The pain is usually described as holocephalic or bilateral, pressure-like in quality, of mild to moderate severity. There are no other associated symptoms. Patients can often continue their usual activities and may not take medication for the pain.

Patients with ETTH often have comorbid mood disorders such as anxiety and depression. ETTH may also coexist with migraine in some patients (6%), and the predominant entity may alternate from time to time. The clinical features of ETTH are summarized in Table 9.11.

Table 9.11 Clinical features of pediatric episodic tension-type headaches

Location	Bilateral, holocephalic
Quality	Pressure-like
Intensity	Mild to moderate
According to frequency	
- Infrequent	1 day/month
- Frequent	1 day/month to <15 days/month
Average duration	30 min. –7 days

Pediatric chronic tension-type headache (CTTH) will be covered in the next section.

The Pediatric Chronic Daily Headaches

Chronic Daily Headache (CDH) is not an ICHD-3 term term, but is one of the most common headache entities resulting in referral to a pediatric neurologist or headache specialist in pediatrics. It often results in significant disability, school absenteeism, and economic burden due to frequent emergency room and office visits, hospitalizations, and unnecessary testing.

CDH, as a primary headache disorder, often results in significant anxiety in patients and parents, as the symptom persists, but no specific etiology is identified. Therefore, one of the keys to successful management of these patients is the ability of the treating health-care provider to be able to provide *confident reassurance* and formulate a comprehensive, often multidisciplinary, treatment plan after a careful evaluation of the patient has been accomplished.

All subtypes of CDH are characterized by being present for at least 3 months, with headache occurring in more than 15 days per month. It may be intermittent or continuous; exacerbations and remissions may occur, and it may be chronic from the time of onset (as in new daily persistent headache, NDPH) or evolve from different forms of primary episodic headache (such as migraine or TTH).

CDH is often accompanied by other symptoms, such as anxiety, depressed mood, dizziness, and fatigue, among others. It has a significant impact in quality of life, as these patients often miss school and withdraw from academic and social activities. Complicating factors, such as medication overuse, also need to be addressed.

Key concept: All forms of CDH may be complicated by medication overuse.

The most frequently encountered forms of CDH in children include CTTH, transformed migraine (TM; now known as chronic migraine, CM), and NDPH. The clinical characteristics of each subtype are summarized below.

Chronic Tension-Type Headache

This type of headache often evolves from ETTH. As in ETTH, it is characterized by bilateral or holocephalic pressure-like pain, of mild to moderate severity. Migrainous features are absent. It may be intermittent (with most episodes lasting at least 4 h), or continuous, occurring at least 15 days per month for 3 months. CTTH in adolescents has been associated with unhealthy habits such as smoking, obesity, and a sedentary life style, and these have been have been recently demonstrated as independent risk factors for this disorder.

Transformed Migraine/Chronic Migraine

It is not infrequent, when evaluating children and adolescents with CDH, to encounter "two different types of headache" in their description of symptoms. Patients often describe a daily headache, of moderate to severe intensity that has exacerbations, sometimes several times per month. These worse headaches are often accompanied by classic migrainous features, such as nausea, vomiting, photophobia, and phonophobia; auras may also occur.

The term "transformed migraine" was initially applied to those patients with a history of episodic migraine who later developed CDH with migrainous features accompanying exacerbations. The ICHD-3 includes the term CM to describe a primary CDH with a link to previous episodic migraine.

New Daily Persistent Headache

Increasingly recognized in clinical practice, New Daily Persistent Headache (NDPH) classically presents in a patient without a prior history of frequent headache as "a headache occurring, out of the blue, that just won't go away."

NDPH manifests as a daily headache with onset from a particular day, within 24 h according to ICHD-3. In adults, half of the patients in one case series had tension-type features and the other half had migrainous features. The ICHD-3 does not characterize the phenotype other than to require the CDH to be primary and have the abrupt onset on the specific day.

The key feature is that patients with NDPH can remember the exact date on which the headache starts. This abrupt onset is the most useful aspect of presentation that helps distinguish NDPH from other forms of CDH.

Epidemiological studies have shown NDPH to be more common in children and adolescents when compared to adults and more frequent in females as well. It is not uncommon to identify certain personality traits in these patients. Adolescent females with NDPH are typically "high achievers," overinvolved in extracurricu-

Table 9.12 Chronic daily headache subtypes in children and adolescents

Feature	CTTH	TM/CM	NDPH
Pattern	>4 h < continuous	Daily, continuous	Should be continuous almost from onset
Evolution	From ETTH	From episodic migraine	Daily and persistent from onset
Associated symptoms	Nausea, pericranial tenderness	Migrainous features during exacerbations	Nausea
Precipitating factors	Stress	Same as for migraine	Viral illness, surgery
Prior history of headache	Yes	Yes	No

CTTH chronic tension-type headache, *TM* transformed migraine, *CM* chronic migraine, *NDPH* new daily persistent headache

lar activities. Patients may experience significant disability, with withdrawal from daily activities. Medication overuse, depression, and anxiety can be consequences of this disorder.

A study by Mack et al. in 2004 in pediatric patients with NDPH found that a physical stressor can be identified in 88 % of patients preceding the onset of headache. The most common identified triggers included (in order of frequency): febrile illness (with Epstein–Barr viral infections being most common), minor head trauma, and extracranial surgery. Although only 12 % of patients had no identifiable precipitant in this series, similar studies in the Japanese literature have reported no identifiable trigger in up to 65 % of patients.

Table 9.12 summarizes the most common types of CDH encountered in the pediatric population.

Less Frequent Primary Headaches in Children and Adolescents

The Trigeminal Autonomic Cephalalgias (TACs) constitute another group of primary headache disorders. This group encompasses cluster headache, paroxysmal hemicrania (PH), short-lasting unilateral neuralgiform headache attacks (SUNHA), and hemicrania continua (HC). Features in common among this group of disorders are the ipsilateral, autonomic manifestations such as conjunctival injection, lacrimation, and nasal congestion.

Although the TACs account for less than 1 % of primary headache disorders in children, these entities are important to recognize because specific therapy such as indomethacin may lead to significant improvement and even resolution of the headache in some of the TACs (PH and HC). More extensive diagnostic descriptions of the TACs are contained in Chap. 2. Pediatric cases have similar features to adults.

Idiopathic Intracranial Hypertension

Previously known as pseudotumor cerebri, idiopathic intracranial hypertension or IIH was first identified as a neurological disease in the 1900s, in patients who presented with signs and symptoms of raised intracranial pressure (ICP) but in whom no tumor was identified. In the 1930s, when ventriculography was in use, David and Dyke described patients with symptoms of increased ICP and negative ventriculography for tumor. Those who underwent cranial decompression showed improvement in symptoms of raised ICP, but it was also observed that papilledema itself could persist for several months. The first diagnostic criteria for this syndrome can be attributed to Dandy and are included in Table 9.13.

Although the exact pathogenesis of this disorder is not entirely clear, it has been postulated that alterations in CSF flow may lead to a buildup of fluid causing increased ICP. With the advent of magnetic resonance venography (MRV), venous sinus stenosis has been identified in some patients, leading to an impaired reabsorption of cerebrospinal fluid (CSF). In some adult patients who are refractory to medical management, stenting of the venous sinuses has been performed. Certain medications, in particular the tetracyclines, may also have toxic effects on the arachnoid villi, resulting in impaired CSF reabsorption.

Epidemiology of Idiopathic Intracranial Hypertension

IIH most frequently affects females, with a female to male ratio of 4:1. Ninety percent of these patients are overweight. Although the exact prevalence in the pediatric population is not known, it has become an increasing health problem in children as obesity rates have risen, causing great concern in light of the potential for permanent visual loss.

Clinical Manifestations of Idiopathic Intracranial Hypertension

Headache is the most common presenting symptom of IIH and affects 90 % of these patients. The head pain may have migrainous features such as photophobia, and is typically retro-orbital and bifrontal in location. It is usually worse in the morning, when the patient is supine, and is aggravated by Valsalva maneuvers.

Table 9.13 Dandy's initial diagnostic criteria for idiopathic intracranial hypertension

- Signs and symptoms of increased intracranial pressure (headache, papilledema, transient visual obscurations)
- No localizing neurological signs although cranial nerve VI palsies may occur
- Normal cerebrospinal fluid analysis
- Normal to small ventricles

Transient visual obscurations are present in 70% of patients, and other visual disturbances such as diplopia, blurred vision, and constriction of peripheral vision may also occur. Pulsatile tinnitus, often described by patients as a "whooshing sound" or a sensation of water running, may also be reported. In children, irritability and rarely, facial diplegia may also occur.

Papilledema is almost invariably present in IIH, and is bilateral in 90% of patients. It may also precede the onset of other symptoms such as headache or visual disturbances. *Papilledema is the single most important predictor of visual loss in these patients*.

Visual loss may occur in 10–16% of children at the time of initial presentation. Visual field defects, present in 70–85% of patients, must be carefully looked for. An inferonasal defect and enlargement of the blind spot may be the initial manifestation.

Diagnostic Evaluation of Idiopathic Intracranial Hypertension

When evaluating patients with suspected increased ICP, secondary causes must be excluded first. In the past, when the term pseudotumor cerebri was used, clinicians would use the term "pseudotumor cerebri complex" (PTC) to distinguish between those patients with IIH and those in whom causes other than tumors or space-occupying lesion resulted in raised ICP. Several infectious, vascular, toxic, and metabolic factors are recognized that can mimic IIH or lead to increased ICP, resulting in a clinical syndrome similar to IIH. These are summarized in Table 9.14, with emphasis on those more frequently encountered in the pediatric population.

Table 9.14 Mimics of idiopathic intracranial hypertension

1. Infectious
   a. Otitis media and mastoiditis resulting in venous sinus thrombosis
   b. Lyme aseptic meningitis
   c. Varicella
2. Endocrine
   a. Hypo- and hyperthyroidism, thyroid hormone replacement
   b. Growth hormone replacement
   c. Addison's disease
   d. Malnutrition and refeeding syndrome
   e. Uremia
3. Medications
   a. Tetracyclines, in particular minocycline
   b. Vitamin A and its derivatives
   c. Corticosteroid withdrawal
4. Craniosynostosis

Ancillary Testing in Idiopathic Intracranial Hypertension

Neuroimaging studies should be obtained in all patients suspected of having increased ICP. Magnetic resonance imaging (MRI) with MRV are the preferred evaluations, as the studies may reveal venous sinus stenosis or thrombosis demonstrating both the cause of the patient's symptoms and a potential route to treatment. As a rule, neuroimaging should be negative in IIH patients, eliminating such causes as tumors, abscesses, and other space-occupying lesions. Due to the elevated ICP, findings such as flattening of the posterior pole of the ocular globes, increased CSF signal surrounding the optic nerve sheaths, tortuous optic nerves, flattening of the pituitary gland, an empty sella, and tonsillar ectopia may be identified with imaging in IIH.

All patients with IIH should have formal visual evaluation that includes standardized visual field testing (either Humphrey visual field testing or Goldman perimetry in young patients who cannot complete Humphrey visual fields). Visual acuity and color vision should also be evaluated.

Recently, optic coherence testing (OCT) has also been used to measure the average nerve fiber thickness to detect nerve edema. No standardized values have been established in pediatric patients as of the writing of this chapter.

Laboratory testing including CBC, CMP, ANA titers, and thyroid function studies should also be drawn in all patients. Lyme serology and vitamin A levels should also be obtained if clinical suspicion warrants it.

The diagnosis is confirmed by obtaining a lumbar puncture in the lateral decubitus position to avoid falsely elevated values when the procedure is done with the patient upright.

What Constitutes a Normal Opening Pressure in the Pediatric Population?

For several decades, a normal adult opening pressure was considered to be below 20 cm H_2O. This number was then extrapolated to the pediatric population, but recent studies have revealed that the normal opening pressure can actually be much higher in children.

In 2010, Avery and colleagues conducted a study in pediatric patients aged 1–18 years of age and measured opening pressures in this group. None of these patients had associated conditions or exposure to medications that could alter the CSF opening pressure (OP), and the authors found a mean opening pressure of 19.8 ± 6.8 cm. A subsequent 2011 study by Lee et al. found similar results with a mean OP of 20.3 cm (SD 7.1), which has led to the acceptance of 28 cm H_2O as the upper limit for a normal opening pressure in the pediatric population, significantly higher when compared to adults (25 cm H_2O by ICHD-3).

Table 9.15 Clinical pearl on normal pediatric opening pressure

• Opening pressures up to 28 cm H_2O can be considered normal in children

In 2011, Avery et al. published another study, this time comparing pediatric patients with papilledema on exam and their OP with control subjects without papilledema and their OP. The mean opening pressure in patients with papilledema was 40 cm H_2O, and all but one patient had opening pressures above 28 cm H_2O (Table 9.15). Interestingly, the only patient in the papilledema group with an opening pressure below 28 cm H_2O was a child who had received a renal transplant, and had been recently restarted on steroid therapy. Lastly, CSF analysis should be normal in the IIH patients.

Treatment of Idiopathic Intracranial Hypertension in Children

Acetazolamide remains the mainstay of treatment for patients with IIH. A carbonic anhydrase inhibitor is thought to reduce CSF production, thereby decreasing CSF volume and lowering CSF pressure. Usual dosing ranges from 20 to 25 mg/kg/day in divided doses, although up to 3 g/day may be needed in some patients.

Side effects such as anorexia, nausea, vomiting, and paresthesias may occur. Electrolytes should be carefully monitored in these patients, and supplementation with sodium bicarbonate instituted if needed, as significant metabolic acidosis can occur. Aplastic anemia and Steven–Johnson syndrome have also been rarely reported.

Furosemide, a loop diuretic in doses of 1–2 mg/kg/day in three divided doses in children and 20–40 mg three times daily in adolescents may be used if there are contraindications to acetazolamide or as adjunct therapy.

Topiramate, an anticonvulsant with weak carbonic anhydrase inhibitor effects, has also been used in these patients as second line therapy, but the appropriate doses for IIH have not been well established. Topiramate has the added benefit of being a good headache prophylaxis agent, as it is not infrequent for patients with IIH to have coexistent migraine or TTH as well.

The use of steroids, such as prednisone and methylprednisolone has also been advocated by some, especially in patients with severe visual impairment at the time of presentation. However, these can cause significant side effects as well as the risk of rebound IIH as the steroid is being tapered.

Treatment should be continued until vision normalizes and papilledema has completely resolved. After this, medications need to be slowly tapered with serial ophthalmological exams performed to detect early recurrence.

Surgical Interventions for Idiopathic Intracranial Hypertension

When medical management fails there is impending visual loss, surgical interventions such as ventriculoperitoneal shunting (VPS) and lumboperitoneal shunting may be used as a last resort. In some centers, optic nerve sheath fenestration is also used when vision is threatened. Fenestration is not effective for the headache but preserves the discs.

Prognosis of Idiopathic Intracranial Hypertension

Permanent visual loss is the most feared complication of this disease. Risk factors associated with irreversible visual loss include recent weight gain, severe papilledema, subretinal hemorrhages, decreased visual acuity, visual field loss at the time of presentation, early optic nerve atrophy, and hypertension. Symptom duration, transient visual obscurations, pulsatile tinnitus, headache severity, and the actual number of the opening pressure have not been shown to influence long-term prognosis.

Overall, 10–20 % of patients will have permanent visual impairment despite normalization of the OP and papilledema resolution. Twenty percent of patients will relapse within 3 years of diagnosis, and it is important to keep in mind that relapse may occur even while patients are receiving medical therapy.

Conclusions

- The episodic syndromes that may be associated with migraine are likely precursors to migraine in adulthood. Each has very specific diagnostic criteria
- Childhood daily headaches, as in adult CDH, often have mixed features. Most can be diagnosed as TM or CM, NDPH, or CTTH
- Medication overuse can complicate CDH in the pediatric population
- IIH is an increasingly prevalent headache disorder in children and should be promptly identified and treated to prevent irreversible visual loss
- A normal opening pressure in children and adolescents is considered to be up to 28 cm H_2O
- Acetazolamide remains the first line of treatment in patients with IIH. Furosemide and corticosteroids may be used as adjunctive therapy or second line of treatment

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Part VI
Treatment of Episodic Headaches

Chapter 10
Acute Treatment of Episodic Migraine

Jennifer S. Kriegler

Introduction

All patients with migraine need to be provided acute treatment, even those on preventive medications. Setting clinical goals and expectations with patients improves adherence and outcomes.

Goals of Treatment of Acute Treatment

The official goals for acute treatment were described by the US Headache Consortium in 2000 (Table 10.1); newer acute guidelines are imminent at the time of this writing. The guideline goals included quick onset of acute treatment with consistent response, low recurrence, restoration of normal function with reduced disability, minimal side effects, and minimal use of rescue medicines, at the lowest possible cost. When patients are surveyed with respect to their desires for acute treatment and given choices, they choose a pain-free response by 2 h.

Clinical Approach to Acute Treatment

The characteristics of each headache determine the most effective acute treatment. Patients should keep a headache diary documenting the frequency, duration, time of onset, rapidity of onset, associated symptoms, prodromes or auras, disability, and triggers. Headache calendars help the clinician provide the most effective therapy

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Table 10.1 US Headache Consortium goals for acute migraine treatment, 2000

- Rapid onset of treatment that works consistently and without recurrence
- Restoration of normal function and reduction of disability
- Minimize rescue medicines
- Optimal self-care translated into reduced consumption of health services
- Lowest possible cost
- Minimal adverse events

Table 10.2 Clinical pearls for acute migraine treatment

- Educate the patient
- Keep a migraine diary
- Use migraine-specific treatment
- Treat early in the attack
- Limit the number of rescue medications to 10 days or less per month

for the patient. Headache education stressing the importance of early treatment is key when providing acute medication.

Acute therapy is divided into specific and nonspecific treatment. The decision on which treatment to use is tailored to patient need, so-called stratified care. Treatment choice is predicated on some characteristic of the headache or of the patient. Often, the extent of disability or impact is the surrogate marker used to determine which class of acute treatment to provide. In the absence of vascular contraindications, more disabled patients merit triptans as first-line acute treatment. Step care, never found to be as effective as stratified care, starts patients with low dose, nonspecific treatment and then escalates to more migraine-specific treatment.

Use nonoral or parenteral therapy, including nasal sprays, for individuals with rapid onset and significant nausea. Orally disintegrating tablets are actually absorbed more slowly than oral agents, but many patients prefer them and believe they work faster since "they dissolve," mistakenly believing that they are absorbed through the oral mucosa. Always take advantage of any placebo effect, since this will enhance the effectiveness of treatment.

Ideally, treatment should be "one and done," that is, one medication with relief of migraine and no recurrence. When asked about acute treatment in a study by Lipton and colleagues, patients prefer a medication that provides complete relief, that is, pain free (87%), rapid onset (83%), and relief of associated symptoms (76%).

Most migraine studies evaluate headache relief at 2 h to judge effectiveness. Some use migraine freedom criteria, that is to say, no headache, nausea, and light or noise sensitivity. This is an important distinction, because it may be necessary to use adjunctive medications to treat associated symptoms such as nausea.

Always limit the number of days that migraine rescue medicines can be used. In general, limit the total number of days to 10 or less to prevent rebound (medication overuse headache, MOH). There is evidence to suggest that 10 days/month of triptans or nonsteroidal anti-inflammatory drugs (NSAIDs), 8 days/month of narcotic analgesics, or 5 days/month of butalbital containing compounds may lead to MOH (Table 10.2).

Table 10.3 Triptan sensations

• Tightening of throat, chest, jaw, neck, limbs
• Paresthesias in limbs and around mouth
• Hot/cold sensations

Table 10.4 Serious concerns with triptans

• Triptans narrow coronary blood vessels by 10–20 %
• Contraindicated in coronary artery and vascular disease, stroke, uncontrolled hypertension, and pregnancy

Migraine-Specific Treatment

Triptans

Except in the presence of coronary artery and vascular disease, stroke, uncontrolled hypertension, and pregnancy, triptans are the drugs of choice for acute migraine management. Triptans not only improve the headache, but the associated symptoms of nausea and photophobia as well.

Triptans were introduced in the 1990s. They are serotonin $(5\text{-HT})_{1B/1D}$ selective agonists (some 5-HT_{1F}), and they block the release of calcitonin gene-related peptide (CGRP), a potent, naturally occurring vasodilator. For the most part, they have a faster time to relief and fewer side effects than ergotamine, which preceded them. Their place in the armamentarium with respect to dihydroergotamine (DHE) or very fast acting NSAIDs is not yet resolved.

Side effects or so-called triptan sensations include tightening of throat, chest, jaw, neck, limbs, paresthesias in the limbs and around the mouth, and hot/cold sensations (Table 10.3). These are attributed to esophageal narrowing, mitochondrial change, or muscular contraction. Tests suggest a noncardiac etiology for most symptoms.

However, triptans do narrow coronary blood vessels by 10–20 % (Table 10.4). In general, always warn the patient about these symptoms, to reduce concern. Reassure them that these tolerable side effects tend to abate (or patients ignore them) over time.

Not every person will have side effects to all the triptans. In general, if the triptan sensations are intolerable, just switch to a different triptan, since many individuals will be able tolerate one member of the class. Subcutaneous (SC) sumatriptan has the most side effects (7.8 %), whereas naratriptan (4 %) and almotriptan (1 %) have the least.

There are seven triptans available in the USA and one combination triptan and NSAID (Table 10.5). Five triptans have a rapid onset and two have slower onset. Sumatriptan, rizatriptan, zolmitriptan, eletriptan, and almotriptan are rapid-acting, whereas frovatriptan and naratriptan have a slower time to clinical effect.

Sumatriptan (brand-name IMITREX, IMIGRAN) is the most versatile of the triptans, as of 2014 with an SC formulation a tablet, a nasal spray, and an electric

Table 10.5 Triptans available in the USA

Brand name	Generic name	Formulation	Onset of action
AMERGE[a]	Naratriptan hydrochloride	Tablet	Slow
AXERT	Almotriptan malate	Tablet	Rapid
FROVA	Frovatriptan succinate	Tablet	Slow
IMITREX[a] (SUMAVEL, ALSUMA, SC forms; ZECUITY, patch)	Sumatriptan succinate	SC, tablet, nasal spray, patch	Rapid
MAXALT[a]	Rizatriptan benzoate	Tablet, orally disintegrating tablet	Rapid
RELPAX	Eletriptan hydrobromide	Tablet	Rapid
ZOMIG[a]	Zolmitriptan	Tablet, orally disintegrating tablet (both generic), nasal spray (not generic)	Rapid
TREXIMET	Sumatriptan succinate 85 mg + naproxen sodium 500 mg	Tablet	Rapid

[a] Generic versions available

Table 10.6 Pearl on triptans

- Use SC sumatriptan or nasal spray zolmitriptan for rapid-onset migraine, migraine upon awakening, or migraine with significant nausea and vomiting from the onset

skin patch. The tablets, traditional nasal spray, and injections are currently available generically in the USA and the tablets available without a prescription in the UK.

At the time of this writing, the other generic triptans available in the USA are rizatriptan (MAXALT), zolmitriptan tablets (ZOMIG), and naratriptan (AMERGE, NARAMIG). Naratriptan is available without a prescription in Germany.

The SC preparation of sumatriptan is the most rapidly absorbed and has the most side effects. It is particularly useful in those individuals who have a rapid onset to peak and who have significant nausea and vomiting from the onset (Table 10.6). There may be a transient increase in headache ("head rush"), for 10–20 min after use of the SC formulation. The SC formulation is currently available with a self-administered needle (generic and brand-name STAT-DOSE, and a different generic autoinjector by Sun Pharmaceutical), in an epipen-like injection (brand name ALSUMA), and in a needle-free injection form (brand name SUMAVEL).

The traditional sumatriptan liquid nasal spray is poorly absorbed through the nasal mucosa (10%) and likely has, at least partly, a gastrointestinal (GI) absorption. It is difficult to use since patient positioning is key, and it has a significantly bitter aftertaste which may make nausea worse. A new nasal spray is under development (see below).

The US Food and Drug Administration (FDA) approved an iontophoretic electric sumatriptan patch (brand name ZECUITY) in 2013.

TREXIMET is the brand name of the combination of sumatriptan (85 mg) and naproxen sodium 500 mg.

Zolmitriptan (brand name ZOMIG) comes as a pill, an orange-tasting orally disintegrating tablet (ODT), and a nasal spray. As noted, the traditional oral tablet and the ODT are both available as generics. The nasal spray (not generic) is

Table 10.7 American Headache Society position paper summary on the risk of serotonin syndrome mixing triptans and SSRIs/SNRIs

"Current available evidence does not support limiting the use of triptans with SSRIs or SNRIs due to concerns for serotonin syndrome"

well absorbed through the nasopharynx (40 %), with the remainder being absorbed through the GI tract (Table 10.6).

Rizatriptan (brand name MAXALT) has both a mint-flavored orally disintegrating tablet and a conventional tablet. Rizatriptan is now available in the USA and Canada as a generic in both the pill and ODT formulation.

Naratriptan (brand name AMERGE) is available in the USA as a generic. The rest of the triptans only come in a pill formulation and are not currently available in a generic form.

In general, a rule of thumb on triptans coined by Dr. Seymour Solomon is that patients vary more than triptans. This means that failure of response to one triptan, because of side effects, inadequate efficacy, slow time to response, or high frequency of recurrence, does not necessarily predict failure of response to another, and multiple trials of different triptans can be necessary and helpful.

Triptan Interactions with Other Medications

Ergots

Both ergots and triptans narrow coronary blood vessels. Triptans should not be used within 24 h of an ergot medication, since there could be a vasoconstrictive synergistic effect. There is no large prospective safety study to support the safety of use of two different triptans within a 24 h period, which is prohibited by labeling.

Serotonin Syndrome

Use of triptans with other serotonin drugs has been called into question due to the serotonin syndrome (SS). This is a potentially life-threatening clinical triad of altered mental status, dysautonomia, and neuromuscular changes. SS may also cause a metabolic acidosis, rhabdomyolysis, seizures, and disseminated intravascular coagulation (DIC). In 2006, the FDA issued an alert warning about SS with use of triptans/ergots and serotonin reuptake inhibitors/serotonin–norepinephrine reuptake inhibitors (SSRIs/SNRIs). Twenty-nine cases were reported between 1998 and 2002.

However, after examining the evidence, the American Headache Society published a position paper in 2010 which states that "the available evidence does not support limiting the use of triptans with SSRIs or SNRIs due to concerns for serotonin syndrome" (Table 10.7).

Table 10.8 Clinical pearls on triptan drug–drug interactions

- Do not use sumatriptan, rizatriptan, or zolmitriptan with an MAOI
- Use no more than 2.5 mg zolmitriptan with cimetidine, quinolones, and fluvoxamine
- Use half-dose eletriptan with clarithromycin, ketoconazole, erythromycin, verapamil, and antiretroviral agents
- Use rizatriptan 5 mg with propranolol

Other Triptan Drug Interactions

Some triptans are degraded by monoamine oxidase inhibitors (MAOIs). There is the potential to cause a hypertensive crisis when sumatriptan, rizatriptan, or zolmitriptan is given in combination with an MAOI. Zolmitriptan should be used at no more than the 2.5-mg dose level when used with cimetidine, quinolones, and fluvoxamine due to a CYP1A2 interaction.

Eletriptan should be used at half-dose with other CYP3A4 potent inhibitor drugs such as clarithromycin (BIAXIN), erythromycin, ketoconazole, verapamil, and certain antiretroviral medications. The typical dose of eletriptan in Europe is 80 mg, so that the maximal dose in the USA (40 mg) is probably safe to use without much risk. The maximal eletriptan dosage per 24 h is 80 mg.

The optimal dose for rizatriptan is 10 mg. Propranolol increases concentrations of rizatriptan by 70%, so the rizatriptan dose should be decreased to 5 mg in combination with propranolol. This interaction is specific only for rizatriptan and propranolol. No dosage adjustment is necessary with other beta-blockers (Table 10.8).

The Future for Triptans

At the time of this writing, there is a flurry of activity in development of new formulations for triptans. This is essentially putting old wine into new bottles.

The first FDA-approved new formulation for a triptan is the previously mentioned skin patch of sumatriptan. This device has a battery and a button, and after putting it on the skin, the patient presses the button and a low-level electrical current pushes the sumatriptan under the skin for absorption. The brand name of the iontophoretic patch of sumatriptan is ZECUITY. The regulatory trials suggest a slow but steady onset of pain relief over 2–4 h, and a faster onset of nausea relief, with 84% of patients without nausea within 2 h of applying and turning on the patch.

In early 2014, a different nasal spray of sumatriptan was submitted to the FDA. This formulation works by the patient blowing dry sumatriptan powder up the nose, which closes the soft palate to prevent the drug from being swallowed. Studies are ongoing to see whether this delivery system offers advantages over other formulations of sumatriptan. There are also other new ideas for triptan deliveries in the works as well, including a dissolvable film of a triptan, oral inhalation, and a spray on the tongue.

Table 10.9 Ergot contraindications

- Pregnancy
- Vascular disease
- Within 24 h of a triptan

Ergots

Ergotamine tartrate has been available since 1925 and DHE since 1945. There are a number of formulations of ergots available around the world: oral, nasal spray, SC, intravenous (IV), and suppository. These were the only migraine-specific drugs available until triptans were introduced in the 1990s.

Ergots do not have receptor specificity. Ergots not only have effects at the serotonin $(5\text{-HT})_{1B}$ and 5-HT_{1D} receptor level, but also at the 5-HT_{1F}, 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B}, dopamine D1 and D2, and adrenergic α1, α2, and β receptor level. This broad range of receptor activity can account for both their side effects and their excellent duration of clinical action.

Ergot half-life is up to 36 h, so ergots may be helpful in long duration migraine. Nausea is the primary side effect. Since it is a common associated symptom in migraine, ergots may increase the nausea instead of improving it.

Other side effects of ergots include lightheadedness and leg cramps. Intranasal DHE (MIGRANAL) causes rhinorrhea and nasal stuffiness in at least 25% of users. The IM/SC formulation of DHE is painful, and there is a 10% chance of injection site reaction; however, DHE can be mixed with 0.25–0.50 mL of 1–2% lidocaine in the same syringe to reduce injection-site burning. This mixture must be prepared just before administration because long-term stability cannot be guaranteed. Since ergots cause uterine contractions, they can cause menorrhagia during the menstrual cycle.

Ergots, as with triptans, are contraindicated in vascular disease including peripheral vascular disease, coronary artery disease, and stroke. Ergots are contraindicated in pregnancy and carry an FDA pregnancy category X (Table 10.9). They may cause retroperitoneal, valvular, and/or pulmonary fibrosis with prolonged daily use of >6 months. This is mediated through 5-HT_{2B} action.

Despite the difficulties with formulations, IV DHE remains a useful medication for terminating status migrainosus and weaning patients from MOH. An orally inhaled DHE, which achieves IV blood levels with minimal nausea, is in development at the time of this writing, and may prove an extremely valuable addition to the acute armamentarium because of the prolonged effects of DHE, and the utility of an inhaled medication in patients with nausea and vomiting.

Table 10.10 Pearls on NSAIDs and migraine

- Use NSAIDs for moderate migraine (diclofenac potassium sachets FDA-approved for moderate-to-severe attacks)
- Use NSAIDs + triptans for migraine in progress, prolonged migraine, or migraine that recurs
- NSAID–triptan combinations can be used synergistically for rapidity of action, improved efficacy, and/or reduced recurrence of the headaches
- Use NSAIDs first-line in triptan-contraindicated patients and for triptan-intolerant or poorly responsive patients
- Patients respond individually to different medications within a category, including triptans and NSAIDs. Try varying acute medications and combinations when one fails for that patient
- Use caution in patients with heart failure, vascular disease, or history of GI bleed. For those at risk for vascular events, naproxen is the safest choice

Nonspecific Acute Migraine Treatment

Nonsteroidal Anti-Inflammatory Drugs

There are at least 20 different NSAIDs available in the USA. All are well absorbed and have a negligible first-pass hepatic effect. They are highly protein bound and may interfere with other protein-bound drugs.

NSAIDs have both a prostaglandin- and non-prostaglandin-mediated mechanism of action. In migraine treatment, NSAIDs prevent prostaglandin formation through the inhibition of cyclooxygenase (COX). Some NSAIDs have more of an anti-inflammatory effect and others an enhanced analgesic effect.

Probably unlike triptans, NSAIDs can reverse central sensitization and so can be useful deep into a migraine attack or for migraine upon awakening, similar to DHE. As with DHE, NSAID use may be associated with decreased likelihood of migraine recurrence, as opposed to triptans.

Randomized, placebo-controlled studies in migraine have shown varying degrees of efficacy with aspirin, ibuprofen, naproxen, tolfenamic acid, and two pivotal phase III studies supported diclofenac potassium for oral solution (brand name CAMBIA in the USA, VOLTFAST in Europe) which dissolves in water and is FDA-approved for acute treatment of episodic migraine. The dissolvable 50-mg sachet was found to be superior to both placebo and conventional diclofenac potassium 50-mg tablets for pain-free response and headache relief at 2 h, as well as onset of analgesic effect, and sustained freedom from pain and pain relief.

There is often benefit to trying different acute medications within a therapeutic category, such as different triptans or NSAIDs, since response to therapy with equipotent doses may vary among individuals. See Table 10.10 for clinical pearls on using NSAIDs and triptans. Table 10.11 lists the classes of NSAIDs.

NSAIDs are suggested for use in moderate headache, although the prescription diclofenac potassium sachets were proven effective and FDA-approved for moderate to severe attacks.

Table 10.11 Chemical groups in NSAIDs

Carboxylic acids
• Aspirin (acetylsalicylic acid): 2.4–6 g/24 h in four to five divided doses (EXCEDRIN MIGRAINE, nonprescription, includes aspirin 250 mg, acetaminophen 250 mg, caffeine 65 mg, FDA-approved for migraine)
• Salsalate: 1.5–3 g/24 h dosed bid
• Diflunisal: 0.5–1.5 g/24 h dosed bid
• Choline magnesium trisalicylate: 1.5–3 g/24 h dosed bid–tid
Propionic acids
• Ibuprofen: 400–800 mg, max 3,200 mg/24 h dosed tid–qid (ADVIL MIGRAINE nonprescription 200 mg, FDA-approved for migraine)
• Naproxen: 500–550 mg bid
• Fenoprofen: 300–600 mg qid
• Ketoprofen: 75 mg tid
• Flubiprofen: 100 mg bid–tid
• Oxaprozin: 600 mg bid
Acetic acid derivatives
• Indomethacin: 25, 50 mg tid–qid; SR:75 mg bid; rarely > 150 mg/24 h
• Ketorolac: 10 mg PO Q6h; NS (SPRIX): 15.75 mg (one spray) each nostril not to exceed 5 days
• Tolmetin: 400, 600, 800 mg; 800–2400 mg/24 h
• Sulindac: 150, 200 mg BID; some increase to tid
• Diclofenac: 50 mg (CAMBIA (diclofenac potassium for oral solution) dissolvable powder sachet 50 mg, FDA-approved for migraine)
Fenamates
• Meclofenamate: 50–100 mg tid–qid
• Mefenamic acid: 250 mg qid
Enolic acids
• Piroxicam: 10, 20 mg/day
• Phenylbutazone: 100 mg TID up to 600 mg/24 h
Napthylkanones
• Nabumetone: 500 mg BID up to 1,500 mg/24 h
Selective COX-2 inhibitors
• Celecoxib: 100, 200 mg/day
Mixed COX-1/COX-2 inhibitors
• Meloxicam: 7.5–15 mg/day

NSAIDs were thought to be less effective in treating migraine-associated symptoms than triptans, but regulatory trials on the diclofenac sachets found rapid benefit for all of the migraine symptoms, and previous trials on NSAIDs including diclofenac often found 2-h equivalence or superiority to triptans.

NSAIDs may be of particular advantage in menstrual migraine, since they target both headache pain and menstrual cramps. Consider use of NSAIDs as first-line therapy in triptan-contraindicated patients and for triptan intolerant or poorly responsive patients.

NSAIDs may also be used in combination with triptans for migraine upon awakening, when the headache is already in progress, for prolonged migraine, and for

migraine that recurs. There is a synergistic effect of NSAIDs with triptans, accounting for the FDA approval of the sumatriptan/naproxen sodium combination pill. Triptan–NSAID combinations such as sumatriptan plus naproxen sodium or, more recently, a triptan washed down with the diclofenac potassium for oral solution may provide synergy in terms of rapidity of action, improved efficacy, and/or reduced recurrence of the headaches.

Ketorolac is available as a pill, IM or IV injection, and a nasal spray (brand name SPRIX). The nasal spray is well absorbed through the nasopharynx with the onset of analgesia within 20 min and half-life elimination at 5–6 h (similar to IM administration). The spray is FDA-approved for moderate-to-severe pain, but not specifically for migraine. Dose is one spray each nostril, yielding approximately a clinical equivalent of a 30-mg IM injection.

As noted, triptans prevent the progression of the migraine by blocking release of CGRP, and NSAIDs block the prostaglandin cascade, a likely promoter of the ongoing migraine. DHE remains an alternative to the NSAID/triptan combination. Some clinical pearls on NSAIDs and migraine are included in Table 10.10.

NSAIDs are not without risk for vascular and GI side effects. A pivotal meta-analysis published in the *Lancet* in 2013, consisting of 280 trials of NSAIDs versus placebo and 474 trials with one NSAID compared with another, found an increased risk with most NSAIDs for major vascular events, heart failure, and GI bleed.

The type of NSAID was an important differentiating statistic for a major vascular event, with the highest odds ratio (OR) for diclofenac with a relative risk (RR) of 1.41 (95% confidence interval, CI, 1.12–1.78) and the COX-2 inhibitors with RR 1.37 (CI 1.14–1.66). Ibuprofen had an RR of 2.22 (CI 1.10–4.48) for major coronary events only but not major vascular events.

Naproxen did not show any increased risk of vascular or coronary events. This meta-analysis did not show any increased risk of stroke with any NSAID, although other studies show comparable risk (see Chap. 17, Tables 17.3 and 17.4).

All NSAIDs were found to double the risk of heart failure and increase the risk of GI irritation and bleed. All NSAIDs, prescription and nonprescription, now carry an FDA black-box warning highlighting the potential for increased risk of cardiovascular (CV) events and GI bleed. In early 2014, the FDA published a review confirming the naproxen had the least vascular risk of any of the NSAIDs.

Acetaminophen

In some individuals, acetaminophen is an effective analgesic and abortive for moderate migraine. It can be effective for mild disability. Acetaminophen can be used alone or in combination with NSAIDs and caffeine. Acetaminophen is commonly paired with butalbital and narcotic analgesics. The effective dose is 1,000 mg at the onset of the headache. However, it is worth remembering that in 2005, a 60-patient, multicenter, randomized controlled trial did not find efficacy for 1 gram of intravenous acetaminophen versus placebo.

Table 10.12 Warning on butalbital

The US Headache Consortium guidelines note no randomized controlled trials prove or refute the efficacy of butalbital-containing compounds for the treatment of acute migraine

Isometheptene

Isometheptene mucate 65 mg is usually combined with acetaminophen 325 mg and dichloralphenazone 100 mg (MIDRIN). This is an older preparation, never fully studied in randomized controlled trials, never approved by the FDA for episodic migraine, and nonspecific for the acute treatment of migraine. Oral dosing: two capsules to start, followed by one capsule every hour until relief is obtained (maximum: 5 capsules/12 h). It has gone in and out of availability over the past few years.

Butalbital

The US Headache Consortium guidelines note that no randomized controlled trials prove or refute the efficacy of butalbital-containing compounds for the treatment of acute migraine (Table 10.12). They are commonly prescribed, but the side effects outweigh the benefits. As few as five doses per month may cause MOH.

Acute side effects of butalbital include incoordination, disinhibition, emotional lability, memory difficulties, and drowsiness. Tolerance occurs rapidly due to its unusual pharmacokinetics. The analgesic half-life is 3–6 h, whereas the pharmacokinetic half-life varies between 35 and 88 h, averaging approximately 61 h.

Patients use frequent dosing due to the short analgesic half-life while building up levels due to the long pharmacokinetic half-life. This increases sedation and leads to tolerance and dependence.

Butalbital withdrawal may be life-threatening, and seizures may begin 24–115 h after the last dose. Delirium tremens can begin in 24 h and last several days. Visual hallucinations are a prominent feature of the withdrawal syndrome. The authors of this manual favor not using butalbital at all for headache and recommend its complete removal from the market.

Narcotic Analgesics

The US Headache Consortium guidelines, with joint participation of the American Academy of Neurology, the American College of Physicians, the American Society of Internal Medicine, and the American Academy of Family Physicians, issued the following statement on opioids for migraine: “Until further data are available, these drugs [opioids] may be better reserved for use when other medications cannot be used, when sedation effects are not a concern, or the risk for abuse has been addressed.”

Despite this position, opioids remain a commonly prescribed medication for migraine. As few as 8 days of narcotic analgesics per month may cause MOH. Narcotic analgesics should be reserved for patients with coronary artery disease

or in pregnant women. Limits on amounts should be clearly defined. As noted in Chapter 5, a careful history for substance and alcohol misuse should be taken before contemplating an opioid prescription. There is concern that single doses may make migraine more refractory to treatment for months.

Antiemetics

Neuroleptics can be remarkably effective in aborting a migraine attack when used alone or when co-administered with an analgesic, triptan, or ergot. They are not FDA-approved for migraine. Neuroleptics antagonize dopamine receptors in the chemoreceptor trigger zone. Commonly used antiemetics are metoclopramide, chlorpromazine, prochlorperazine, promethazine, haloperidol, and droperidol.

Chlorpromazine

When used intravenously, chlorpromazine 10 mg is an effective migraine abortive. It can be used to treat both migraine without and with aura and is extremely useful in the patient with nausea and vomiting. Most common side effects include sedation and drowsiness. Dystonia and akathisia may be seen following the first IV dose and can be treated with benztropine or diphenhydramine. Chlorpromazine can induce orthostatic hypotension. There are also suppository and oral formulations that are useful adjunctives for patients with significant nausea and vomiting to keep them out of the emergency room.

Prochlorperazine

Prochlorperazine is no longer approved for IV use due to significant risk of venous thrombosis. It should also not be used IM. Prochlorperazine may be used per oral (PO) or per rectum, and has similar effectiveness to chlorpromazine, although it is a bit less sedating. Side effects are also similar, although anecdotally the risk of dyskinesias and akathisia appears to be greater.

Metoclopramide

In pooled data, IV metoclopramide proved an effective migraine abortive. Data show that metoclopramide 20 mg IV (a higher dose than the conventional 10 mg) given every 20 min for four doses (with diphenhydramine 25 mg every hour to prevent akathisia) has comparable effectiveness to sumatriptan 6 mg SC, but many more side effects. Metoclopramide 10 mg given orally every 6 h is a good alternative in patients who are not able to use triptans, and metoclopramide is Category B for use in pregnancy. Used in combination with other medications, metoclopramide can improve medication absorption due to its prokinetic effect on gastroparesis.

Table 10.13 Treatment of intractable migraine/status migrainosus (emergency department or office infusion room)

- Rehydrate with 1 liter D5 1/2 N saline
- Antiemetic: metoclopramide 10 mg IV OR chlorpromazine 10 mg IV over 20 min OR ondansetron 4–8 mg IV over 20 min
- Diphenhydramine (BENADRYL) 25 or 50 mg IV for akathisia
- DHE 1 mg IV (for naïve patient use 0.25 mg over 20 min × 4). The subnauseating dose is the effective dose or
  Sumatriptan 6 mg SC and/or
  IV valproic acid (loading dose 15 mg/kg, maintenance dose 11 mg/kg) over 20 min
- Magnesium sulfate 1–2 g IV over 1 h
- Corticosteroid (dexamethasone 10 mg IV) or methylprednisolone 500–1,000 mg IV over 20 min
- Ketorolac 30 mg IV over 20 min

Additional notes

- IV magnesium may decrease efficacy of IV metoclopramide
- Obligatory disclaimer: There are almost no controlled comparisons for migraine status management. This is mostly recipe swapping! However, please see the 3-part series on rescue medications for acute migraine by Kelley and Tepper in the suggested readings for a comprehensive discussion of controlled trials

Droperidol

Droperidol has a "black box" warning, due to prolonged QT effects which can cause torsades de pointes. Although this event is extremely rare, droperidol should probably not be given unless a patient is being monitored for cardiac events.

Atypical Antipsychotics

Quetiapine and olanzapine are also not FDA-approved for treatment of migraine. They can be useful to abort a migraine when agitation is prominent or when the pain prevents sleep.

Corticosteroids

In general, corticosteroids should be reserved for intractable migraine or status migrainosus. Usually, a rapidly tapering dose of prednisone beginning with 60 mg or a 3-day burst of dexamethasone (4 mg tid, bid, qd) is effective in terminating prolonged migraine. IV dexamethasone 10 mg may be given as a rescue in an emergency room situation. The methylprednisolone dose pack is generally too low a dose to be effective (Tables 10.13 and 10.14)

Table 10.14 Clinical pearls on outpatient management of status migrainosus

- Stop if headache free for 24 h
- Prednisone 60 mg po with rapid taper over 7 days
- Dexamethasone 4 mg tid, bid, qd
- Ketorolac 30 mg IM followed by 10 mg orally: up to QID × 5 days
- The methylprednisolone dose pack is too low a dose to be generally effective

Neuromodulation for Acute Migraine Treatment

In December of 2013, the FDA approved use of a Transcranial Magnetic Stimulator (Cerena, eNeura) for acute treatment of migraine with aura. This is a portable device held at the back of the head and turned on to pulse and terminate attacks. The manufacturing company has elected not to market the Cerena device, but has instead submitted a follow-on similar device to the FDA at the time of this writing.

Other neuromodulation techniques being studied for acute treatment of migraine at the time of this writing include a non-invasive hand-held vagal nerve stimulator and an implantable sphenopalatine ganglion stimulator. Each of these devices will require randomized controlled trials before receiving FDA approval.

Conclusions: Key Clinical Pearls in Acute Migraine Management

- Use migraine-specific medication such as triptans or DHE in the absence of vascular risks
- NSAIDs offer an alternative as monotherapy to triptans with some evidence for similar effectiveness at 2 h, and also evidence for reversal of central sensitization
- Treat early in the attack
- Add an NSAID to the triptan if migraine recurs, or there is not an appropriate 2-h response to the triptan alone. DHE is also an alternative
- Avoid opioids and butalbital
- Do not use acute medications more than 10 days/month. Simplicity leads to the recommendation to treat acutely no more than 2 days per week
- Encourage patients to keep a diary to help understand the characteristics of their headache and to evaluate response to treatment

Suggested Reading

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Chapter 11
Preventive Treatment of Episodic Migraine

Cynthia C. Bamford and Emad Estemalik

Introduction

Migraine pain should be treated with abortive or acute, as-needed, therapies, but when the migraines are frequent or disabling, preventive therapy should be considered. Preventive therapy is typically pharmacologic, but nonpharmacologic therapies are available as well.

As discussed in previous chapters, the patient is on the road to medication overuse once abortive treatment exceeds 9 days a month with nonsteroidal anti-inflammatory drugs (NSAIDs) or triptans, 7 days a month with opiates, or 4 days a month with compound analgesics containing butalbital. Therefore, preventive measures should be initiated while a patient still has episodic migraine to prevent headaches from becoming increasingly frequent leading to medication overuse (see Table 11.1).

This chapter addresses preventive treatment of episodic migraine. When to begin preventive treatment depends on a number of factors: frequency, severity, patient's preference, medication overuse, and disability or impact.

Medications Used for Prevention of Migraines

Preventive medications commonly used for prophylaxis can include antihypertensives, antidepressants, antiepileptic drugs (AEDs), NSAIDs, and supplements (see Table 11.2). Only five drugs are approved by the Food and Drug Administration (FDA) for episodic migraine prevention in the USA: propranolol, timolol, valproic

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S. J. Tepper, D. E. Tepper (eds.), *The Cleveland Clinic Manual of Headache Therapy, Second Edition,* DOI 10.1007/978-3-319-04072-1_11,

Table 11.1 Clinical pearls: When to initiate daily pharmacological prophylaxis. (Adapted from Silberstein and Goadsby 2002)

- Recurring migraines that interfere with daily routine despite acute therapy
- Frequent migraines (> 3/month)
- 10–14 headache days/month
- Patient preference
- Adverse effects from abortive therapies
- Uncommon conditions, such as hemiplegic migraine, migraine with brainstem aura (formerly called basilar-type migraine), prolonged migraine aura
- Medication overuse
- Severe, disabling attacks

Table 11.2 Classes of drugs used for prevention of migraines

- *Antihypertensive drugs*
  - Beta-blockers
  - Calcium channel blockers
  - ACE inhibitors
  - ARBs
- *Antiepileptic drugs*
- *Antidepressants*
  - Tricyclic antidepressants
  - Serotonin norepinephrine reuptake inhibitors (SNRIs)
  - Selective serotonin reuptake inhibitors (SSRIs)
  - MAO inhibitors
- *Nonsteroidal anti-inflammatory drugs (NSAIDs)*
- *Serotonin (5-HT) antagonists*
- *Herbal, vitamin, and mineral supplements*

acid, topiramate (TPM), and methysergide (no longer available in the USA). All other drugs for prevention are used off-label. OnabotulinumtoxinA has FDA approval for chronic migraine (defined in the prescribing information as headache of at least 15 headache days per month at least 4 h per day) but not episodic migraine.

Mechanisms of action for preventive medication comprise a variety of not mutually exclusive pathways. These include inhibition of cortical spreading depression, raising the threshold to migraine activation by stabilizing the hyperexcitable migraine brain, enhancement of antinociception, inhibition of central and peripheral sensitization, and modulation of sympathetic, parasympathetic, or serotonergic tone.

The US Headache Consortium published the first episodic migraine preventive guidelines in 2000 based on quality of evidence, scientific effect, clinical impression of effect, adverse effects, and efficacy. In 2012, a follow-up set of guidelines with an evidence review on preventive medications was published. A second set of guidelines provided evidence on NSAIDs, herbs, minerals, and vitamins for prevention of episodic migraine (see Tables 11.3 and 11.4).

The definitions for the quality of trials are listed in Table 11.5 and the rating system for the 2012 guidelines is listed in Table 11.6.

Table 11.3 2012 American Headache Society evidence–based guidelines of preventive therapies for migraine

Level A: Medications with established efficacy (at least two class I trials)
- Divalproex Sodium/Sodium Valproate
- Topiramate
- Metoprolol
- Propranolol
- Timolol

Level B: Medications that are probably effective (one class I or ≥2 class II studies)
- Amitriptyline
- Venlafaxine
- Atenolol
- Nadolol

Level C: Medications are possibly effective (one class II study)
- Lisinopril
- Candesartan
- Clonidine
- Carbamazepine
- Nebivolol
- Pindolol
- Cyproheptadine

Level U: Medications with inadequate or conflicting data to support or refute medication use
- Acetazolamide
- Warfarin
- Fluvoxamine
- Fluoxetine
- Gabapentin
- Protriptyline
- Bisoprolol
- Nicardipine
- Nifedipine
- Nimodipine
- Verapamil
- Cyclandelate

Other: Medications that are possibly or probably ineffective
- Lamotrigine
- Clomipramine
- Acebutolol
- Clonazepam
- Nabumetone
- Oxcarbazepine
- Telmisartan

Although the 2012 guidelines list NSAIDs for daily migraine prevention, NSAIDs are not currently recommended as daily prophylaxis, due to the potential to develop medication overuse headache (MOH), gastritis, and renal insufficiency. The NSAIDs should be considered for short-term prevention, used at the time of exposure to a trigger, or treatment just before and during menses to avert menstrual migraine.

Table 11.4 Over-the-counter and NSAID preventive medications, 2012 American Headache Society guidelines-2

Level A: Medications with established efficacy (≥2 class I trials)
- Petasites

Level B: Medications are probably effective (one class I or two class II studies)
- Fenoprofen
- Ibuprofen
- Naproxen and naproxen sodium
- Magnesium
- Feverfew
- Riboflavin

Level C: Medications are possibly effective (one class II study)
- Flurbiprofen
- Mefenamic acid
- Co Q10
- Estrogen
- Cyproheptadine

Level U: Medications with inadequate or conflicting data to support or refute medication use
- Aspirin
- Indomethacin
- Omega 3
- Hyperbaric oxygen

Other: Medications that are possibly or probably ineffective
- Montelukast

Table 11.5 Definitions for quality of trials in the 2012 American Headache Society guidelines

Class I: Randomized controlled trial (RCT) with masked or objective outcome assessment(s) with:
- Baseline characteristics substantially equivalent among treatment groups or appropriate statistical adjustment for differences
- Concealed allocation; Primary outcome(s), exclusion/inclusion clearly defined
- Adequate accounting for dropouts (≥80% enrolled subjects completing)
- Explicitly defined threshold for equivalence or non-inferiority
- Standard treatments, inclusion/exclusion criteria, outcomes used similar to those previously used
- Study interpretation per protocol analysis taking into account dropouts or crossovers

Class II: RCT with masked/objective outcome assessments lacking one of the above criteria

Class III: Other controlled trials (e.g., natural history controls or patients are own controls); outcome independently assessed by objective outcomes

Class IV: Studies not meeting class I, II, or III criteria including consensus or expert opinion

Table 11.6 Rating system for evaluating preventive medications in the 2012 American Headache Society guidelines

Level A: Medication has established efficacy (≥2 Class I trials)

Level B: Medication is probably effective (one Class I or ≥2 Class II studies)

Level C: Medication is probably effective (one Class I or ≥2 Class II studies)

Level U: There are inadequate or conflicting data to support or refute medication use

Other: Medications that are possibly or probably ineffective

Table 11.7 Preventive treatment goals: the basics

• A 50% decrease in frequency of headaches with diminished intensity and duration
• Decreased disability
• Improved responsiveness to abortive treatment

How to Set Up Preventive Treatment: Active Tips

Look at each patient individually to determine an appropriate preventive regimen. Set realistic expectations. Emphasize a healthy lifestyle with aerobic exercise daily, good sleep hygiene, and limiting caffeine intake to the equivalent of two 8 oz cups of coffee a day or less. Use the most efficacious drugs.

All drugs have potential adverse reactions. Most side effects are minor, but some are life threatening, such as anaphylaxis or Stevens–Johnson syndrome.

Worsening of headache may occur with the very drugs we use to treat headaches. Consider patients' comorbidities and the adverse effects of the medications.

Amitriptyline is efficacious but may not be the first choice in an obese patient because of increased appetite and weight gain associated with the drug. It may be a great choice for a patient who suffers from insomnia or chronic diarrhea, as it may cause sedation or constipation.

Only a few preventive medications cause weight loss or are weight neutral: topiramate (TPM), zonisamide, venlafaxine, and duloxetine. Zonisamide and duloxetine, although used in prophylaxis, have no randomized controlled evidence for efficacy. TPM, which is widely used for migraine prevention, may also have significant side effects and is FDA Category D for pregnancy. Pay attention to cognitive side effects and the risk for nephrolithiasis.

Start low, go slow, and be patient. It is by trial and error that one finds a drug that works with minimal adverse effects. Educate patients that each preventive medication may take at least 2–3 months to be effective. Success may take several medication trials.

In some patients, headaches are refractory to treatment and may require many trials and polytherapy. Combine medications with different mechanisms of action, i.e., TPM and amitriptyline.

Do not continue drugs that are ineffective, but withdraw these medications slowly. Do not stop medications abruptly unless there is an allergic reaction.

Be sure to set reasonable expectations. A 50% decrease in frequency is a good response to daily preventive medication. See Table 11.7 for the basics on preventive treatment goals.

Provide the patients with headache diaries to determine if preventive therapy is effective and to monitor the frequency of abortive therapies used. Many diaries are available on line; there are several smartphone apps. The diary should include, at the least, frequency of headaches, frequency of the abortive medications taken, effectiveness of the abortive therapy, and preventive therapies and doses. Triggers and disability ratings may also be included.

Table 11.8 Key preventive treatment clinical pearls (Adapted from Silberstein 2006)

- Start with a low dose
- Give at least a 2–3-month trial; make sure the preventive trial is long enough
- Avoid drug–drug interactions, overused rebound medications, and medications which are contraindicated or worsen comorbid conditions
- After reviewing the diary, if there is no reduction, reevaluate treatment. If multiple treatments fail, reevaluate the diagnosis or look again for rebound
- Most migraine patients are women in their childbearing years. Discuss with patients risks of medications to fetus, discuss contraception, and potential drug–drug interactions with oral contraceptives. Avoid valproic acid due to teratogenicity and propensity for causing polycystic ovaries. Topiramate, too, is FDA Category D in pregnancy. Consider, if appropriate, discontinuation of hormonal therapy
- Create an active therapeutic alliance with patients to improve adherence
- Go for a two-fer! Consider using one medication to treat two or more comorbid conditions when possible
- Choose a drug based on level of evidence for effectiveness, patient's own preference, characteristics of the patient's headaches, side effects, and coexisting or comorbid disease
- Provide realistic expectations when starting daily treatment. There is no cure

Table 11.9 Tricyclic antidepressants

• Amitriptyline	10–150 mg daily at bedtime
• Nortriptyline	10–150 mg daily at bedtime
• Imipramine	10–150 mg daily at bedtime
• Doxepin	10–150 mg daily at bedtime
• Protriptyline[a]	10–150 mg daily in divided doses
• Desipramine[a]	10–150 mg daily

[a] Stimulating rather than sedating

Table 11.8 summarizes some key preventive clinical pearls as prevention is initiated and monitored.

Antidepressants

Tricyclics

A tricyclic antidepressant (TCA) is a good choice for patients with other chronic pain disorders or insomnia, or in patients without prescription coverage because they are inexpensive (see Table 11.9). Always start at the lowest dose and gradually increase. Start with 10 mg and titrate up to 50 mg at bedtime slowly. Titrate up further and maximize therapy if there are partial benefits evident.

The effective doses for migraine prevention are typically less than doses needed for the treatment of depression. None of the TCAs has FDA approval for migraine.

In the 2012 guidelines, amitriptyline is no longer classified as a proven effective drug in migraine prevention. Nortriptyline is felt to be effective by a consensus

Table 11.10 Side effects of tricyclics: the basics

• Dry mouth
• Constipation
• Sedation
• Weight gain
• Tachycardia and arrhythmias with QTc prolongation
• Orthostatic hypotension
• Urinary retention
• Confusion in the elderly
• Syndrome of inappropriate ADH secretion (SIADH)
• Mania

ADH antidiuretic hormone

of expert opinion rather than randomized controlled trials (RCTs) and has fewer anticholinergic adverse effects. Also of note, nortriptyline is available in an elixir form (10 mg/5 cc). Patients who are sensitive to medications may tolerate smaller doses of nortriptyline, starting at 2.5 mg (1.25 cc) at bedtime. If fatigue is an issue, protriptyline may be stimulating rather than sedating, can be administered in the morning, and is usually not associated with weight gain.

Remember that TCAs often interact with selective serotonin reuptake inhibitors (SSRIs) through the cytochrome P450 metabolism when administered together. SSRIs can raise TCA levels, which may lead to serotonin syndrome, encephalopathy, cardiac arrhythmia with QTc prolongation, or intoxication.

Some headache physicians obtain electrocardiograms (EKGs) on all patients started on TCAs due to their potential for cardiac effects. Side effects of TCAs are summarized in Table 11.10.

SSRIs and SNRIs

The SSRIs and serotonin–norepinephrine reuptake inhibitors (SNRIs) can be effective and are useful for patients with comorbid anxiety and depression or other chronic pain syndromes, including fibromyalgia. Venlafaxine is probably effective in migraine prevention and is also possibly as effective as amitriptyline. There is conflicting Class II evidence for fluoxetine. We find clinically that SNRIs appear to be more effective than SSRIs both for prevention of migraine and for pain syndromes, but comparison trials are not available.

In the 2012 guidelines, as noted, venlafaxine is rated as a level B drug. A Class II comparative study demonstrated both venlafaxine and amitriptyline to be similarly effective in reducing headache frequencies. The noradrenergic effect of venlafaxine kicks in at 150 mg. Doses below 150 mg daily are generally not effective in migraine prevention. Venlafaxine may be stimulating and may increase blood pressure.

Duloxetine tends to be stimulating and also weight neutral, but may also increase blood pressure. Nausea is a significant side effect in the first few weeks. Neither duloxetine nor any of the other SNRIs (desvenlafaxine, minalcipran) has been stud-

Table 11.11 SNRIs and SSRIs

• *SNRIs*	
○ Venlafaxine[a]	150–225 mg/day
○ Duloxetine	20–120 mg/day
○ Desvenlafaxine	50–100 mg/day
○ Minalcipran	100–200 mg/day
• *SSRIs*	
○ Fluoxetine	10–80 mg daily
○ Paroxetine	10–60 mg daily
○ Fluvoxamine	50–300 mg daily at bedtime
• *Mirtazapine* (not an SSRI/SNRI)	7.5–45 mg/day at bedtime (for CTTH)

[a] Only SNRI with an RCT showing efficacy, at the dose of 150 mg/day

Table 11.12 Adverse effects of SNRIs and SSRIs

- Weight gain (generally not seen with SNRIs)
- Sexual dysfunction (reported less frequently with duloxetine)
- Withdrawal
- Lowering of seizure threshold
- Serotonin syndrome
- Mania
- SIADH
- GI symptoms
- Sweating
- Sedation or insomnia
- Dry mouth
- Nervousness
- Tremor

ied in the prevention of migraine in an RCT. These drugs may be helpful in treating patients who also have autonomic problems such as orthostatic intolerance or paroxysmal orthostatic tachycardia syndrome (POTS), depression, and/or anxiety.

Mirtazapine, not an SSRI or an SNRI, has been found in one RCT to be effective in chronic tension-type headache (CTTH). Mirtazapine is sedating and may benefit patients with insomnia, although weight gain can be a problem.

All of the above medications and their doses are summarized in Table 11.11. Their adverse events are included in Table 11.12.

Monoamine Oxidase Inhibitors

Under the rubric of "when all else fails" are the monoamine oxidase inhibitors (MAOIs). These antidepressants were used extensively in the 1980s and early 1990s for migraine prevention before the advent of the use of AEDs for prophylaxis. There are few trials that demonstrate efficacy, but consensus among headache specialists

is that they are effective. Their use is limited by their propensity for serious side effects.

Phenelzine, in particular, may be used in headaches refractory to other treatments. This requires a cooperative, intelligent, and compliant patient because of numerous drug and food interactions that can result in hypertensive crisis, myocardial infarction (MI), or stroke. SSRIs, SNRIs, and TCAs must be discontinued at least 2 weeks prior to initiation of any MAOI. Fluoxetine, because of its multiple active long-lasting metabolites, must be discontinued at least 5 weeks before initiation of therapy. Dosing for phenelzine begins at 7.5 mg (tid, three times a day) and may be titrated to 30 mg tid (max 90 mg daily, 60 mg in elderly).

Besides hypertensive crisis, MAOIs can cause hypotension with use, excessive activation, diaphoresis, weight gain, sexual dysfunction, and urinary retention. Thus, their use is generally limited to the cognoscenti when simpler preventive measures have failed.

Antiepileptic Drugs

Topiramate

TPM is FDA-approved for the prevention of episodic migraine. No RCTs were initially available for TPM when the US Headache Consortium guidelines were published in 2000. Since then, there have been 11 RCTs. TPM is included as a Level A drug in the 2012 guidelines. Topiramate is Category D for pregnancy.

One advantage of TPM is that it does not cause weight gain and may cause weight loss. Weight loss occurred in about 10% of patients in the regulatory trials, with a mean weight loss of about 3% of body weight over 1 year. However, the weight loss may not be sustained.

A common side effect is paresthesias of fingers, toes, and face, typically coming and going, but occurring in around half of the people who take TPM. These paresthesias usually resolve over months of treatment but may recur when doses are adjusted. Paresthesias are usually benign, but some patients will be distressed by these symptoms, so warning them ahead is a good idea. Reassurance and an oral potassium supplement may help if the tingling is bothersome to the patient.

Cognitive dysfunction is a potentially serious adverse effect with TPM, occurring in 5–13% of patients at 100 mg in clinical trials. Symptoms include word-finding difficulty and problems with concentration and memory. If severe enough, cognitive side effects may require weaning off the TPM, as they rarely improve with continuation of the medication. Occasional affective and psychiatric changes can also occur, including worsening depression, anxiety, mania, and even psychosis.

Sedation can accompany use of TPM, so dosing in a single dose at night may be of benefit to patients who have difficulty sleeping. Other rare adverse effects include calcium phosphate renal calculi, hyperchloremic acidosis, oligohydrosis in younger patients, and allergic narrow-angle glaucoma, an ophthalmologic emergency.

TPM is primarily renally excreted and not very hepatically metabolized. It is safe to use with oral contraceptives at doses less than 200 mg/day. Typical dosing begins at 25 mg at bedtime, with increases of 25 mg/week to 50 mg twice daily. For patients sensitive to medications, there is a 15-mg capsule or patients can be instructed to cut the 25-mg tablet in half. There is also a long acting gradual release brand name topiramate that can be dosed in a single dose, brand name Trokendi XR.

The regulatory trials found that in episodic migraine patients tested, 50 mg was no better than placebo and 200 mg no better than 100 mg, but had more side effects. Still, TPM can be titrated to 200 mg at bedtime or divided into two doses daily, and some patients do better at higher doses.

Valproate

Valproate (VPA) is FDA-approved for the prevention of episodic migraine. Although it is a very effective preventive therapy, VPA should not be used in women in their childbearing years because of teratogenicity and increased risk of developing polycystic ovarian syndrome. Valproate is Category D for pregnancy. It can cause weight gain and hair breakage. Hair breakage may be prevented in some patients with supplementation of selenium 10–20 mcg daily and zinc 25–50 mg daily.

Rare adverse effects of VPA include pancreatitis, hepatitis, bone marrow suppression, and renal toxicity. Blood monitoring is recommended. It is less toxic when used in monotherapy.

The usual dose of VPA is 500–1,500 mg at night, generally in the extended release formulation. Onset of effect can be within the first month, and level of effectiveness is comparable to TPM.

Gabapentin

Gabapentin (GBP) has been used in migraine prevention as well. There was one Class III study since the 2000 guidelines' release, and in the 2012 guidelines it is listed as Level U, inadequate or conflicting data making a clear recommendation difficult. However, a Cochrane meta-analysis of all data available as of the summer of 2013 concluded that gabapentin was likely ineffective in migraine prevention.

Typical dosing used has ranged from 900 to 2,400 mg daily, with the higher dose found to be the effective dose in one RCT. Start low with 100 mg tid and titrate gradually. Some patients will benefit with lower doses.

The significant adverse events with GBP are the two Ds, drowsiness and dizziness. Beyond that, GBP has the advantage of having no drug interactions and is excreted unchanged by the kidneys. It has the disadvantage of requiring tid dosing and being of questionable efficacy.

Other AEDs

There are no large RCTs for the other AEDs. Smaller RCTs have shown lack of efficacy for levatiracetam, lamotrigine, and lacosamide in episodic migraine prevention. Lamotrigine may be effective in aura, according to one open-label European trial. Levatiracetam and pregabalin may be effective in chronic migraine, according to small open-label trials.

Only open-label studies have showed benefit for zonisamide, and these studies have been exclusively in refractory patients, or those who could not tolerate TPM. Therefore, clinically, zonisamide is an option if there are adverse effects to TPM, especially in TPM responders.

Zonisamide is so well tolerated that patients can generally be started with 100 mg at night. Most headache specialists will then increase the dose to 200 mg or higher if the lower dose is ineffective. Given the absence of RCTs or dose-ranging studies, the optimal dose of zonisamide for the prevention of episodic migraine is not known.

This drug contains a sulfa moiety and should be avoided in patients with known sulfa allergies. As with TPM, zonisamide has a carbonic anhydrase effect and therefore may also cause renal calculi. Zonisamide will interact with oral contraceptives, lowering efficacy of the birth control pills, potentially causing breakthrough bleeding or unwanted pregnancy, as will TPM at doses >200 mg/day.

Lamotrigine has calcium-channel-blocking effects and, as noted above, may be effective for treating migraine with aura. Caution must be taken with lamotrigine titration as other drugs will affect its concentration, and because quick increase has been associated with severe rash. Three titration packs are available depending on whether the patient is on enzyme-inducing medications. Effective doses range from 25 mg daily to 100 mg daily.

The big problem with lamotrigine, as noted, is its potential to cause Stevens–Johnson syndrome, which can be fatal. The manufacturer's recommended slow titration lowers this risk, but any rash necessitates immediate discontinuation of the medication.

Lamotrigine is rated level U in the 2012 American Academy of Neurology (AAN) guidelines with adjunctive commentary saying it is possibly or probably ineffective for migraine prophylaxis. The guideline authors suggest that it not be offered or considered for patients requiring migraine prevention. As noted, there is some open-label evidence that it may be effective for treating prolonged or intractable aura, perhaps through its glutamate inhibition.

Clinical pearls on the use of AEDs for prevention of migraine are summarized in Table 11.13.

Antihypertensives

The antihypertensives as a group are summarized in Table 11.14. Their adverse events are listed in Table 11.15.

Table 11.13 Clinical pearls on use of the antiepileptic drugs

- *Topiramate* (FDA-approved for episodic migraine, effective but not approved for chronic migraine)
  - Start with 25 mg qhs and titrate gradually to 50 mg twice daily (some patients go as high as 200 mg in divided doses)
  - Common side effects: paresthesias, weight loss, fatigue, cognitive dysfunction
  - Less common side effects: renal calculi (calcium phosphate composition), narrow angle glaucoma, oligohydrosis, hyperchloremic acidosis
  - Category D for pregnancy
- *Divalproex* (FDA-approved for episodic migraine, possibly effective for chronic migraine)
  - Start with 250 mg and titrate as high as 1500 mg/day
  - Avoid use in patients with liver disease
  - Avoid use in children age 10 or younger
  - Avoid use in women of childbearing years-it is a known teratogen
  - May cause pancreatitis, hepatitis, bone marrow suppression, renal dysfunction. Monitor with blood work
  - May cause polycystic ovary syndrome
  - Other adverse effects include weight gain, tremor, somnolence, GI symptoms, hair loss, nystagmus, rash, edema
- *Gabapentin* (level U)
  - Start with 100 mg tid and titrate gradually up to 2400–2700 mg daily in divided doses
  - No drug –drug interactions
  - Renally excreted
  - Adverse effects: somnolence, mood alterations, sexual dysfunction, pedal edema, constipation, dry mouth, weight gain
- *Lamotrigine*
  - Level U in 2012 AAN guidelines with adjunctive commentary saying possibly or probably ineffective for migraine prophylaxis. The guideline authors suggest that it not be offered or considered for patients requiring migraine prevention. There is some evidence that it is effective for treating prolonged or intractable aura, perhaps through its glutamate inhibition
  - Start with 25 mg and titrate gradually to 100 mg. Titration is dependent on whether patient is on enzyme-inducing AEDs or non-enzyme-inducing drugs or valproate. Please refer to the prescribing information for appropriate titration schedules
  - Slow titration is necessary to avoid Stevens-Johnson syndrome
  - Adverse effects: severe rash, Stevens–Johnson syndrome, angioedema, dizziness, GI symptoms, somnolence, tremor, mood alterations, hair loss, nystagmus
- *Zonisamide* (Not rated in 2012 guideline, but because of its close similarity to topiramate in composition, it is used by consensus by many headache specialists for migraine prevention. Evidence is only by open-label studies)
  - Start with a dose of 100 mg QHS. Consider increasing to 200 mg QHS if the lower dose is ineffective. For patients who are sensitive to medications, start with 25 or 50 mg and gradually increase to 100–200 mg QHS
  - Contraindicated in patients with sulfa allergies
  - Common adverse effects: weight loss, GI symptoms
  - Less common adverse effects: renal calculi, possible narrow angle glaucoma, fatigue, very rare cognitive dysfunction

Table 11.14 The antihypertensives

• *Beta-blockers*	
○ Propranolol	40–480 mg daily (optimal dose 80–240 mg)
○ Timolol	10–30 mg daily
○ Atenolol	50–100 mg daily
○ Metoprolol	50–100 mg daily
○ Nadolol	10–160 mg daily
• *Calcium channel blockers*	
○ Verapamil	120–480 mg daily
○ Diltiazem and amlodipine	(doses not established)
• *ACE inhibitor*	
○ Lisinopril	20 mg daily
• *ARB*	
○ Candesartan	16 mg

Table 11.15 Adverse effects of antihypertensives

• *Beta-blockers*	
○ Depression	○ Fatigue
○ Bradycardia	○ Sexual dysfunction
○ Hypotension	○ Bronchospasm
○ Raynauds	
• *Calcium channel blockers*	
○ Hypotension	○ Dizziness
○ Bradycardia	○ Fatigue
○ Constipation	
○ Cardiac arrhythmias	
• *ACE inhibitors*	
○ Cough	○ Angioedema
○ Hypotension	
• *ARB*	
○ Dizziness	
○ Hypotension	
○ Angioedema	
○ Back pain	
○ Fatigue	
○ URI (upper respiratory symptoms)	

Beta-blockers

Propranolol, metoprolol, and timolol are Level A drugs in the 2012 guidelines. Other beta-blockers commonly used include nadolol and atenolol. Doses are listed in Table 11.14. These drugs may be beneficial in patients who suffer from anxiety without depression. Caution must be taken in patients with depression, as this class of drugs may worsen their condition.

Beta-blockers should be avoided in diabetics, those with Raynauds, and asthmatics. These drugs lower blood pressure and slow the heart rate, blunting the maxi-

mum aerobic capacity, and have potential for causing exercise intolerance, asthenia, erectile dysfunction, and constipation. They are good choices in patients without insurance, as they are generic and inexpensive.

Calcium Channel Blockers

Flunarazine is a Class 1 drug but is not available in the USA. Verapamil is a Level U drug in the 2012 guidelines, with inadequate evidence for a recommendation. It is fairly well tolerated, and may be effective for migraine aura. Start with 80–120 mg daily and titrate as high as 480 mg daily in TID divided doses. Always use the short acting verapamil, as the SR has irregular pharmacokinetics, generally lasting the same duration as the short acting form. An EKG should be obtained prior to starting the drug and regularly in follow-up. Adverse effects include syncope, constipation, cardiac arrhythmias, and pedal edema. Verapamil is available generically and is inexpensive.

There are small trials suggesting effectiveness for diltiazem and several open-label studies proposing amlodipine as effective in episodic migraine prevention. Neither of these have a level of effectiveness to be rated in the guidelines, and diltiazem was taken off the 2000 AAN guidelines because of this.

Other Antihypertensive Drugs

The angiotensin-converting enzyme inhibitor (ACE inhibitor) lisinopril was studied in a small RCT (47 patients) and was found to reduce headache frequency and severity at a dose of 20 mg daily. Cough was the major side effect.

The angiotensin 2 receptor blocker (ARB) candesartan has now been studied in two excellent published RCTs and found to reduce headache frequency and severity at a dose of 16 mg daily. The second study, published in December of 2013, found comparable effectiveness to propranolol at 160 mg. An RCT for telmisartan was negative, raising questions about whether ARBs as a class are preventive. As of now, the only ACE inhibitor to have an evidence level of possibly effective (Level C) is lisinopril, and the only ARB to be rated effective is candesartan, which has at least Level B, and could be argued to have Level A evidence.

OnabotulinumtoxinA

OnabotulinumtoxinA (onabot, BOTOX) is US FDA-approved in the prevention of chronic migraine, which is defined in the prescribing information as headache at least 15 days per month and at least 4 h per day. It has Level A evidence of effectiveness. This treatment is of benefit when these criteria are met.

When a patient with chronic migraine has failed different drugs from different classes, it may be time to consider onabot. It is also of benefit for patients prone to

Table 11.16 Vitamins, supplements, and herbal therapies

- *Riboflavin (vitamin B2) (Level B, 2012 guidelines)*
  - 25–400 mg
  - Will discolor urine
  - May be energizing
- *Coenzyme Q10 (CoQ10) (Level C, 2012 guidelines)*
  - 150–200 mg bid
  - May be energizing
- *Magnesium (Level B, 2012 guidelines)*
  - 400–600 mg daily
  - Use limited by diarrhea
- *Petasites hybridus (butterbur root extract) (Level A, 2012 guidelines)*
  - 150 mg daily in divided doses (50 mg tid or 75 mg bid)
  - May cause burping
  - Bid to tid

many side effects with different preventives or in patients with serious comorbidities, such as those in which drug–drug interactions are of concern, or those who have gastrointestinal (GI) disorders preventing effective use of daily oral medications.

Vitamins, Supplements, and Herbal Therapies

Herbal therapies are generally safe with few adverse effects, and some have been shown to be effective for migraine prevention. They can be used as first-line prevention before starting other pharmacological drugs, or as adjunctive therapy. Doses and side effects are listed in Table 11.16.

Other Pharmacological therapies

Serotonin (5-HT) Antagonists

Cyproheptadine is safe and effective in the pediatric population and may be used in adults as well for migraine prevention. It can be safely used during pregnancy, but is not safe during lactation. Dosing is up to 4–8 mg tid. Adverse effects include drowsiness, dry mouth, constipation, and weight gain.

Methysergide was an effective FDA-approved preventive agent no longer available in the USA. This drug required a 1-month drug holiday every 6 months in the hopes of preventing fibrotic complications.

Methylergonovine is similar to methysergide and is the active breakdown product of methysergide. Both are long-acting ergots, and the admonition for a 1-month drug holiday every 6 months for methysergide is clinically applied to methyler-

Table 11.17 The 5-HT antagonist doses

- *5-HT antagonists*
  - Cyproheptadine 4–8 mg tid
  - Methylergonovine 0.2–0.4 mg bid to tid
  - Methysergide (no longer available in the USA) 2–4 mg tid to bid
  - Pizotifen (not available in the USA) 0.5–1.5 mg QHS or in divided doses up to 6 mg/day

gonovine as well. This is hoped to prevent the serious irreversible retroperitoneal, pericardial, pulmonary, or subendocardial/valvular fibrosis that can be seen with continuous use. Methylergonovine is dosed 0.2–0.4 bid to tid. As it is an ergot, triptans cannot be used acutely in patients on methylergonovine prophylaxis.

The 5-HT antagonist doses are listed in Table 11.17.

The Future of Prevention

The clear need in migraine treatment is for better prevention, and this area has been very disappointing, with many medications and new classes failing for reasons of lack of efficacy or toxicity. At the time of this writing, four companies are studying monoclonal antibodies against calcitonin gene-related peptide (CGRP) or its receptor.

CGRP is the most potent naturally occurring vasodilator, and it is implicated in migraine genesis. Five CGRP receptor antagonists have been studied in humans as acute medications, and all worked, but none has made it to the market for various reasons, one of which was hepatotoxicity.

Of the four medications being studied in migraine prevention, three are monoclonal antibodies to the CGRP peptide itself, and one is a monoclonal antibody to the CGRP receptor. All are parenteral, three to be self-injected, bi-weekly or monthly and one to be given intravenously for migraine prevention. Some of these biologics are being studied for episodic migraine, and some for chronic migraine.

The other area of study in prevention is with devices. Occipital nerve stimulators have been approved in Europe for the prevention of chronic migraine; studies are in the works for the USA on these devices. Other stimulators, for example non-invasive hand-held vagal nerve stimulators and implanted sphenopalatine ganglion stimulators are also being studied in migraine prevention. In March 2014, a TENS unit to be worn on the head for 20 minutes daily by the company Cefaly was approved by the FDA for migraine prevention.

It is clear from the above discussion that new options for migraine prevention are limited and no longer conventional. Migraine prevention that is safe and effective is truly the Holy Grail in headache medicine.

Conclusions on Preventive Treatment of Episodic Migraine

- When migraines become frequent or disabling, pharmacological prevention should be initiated to prevent chronification of headache to MOH, to decrease disability, and to improve function
- Many preventive options are available, and treatment should be individualized with consideration of each patient's comorbidities. Use the highest-level evidence preventive medication available when possible
- There is not one drug that is effective in all patients, and it is often by "trial and error" that one finds the most effective drug for each patient
- Remember to give each drug at least a 2–3-month clinical trial at optimum doses
- Educate patients about medications, and set realistic goals
- Have patients maintain a headache diary to accurately determine if therapy is beneficial
- Successful preventive treatment is a "win–win," with decreased disability and improvement in quality of life for patients, and with gratification for the physician

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Chapter 12
Treatment of Trigeminal Autonomic Cephalalgias and Other Primary Headaches

Mark J. Stillman

Introduction

This chapter is the bookend to Chap. 2, "Diagnosis of the Trigeminal Autonomic Cephalalgias" and Chap. 3, "Diagnosis of Other Primary Headaches." Because Trigeminal Autonomic Cephalalgias (TACs) are so severe, treatment must be very aggressive. Treatment comprises acute treatment, preventive treatment, and, in the case of cluster headaches (CH), transitional or "bridge" therapy.

Acute treatment is of the essence, as attacks peak in seconds to minutes. Prevention is mandatory for TACs as well, when feasible. Transitional therapy is a bridge between abortive therapy and the (successful) establishment of preventive therapy and plays an important role in managing CH. Because cluster attacks are so terrible, transitional therapy is a compassionate act in between acute and preventive treatment.

Treatment of the Trigeminal Autonomic Cephalalgias

Cluster Headache

The treatment goals for cluster are (1) to terminate an attack within 15 min or less acutely, (2) to induce remission with preventive treatment, and (3) to offer a transitional treatment to buy headache freedom long enough to get the effective preventive treatment in place (Table 12.1).

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Table 12.1 Goals for treatment of cluster headache

- To abort a cluster headache (CH) as quickly as possible (within 15 min or less). This is the *acute or abortive therapy*
- To induce a remission, preferably a lasting remission. This is the *preventive therapy,* and it may take weeks to induce
- Initiate *transitional* or *bridge therapy* that "buys" headache freedom and enough time for the preventive therapy to work

Table 12.2 Level A-recommended acute treatment of cluster headache attacks

Level A-recommended abortive measures for acute cluster headache attack on the basis of Class 1 studies

- Sumatriptan 6 mg subcutaneously → headache relief[a] in 15 min (FDA approved)
- Sumatriptan 20 mg nasal spray → headache relief in 30 min
- Zolmitriptan 5 mg nasal spray → headache relief in 30 min
- Oxygen 100 % (high-flow mask)
  - 12 L/min → pain-free[b] at 15 min

[a] Headache relief is defined as the transition of a moderate or severe headache to a mild or no headache at the measured time point

[b] Headache- or pain-free indicates the complete termination of pain in a moderate or severe headache at the measured time point

Acute or Abortive Therapy of Cluster Headache

To the patient in the throes of a CH attack, the most important goal is to abort the unrelenting pain. For most patients, the interictal period between attacks is pain-free or only mildly uncomfortable, but the seasoned cluster veteran fears that the headaches, brief though they may be, will return, recur, and persist. Many patients will voice their trepidation about falling asleep at night, as headaches commonly "crash" into the rapid eye movement (REM) sleep onset. Because alcohol triggers CH, I have seen a male patient with well-entrenched alcoholism opt to suffer delirium tremens rather than *look* at a bottle of gin, much less take a drink from it, during a cluster period!

This section will discuss treatments that are effective and safe, using the principles of evidence-based medicine (EBM), in which prospective, randomized, controlled trials with clearly defined outcomes and inclusion/exclusion criteria (i.e., Class 1 studies) are included, and treatment groups are large and similar enough in clinical characteristics to allow a comparison of effects. In certain situations, agents will be recommended based not on controlled studies, but on a long history of clinical experience by established clinics in the field of headache medicine.

The following acute cluster medications, listed in Table 12.2, are supported by at least two Class 1 studies with end points of either pain freedom or pain relief (≥ 50 % pain reduction from baseline) at either 15 or 30 min, depending on the study. They are granted a Level A recommendation ("Established as effective…or established as

Table 12.3 Other acute treatments of cluster headache attacks

Abortive medications that do not meet Level A (due to inadequate studies or only one Class 1 study)
• Zolmitriptan 5 mg or 10 mg oral tablet → headache relief in 30 min
• Nasal cocaine
• Nasal lidocaine
• Octreotide subcutaneously
• Intravenous (IV) somatostatin
• Nasal dihydroergotamine (DHE; DHE is FDA approved for cluster)
• Parenteral DHE
• Intravenous magnesium sulfate 1–2 gm
• Intravenous valproate 500–1,000 mg
• Quetiapine 25–50 mg

Table 12.4 Clinical pearls on acute treatment of cluster

• Acute treatment must be very fast, as cluster attacks peak rapidly. Never prescribe tablets for acute treatment of cluster! Do not overlook the efficacy of parenteral dihydroergotamine (DHE)
• Oxygen is the first-line acute treatment. Give the patient a nonrebreathing mask, deliver 100% oxygen at a rate of 10–15 L/min, and have them take the oxygen in a sitting position like Rodin's "The Thinker," while holding the mask loosely. Never resort to nasal cannula!
• Nonoral home acute treatments for cluster include sumatriptan subcutaneous (FDA approved), nasal zolmitriptan, DHE self-administered (FDA approved), and, last, nasal sumatriptan
• A useful rescue, which puts the patient to sleep and may not necessarily abort the pain, includes oral atypical neuroleptics such as olanzapine or quetiapine

useful/predictive…for the given condition in the specified population") and are derived from the American Academy of Neurology Practice Guidelines for treatment of CH. Other treatments for acute treatment of cluster are included in Table 12.3.

Comments on Acute Treatment of Cluster Headache

The emergent nature of a CH attack necessitates rapid therapy, and often calls for *combination therapy*. Acute treatment must demonstrate rapid onset, as cluster attacks peak very fast (Table 12.4). Never prescribe a tablet for acute treatment of cluster, even zolmitriptan (see above)!

If this is new-onset CH, and the patient has never tried oxygen therapy, high-flow oxygen at the onset of an attack should be attempted first line, either in the office or at home. The oxygen is given by a high-flow mask—not nasal cannula—and provided at a flow rate of 10–15 L/min for 20 min, barring any medical contraindications. Have the patient sit in a position similar to Rodin's The Thinker, holding the mask loosely over the face.

Some form of parenteral therapy should be available should oxygen prove ineffective or too slow, or the situation warrants it: subcutaneous or nasal sumatriptan;

nasal, intravenous (IV), subcutaneous, or intramuscular dihydroergotamine (DHE); nasal zolmitriptan; and/or IV valproate and/or magnesium sulfate (barring any medical contraindications). Our experience is that injectable sumatriptan is optimal, using either the generic Statdose or other needle-free (but not pain-free) injection SUMAVEL system. The latter is marketed in boxes of six, which may be of greater convenience for cluster patients while prevention is adjusted. In addition, the simplicity of the needle-free system is useful for cluster patients during the agitation of an attack, when loading the Statdose device can be challenging.

In our hands, nasal zolmitriptan is next on the utility list, then self-administered DHE, with nasal sumatriptan dead last (after oxygen, sumatriptan subcutaneously, zolmitriptan nasal, and DHE). There are no comparative studies.

For rescue of patients, instead of using opioids orally or parenterally, we resort to atypical neuroleptics in the form of oral quetiapine (25–100 mg with repeat dose, as needed) or olanzapine (5–10 mg with a repeat 5-mg dose, as needed). These medications induce sleep and sedation.

Just because a medication has failed to achieve a Level A recommendation does not mean it is ineffective. DHE remains one of the most versatile medications available for aborting and preemptively treating future attacks, and is, in fact, Food and Drug Administration (FDA) approved for cluster. IV DHE, in experienced hands, is as fast as parenteral sumatriptan and has a long duration of action. The metabolites of DHE, like the parent drug, are believed to be active and lipophilic and to readily penetrate brain substance where they bind to serotonin and dopamine receptors. The development of orally inhaled DHE may revolutionize the treatment of cluster, as it promises an effective, more patient-friendly, nonoral route for this drug.

The treating clinician should not overlook the opportunity to initiate bridge or transitional therapy and preventive therapy at the earliest opportunity.

The future holds promise of new therapies in the next few years. As discussed below, occipital nerve stimulators, sphenopalatine ganglion stimulators, handheld vagal nerve stimulators, and deep brain stimulation are being studied for the treatment of refractory and chronic CH. One controlled study demonstrated that high-frequency stimulation of the sphenopalatine ganglion can terminate an acute attack, and further studies are under way.

Transitional or Bridge Therapy for Cluster Headache

Transitional or bridge therapy is an attempt to prevent cluster attacks while awaiting onset of (successful) prevention. The purpose of transitional therapy is to buy time, since preventive medication often takes weeks for titration to optimal dose (Table 12.5). Without transitional therapy, the patient is likely to use injectable sumatriptan daily and run out of insurance allotments, even with oxygen provided.

Transitional therapy of cluster is the most poorly understood and studied phase of treatment, and the majority of the approaches involve the use of steroids, either

Table 12.5 Transitional treatment of cluster headache

- The purpose of transitional treatment in cluster headache is to buy time while waiting for the preventive medications to kick in
- Barring medical contraindications, these are three options:

  Option 1. *Ipsilateral greater occipital nerve (GON) block/suboccipital steroid injections:* In patients with tenderness in the GON region ipsilateral to the CH, inject 40 mg triamcinolone or equipotent injectable glucocorticoid mixed with 3 ml of 0.5 % bupivicaine. Leroux and colleagues published a double-blind randomized controlled study demonstrating the efficacy of 3 days of consecutive GON blocks with betamethasone and lidocaine in inducing remission of CH attacks that occur two or more times/day

  Option 2. *Systemic steroids:* Give a high dose of methylprednisolone, dexamethasone, or prednisone daily for 10 days to 2 weeks as preventive medications are adjusted. Do not use MEDROL dose packs (dose too low)

  Option 3. *DHE:* Have the patient inject DHE 1mg subcutaneously nightly, until the patient is headache-free for 2 weeks, whereupon the patient may skip the injection for a day to see if he is in remission. An alternative is nightly oral ergotamine tartrate

injected into the greater occipital nerve (GON) vicinity ipsilateral to the headache or taken systemically. Three approaches and their rationales will be discussed below.

1. Ipsilateral GON block/suboccipital steroid injections

Small studies have demonstrated induction of remissions in episodic and a few chronic CH patients within 1 week of a GON injection of lidocaine and betamethasone. None of the placebo group, injected with just lidocaine, achieved pain freedom. More than 50 % of the steroid-injected patients achieved a 4-week or greater remission. Another retrospective study also demonstrated greater than 50 % of CH patients achieving a complete or partial response lasting for a median of 17 days (for the partial response).

A predictor for a successful response was tenderness in the region of the GON on the side ipsilateral to the CH. No relationship was shown between the response and the level of induced dermatomal anesthesia from the injection.

Recommendation: Barring medical contraindications, in patients with tenderness in the GON region ipsilateral to the CH, inject 40 mg triamcinolone or equipotent injectable glucocorticoid mixed with 3 ml of 0.5 % bupivicaine.

2. Systemic steroids

Years of anecdotal experience support the use of oral prednisone or equivalent steroid in an attempt to "buy enough time" for the preventive therapy to work or the patient to spontaneously remit. We know of no studies that support the assertion that this is effective. However, in patients who can tolerate the innumerable possible adverse effects of glucocorticoid therapy over a period of 2 weeks, or who are not candidates for GON blocks or for whom GON blocks were ineffective, we utilize systemic steroids.

The dose and route of steroids are both empirical: pulse methylprednisolone as in an exacerbation of multiple sclerosis, IV dexamethasone 8 mg for 1–3 days, or oral dexamethasone, prednisone, or methylprednisolone. The commercially marketed

methylprednisolone oral dose pack, commonly utilized to treat poison ivy-induced dermatitis, is too low a dose to be effective in both CH and status migrainosus.

Recommendation: Barring medical contraindications, a trial of oral prednisone, starting at 60 mg daily and tapering off over a period of 2 weeks.

3. Daily preemptive DHE injections at bedtime

As mentioned above, DHE, the progenitor of the triptans, is as effective in aborting CH as subcutaneous sumatriptan and perhaps is more durable. In our clinic, we utilize a modified Raskin protocol (see Chapter 14, Table 14.13 for details) to treat a cluster period.

The patient will come in for a DHE infusion, and if successful, can be sent home with 8-hourly DHE self-injections or with a continuous subcutaneous DHE pump until 24 h of being headache-free. We will then initiate *preemptive* subcutaneous DHE injections 1 mg at bedtime since REM-onset cluster attacks are so predictable. We continue this until the patient is completely headache-free for at least 2 weeks, whereupon the patient will skip a day of self-injection to see if he is in remission.

If a headache breaks through, the patient will use the DHE injections every 8 h as needed to abort the headache. If the patient enters remission, he or she can continue the prevention for a certain amount of time and eventually taper off the preventives.

DHE has replaced nighttime doses of ergotamine tartrate preventively, which can also be used in this manner. A disadvantage is that the use of the ergots means the patient cannot treat breakthrough attacks with a triptan. However, there is always an extra DHE dose or oxygen for this need.

Recommendation: Barring medical contraindications with DHE, have the patient inject DHE 1mg subcutaneously nightly, until the patient is headache-free for 2 weeks, whereupon the patient may skip the injection for a day to see if he is in remission. When orally inhaled DHE becomes available, self-injected DHE may no longer be necessary.

Preventive Therapy of Cluster Headache

Considering that CH periods last weeks to months, the institution of preventive therapy is usually indicated. For the lucky ones who respond to GON blocks or who have short cluster periods, prophylaxis may not be necessary. For the chronic CH sufferer, tolerable preventive therapy must be fashioned over a period of years or indefinitely. Unfortunately, there are little data to support any specific protocol; again, this does not mean none exists. In addition, novel approaches are currently being studied, and they make use of a better understanding of pathophysiology of CH.

As noted above, the American Academy of Neurology Practice Guidelines did a very thorough review of all treatments for CH in the literature. Table 12.6, adapted from these guidelines, lists the oral medications utilized for preventive therapy. Few studies deemed Class 1 succeeded in providing evidence of efficacy, and many of

Table 12.6 Preventive therapies for cluster headaches. (Adapted from Francis et al. 2010)

Treatment	Efficacy	Level of evidence	Comment
Civamide	One small randomized controlled trial (RCT) of intranasal therapy demonstrated efficacy	Class 1	100 μl intranasal for prevention of CH/induction of remission; not available yet in the US
GON injections—steroids	Demonstrated efficacy in one study	Class 1	For the prevention/induction of remission
Sodium valproate	500 mg did not prevent CH	Class 1	Not recommended
Sumatriptan	Studies did not confirm role in prevention	Class 1	Not recommended for prevention or preemptive therapy
Melatonin	Evidence that doses greater than 10 mg may help induce remission when added to verapamil	Class 2	May be used in conjunction with other preventives, especially verapamil
Verapamil	Evidence that doses of 360 mg were effective in improving headache response	Two studies: Classes 2 and 3	May cause bradycardia and heart block in doses higher than 240 mg/day. Follow ECG; constipating
Lithium	Dose of 900 mg a day effective in CH prevention	Two trials Class 2 evidence	Side effects include CNS toxicity with therapeutic levels, hypothyroidism, and polyuria
Oxygen 100%	Hyperbaric oxygen not effective	Class 2 evidence	In contrast to evidence supporting its use for aborting acute cluster headaches
Capsaicin nasal	Insufficient evidence	Class 3 trial	Insufficient evidence. Painful to the nasal mucosa
Prednisone 20 mg qod	Insufficient evidence	Class 3 trial	In contradistinction to its efficacy for transition or bridge therapy
Ergot therapy	Insufficient evidence	None	While used by experienced clinicians as DHE subcutaneously or ergotamine tartrate rectally once or twice a day, this has not been studied

CH cluster headache, *CNS* central nervous system, *DHE* dihydroergotamine, *ECG* electrocardiogram, *qod* every other day

the medications presently used are Level B or C and derive from experience and consensus.

Only civamide, an intranasal analogue of capsaicin not available yet in the US, and GON injections with steroids were Class 1 and recommended (Table 12.7). Conventionally, many medications not recommended or with poor evidence, are widely used clinically: verapamil, lithium, melatonin, valproate, and topiramate.

Table 12.7 Clinical recommendations for cluster prevention

- Institute prevention utilizing rational polypharmacy, and start with the least toxic approach
- While the evidence for verapamil fails to meet Class 1 evidence, start with immediate- release verapamil provided on a three times daily basis: 80 mg orally TID, and increase by 80–160 mg from every 2 or 3 days to every 2 weeks
  1. Have a baseline ECG, and check for first degree (and complete) AV block during titration of verapamil above 240 mg a day. Titrate verapamil as high as 1,000 mg if needed and tolerated in terms of adverse events
  2. Addition of magnesium oxide 400–1,000 mg a day to offset constipation. Any absorbed magnesium may, in theory, suppress trigeminal nucleus caudalis nociceptive activity. There are almost no data on its use in CH
  3. Addition of melatonin, for which data are also limited. Given in the late evening before bed, doses may be titrated quickly as high as 25 mg, starting with a minimum of 10 mg. During a cluster period, both ictally and interictally, cluster sufferers have measurably low cerebrospinal levels of melatonin. For more details, see suggested reading on the neuroendocrinology of cluster headaches
- If no remission or reduction in the frequency of the headaches ensues in 2 or more weeks after institution of the highest tolerated doses, add another medication(s):
  1. Divalproex sodium 500–1,500 mg per day, and/or
  2. Topiramate 100–200 mg at night (titrate up by 15–25 mg every week), and/or
  3. Lithium carbonate in doses to build a therapeutic blood level
- In our clinic, I routinely investigate the hormonal levels of all chronic CH patients, as I have been surprised to find low bioavailable testosterone levels in these seemingly hyperandrogenized men. If there are no contraindications (i.e., prostate disease, lipid disorders), I provide testosterone replacement therapy for hypogonadal individuals and have been able to induce complete remission or a reversion to an episodic CH pattern (see references below) in a number of them
- Anecdotal reports of the herb kudzu suggest doses of 1,500 mg TID may reduce the frequency and severity of the attacks. This is an otherwise harmless over-the-counter approach

TID three times a day

Treatment of Refractory Cluster Headaches

Refractory CH occur in either (a) episodic CH patients who fail to respond to any abortive therapies or (b) chronic CH patients who cannot revert to an episodic pattern or who have never been able to go into remission despite concerted medication trials. Until recently, there were few options other than chronic opioid therapy or a destructive neurosurgical procedure. Multiple surgical and pain anesthesia procedures have been described for CH and are listed in Table 12.8.

None of these therapies offers more than modest results; none has met the rigors of randomized controlled trials, and all carry risk of failure of response and delayed deafferentation pain syndromes. Recent knowledge culled from functional neuroimaging combined with advances in neurostimulatory procedures promise chances for new therapies. For refractory CH patients, *after expending all attempts at medical management,* we consider the patient for sphenopalatine block, then nondestructive neurostimulatory (neuromodulatory) procedures (Table 12.9). These await the studies needed for FDA approval.

Because CH patients are so desperate, numerous unusual approaches to treatment have been tried or championed. We summarized some of these approaches in

Table 12.8 Surgical procedures for refractory cluster

- Radiofrequency ablation of the trigeminal nerve
- Glycerol trigeminal rhizotomy
- Trigeminal nerve sectioning
- Balloon compression of the trigeminal ganglion
- Microvascular decompression of the trigeminal nerve
- Sphenopalatine gangliolysis
- Superficial petrosal neurectomy
- Sectioning of the nervus intermedius
- Gamma Knife radiosurgery of the trigeminal ganglion

Table 12.9 Last-resort options for refractory cluster

- Sphenopalatine (SPG) block followed by radiofrequency ablation was effective in an open study of intractable chronic cluster headache patients followed for more than 18 months. Note that this is an ablative procedure of a parasympathetic ganglion and is not reversible, although clinical response was generally transient
- SPG stimulation was effective in a European study for aborting and preventing acute CH attacks. An implantable SPG stimulator is now approved in Europe for chronic CH, and studies are planned in the USA
- Occipital nerve stimulation (ONS) is frequently successful in CH. Clinical response often takes months to reach full effect, and technical difficulties (lead migration, infection, battery failure) can plague this approach. For more information, please see reference below on potential options in CH for medically refractory patients
- A non-invasive, hand-held vagal nerve stimulator is being currently studied for acute treatment of cluster attacks
- Deep brain stimulation (DBS) of the posterior hypothalamus has been in use for more than 10 years to prevent CH attacks. Serious adverse effects can include intracranial bleeding, stroke, infection, vertigo, and syncope, and there was one death reported, making DBS the very last resort

Table 12.10 Diagnostic and therapeutic trial of indomethacin for paroxysmal hemicrania

- Start with 25 mg of indomethacin TID for 48 h to 1 week
- Place the patient on a proton pump inhibitor and have the indomethacin taken with meals
- Increase to 50 mg TID for 48 h to 1 week
- If there is no response, the dose is then increased to 75 mg TID and maintain for 72 h to 2 weeks
- If there is a partial response, increase to 100 mg TID if the patient can tolerate it
- If there is no response or if the patient has intolerable adverse effects, stop indomethacin

a review entitled “Cluster Headache: Potential Options for Medically RefractoryPatients (When All Else Fails)”, and the reference is included in the suggested reading.

The Paroxysmal Hemicranias

The paroxysmal hemicranias (PH) are defined by an absolute responsiveness to indomethacin. The approach is similar to that used for hemicrania continua (HC) and is repeated here in Table 12.10.

Table 12.11 Other treatment for indomethacin-intolerant patients with paroxysmal hemicrania or hemicrania continua

• Celecoxib or another NSAID (e.g., piroxicam, diclofenac, etc.)
• Melatonin, which is structurally similar to indomethacin
• Topiramate or gabapentin in escalating doses, as used for migraine prophylaxis
• Greater Occipital Nerve block with 'caine + steroid' as described above for CH. Currently, I approach all patients with any form of TAC with this approach initially, and, when necessary, will provide 3 consecutive days of blocks, as described by Leroux et al. in 2011 (see references)
• A trial of deep brain stimulation of the ipsilateral posterior hypothalamus.

Alternatives for patients intolerant to indomethacin or for whom it is contraindicated are listed in Table 12.11. These generally include other nonsteroidal anti-inflammatory drugs (NSAIDs) or anticonvulsants.

Short-Lasting Unilateral Neuralgiform Headache Attacks (SUNHA) with Conjunctival Injection and Tearing (SUNCT)/ Short-Lasting Unilateral Neuralgiform Headache Attacks with Cranial Autonomic Symptoms (SUNA)

These rare, short-lasting headaches with prominent cranial autonomic symptoms can deceive the clinician because, as with trigeminal neuralgia, they can be triggered by cutaneous stimuli. Unlike trigeminal neuralgia, however, they are recognized by the autonomic features and by the location of pain around the eye in V1. They present with single stabs, many (more than a hundred) separate single stabs anywhere in the head, or groups of stabs (sawtooth pattern) separated by complete or partial resolution of the pain (see Chap. 2).

SUNCT and SUNA do not respond to indomethacin in any dose—eliminating PH from the differential diagnosis—nor do they respond to high-flow 100% oxygen, or serotonin agonists (DHE or triptans), eliminating the diagnosis of CH. Oxcarbazepine and carbamazepine may be effective, further complicating differential diagnosis from trigeminal neuralgia. However, unlike in trigeminal neuralgia ablative neurosurgical procedures generally have poor outcomes.

Treatment described as useful in SUNCT and SUNA, listed in Table 12.12, relies on anticonvulsant therapy. Note that these options actually include lidocaine, which was used by neurologists to treat refractory status epilepticus in a time before the introduction of newer parenteral anticonvulsants and before attempting a trial of general anesthesia.

For patients refractory to the above, there are few options. One patient responded in an on–off fashion to ipsilateral posterior inferior hypothalamic deep brain stimulation, parallel to the turning on and turning off of the stimulator. Occipital nerve stimulation is an option that could be pursued, as it is obviously less dangerous.

Table 12.12 Treatments for SUNHA (SUNCT and SUNA)

- Lamotrigine (100–400 mg/day) → relief in up to 2/3 of patients (drug of choice for SUNCT)
- Topiramate (50–400 mg/day) → response in ~50% of patients
- Gabapentin (600–3,600 mg/day) → response in ~45% of patients (drug of choice for SUNA)
- Oxcarbazepine and carbamazepine may be effective, complicating differential diagnosis from trigeminal neuralgia
- IV lidocaine 1.3–3.3 mg/kg/h. Lidocaine infusion will require cardiac monitoring and drug levels should be followed. No trials of mexiletine or tocainide have been reported, but doses of 400–600 mg of mexiletine have been given in two to three divided doses a day. Levels of mexiletine also should be measured to avoid potential toxicity
- GON steroid block may abort attacks in up to 2/3 of all patients

Table 12.13 One indomethacin titration schedule for hemicrania continua

- Start with 25 mg of indomethacin TID for 48 h to 1 week
- Place the patient on a proton pump inhibitor and have the indomethacin doses taken with meals
- Increase to 50 mg TID for 48 h to 1 week
- If there is no response, the dose is then increased to 75 mg TID and maintained for up to 2 weeks
- May increase to 100 mg TID if the patient can tolerate it
- If no response, and the clinician really thinks this is HC, consider increasing the dose to 450–500 mg over 1–2 weeks and maintain the patient on this for an additional 1–2 weeks
- If the patient has intolerable adverse effects, stop trial

Finally, one additional word on SUNHA. There are a number of case series showing that SUNHA can be associated with pituitary lesions, specifically pituitary adenomas. There are also descriptions of SUNCT cured by surgical extirpation of these tumors. A careful MRI search for lesions of the adenohypophysis is in order for SUNHA. When medical therapy is ineffective in a SUNHA patient with one of these tumors, a surgical approach should probably be considered.

Hemicrania Continua

The diagnosis of Hemicrania Continua (HC) is made by a combination of the clinical headache features *plus a complete* therapeutic response to indomethacin at pharmacological doses. There is debate about how long to wait before abandoning indomethacin. Some studies suggest the response should be complete and rapid within 48 h of reaching the therapeutic dose of indomethacin, but other researchers feel that the trial of large doses (doses as high as 500 mg/day; see Cittadini et al.) should be extended a full 2 weeks before abandoning the drug. Fortunately, for many patients, when HC remits once the therapeutic dose is reached, the dose of indomethacin can be tapered down to a lower dose that is maintained indefinitely (Table 12.13).

Clearly, some patients cannot tolerate the central nervous, gastric, or renal side effects of this harsh drug; additionally, there are patients, such as those with diabe-

tes, renal, and/or hepatic dysfunction, or those with bleeding issues, who will never be able to take the medication. For these patients, there are rays of hope in the case reports showing benefit from large doses of melatonin or trials of gabapentin, topiramate, and celecoxib.

As mentioned above with other TACs, there is usually no harm in initiating therapy with an ipsilateral local anesthetic/steroid GON block(s) and waiting expectantly 72–96 h before starting indomethacin therapy. Some patients—particularly those with tenderness over the site—will respond to this approach, at least temporarily. Ipsilateral occipital nerve stimulation and GON blocks are other approaches that can be utilized.

Treatment of Other Primary Headaches

Some of the Other Primary Headaches are not well studied and, after preliminary comments, will allow a summary in the form of a table. Not surprisingly, the recommendations summarized in this table will be an amalgam of recommendations and time-tested therapies. There are no data remotely approaching Class 1 status.

The first and foremost therapeutic approach to these headaches—particularly, cough headache, exercise headache, headache associated with sexual activity, and thunderclap headaches—is to investigate and rule out causation. Similar to primary stabbing headaches, if deemed "primary," these headaches are best treated by prevention of the inciting cause (of course, with the exception of thunderclap and sex headaches).

As expected, a recommendation to patients to modify behavior drastically often does not sit well. In such cases, after an appropriate workup, reassurance that a short-lived but severe headache is primary, and thus benign, might suffice.

Primary thunderclap headache necessarily distinguishes itself from the rest of other headaches, due to its random and unexpected presentation. As expected, treatment is palliative while a workup ensues to rule out an ominous cause.

Table 12.14 summarizes the treatment of the listed Other Primary Headaches. Hypnic headache is discussed below separately. Primary thunderclap headache is not listed, as explained above. Treatment of new daily persistent headache is discussed in Chap. 14.

Hypnic Headache

Treatment of hypnic headache is as unusual as the headache itself and is listed in Table 12.15. The most important three treatments are caffeine, lithium, and indomethacin.

It seems counterintuitive to recommend caffeine before a patient goes to sleep or takes a nap, but remember the English traditionally have a cup of tea before bed-

Table 12.14 Treatment of Other Primary Headaches

Headache	Therapy	Comments
Primary stabbing	– Indomethacin: 25–250 mg/day in divided doses – Celecoxib 100–400 mg/day in divided doses – Melatonin 3 mg at night; titrate to higher dose – Nifedipine or verapamil	– Sharp stabs of pain last 1–10 seconds and cannot be effectively treated once they occur – Indomethacin is most commonly used when the stabs occur in volleys – Celecoxib is used in indomethacin intolerance – Calcium channel blockers can be used as well (anecdotal)
Cough headache	– Indomethacin: 25–250 mg/day in divided doses – Acetazolamide 250–500 mg twice daily	– Lasts seconds to minutes after Valsalva – Primary form not commonly seen in patients under 40 – Not usually seen with nausea and vomiting – Up to 40% of patients have a secondary cause (Chiari, posterior fossa lesion) – Responds to indomethacin or high-volume CSF removal
Exercise headache	– Indomethacin: 25–250 mg/day in divided doses – Beta blocker: proprano-lol 40–240 mg/day or equivalent	– May last minutes to 2 days – Unlike primary cough headache, more common in young adults and in those with migraine – May masquerade as cardiac ischemia – Try tapering therapy after several months
Headache associated with sexual activity	– Indomethacin: 25–250 mg/day in divided doses – Beta blocker: proprano-lol 40–240 mg/day or equivalent – Diltiazem 180 mg/day for beta blocker intolerance	– Advising the patient to be more passive during intercourse may help prevent the headache – Try tapering therapy after several months to test for recurrence
Cold-stimulus headache		– Advise the patient to avoid rapid ingestion of cold drinks or solids
External-pressure headache		– No specific therapy other than avoidance and treatment similar to early migraine treatment (indomethacin or some other NSAID) – Migraine prevention may work for this type of headache as the pain is reminiscent of allodynia and hyperpathia seen in migraine
Nummular headache	– Carbamazepine or gabapentin have been used in anecdotal reports – OnabotulinumtoxinA has been used successfully in a few patients – There are reports of an occasional patient who responds to local anesthetic injection	– Reassurance after a negative exam and workup may be all that is needed

Table 12.15 Medications for the treatment of hypnic headache

Medication	Dose	Comments
Caffeine	40–60 mg as tablet or coffee at hour of sleep	First and easiest approach
Lithium carbonate	300–600 mg at bedtime	Watch for toxicity: tremors, chorea, ataxia, hyperthyroidism, electrolyte disorders
Indomethacin	25–75 mg at bedtime	May be more effective if the headache is unilateral and side-locked

time. The fact that this simple, inexpensive treatment frequently works should make clinicians pine for the days when Britannia ruled the seas.

Lithium has been most studied for this disorder, but comes with an assortment of toxicities, some of which do not correlate with toxic blood levels, such as renal and thyroid abnormalities. Recent case reports suggest potential benefit with indomethacin. There are no randomized controlled trials.

Conclusions on Treatment of TACs and other Primary Headaches

- For the TACs and Other Primary Headaches, the correct diagnosis is vital to choosing proper therapy. Proper treatments are often disorder specific
- New insights into the pathophysiology of these headaches has opened the door to novel treatment approaches including neuromodulation such as deep brain, occipital nerve, non-invasive hand-held vagal nerve, and implantable sphenopalatine ganglion stimulation
- Several of the headaches discussed are so uncommon or so unpredictable in onset, no evidence-based recommendations exist for treatment

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Part VII
Treatment of Chronic and Refractory Headaches

Chapter 13
Treatment of Medication Overuse Headache

Stewart J. Tepper and Deborah E. Tepper

Introduction

The treatment of medication overuse headache (MOH, rebound) is often the bane of a clinician's existence. This need not be the case with simple and direct approaches based on a number of key points: (1) Prevention of MOH is always better than treating it after it occurs. (2) Treatment is predicated on absolute detoxification from overused medications. Partial measures are doomed to failure. (3) Prevention will not work fully, and migraine-specific medications will not work fully until the wean is completed. (4) Do not get fancy. Use preventive medications that have evidence for effectiveness in prevention of episodic migraine, the underlying disorder behind MOH. (5) Multiple visits with education and reinforcement will be necessary during the wean and after. (6) Strict limits on as-needed acute medications are key.

The general story for MOH is that a patient with episodic migraine transforms to chronic daily headache (CDH), that is headache at least 15 days per month, in the setting of overuse of acute medications. Once that patient crosses the Rubicon to CDH, a number of clinical changes occur that interfere with treatment. These include reduced responsiveness to preventive and migraine-specific acute medications, non-restorative sleep disturbances, worsening of comorbid psychiatric issues, neck pain, vasomotor instability, and variability of headache symptoms across time.

Weaning the patient off the overused medications, providing preventive medication, initiating behavioral support, and prescribing acute medications with strict limits usually cuts the Gordian knot of CDH, restoring the effectiveness of prophylaxis and acute medications. General principles of treating MOH are listed in Table 13.1.

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Table 13.1 General principles of treating medication overuse headache (MOH)

- Prevention of MOH is always better than treating MOH after it occurs
- Treatment is predicated on absolute detoxification from overused medications. Partial measures are doomed to failure
- Prevention will not work fully, and migraine-specific medications will not work fully until the wean is completed
- Do not get fancy. Use preventive medications that have evidence for effectiveness in prevention of episodic migraine
- Multiple visits with education and reinforcement will be necessary
- Strict limits on as-needed acute medications are key

Prevention of MOH

Almost all patients who complain to care providers about episodic headaches have disabling migraines. This remarkable fact has been shown over and over again, as those with pure tension-type headaches do not generally present in medical offices. The disability or impact of disabling migraines drives patients to the office to seek help, and the average patient in the average primary care provider who is complaining of stable, episodic headache has disabling episodic migraines until proven otherwise.

Optimal treatment of episodic migraine is with migraine-specific medication for disabling migraine. Stepping patients through lower-level treatments in the hopes of finding less-expensive treatment has been shown to be a bankrupt strategy. The best approach is to match patient need and disability to level of treatment, so-called stratified care.

The consequence of not matching intensity of treatment to severity of disability is lack of complete response. That is, if a patient with disabling migraine is given a subtherapeutic medication, the likelihood is that the patient will only get partial relief and not obtain a pain-free or migraine-free response. Partial relief of migraine is linked to headache recurrence and, therefore, to repeat dosing. Repeat dosing propagates the attack, prolonging the attack.

The likelihood of transformation from episodic migraine to CDH is predicted by the interaction of two major factors, the number of headache days per month and the number of days of acute treatment per month. As the headache days increase above 10 per month, the probability for transformation to CDH dramatically increases.

If a patient begins the year with 6–10 headache days per month, the odds ratio for developing rebound over the next year is 6 compared with lower frequencies of headache. If a patient begins the year with 11–14 headache days per month, the odds ratio for transforming to MOH goes up to 20. And as the number of acute treatment days goes up, so too does the risk of MOH.

Therefore, if a patient with a tendency to multiday migraine is given an inadequate treatment, the outcome will be a prolonged attack and several days of acute treatment. If that patient had been given an adequate triptan or ergot, or migraine-specific medication plus nonsteroidal anti-inflammatory drug (NSAID), the outcome would have likely been a sustained pain-free response, one and done, with a

Table 13.2 When to add daily preventive medication to prevent medication overuse headache (MOH)

- Odds ratio for developing MOH:
  - 6–10 headache days per month, odds ratio 6
  - 11–14 headache days per month, odds ratio 20
    - Therefore, add daily prophylaxis at 10 headache days per month, and consider at 6–10 headache days per month
- Add daily prophylaxis when acute treatments exceed 2 days per week (5/month for butalbital)
- Acute medication days are additive. Add the number of days of each acute treatment, and if this exceeds 10 days per month, add prevention

truncated duration of attack and fewer acute treatments. That appropriate intervention helps prevent MOH.

If headache days per month climb above 10 days per month, it is mandatory to start preventive medication and drive the number of headache days per month down. If acute treatment days reach a critical level associated with risk for transformation and chronification, once again, prophylaxis is indicated. This requires knowing which medications appear to be associated with precipitation of MOH at which frequency.

Also, acute treatment days are additive. It is important to add all of the acute treatment days together. If a patient is taking 5 days of aspirin–acetaminophen–caffeine tablets, 5 days of opioids, and 2 days of triptans, it adds up to 12 days of acute treatment per month which places that patient in a critical danger zone for transformation into rebound. Intervention with prophylaxis becomes imperative. Some thoughts on translating these facts in terms of when to add daily preventive medication to prevent MOH are listed in Table 13.2.

A large multiyear, population-based study, the American Migraine Prevalence and Prevention (AMPP) study, followed up patients with episodic migraine over time to evaluate who was taking what medication for how long and who developed MOH. Butalbital use appeared most complicit in precipitating MOH, associated with transformation in as little as 5 days of use per month. Next came opioids, associated with rebound at as infrequent as 8 days per month. Triptans and combination analgesics seemed to trigger MOH at 10 days per month.

NSAIDs had a double-peak effect. With use of <5 days per month, NSAID use appeared protective against development of MOH. At use somewhere between 10 and 15 days per month, NSAIDs appeared to provoke rebound.

The hierarchy is important to bear in mind, because with butalbital, use even less than 2 days per week can trigger MOH, while for other acute medications, vigilant monitoring on frequency of acute medication use will yield dividends in alerting the clinician on when to pull the trigger on preventive medication (see Table 13.3).

Four simple rules in preventing rebound are as follows: (1) Use migraine-specific treatments (triptans, ergots) in the absence of vascular disease for acute treatment of episodic migraine. NSAIDs can be added for synergy and also can work in monotherapy. (2) Keep acute treatment days to no more than 2 days per week. (3) Add prevention at 10 headache days per month or when acute treatment days

Table 13.3 Hierarchy of acute medication days and risk for medication overuse headache (MOH)

- Butalbital, as little as 5 days/month
- Opioids, as little as 8 days/month
- Triptans, NSAIDs, analgesics, as few as 10 days/month

Table 13.4 Four simple rules to prevent rebound

1. Use migraine-specific treatments (triptans, ergots) in the absence of vascular disease for acute treatment of episodic migraine. NSAIDs can be added for synergy and will sometimes work in monotherapy
2. Keep acute treatment days to ≤2 days/week. Butalbital can cause MOH at 5 days/month
3. Add prophylactic medication at 10 headache days/month or >2 acute treatment days per week. Consider prevention when headache frequency appears to be climbing and is in the 6–10-day/month range
4. Do not use butalbital or opioids as acute treatments for migraine. Period. Neither occasionally nor repeatedly

Table 13.5 Seven steps in the treatment of medication overuse headache (MOH)

1. Educate the patient
2. Wean the offending medication
3. Initiate prophylaxis
4. Initiate non-pharmacologic/behavioral interventions where appropriate
5. Set a quit date after which patient will not treat low-level headaches
6. Establish acute treatment with limits on usage
7. Establish a time to follow up, more frequently during acute withdrawal, regularly for several years after withdrawal

exceed 2 days per week. Consider daily prophylaxis if headache frequency is climbing in the 6–10-headache-day/month range. (4) Do not use butalbital or opioids as acute treatments in migraine, either occasionally as rescue or repeatedly. The four rules are listed in Table 13.4.

Treatment of Established MOH

There are seven steps to the treatment of MOH : (1) Educate the patient. (2) Wean the offending medication. (3) Initiate prophylaxis. (4) Initiate non-pharmacologic/behavioral interventions where appropriate. (5) Set a quit date after which the patient will not treat low-level headaches. (6) Establish acute treatment with limits on usage. (7) Establish a time to follow up, more frequently during acute withdrawal, regularly for several years after withdrawal (Table 13.5).

Educate the Patient

Education requires differentiating overuse, abuse, dependence, and addiction. Most patients who transform to rebound do so inadvertently and are not addicts. Early on, reassuring the patient, when appropriate, that he or she is not being accused of being a drug abuser or addict is critically important.

It is key to manage expectations in several ways during the education discussions. Improvements require time. Remind the patient that it took a long time to get into MOH and may take months to exit daily headache.

Emphasize that the treatment of MOH does not eliminate migraine. Rather, it reduces daily headache, and may reduce frequency, severity, and duration of acute attacks.

The analogy frequently made to MOH/CDH patients is that in rebound, in their transformed state, they have raisin bread, that is, background headache, the bread studded with the raisins of migraine. What clinicians hope to accomplish is to dissolve away the bread and leave just the raisins, the episodic migraines, to treat. Point out that successful treatment of MOH involves the "re-transformation" back to episodic from chronic and daily but does not eliminate episodic migraine attacks.

Headaches may get worse for several weeks before they get better, so patience is a necessity. Treatment plans try to mitigate increased pain, but some persistence and motivation by a patient is required.

Explain the importance of sticking to the program and the need for long-term follow-up. Recidivism and falling back into MOH can occur, so return visits are necessary to address issues as they arise.

To enhance support, educate the family and significant others. They can be quite helpful.

Remember, the patient needs to want the plan. You may know the patient needs to be weaned, the family may recognize the need for a wean, and the referring doctor may want you to help get the patient out of rebound, but unless the patient is invested in complete detoxification and appropriate treatment, proceeding is futile. You cannot detoxify a patient against their will.

Playing tough love is often useful. Another point well made is that unless the patient puts the clinician up against the wall and insists on being detoxified, it is well worth resisting.

Remember, preventive medications are unlikely to be effective unless a wean takes place. Previously ineffective prophylaxis will miraculously become effective after wean. Taking a strong stance that wean is paramount, and obtaining a strong patient buy-in, is necessary for successful treatment of MOH.

Therefore, allow the patient to try other approaches to the treatment of MOH. Most will go into a Halley's comet-like orbit, availing themselves of a myriad of interventions before ending up, sometimes years later, back in the clinician's office, ready, finally, for the wean and overall plan.

There is no spontaneous remission from rebound. Only a carefully planned and implemented treatment strategy that involves complete detoxification from overused medications will work. Table 13.6 is a summary of education of the patient in MOH.

Table 13.6 Education of the patient in medication overuse headache (MOH)

- Differentiate overuse, abuse, dependence, and addiction, and reassure the patient (when appropriate) that they are not being accused of being a drug abuser or addict
- Manage expectations
  - Improvements require time
  - Treatment does not eliminate migraine. Rather, it reduces daily headache, and may reduce frequency, severity, and duration of acute migraine attacks
  - Headaches may get worse for several weeks before they get better
- Explain importance of sticking to the program and long-term follow-up
- Arrange for follow-up visits
- Educate family and significant others to enhance support
- Insist on patient commitment to the program. Allow patients to leave and explore other alternatives if they are not fully invested
- There is no spontaneous remission from rebound

Weaning the Overused Medications

The entire Cleveland Clinic Headache Center and all authors of this manual believe that absolute detoxification or wean from overused medications is the crucial step in treating patients in MOH. Any compromise in this regard will increase the likelihood of failure.

Is Wean Really Necessary?

Four randomized controlled studies have been run on patients with daily headaches, two each for topiramate and onabotulinumtoxinA (onabot, Botox), in which patients with MOH were not completely excluded. That is, these studies examined whether topiramate and onabot could reduce headache days in a mixed group of patients, those with primary International Classification of Headache Disorders (ICHD) chronic migraine and those with secondary MOH. Patients with opioid and barbiturate MOH were mostly excluded from the studies, and in the onabot studies, patients with continuous headaches without any headache-free time in a given month were also excluded. Thus, these were not studies of all typical MOH patients.

In post-hoc analyses, since this issue was not the primary end point, the studies found that topiramate in one study and onabot in both did reduce the number of headache days, compared to placebo or sham, in those patients with MOH. Thus, it is established that these medications can have some benefit even without a wean.

However, there are a number of concerns, first about interpretation and then about clinical recommendations. It is wise to remember that the benefit data were post-hoc analyses, and the studies were not powered specifically and primarily to examine the effectiveness of these interventions in MOH patients. Large groups of typical rebound patients were excluded, namely those with opioid and barbiturate overuse, and those with continuous headache. Finally, the studies did not examine

Table 13.7 Four levels of weaning patients in medication overuse headache (MOH)

1) Conventional outpatient slow wean with slow addition of preventive medication
2) Conventional outpatient quick discontinuation with bridging medications and quick addition of preventive medication (cold turkey of rebound meds with bridge)
3) Day-hospital approach using infusions as the bridge and quick addition of preventive medication
4) Inpatient wean using infusions as the bridge and quick addition of preventive medication

whether the patients would have done better with topiramate or onabot *plus* a wean from overused medications rather using those medications without the wean.

There are numerous reasons to vigorously wean patients from acute medications in MOH. The first is the relatively well-established observation that wean alone can be very helpful in restoring episodic headache in the majority of patients weaned. The second is that well-designed studies have shown that patients who are weaned and given preventive medications and other interventions for their daily headache do better than those left alone, who generally do not improve. The third reason to wean patients is overall health, that is, to avoid other potential medical consequences of overuse, such as gastrointestinal (GI) bleeds, analgesic nephropathy, barbiturate-worsened depression, and so forth. Finally, medication overuse often results in a tussle with the care provider, impeding a therapeutic alliance.

For all of these reasons, it remains the consensus that the wean of overused medications is the single most crucial step in the care of MOH patients.

Which Setting is Best for the Treatment of MOH?

One of the first questions in approaching the wean is the determination of how much can be done in a conventional outpatient setting. There are basically four levels of treatment: (1) conventional outpatient slow wean with slow addition of preventive medications, (2) conventional outpatient quick discontinuation with bridging medications and quick addition of preventive medication, (3) day-hospital approach using infusions as the bridge, and (4) inpatient wean using infusions as the bridge. The four levels of treatment for weaning patients in MOH are summarized in Table 13.7.

How does one determine which level a patient with MOH will require? A few clinical guidelines may be helpful.

Patients who can usually be treated as conventional outpatients include those who have a shorter duration of medication overuse, use only one to two substances at low doses, have the support of family or friends, and/or are highly motivated themselves.

Non-opioids and triptans can be abruptly discontinued in some people, and this plays into using a conventional setting. Opioids, barbiturates, caffeine, ergots, and benzodiazepines can sometimes be withdrawn slowly, often over about 5 weeks, depending on duration of use and dosage.

Table 13.8 Conventional outpatient slow wean with slow addition of preventive medications

1. Slow taper of rebound medications and caffeine over about 4–6 weeks
2. Begin onabotulinumtoxinA (this is the only FDA-approved medication for chronic migraine)
   – 155 units at onset of taper and q 3 months thereafter *OR*:
3. Add preventive medications slowly over the same 4–6 weeks
   A. Tricyclics (e.g., amitriptyline (Level B evidence for episodic migraine); nortriptyline and doxepin by consensus):
      – 10 mg at night; increase by 10 mg per week to target dose of approximately 50 mg qhs
   B. Beta-blockers (e.g., propranolol or timolol (FDA approved and Level A evidence), metoprolol (Level A evidence), nadolol (Level B evidence))
      – For example, nadolol, begin with 40 mg and increase by 40 mg per week
   C. Anti-epilepsy drugs
      – Topiramate (FDA approved, Level A for episodic migraine, Category D in pregnancy)
      – 25 mg qhs and increase by 25 mg per week to target dose of 50 mg BID
      – Valproate (VPA; FDA approved, Level A evidence for episodic migraine)
      – 250 mg extended release at night, increase by 250 mg to target dose of 500 mg to 1 g qhs. VPA should not be used in women of child-bearing age or patients withdrawing from butalbital or benzodiazepines with liver induction
4. Set a quit date, generally in week 4. Following this date, the patient should no longer treat low-level headaches with the previously overused rebound medication or the newly provided acute migraine-specific medication
5. Provide migraine-specific acute treatment for severe migraines, maximum 2 days per week. Never use the same medication that is being weaned, and if possible, change classes of acute medication
6. In difficult weans, a steroid course can put a patient over the hump

As dosage escalates, intensity of treatment may increase as well. As number of acute medications overused goes up, so too does the complexity of the withdrawal and the potential for drug–drug interactions as preventive medications are added.

Comorbid medical and psychiatric conditions can complicate preventive treatment strategies. For example, asthma precludes use of beta-blockers, obesity mitigates use of weight-gaining medications such as tricyclics and valproate, and kidney stones and glaucoma suggest extreme caution for the use of topiramate (if it should be used at all). Vascular disease contraindicates the use of triptans and ergots, and a history of a GI bleed precludes use of NSAIDs. The more the comorbidity, the more attractive onabotulinumtoxinA appears, as the only Food and Drug Administration (FDA)-approved preventive medication for chronic migraine.

Conventional Outpatient Slow Wean with Slow Addition of Preventive Medications

The trick for this approach is gradual wean of the rebound medications at the same time titrating prophylaxis upward to a target dose. Conventionally, this is done over 4–6 weeks, although onabot can be substituted on day 1 and given q 3 months (see Table 13.8).

Butalbital mixtures, aspirin–acetaminophen–caffeine combinations, and hydrocodone–acetaminophen combinations, all frequently overused medications, can be tapered by reducing the number of tablets per day by 1 per week. Tricyclics and topiramate fit this schedule nicely for prevention, increasing by 1 tablet per day per week. Tricyclics allow for dosage escalation by 10 mg per week and topiramate by 25 mg per week. Once again, a reasonable alternative is administration of onabotulinumtoxinA instead on day 1 and q 3 months thereafter instead of using daily preventive medications.

A "quit date" is also set for the patient, following which the patient is instructed not to treat any low-level headache. Acute, migraine-specific drugs are provided for treating severe headaches, with limits on frequency of use.

The quit date means that the patient should not use the weaned rebound medication or the newly introduced acute migraine-specific as-needed medication to treat low-level headaches. In general, when selecting the new medication, try to avoid the class of medication previously overused. For example, if a patient is in triptan rebound and can tolerate dihydroergotamine in its various forms, that is a good switch. If a patient is in NSAID rebound, avoid combinations containing NSAIDs.

For simplicity's sake, limit the new acute as-needed medications to 2 days of use per week. It is simple to remember and execute.

Occasionally, a patient will "hit the wall" during the taper of rebound medications, or go into a particularly nasty withdrawal headache. In those circumstances, a run of high-dose oral steroids can sometimes put the patient over the final hump of detoxification.

Conventional Outpatient Quick Discontinuation with Bridging Medications and Quick Addition of Preventive Medications

In this technique for getting patients off of rebound medications, the key clinical feature is that the patient is not on high doses of potentially dangerous acute medications, because this approach depends on a "cold turkey" of the overused drugs. Following this abrupt discontinuation of the rebound medications, the patient is placed on a bridge of medications for a week to 10 days to blunt the withdrawal symptoms and the withdrawal headaches. At the same time, the patient is quickly placed on migraine preventive medication. This quick establishment of prophylaxis is limited by what prevention can be safely and tolerably established in a matter of days.

If the patient is on high-dose opioids, the chance for precipitating acute narcotic withdrawal is high, so this approach is not acceptable.

If the patient is on high-dose butalbital, the chances for incurring acute barbiturate withdrawal with status epilepticus and the risk of death are also high.

Accordingly, precipitous discontinuation of rebound medications should be limited to patients on no more than three tablets of opioids or butalbital per day. Any

uncertainty on the total number of tablets per day should put a brake on this approach in favor of the slower-taper approach.

If the state of medical practice has a prescription monitoring program (PMP) in which a clinician can look up the number, frequency, and doses of scheduled medication a patient has received in the last year, this registry must be consulted prior to initiation of the wean. These registries include the Ohio OARRS, the Kentucky KASPER, the Michigan MAPS, etc. The health-care provider can find a link as to whether the state offers an accessible PMP at http://www.pmpalliance.org. PMPs are described in greater depth in Chap. 5.

Very often, patient history and the PMP will be in conflict. Always err on the side of the registry when calculating the intake of scheduled medication. This maximizes the likelihood of success without clinical mishap during the wean.

If the clinician is confronted with a patient using only over-the-counter medications or NSAIDs and at low number of tablets per day, this type of rebound is made to order for a quick wean (see Table 13.9). The process, as noted above, has four steps: (1) abrupt discontinuation of the overused medication, (2) bridging medication for 7–10 days to blunt withdrawal and reduce withdrawal headache, (3) establishing preventive medication in the first few days of withdrawal, and (4) providing acute as-needed migraine-specific medication with strict limits on use at the end of the bridge.

Key Points:

- Cold turkey is potentially dangerous in patients on ≥3 tablets per day of butalbital, and can precipitate withdrawal in patients on opioids ≥3 tablets per day
- If your practice is in a state with a Prescription Monitoring Program (PMP) of scheduled medications for every patient, look up the patient and quantify use before initiating a cold turkey (e.g., in Ohio, OARRS; in Kentucky, KASPER; in Michigan, MAPS, etc.). Find the link to your state's PMP at http://www.pmpalliance.org.

Interdisciplinary Day-hospital or Inpatient Approaches with Bridging Infusions and Quick Addition of Preventive Medications

When the complexity of the patients is too great, or the doses of medications too high, it can become obvious that neither traditional outpatient approach will work for a given patient in MOH. Sometimes, the patient will have already failed in trying to do the wean at home. Sometimes the comorbid medical and psychiatric issues combine to make it very difficult to construct a reasonable outpatient plan. Sometimes drug interactions, allergies, contraindications, or intolerances are such that it appears too daunting to engage in the outpatient wean.

Table 13.9 Cold turkey of rebound medications with bridge

1. Day 1: Cold turkey abrupt termination of acute rebound medications
2. Day 1: Initiate a therapeutic bridge therapy for 7–10 days
   - NSAIDs can be used repetitively and in a scheduled manner. They are not good options in patients in NSAID rebound, obviously. Options include, among others:
     - Nabumetone: 750 mg per day
     - Naproxen: 500 mg b.i.d.
   - Steroids can be used, such as:
     - Dexamethasone 4 mg b.i.d. for 4 days, qd for 4 days
     - Prednisone: 80 mg qd (days 1 and 2), 60 mg qd (days 3 and 4), 40 mg qd (days 5–7); this is a 1-week bridge. Note that a methylprednisolone dose pack is probably too low a dose for use as a bridge
   - Triptans can be used repetitively and in a scheduled manner. They are not good options in patients in triptan rebound, and this is not an FDA-approved use of triptans. Reported protocols include:
     - Sumatriptan: 25 mg t.i.d. for 10 days or until the patient is 24 h headache-free, whichever comes first
     - Naratriptan 2.5 b.i.d. for 1 week
   - Ergots:
     - DHE nasal spray b.i.d. or t.i.d. for 7–10 days
     - Methylergonovine 0.2 mg b.i.d. or t.i.d. for 7–10 days
3. Also beginning on Day 1: Initiate onabot or start daily prophylaxis over 2 days. This quick start is limited by tolerability issues, and probably excludes topiramate, for example. Among preventive agents, it should be possible to add rapidly:
   - Tricyclics:
     - Doxepin or nortriptyline 25 mg qhs (day 1), 50 mg qhs (day 2)
   - Beta-blockers:
     - Metoprolol 25 mg day 1, 50 mg day 2
     - Nadolol 40 mg qd day 1, 80 mg day 2
   - OnabotulinumtoxinA:
     - With this approach, the onabot is administered on day 1 and q 3 months
4. At the end of the bridge, provide migraine-specific treatment such as a triptan with strict limits, maximum 2 days per week
5. If the patient has difficulty, and steroids were not used as the bridge, an additional steroid run can sometimes put the patient over the hump

In these circumstances, an interdisciplinary headache program with infusion capabilities becomes the reasonable way to go. These programs are spread out in the USA, and some are available in Europe. They generally include participation by, at a minimum, a team consisting of neurology, primary care, psychology, skilled nursing, and physical therapy. Some teams include psychiatrists, pharmacists, nutritionists, occupational therapists, pain medicine specialists, rehabilitation specialists, pain anesthesiologists, and others.

The overall game plan in these programs is to (1) wean the rebound meds as quickly as safe, (2) use intravenous medications as the bridge during the withdrawal, (3) use the interdisciplinary team to work with the patient and put together a menu of preventive and acute medications and behavioral treatments for the post-wean

Table 13.10 Interdisciplinary headache program with infusions

1. Stop the overused acute medications as quickly as possible
   - Benzodiazepines, butalbital, and opioids require special handling
   - 100 mg butalbital = 30 mg phenobarbital
   - Each butalbital combination tablet contains 50 mg butalbital
   - Convert and taper the phenobarbital
2. Start intravenous bridge and choose from a menu such as:
   - Repetitive intravenous (IV) dihydroergotamine (DHE; contraindicated with vascular disease)
   - Repetitive antinauseant such as a neuroleptic (e.g., metoclopramide), a 5-HT_3 antagonist (e.g., ondansetron), and/or antihistamine (e.g., diphenhydramine)
   - Repetitive valproate
   - Repetitive ketorolac
   - Repetitive steroids
3. Start daily prophylaxis medication or onabotulinumtoxinA as quickly as possible
4. Interdisciplinary education
5. Behavioral evaluation and treatment
6. Limit acute as-needed medications to 2 days per week at discharge

Table 13.11 Partial list of interdisciplinary headache programs for referral

- Albert Einstein/Montefiore Headache Program, the Bronx, NY (inpatient)
- The Interdisciplinary Method for Assessment and Treatment of Chronic Headache (IMATCH), Cleveland Clinic (day hospital)
- The Michigan Headpain and Neurological Institute (MHNI), Ann Arbor, MI (inpatient)
- The Diamond Headache Clinic, Chicago, IL (inpatient)
- The University of South Florida, Tampa, FL (day hospital)
- Cedars Sinai Inpatient Headache Program, Los Angeles, CA (inpatient)
- Instituto Neurologico “C Besta” Headache Program, Milan, Italy (day hospital)

episodic migraine state, and (4) teach healthy habits to maximize the likelihood of success (see Table 13.10).

These programs, as noted, can be inpatient or provided in a day-hospital setting (see Table 13.11 for a partial list). Outcomes for the patients who complete the programs are generally favorable. When concern over safety is paramount, an inpatient program with round-the-clock monitoring should be selected. When the wean is expected to be more conventional, day-hospital programs offer similar treatment, similar outcomes, and lower costs.

The trick is recognizing when to initiate the referral to one of these programs. If the therapeutic alliance is strong enough to withstand a failure of conventional outpatient wean, an outpatient trial of weaning is reasonable. If the clinician feels there is only one shot at getting a patient detoxified and turned around, an interdisciplinary program is more likely to be successful.

Behavioral Treatment of MOH

Almost all patients who have ended in MOH will benefit from behavioral evaluation and treatment. These interventions, which are pillars of the wean and restoration of the episodic migraine pattern, are covered extensively in Chaps. 15 and 19.

Follow-up and Prognosis of MOH

There is a fixed rate of recidivism after a patient returns to an episodic pattern of migraine following a wean from MOH. That is, patients can fall back into rebound again, and do so frequently unless properly followed.

There are a few clinical pearls that may prevent this recurrence of overuse. The first is that MOH occurs regardless of what ailment for which the acute medications are used.

A patient who has been in opioid rebound, weaned, and back in episodic migraine, treated with tramadol for a bad back, will develop MOH again if the opioid use reaches 8 days per month or more, regardless of the fact that it is being taken for the back pain.

Frequently, patients do not understand this, and careful monitoring and guidance is necessary to prevent accidental overuse for another problem. A headache diary is crucial to counting the number of days of intake of acute relief medications per month.

The second is that patience is a virtue. It takes at least 3 months for patients to come out of rebound, longer for opioids. Counseling on the time necessary for recovery is a crucial part of follow-up.

The third pearl is that the prognosis for recovery from MOH is good. Across multiple studies, more than half of the patients weaned and cared for were still in an episodic pattern at 5 years. Sharing this good prognosis is an important part of treatment.

Finally, for those patient requiring an interdisciplinary program, prognosis overall is also good. Most get relief during the actual program, and the majority hold on to the recovery if follow-up is adequate.

A few further clinical pearls on prognosis and follow-up of MOH are listed in Table 13.12.

Table 13.12 Further clinical pearls on prognosis and follow-up of medication overuse headache (MOH)

• It does not matter what a patient takes acute relief medications for; if the frequency of use exceeds a critical number of days per month, daily headache can ensue
• Carefully monitor patient intake of acute relief medications with a diary
• Complete restoration to an episodic pattern of migraine following wean can take 3 months or more
• Prognosis for recovery from MOH is good

Conclusions

- The best way to view a patient coming into the office in MOH is not as a CDH person, but as an episodic migraine patient trying to come out. The job of the clinician is to provide guidance enabling the reverse transformation from daily headache back to an episodic pattern
- The accomplishment of this clinical reversal is one of the most satisfying endeavors in clinical medicine. Patients are immensely grateful at getting their lives back and being provided skills and tools for avoiding another plunge back into rebound
- MOH can be prevented by simple steps, beginning with having patients keep a headache diary to monitor frequency of acute medication use
- Avoidance of butalbital and opioids greatly enhances likelihood of avoiding rebound
- Use of migraine-specific medications, such as triptans and DHE, should be limited to no more than 2 days per week. When use begins to climb, or headache days per month approaches 10, preventive medication should be added to drive down frequency, severity, and duration of migraine attacks, and to make them more amenable to treatment
- Treatment of MOH patients requires absolute detoxification or wean, establishment of daily preventive medication or onabotulinumtoxinA, behavioral evaluation and treatment, and, after the wean, acute migraine-specific treatment used no more than 2 days per week
- Follow-up of MOH patients is important to avoid a backslide into rebound. Remember that overuse of acute medications, regardless of what illness is being treated, can reignite rebound

Suggested Reading

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Chapter 14
Medical Treatment of Refractory Daily Headaches, Including Interdisciplinary Management

Mark J. Stillman

Introduction

This chapter discusses the medical management of the refractory headaches that occur on a daily or near-daily basis. The diagnostic criteria for these headaches have been addressed in Chap. 4.

While the headaches to be discussed have been classified in the International Classification of Headache Disorders, 3rd edition, beta (ICHD-3) in different sections of the manual, for therapeutic purposes it is reasonable to discuss these headaches in one chapter. The exception is hemicrania continua (HC), which has now been included in the section on treatment of trigeminal autonomic cephalalgias. Note that medication overuse headache (MOH), the most common refractory headache disorder, is technically a secondary headache disorder, but its progenitor is usually episodic migraine, and it phenotypically looks very much like chronic migraine (CM) or chronic tension-type headache (CTTH) punctuated by migraine-like exacerbations.

The headaches to be discussed are listed in Table 14.1.

Treatment of Chronic Migraine

A reasonable treatment approach for CM incorporates the techniques used in aborting and preventing episodic migraine. We initially attempt to alter and eliminate modifiable risk factors, at the same time educating the patient to avoid any overreliance on immediate relief medications, which may additionally induce further transformation to MOH (see below).

Treatment routinely includes addressing the modifiable risk factors associated with the development of CM (Table 14.2): dietary consultation and counseling for patients with obesity, investigation for sleep disorders including history and

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Table 14.1 The refractory daily headaches

• Chronic migraine (CM)[a]
• Chronic tension-type headache (CTTH)[a]
• New daily persistent headache (NDPH)[a]
• Medication overuse headache (MOH)[b]

[a] Primary headache disorder
[b] Secondary headache disorder

Table 14.2 Modifiable and non-modifiable risk factors for chronic migraine (*CM*)

Non-modifiable risk factors for CM
• Poverty
• Female gender
• Single marital status
• History of head and/or neck trauma
• Comorbid pain syndromes
Modifiable factors for CM
• Obstructive sleep apnea and snoring
• Obesity
• Caffeine intake

polysomnography with multiple sleep latency testing where indicated, and assessment of anxiety and depression. The latter requires astute history taking, which is difficult considering the current time constraints of daily practice.

In order to uncover psychiatric comorbidities, a variety of screening tests may be administered to the patient before he or she enters the examination room. We utilize the Patient Health Questionnaire 9 (PHQ-9) and the European Quality of Life, a five-question screen. Anything more than mild depression and anxiety can be addressed with a semi-structured psychological interview and consultation (see below).

Treatment aims to reduce chronicity and return the patient to the episodic headache pattern. We have no presumptions about making a migraineur headache-free, as migraine headaches are a condition one is born with and are likely be found to be the result of an inherited deficiency in the central nervous system's modulation of pain. As such, success in clinical research and clinical practice is defined as at least a 50% reduction in headaches frequency for the individual patient.

Many studies utilize different measures of outcomes: headache days per month, headache episodes per month, or a calculated headache index. We use the number days of headaches per month, as measured in a headache diary, and combine this with satisfaction ratings comparing the present visit with the last visit and/or the first visit to clinic.

Drug Therapy

Medical therapy of CM incorporates the same preventive medications used to treat episodic migraines and frequent migraines with and without aura. The classes of

Table 14.3 Clinical pearls for treating chronic migraine

- Start low and go slow enough to minimize adverse effects and allow enough time to assess therapeutic efficacy
- Practice polypharmacy by layering on additional medications if one drug is not sufficiently efficacious
- Utilize medications whose mechanisms of action may be complimentary

medications are, not surprisingly, medications shared with the fields of neurology and psychiatry, and all the medications target the central nervous system. Included are the antiepileptics, anticonvulsants, and antidepressants. In addition, some supplements and vitamins can be utilized as adjuvants.

Two drugs have now been studied rigorously in the management of CM and will be described first. OnabotulinumtoxinA is the only FDA-approved medication for prevention of CM. Topiramate has been studied in two randomized controlled trials for CM.

As with many of the drugs listed here, they can be used in isolation or combined with other drugs, with their effects amplified by other pain-relieving techniques in a multidisciplinary plan (see below). The same clinical pearls and medications used to treat episodic migraines apply to the treatment of CM, listed in Tables 14.3 and 14.4.

Outcome of Treatment

With prolonged preventive treatment, 3–6 months or longer, the chances for reverting to episodic migraine and remaining episodic at 1-year run 50–70%. Success is better assured if patients:

1) Comply with preventive therapy
2) Strictly avoid overusing analgesics for symptom relief
3) Remain physically conditioned with regular exercise.

Treatment of Chronic Tension-Type Headache

The treatment of CTTH is similar to that of CM. CTTH is less well studied in the literature, and, appears to respond less well to therapy than CM.

Treatment of New Daily Persistent Headache

There is no known effective medication protocol for new daily persistent headache (NDPH). There are no studies for efficacy of the newer agents such as the serotonin–norepinephrine reuptake inhibitors (SNRIs) or onabotulinumtoxinA. We

Table 14.4 Medications used in chronic migraine treatment

Medication	Dose	Comments
OnabotulinumA (FDA-approved for chronic migraine)(Botulinum toxin A)	155–195 units	Injected in a fixed-site fashion as outlined in PREEMPT FDA-approved protocol and also "following the pain" for problem areas. Can be effective in some patients with medication overuse headaches
Topiramate	100–150 mg in 1–2 divided doses	Also somewhat effective in one of two studies of patients with medication overuse headaches
Gabapentin	1,800–2,400 mg in 3–4 divided doses	One study for CM; no further studies since going generic. Rated Level U for conflicting or inadequate evidence of efficacy or with evidence indicating lack of efficacy in 2012 AHS/AAN guidelines
Valproic acid	500–2,500 mg in divided doses	FDA-approved for episodic migraines; may be given intravenously as a loading dose or for acute exacerbations
Levatiracetam	500–1,000 mg BID	May be given intravenously as a loading dose or for acute exacerbations. Specifically not recommended for migraine prevention per 2012 AHS/AAN guidelines commentary
Amitriptyline	10–75 mg qhs or higher as tolerated	Effective with or without fluoxetine in one study; anxiolytic and sleep promoting. Other antidepressants (nortriptyline, protriptyline, doxepin, or imipramine) have been used in our clinic and are most effective when utilizing their assets to treat comorbid conditions: insomnia, nocturia, anxiety, and/or depression, muscle and neck pain, fibromyalgia, etc.
Fluoxetine	10–80 mg qd	Effective for CM in one controlled blinded study but rated Level U for conflicting or inadequate evidence of efficacy or with evidence indicating lack of efficacy in 2012 AHS/AAN guidelines
Venlafaxine, duloxetine, milnacipran, and desvenlafaxine	Doses used for depression	Not studied for CM. Venlafaxine Level B as per 2012 guidelines, meaning probably effective for episodic migraine. The SNRIs have been studied for fibromyalgia, depression, and postherpetic neuralgia. Effective analgesic antidepressants
Memantine	10 mg BID	Excitatory amino acid receptor (NMDA glutamate) antagonist used for Alzheimer's disease. One positive open-label study. Not rated for effectiveness 2012 guidelines

AHS American Headache Society, *AAN* American Academy of Neurology, *NMDA N*-methyl-D-aspartate

Table 14.5 Medications used in chronic tension-type headache (*CTTH*) treatment

Drug	Dose	Comments
Amitriptyline Nortriptyline	10–75 mg qhs, or as tolerated	Similar to episodic tension-type headache, amitriptyline is the drug of choice. Nortriptyline is its derivative, as effective with less sedation and anticholinergic side effects
Protriptyline	5–30 mg qam	Related to above; less sedating. No studies
Mirtazapine	15–45 mg qhs	Studied in small controlled trials. Sedating, weight gain
Valproic acid	See CM	Studied and effective
Topiramate	See CM	Not studied for CTTH but used in our clinic
Tizanidine	2–24 mg in divided doses	One randomized controlled trial in chronic daily headache; one study suggesting effectiveness in wean in medication overuse headache
Venlafaxine, duloxetine, milnacipran, and desvenlafaxine	Doses used for depression	No studies to date, but we suspect they will be as effective as amitriptyline, similar to other chronic pain conditions
OnobotulinumA (Botulinum Toxin A)	See above	Not found to have benefit in CTTH studies but anecdotal benefit described. Better-designed studies needed to prove or disprove

recommend trials adapted from the discussions above for CM and CTTH depending on the clinical characteristics of the individual patient's NDPH pattern. We carefully screen our patients for comorbidities in order to find any hook to hang our hat on, and that includes looking for sleep disorders with a polysomnogram.

The case series by Robbins and colleagues of 71 patients reported four patients who remitted while on topiramate and six patients who remitted while on nortriptyline.

If there were one headache type deserving of a multidisciplinary approach, based on its impact on quality of life and its tenacity, it is NDPH. We routinely recommend either an inpatient or an outpatient chronic headache pain program to the patients with NDPH.

Treatment of Medication Overuse Headaches (MOH; Also Referred to as Chronic Migraine with Medication Overuse and Rebound Headache)

Introduction

The 3rd edition of ICHD lists the number and types of medications overused necessary for transformation from episodic migraine to CM/chronic daily headache (CDH). Chronification may come from central sensitization of a central nociceptive system.

Table 14.6 Risks for transformation to medication overuse headache/chronic migraine from the American Migraine Prevalence and Prevention Study

- Butalbital use – 5 or more days a month; a single dose was found to increase risk of chronification in the population as a whole
- Opioid use – 8 or more days a month; a single dose was found to increase risk of chronification in the population as a whole
- Triptans – 10 days a month
- Nonsteroidal anti-inflammatory use – At uses < 5 days a month, NSAID use is protective against chronification; at uses from 10 to 14 days per month, NSAID use becomes provocative for transformation

Table 14.7 Clinical pearls for avoiding medication overuse headache in practice

1. Do not use opioids or butalbital as acute medications for treatment of episodic migraine
2. Keep as-needed acute medications to no more than 2 days of use per week

Our studies (Stillman et al. unpublished data) show that patients with presumed MOH overexposed to many of the above analgesics exhibit psychometric markers of central sensitization of trigeminal nociceptive pathways. With successful detoxification and headache remission, these markers return to levels close to those seen in a non-MOH control cohort.

Several epidemiological studies have shed the brightest light to date on the subject. In over 2,500 patients, approximately two-thirds of the MOH patients had episodic migraines as a substrate, and in one-fourth episodic tension-type headaches were present historically.

Some patients with MOH have headaches that exhibit migraine features occurring intermittently and punctuating an otherwise monotonous daily headache pattern. However, in the regulatory trials for onabotulinumtoxinA (onabot) for CM/MOH, the majority of patients had at least 17 days reaching migraine levels out of their daily headaches.

The risk of transformation to MOH varies with different medications at different frequencies of intake. Some medication classes have never been well studied; there is no consensus on benzodiazepines.

Bigal, Lipton, Buse, and colleagues have published seminal data from a prospective, population-based study, the American Migraine Prevalence and Prevention Study (AMPP). They confirmed a high risk of transformation with caffeine-containing combination analgesics, opioids, and butalbital. Triptans have moderate risk with overuse.

Nonsteroidal agents exhibit a biphasic pattern. At uses of less than 5 days per month, nonsteroidal anti-inflammatory drugs (NSAIDs) protect against transformation to MOH. At uses somewhere from 10 to 15 days per month, they interact with high headache frequency to provoke chronification.

Table 14.6 lists the frequencies of use from AMPP found associated with transformation to MOH transformation. A useful pearl is to recommend patients not use acute medications more than twice weekly. If use climbs to that level, optimizing acute medications to achieve a sustained pain-free response (one and done) and interventions for prevention are in order.

Table 14.8 Principles of an integrated approach to treatment of medication overuse headache

No therapeutic maneuver can stand alone and must be part of a larger program that incorporates
• Absolute elimination of offending medications or substances
• Addition and continuation for a period of time of new preventive therapy
• Paced physical reconditioning
• Patient education, including use of adjuvant non-medicinal therapies
• Follow-up and reassessment are necessary as with any serious pain issue in order to prevent reversion to medication overuse

Table 14.9 Stratification of characteristics for treatment of medication overuse headache

• Medication or medications/substances being overused (abused) and their tendencies to cause medically serious withdrawal syndromes
• Comorbid medical and pain conditions
• The psychological makeup, including major psychiatric disorders, and personality disorders and traits
• Socioeconomic status and needs of the patient

It must be stressed that these are population data and not based on specific information of the mechanism or biology of headache induction. Based on the AMPP data, some researchers in the field feel that even one opioid dose or barbiturate can throw a wrench in the works and set the patient back significantly.

Treatment of Medication Overuse Headache

Treatment of MOH is as varied and complicated as there are proposed revisions to its definition, due in large part to the lack of understanding of the natural biology and history of this headache disorder. Certain principles must be observed in any attempt to treat this ailment, as listed in Table 14.8.

In practice, the treatment of MOH should be *stratified* to the individual needs and requirements of each case. This individualization will depend on the characteristics of the disorder and the patient, as listed in Table 14.9.

The use of a particular treatment approach is not based so much on firm head-to-head data (which hardly exist) as it is based on the perceived risk of relapse. In other words, the approach is based on the clinical perception of how ingrained and refractory the medication overuse problem is. This depends on the above principles, especially the first three.

In our practice we have two basic treatment approaches, both of which provide the same principles of care: (1) a simple outpatient protocol for patients who have inadvertently fallen into the cycle of medication overuse and (2) a structured, 3-week, outpatient interdisciplinary chronic headache or pain program that includes a physical therapy component, a medical component, and a psychological component. Other institutions may provide an inpatient program, lasting weeks. The provisions of these treatment programs are schematized in Table 14.10.

Table 14.10 Components for treatment of medication overuse headache

1. *Detoxification (wean)*
   - Simple analgesics and combination analgesics
   - Butalbital-containing analgesics
   - Benzodiazepines and other sedatives that cause physical dependence
   - Opioids
2. *Bridge therapy*
   - Dihydroergotamine (DHE) protocols
     - Raskin protocol
     - Continuous IV
     - Continuous subcutaneous (SQ)
     - Intermittent SQ injection
   - Oral bridge therapy with triptans
   - Steroid bridges
     - Oral
     - IV
3. *Preventive therapy*

Regimens for Detoxification, Bridge Therapy, and Prevention of Relapse

Successful treatment of MOH, whether as an outpatient or in a multidisciplinary outpatient or inpatient program, requires the integration of three components: detoxification from the offending agents, bridge or transitional therapy, and preventive therapy. Choosing a protocol for the individual patient will depend on the patient's individual needs. These components are outlined in Table 14.10, and a description of the protocols follows below.

Choosing a Protocol and Medical Treatment Plan

Detoxification (Wean)

Outpatient oral regimens can be used for the common analgesic/combination analgesic-induced MOH where there is no potentially dangerous withdrawal syndrome expected. This applies also for low dosages of opioid and sedative hypnotics.

Barbiturates

If the patient does not take butalbital daily, or just one or two tablets a day, and reports that he or she has days of not taking any at all, an attempt at outpatient oral therapy can be made. The problem occurs if the patient reports (or the clinician has reason to suspect) there is large or escalating butalbital usage.

Table 14.11 Protocol for butalbital wean

• Replace each 100 mg butalbital ingested daily with 30–60 mg of phenobarbital provided daily in two divided doses (orally or intravenously, depending on patient status)
• Taper the patient by 15 mg of phenobarbital until off completely

Table 14.12 Clinical pearls on planning butalbital, barbiturate, benzodiazepine, or other scheduled medication weans for medication overuse headache

• Always check your state's prescription-monitoring program (PMP) before planning a wean of scheduled medications
• Explicitly ask your patient to overestimate his or her usage
• Explicitly ask your patient if he or she is accessing any other sources for scheduled medications, such as the Internet or someone else's medications

Butalbital withdrawal is potentially lethal and is more dangerous than opioid withdrawal; it resembles acute alcohol withdrawal, replete with withdrawal seizures that can lead to status epilepticus. It is therefore prudent to assume that a patient with a long history of butalbital ingestion is *under*estimating his usage. Caution is the better part of valor.

I have had to admit a patient using 12–16 butalbital-containing tablets a day for observation and carefully governed detoxification. In such cases, one useful detoxification protocol is listed in Table 14.11. Doctors Elizabeth Loder and David Biondi published their widely used protocol, listed in the suggested reading.

Some clinicians have adopted an inpatient loading protocol using intravenous (IV) phenobarbital on the day the patient's access to butalbital is discontinued. The dose is repeatedly provided every 1–2 h until the patient becomes drowsy. The cumulative dose is usually less than 700 mg. Once the patient is loaded, there is no further need to provide further phenobarbital, as the blood phenobarbital level will decrease slowly due to a long half-life. The phenobarbital tapers itself this way.

There is one extremely important point worth reiterating. Since patients usually underreport their intake, check your state's prescription-monitoring program (PMP). These programs usually, but not always, list the butalbital prescriptions for patients, allowing the clinician to check the amounts and make appropriate clinical decisions on the wean. However, patients do purchase scheduled medications on the internet, and a cautionary tale is reported in the paper by Romero and colleagues in the suggested reading.

Dihydroergotamine Bridge Therapy

Despite no head-to-head randomized controlled trials of one bridge therapy with another, dihydroergotamine (DHE) treatment is the gold standard of therapy for bridging the patient as painlessly as possible through the "rebounding" turbulent waters of detoxification. This may, in part, be due to the pharmacology of the DHE, its long half-life, and low recurrence rate.

Table 14.13 Modified Raskin DHE protocol

1. *Establish IV access.* May provide volume repletion with D5/NS, NS, or D5/½ NS as needed if the patient is vomiting
2. *Provide antiemetic* (will be needed every 8 h for at least the first 24 h, as IV DHE can be nauseating)
   a. Choices: metoclopramide, prochlorperazine, promethazine, haloperidol, chlorpromazine, droperidol, or a $5HT_3$ antagonist such as ondansetron as per hospital formulary and patient tolerance
3. *DHE titration*
   a. After pretreatment with antiemetic, provide 0.25 mg DHE in 50 ml NS over 15 min. Wait for 30 min to see if headache remits or the headache worsens or if the patient becomes nauseated
   b. If the headache is still present, repeat the infusion of 0.25 mg DHE and wait 30 min for response
   c. Repeat step 3b until a total of 1.0 mg of DHE infused, unless
      i. The headache completely remits at a lower cumulative dose than 1.0 mg; that will be the dose infused q 8 h around the clock.
      ii. The headache worsens or nausea appears; then the cumulative dose may be too high, so lower the cumulative dose by 0.1–0.25 mg. Infuse the lower cumulative dose every 8 h around the clock
4. *DHE infusion* after finding the highest-tolerated dose or reaching a maximum of 1.0 mg DHE: infuse that dose in 50 ml of NS every 8 h around the clock until the patient is headache free for 24 h
   a. Provide the antiemetic pre-DHE for at least the first three infusions of DHE (24 h), and use as needed for nausea or as an abortive agent

D5/NS 5 % dextrose in normal saline

The Neil Raskin protocol for refractory migraine has been adapted and refined through years of experience. It can be provided to all patients without vascular disease in need of detoxification, whether they are going to go home and taper/stop the analgesics, are in an outpatient multidisciplinary program, or in an inpatient program. It can be the jump-start of a wean that will be conducted as an outpatient, or an 8-hourly continuous regimen. Patients will need to be educated that DHE should not be used within 24 hours of a triptan if they are going home. Our approach is outlined in Table 14.13. Some alternatives to the 8-hourly DHE protocol can be found in Tables 14.14 and 14.15.

Oral bridge therapy represents a useful, although unproven, alternative to DHE bridge therapy, for those patients unwilling or unable to get parenteral DHE. It is a technique we use for relatively uncomplicated MOH, from common analgesics and combination tablets. Abrupt discontinuation of the analgesics and or caffeine is combined with the "preemptive" use of daily use of a triptan such as naratriptan or sumatriptan in divided doses, headache or not, until the patient is headache-free for 24 h or day 7, whichever comes first. The patient may take co-analgesics such as antiemetics and nonsteroidal agents along with the triptan, unless that was a class they were taking in rebound. It is worth repeating strongly again that whatever class of medication the patient was overusing should not be used as the bridge.

The patient will initiate preventive therapy at the same time, as discussed below. In our hands, about 50 % will break the daily headache cycle this way and continue on preventive therapy and prn triptan therapy.

Table 14.14 Alternatives and variations to the Raskin DHE protocol

1. *Continuous IV DHE:* Once the dose titration has been completed, wait for several hours and start infusing that amount by continuous IV infusion over an hour period. This will require a volumetric infusion pump and inpatient status
   a. Continue this infusion until headache free
   b. Use antiemetics and co-analgesics as needed
2. *Continuous SQ DHE:* Instead of providing a continuous IV infusion, place a small-gauge butterfly in the abdominal or chest subcutaneous tissue
   Place 3 mg DHE in 25 cc saline in the pump and infuse at 1 cc an hour using a portable volumetric (insulin-type) pump. This is approximately 1 mg over an 8-hour period and allows the patient to be ambulatory and go to work. Continue daily, with the help of a home-care company, until the patient is 24 h headache free. Range of treatment is 3–9 days
3. *Intermittent self-administered parenteral DHE:* Following the initial IV infusion, or after an initial test dose and education session in the office, the patient can self-administer DHE 1 mg SQ q 8–12 h round the clock until 24 h headache free
4. *Intermittent self-administered intranasal DHE:* Following the initial IV infusion, the patient uses four sprays of intranasal DHE (Migranal) BID or TID until 24 h headache free

Table 14.15 Intravenous (*IV*) adjunctive treatments used for bridge therapy

Agent	Dose	Comment
Magnesium sulfate IV	1–4 g IV over 1–2 h	Provided in infusion suite at time of DHE infusion. 1 g may be given over 1 h. May be given daily
Valproic acid IV	500–1,000 mg	May be given in 50 ml of saline or D5 over 20–30 min daily
Antiemetics (see above)	Varies	May be given IV q 8 h; dopamine antagonists have abortive potential. Check with pharmacy to see which one requires ICU monitoring for QTc prolongation. $5HT_3$ antagonists are safer, but may be less effective for pain
Ketorolac	30 mg	May be given in 50 ml of saline or D5 over 20–30 min daily
Steroids	Variable; either po or IV	Dexamethasone 8 mg IV × 1; methylprednisolone 250–500 mg IV× 1; or oral prednisone starting at 60 mg a day and tapering off over 10–14 days

ICU intensive care unit

Preventive Therapy

In almost every case, it is necessary to initiate, update, or add more preventive therapy as part of MOH treatment. Zeeberg and colleagues, as well as others, have demonstrated that detoxification from immediate-relief analgesics leads to greater responsiveness to preventive therapy, and several other studies have confirmed that compliance with preventive therapy assures lower risk of relapses. Duration of preventive therapy is empirically continued at least 3–12 months after successful remission from MOH.

Relapse Rates and the Need for Follow-up

Relapse rates of these approaches are not easy to find, and available head-to-head comparisons have been open-label studies. Research from Italy has found no difference between outcomes at 6 months when comparing day hospital care and inpatient therapy. About 40 % had at least a 50 % drop in headache frequency and 53 % reduced abortive drug intake by more than 50 % when the two populations were combined. Other studies have demonstrated that most relapses occur within the first year after successful detoxification, and that the type of drug use responsible for MOH may determine the risk of relapse. The German investigators found a 5-year relapse rate of 33 %.

Conclusions on Medical Treatment of Chronic Daily Headaches: Chronic Migraine, Chronic Tension-Type Headache, New Daily Persistent Headache, and Medication Overuse Headache

- This chapter has discussed the treatment of refractory primary headache disorders as well as revisiting the common secondary daily headache disorder, MOH
- Treatment of MOH is predicated on the absolute wean from overused medications, appropriate selection of preventive medication, and, on occasion, bridge therapies
- Education and interdisciplinary treatments can help in augmenting these medical treatments

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Chapter 15
Psychological Comorbidities, Assessment, and Management of Refractory Daily Headaches

Steven J. Krause

Introduction

The practicing physician encounters depression and anxiety disorders as the most common psychological comorbidities of headaches. Medication overuse headache (MOH) patients exhibit substantially more frequent depression than other headache patients. The same may also be true of anxiety disorders. Thus, behavioral treatment is often aimed at both the headaches and the psychological comorbidities, and crossovers between them.

This chapter reviews the comorbidities associated with refractory daily headaches, specifically MOH, and suggests approaches for assessment and management, including when to refer to existing structured interdisciplinary headache programs (Table 15.1).

Sleep Disturbances and MOH

Headache patients frequently suffer from sleep disturbances, both as a contributing factor and as a consequence of their headaches (Table 15.2). Once again, behavioral treatments need to take this into account, with sleep hygiene training and other behavioral interventions.

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Table 15.1 Psychological comorbidities of medication overuse headache (MOH)

- Depression is 35 times more common in MOH patients than in the non-headache population, and nearly 7 times more common than in headache patients without MOH
- There appears to be a reciprocal relationship between depression and migraine, with each disorder increasing the likelihood of developing the other, probably due to common underlying factors
- Panic attacks and generalized anxiety both occur three times more frequently in migraine patients than in controls
- Longitudinal studies suggest that prior diagnosis of migraine increases the risk of developing panic attacks

Table 15.2 Clinical pearls on sleep and headache

- Individuals suffering from obstructive sleep apnea or heavy snoring are 3.6 times more likely than the general public to develop headache, with a greater risk for daily headache than episodic headaches
- Sleep-related breathing disorders occur in 15–29% of chronic headache patients
- Insomnia is the most common sleep disturbance in headache patients. This may result directly from the headache, or may be a symptom of comorbid depression. Insomnia is extremely common in daily headache and MOH

Table 15.3 Case selection for intensive structured interdisciplinary treatment of MOH

In order to be appropriate for intensive interdisciplinary treatment, patients should meet each of the following criteria:

1. Patient suffers from headaches occurring at least 15 days per month
2. Headaches have been present for at least 3 months
3. Patient has received standard medical care for headaches without adequate benefit
4. *At least one* of the following must be present:
   - Significant impairment of functioning in either home or work environment
   - Functioning is maintained only through the use of medications at doses known to induce medication overuse headache, or through the use of controlled substances
   - Patient experiences significant emotional distress associated with headache and/or psychiatric comorbidities

Patient Selection for Intensive Interdisciplinary Medication Overuse Headache Treatment

Patients should be selected for interdisciplinary MOH treatment when the severity of their headaches disorder and the resulting functional impairment prevent effective treatment on a less intensive basis. They must have the requisite attributes and motivation to make such treatment effective. Referrals are often driven by comorbid psychiatric and medical illnesses, resulting in multiple medication contraindications, as well as the types and amount of overused medications. Previous outpatient failures can also impel referrals to an interdisciplinary program (Table 15.3).

Patients should *not* be enrolled in intensive interdisciplinary structured treatment programs when there are warning signs. These are listed in Table 15.4.

Table 15.4 Patients inappropriate for interdisciplinary headache programs

1. Patient suffers from other non-headache medical conditions that would preclude full participation in treatment
2. Patient lacks the cognitive ability to benefit from education, due to enduring conditions such as dementia or mental retardation. Such patients should be offered appropriate medical treatment, and their caretakers instructed in appropriate behavioral management techniques as outlined in Table 15.3
3. Patient suffers from a psychiatric disorder causing *current* hallucinations and/or delusions. Patients with a history of hallucinations and/or delusions may be considered if they are currently psychiatrically stable
4. Patient is involved in litigation related to the cause of their headaches (e.g., suing another motorist regarding a motor vehicle accident that was associated with the headaches, positing causation, blame, and restitution)
5. Patient currently abuses illegally obtained drugs. This does not include overuse of legally prescribed medications. Patients exhibiting addictive behavior patterns should be referred for appropriate alcohol and/or drug abuse services. When sobriety has been established, intensive interdisciplinary treatment may be appropriate
   a. Note: Some pain medicine interdisciplinary programs include substance use/addition arms and address headache and MOH as well
6. Patient is unwilling to eliminate use of inappropriate medications
7. Patient is unwilling to participate in the *entire* treatment program
8. Patient has no goals for increased activity or improved psychological functioning
9. Patient is disabled by a non-headache medical and/or psychiatric disorder. Such patients can be reconsidered for intensive interdisciplinary treatment following resolution of the non-headache disorder(s)

The Paradigm Shift in Behavioral Treatment of Medication Overuse Headache

Intensive interdisciplinary treatment for MOH begins by addressing traditional approaches to headache management, and how they have not only failed to resolve the patient's headaches but also frequently exacerbated them. While common sense and much pharmaceutical marketing suggest that the pain should always be treated promptly with medications, patients must be educated in the mechanisms by which their too-frequent medication use has in fact exacerbated their headaches.

Likewise, the means by which excessive rest, avoidance of normal light and sound levels, and the ordinary solicitous responses of friends and family have exacerbated headaches should be elucidated as well. The means by which headaches are exacerbated by excessive rest, light and sound avoidance, and the frequent solicitous responses of friends and family should be explained as well. A new treatment paradigm for chronic headache is introduced when the patient becomes aware that these well-intended responses to headache in fact escalate the problem. This approach rests on *restoration of functioning as the primary treatment goal,* rather than analgesia.

An interdisciplinary treatment program thus becomes necessary in refractory daily headache patients without the above contraindications. Suggestions regarding how to introduce patients to the need for interdisciplinary treatment are described in Table 15.5.

Table 15.5 Introducing the patient to the need for intensive interdisciplinary treatment

- The patient is told directly and unequivocally that they will not become pain free at the end of treatment
- The primary goal of treatment is not analgesia, but improvements in functioning
- Treatment requires that patients risk temporarily increased pain, but that they will be given tools to allow increased activity without pain escalation
- The failure of prior treatment should be explicitly framed as the fault of the treatment itself, neither of the patient nor of previous care providers
- Patients consider which values and life goals have the greatest salience for them. These functional goals then form the basis of treatment planning. Individualized training in pain management skills enables patients to achieve their chosen goals

Table 15.6 Advantages of goal-focused interdisciplinary care

- Goal-focused care frees the treatment team from patients' rejection of increased functioning on the grounds that it causes headache worsening
- An appropriate regimen of medications can be instituted without the expectation that every headache will disappear, or that medications should be changed on the basis of transient pain fluctuations
- Goal-focused care provides a basis upon which to instruct the patients not to discuss pain, except when asked by their health-care provider. This begins to turn attention away from pain levels and toward resumption of appropriate activity, providing a useful distraction that indirectly diminishes headache
- Goal-focused treatment provides measurable goals rather than basing outcomes solely on subjective experience of pain. This allows the treatment team to define endpoints for treatment, and sets standards for the progress necessary to continue care
- Care continues only when the patient demonstrates measurable progress toward his or her previously defined goals
- Progress toward treatment goals can be assessed by direct staff observation, as well as through self-assessment
- Goal-focused treatment reduces provider frustration and burnout, by eliminating the need to chase the elusive and frequently unobtainable goal of complete pain relief

Most patients requiring an interdisciplinary treatment program will have failed previous outpatient attempts to help their chronic daily headaches. Goal focused interdisciplinary programs offer the advantages listed in Table 15.6.

Within such programs there is less importance placed on rescue headache medications, and more emphasis on preventive strategies for managing headaches, and ways to improve daily function.

The interdisciplinary program provides the patient with self-help skills, and furthers self-reliance. There is a shift in locus of control, educating the patient on how they can appropriately manage their medications. Guidelines are given in Table 15.7.

Table 15.7 Guidelines for medication management

• The appropriate use of rescue medications should be addressed with the patient prior to any significant headache flare-up
• Do not alter the previously agreed upon medication regimen during a headache flare-up, unless the patient experiences intolerable side effects or other adverse drug reactions. Otherwise the patient rapidly learns from the health-care provider's behavior that alterations of medication use are necessary in the context of severe pain
• Remain calm. To the extent that the staff becomes frightened by patients' headache flare-ups, patients become frightened as well. This only serves to escalate the headache and diminishes confidence in the treatment offered

Table 15.8 Guidelines for making a psychological referral for an MOH patient

• Reassure the patient that the pain is real and a consequence of a medical disorder rather than a psychosomatic one
• Educate the patient in the ways that lifestyle choices, emotional responses, and social context can influence the long-term outcomes of care. An attitude of "you need to alter your lifestyle precisely *because* your pain is real" tends to be most productive

Table 15.9 Relaxation training and biofeedback basics

• Relaxation training includes progressive muscle relaxation, autogenic relaxation, diaphragmatic breathing, guided imagery, and similar techniques intended to reduce autonomic arousal accompanying headache
• The efficacy of such techniques in reducing headache is comparable to that of pharmacological treatment
• Biofeedback provides patients with real-time information regarding surface electromyographic (EMG) tension, peripheral temperature, skin conductance, the ratio of chest wall to diaphragmatic breathing, heart rate reactivity, and other physiological indices of stress. This is most effective when coupled with relaxation training

The Role of the Psychologist

The role of the psychologist within intensive interdisciplinary chronic headache treatment consists only partly in the assessment and treatment of mental disorders. Additionally, it encompasses training the patient in behavioral pain management skills and assisting the patient in making lifestyle changes appropriate to reducing headache-related functional impairment. Understanding this role allows for appropriate referrals from doctor or health-care provider to psychologist, and appropriate referral, in turn, benefits patients (see Table 15.8).

Relaxation-based Treatments

A number of relaxation-based approaches are used to diminish arousal, divert attention from pain, and reduce anxiety (Table 15.9).

Table 15.10 Use of cognitive-behavioral therapy (CBT): the basics

- CBT begins with the acknowledgment that individual mood states result from a combination of life events and the patient's *beliefs* about their significance
- The intense focus on nociception experienced by chronic headache patients narrows their ability to consider alternate understandings of their experience, exacerbating both anxiety and depression
- CBT assists the patient in identifying and evaluating their own thoughts about a variety of stressful situations, including but not limited to their headache
- Patients are encouraged to identify irrational thoughts and to systematically replace these with realistic alternatives

Treatment of Anxiety and Depression

Comorbid depression and anxiety are treated with a combination of cognitive-behavioral psychotherapy (CBT) and antidepressant and anxiolytic medication (Table 15.10). Antidepressants with anxiolytic effects that also have headache preventive properties, such as the serotonin–norepinephrine reuptake inhibitors (SNRIs), can be particularly appropriate choices.

Activity Pacing and Time Management

Difficulties with activity pacing are treated as described in Chaps. 19 and 23. The need to both pace activities appropriately and find time for self-care techniques such as relaxation and exercise often creates difficulties for patients lacking skills in time management. Patients are taught the guidelines given in Table 15.11 to assist them in this regard.

Table 15.11 Time management recommendations for patients

- Begin each day with a brief organizational period, in which daily tasks are identified and prioritized based on the degree to which they contribute to the goals articulated earlier
- Avoid the temptation to fill that day with tasks important to others that do not contribute to these goals. Assertiveness training, as described below, is useful to politely but successfully avoid commitment to unnecessary tasks
- Remember to complete tasks that lack deadlines, but which contribute substantially to the patient's well-being, or to the well-being of those important to the patient. Self-care tasks such as relaxation and exercise are particularly easy to neglect, but the long-term consequences of doing so can be severe
- Complete tasks in the order of their importance, rather than on the basis of ease. In this manner, should the patient be unable to complete everything he or she intended, at least the most important tasks will have been addressed

Sleep Hygiene Training

Given the frequency with which pain and headache patients suffer comorbid sleep disorders and the impact of reduced sleep on headache itself, sleep hygiene training can substantially benefit MOH patients. Once again, sharing guidelines to help patients establish regular sleep is a very important behavioral intervention (Table 15.12).

With use of these methods, patients frequently experience a significant improvement in sleep over a 2–3-week period. Patients with more refractory sleep difficulties can be referred for a polysomnogram or additional sleep disorders evaluation.

Other Psychological Treatments

Assertiveness training is often a useful adjunct to the behavioral management techniques described in Chap. 19. Social and emotional support that results from pain displays may be particularly salient for those patients who lack the skills of asking for what they want, resolving conflicts, and refusing inappropriate demands by others. As distinct from aggression, assertiveness consists in simultaneously treating both others and one's self with respect (Table 15.13).

Family education is vital to implementing behavioral strategies. The underlying rationale for the guidelines given in Table 15.14 must be explained, because family members may see the injunction against reinforcing pain behavior as going against their natural compassion toward the ones they love.

Table 15.12 Patient guidelines for sleep hygiene

- Set a stable waking time each day, regardless of how much sleep you had the prior night
- Avoid naps, and stay out of bed during the day
- If not asleep 20 min after going to bed, get up and pursue monotonous activities. Turn on only enough light to ensure personal safety. Return to bed when drowsy. The same guideline applies if you waken during the night prior to your designated waking time
- Avoid the use of stimulants such as caffeine or nicotine
- Exercise regularly as an aid to sleep
- Establish a routine of pre-bedtime habits
- Avoid using your bed for any activity except sleep or sexual intimacy
- Avoid the use of television or computers for at least 1 h prior to bedtime
- Dietary sources of L-tryptophan such as poultry, warm milk, or honey can be consumed 1 h before bed as an aid to sleep. The safety of tryptophan supplements has not been confirmed since the problem of eosinophilic myositis was linked to tryptophan supplements in the 1980s

Table 15.13 Guidelines for assertive behavior

- Honestly state your own desires and opinions
- Directly address those with whom one has concerns
- Communicate courteously with due regard for the well-being of others

Table 15.14 Guidelines for families and significant others of patients with MOH/chronic migraine/refractory headache

- Discontinue all questions about the presence or severity of patient headaches
- Should the patient display evidence of headache, change the subject or discontinue the conversation without comment. Criticizing pain displays is a form of attention just as sympathizing with them, and should be discontinued for the same reason
- Conversely, family members should provide encouragement and support whenever they observe patients engaging in constructive activities such as work or recreation. These "healthy behaviors" should be rewarded with additional attention
- Decide upon appropriate responsibilities for each family member. These should be consistent with guidelines for patient activity pacing described earlier
- Once established, family responsibilities are not altered due to the presence or absence of a severe headache. For example, if prior agreement requires the patient to cook dinner, they should do so regardless of pain level
- Avoid protecting the patient from normal levels of light and sound, as this will gradually increase sensitivity
- If the patient displays pain behavior despite instructions, families are instructed to maintain their normal schedule nonetheless. For example, family members should persevere with planned social activities, even if the patient refuses to participate. Canceling such activities risks rewarding the headache with additional attention, as well as creating a source of resentment for the family and guilt for the patient, which is destructive of relationships
- The above guidelines apply only to management of headache. Should the patient experience an acute illness such as an injury or a viral infection, they should be treated the same as any other family member

Nursing Role

Within an intensive interdisciplinary treatment program for MOH, the role of the nurse requires a wider scope and greater autonomy than in most outpatient clinical settings. Nursing responsibilities are delineated in Table 15.15 and discussed in greater detail in Chap. 23.

Table 15.15 Nursing roles within an intensive interdisciplinary treatment

- Educating patients about the pathophysiology underlying headaches and the role of various medical treatment approaches in their management
- Medication education
  - Proper use and timing of both preventive and rescue medications
  - Side effects and their management
- Education regarding dietary issues and headache, including food triggers, and the comorbidity of migraine with obesity
- Sexual consequences of headaches and of headache medications
- Instruction in assertively communicating with physicians, nurses, and other health-care providers, including the need to accept primary responsibility for one's own health care
- Case management and discharge planning

Table 15.16 Guidelines for interdisciplinary team interactions

- Maintain a stable roster of professionals dedicated to treatment of MOH cases whenever possible
- Establish a consistent case planning meeting where treatment team members can openly discuss consistencies and differences in their interactions with patients
- Communicate among team members to ensure a consistent set of recommendations to the patient
- Treatment team members should be well versed in each other's roles and functions and be willing to guide the patient appropriately regardless of one's own professional discipline. Over time, greater familiarity with one's colleagues professional skills will facilitate coordination
- Meet regularly with each patient to discuss patient progress toward the functional goals established at the beginning of treatment. Identify areas of success as well as necessary improvements

Table 15.17 Follow-up care

- Patients are scheduled for follow-up appointments with each treating discipline
  The frequency of these depends on individual circumstances, but should occur at a minimum of every 3 months for the first year
- Coordination with the primary care physician substantially increases the likelihood of long-term success
- Prior to discharge, staff members assist each patient in developing a crisis plan for managing severe headache. Should patients attempt to contact the clinic subsequently, reference is made back to this plan, rather than offering additional diagnostics or rescue medications

Coordination of care

For maximum efficacy, the professionals involved in interdisciplinary care must coordinate their efforts on behalf of the patient (Table 15.16). This allows team members to act with greater confidence, knowing that their efforts will be supported by their colleagues. A consistent message emphasizing the necessity of healthy functioning is imperative, as any discrepancies among the professional team will rapidly increase patient anxiety.

Follow-up Care

Perhaps the most difficult portion of interdisciplinary headache care comes in the first weeks following treatment. While enrolled in care, the patient receives extensive support and structure from the treatment team. Upon discharge, the habits developed during treatment must be maintained in the absence of external structure. Patients commonly feel anxious about this prospect, with frequent minor crises.

Follow-up care is mandatory to prevent recidivism. This involves an ongoing commitment from the staff. These requirements are listed in Table 15.17.

This interdisciplinary model can be nearly as challenging for the health-care provider as for the patient, in that it disrupts normal physician–patient interactions. While patients must learn to rely less on medications and more on their own pain management resources, the health-care provider must correspondingly abandon the "doctor knows best" approach.

Medical training perhaps emphasizes competence and responsibility more than collaboration and humility, but the latter two play a greater role in this model. Likewise, the choice not to focus on symptoms may strike both patients and health-care providers as lacking compassion, leading patients to anger and physicians to guilt. Both can be alleviated by frequent reminders that incomplete improvement is still preferred over a fruitless pursuit of the ideal but unobtainable absence of pain.

Conclusions on Behavioral Treatment of Refractory Headaches

- With exceptions, refractory headaches are accompanied by complex psychosocial issues that can mandate multi- or interdisciplinary therapy exceeding the capacity of many neurological offices.
- Combining medical, psychological, and rehabilitative measures can provide a comprehensive approach to these very difficult patients. Interdisciplinary programs can be inpatient or provided in a day-hospital setting.
- Refractory headaches are chronic problems that require long-term interdisciplinary therapy in order to promote well-being and prevent relapse.

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Chapter 16
Detoxification or Wean Treatment of Opioids and Sedatives in Headache and Pain Disorders

Jennifer S. Kriegler, Edward C. Covington and Mark J. Stillman

Introduction

This chapter discusses the outpatient drug detoxification or wean from opioids and sedative medications. Inpatient management and alcohol detoxification are beyond the scope of this section. We offer a "how to" of procedures for weaning patients off opioid analgesics and sedative/hypnotic medications. Detoxification from alcohol is not discussed, since this should never be attempted except by those skilled in alcohol rehabilitation.

Opioids can be effective for the management of acute pain and cancer pain where unlike nonsteroidal anti-inflammatory drugs (NSAIDs) and lower level mu-opioid agonist combinations such as tramadol/acetaminophen, most opioids have almost no ceiling effect. The exceptions are codeine, tramadol, and propoxyphene; the latter is no longer available in the US market.

Opioid tolerance occurs rapidly to sedation, intoxication, and respiratory depression, but slowly to analgesia and constipation. There is minimal organ toxicity and in acute pain management, iatrogenic addiction is less common.

Opioid use in chronic nonmalignant pain, especially headache pain, should be avoided. Opioids can cause medication overuse headache (MOH) quickly. As the use of prescription opioids has increased, so have the problems of diversion and death as a consequence. Between 1999 and 2006, fatal opioid overdoses more than tripled from 4,000 to 13,800 instances per year.

There are no controlled comparisons of medication weaning strategies. Most of us adapt and adopt from colleagues. The three phases of weaning are (1) establishing a baseline, (2) planning the dosage reduction schedule, and (3) treatment of withdrawal if it occurs (Table 16.1).

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Table 16.1 Three key steps for a weaning strategy of controlled substances

1. Establishing a baseline
2. Anticipating and planning a dose reduction schedule
3. Treating protracted post-acute withdrawal

Table 16.2 Stopping opioids once the amounts are low

• Wean opioid to a low level, preferably with a long-acting form, e.g., oxycodone 30 mg/day, or long-acting morphine sulfate 50 mg/day, then stop it
• Add clonidine 0.1 mg tid
• If evidence of opioid withdrawal occurs, that is, systolic blood pressure ≥150, diastolic ≥90, or pulse ≥90, add an additional 0.1 mg clonidine prn
• Maintain patient for 5–7 days on the clonidine dose, then decrease the clonidine dose by 0.1 mg daily
• If withdrawal symptoms recur, continue the previous clonidine dose for 5–7 days and try to taper again at oxycodone 30 mg/d, or long-acting morphine sulfate 50 mg/day

All pure mu-opioid agonists are effective to use for weaning from other opioids. Preference is to use a drug with a long half-life which will allow for a smoother wean by eliminating peaks and troughs. These are expensive drugs, so that may preclude use.

Long-acting morphine (24 h) is ideal, as generic preparations are available. Some clinicians very familiar with interchanging opioids in clinical practice use methadone; it can be given as a pill or a liquid (disguised in sweetened syrup) once a day due to its long serum half-life. Corrected QT interval of electrocardiography (EKG QTc) must be monitored if use of methadone is contemplated, as it can cause QTc prolongation.

Once the amount of opioid is decreased to a low level (e.g., oxycodone 30 mg/day, or long-acting morphine sulfate 50 mg/day), it may be stopped with the protocol listed in Table 16.2.

Establishing a baseline of the patient's daily average consumption is sometimes difficult, as the patient may exaggerate, minimize, forget, or be too intoxicated to remember how much medication he or she is taking. You must check your state's prescription monitoring program (PMP) when available. You can find a link to the accessibility or your state's PMP at http://www.pmpalliance.org. A fuller discussion of PMPs is included in Chapter 5.

Always remember to individualize your treatment; there is no one-size-fits-all formula for these potentially toxic drugs. The wean may be affected by age, concurrent medical conditions, or other medications taken (see Table 16.3).

When weaning opioids, it is always safer to undershoot the amount of medication at first. Evaluate the patient often, daily, if possible. Always evaluate the patient for withdrawal symptoms such as somnolence, tremor, autonomic arousal, myoclonus, inability to sleep at night, and irritability.

As a rule, one may wean by 25% of the previous day's dose. If the patient is uncomfortable, either reduce the rate of the wean to every other day or decrease the

Table 16.3 Clinical pearls on weaning from opioids

- Individualize treatment using oral morphine equivalents per day. This requires knowledge of equi-analgesic charts for the opioid class of medications
- Weaning may be affected by
  - Age of the patient
  - The patient's concurrent medical conditions
  - Other medications being used (e.g., sedatives)
- Wean opioids by ~25% of the previous day's dose, unless there is a contraindication to this rate
- Avoid weaning during holidays, weekends, or when there is limited access to care
- Make use of adjuvant medications such as antiepileptic analgesics (e.g., gabapentin, pregabalin, valproate), NSAIDs, antidepressant analgesics (tricyclic agents, serotonin–norepinephrine reuptake inhibitors), and atypical antipsychotics

NSAID nonsteroidal anti-inflammatory drug

rate to 10% of the previous day's dose. In general, do not decrease the dose on a weekend or holiday, since access to care is limited.

Use generous adjuvant medications including tricyclic antidepressants, trazodone, doxepin, antiepileptic agents (gabapentin and valproate are particularly effective), and atypical antipsychotics (quetiapine). Alpha-2 agonists can be useful to block withdrawal symptoms from opioid withdrawal. As noted above, clonidine is the most effective, tizanidine less so.

Clonidine may be given 0.1 mg as necessary if the blood pressure diastolic is ≥100. Tramadol has been utilized effectively for low-level opioid withdrawal and can usually be tapered easily, although it, too, is a mu-opioid agonist that can cause MOH.

If nausea is a problem, antiemetics such as ondansetron may be used. Use loperamide for diarrhea.

Monitoring for withdrawal is crucial in the wean. Polysubstance abuse should be assumed and never overlooked. The acute manifestations of withdrawal of sedatives (alcohol, barbiturates, and even benzodiazepines) are best managed in hospital by a team familiar with their potential serious consequences during withdrawal, such as seizures, dysautonomia, and death.

Withdrawal from a given medication tends to be the opposite of its pharmacologic effect. For example, alcohol, benzodiazepines, and barbiturates are all central nervous system (CNS) sedatives, so withdrawal manifests as CNS excitation and agitation. Opioids, as sedating analgesics with strong anticholinergic side effects, exhibit an acute withdrawal consisting of agitation, hypervigilance (and lowered pain threshold), and cholinergic discharge (abdominal cramps, diarrhea, sweating, salivation, and tearing). Cocaine and methamphetamine as stimulants manifest withdrawal as sedation (see Table 16.4).

Benzodiazepines are useful for treatment of short-term anxiety, but in general are counterproductive when managing chronic headache or pain. There is some evidence that diazepam decreases the central antinociceptive effect of both morphine sulfate and indomethacin.

Table 16.4 Clinical pearls on signs of withdrawal

- *Withdrawal from a medication tends to be the opposite of its pharmacologic effect*
  - Alcohol, benzodiazepines, and barbiturates are all CNS sedatives, and withdrawal manifests as CNS excitation and agitation
  - Opioids, as analgesics with strong anticholinergic side effects, exhibit an acute withdrawal consisting of agitation, hypervigilance (and lowered pain threshold), and cholinergic discharge (abdominal cramps, diarrhea, sweating, salivation, and tearing)
  - Cocaine and methamphetamine withdrawal manifests as sedation
- Polysubstance abuse should be assumed and never overlooked
- The acute manifestations of withdrawal of sedatives (alcohol, barbiturates, and benzodiazepines) are best managed in hospital by a team familiar with their serious consequences

CNS central nervous system

Acute alcohol withdrawal should never be attempted as an outpatient, and patients should be referred to an appropriate drug and alcohol rehabilitation program.

Butalbital Weaning

Butalbital, a barbiturate that is no longer on the market in Europe but continues to be used in the USA, has an unusual pharmacology that easily leads to dependence. The serum half-life varies and can be as long as 72 h depending on age, but the therapeutic or analgesic half-life is 4–6 h. Therefore, the patient re-doses as the analgesia wears off and quickly accumulates high blood levels when it is regularly used for pain.

Phenobarbital, its relative still used in epilepsy management, has a 36-h serum half-life. For clinical purposes, each 100 mg of butalbital used per day is pharmacologically equivalent to about 30 mg of phenobarbital a day. The replacement dose of phenobarbital should be administered at night, as it will help induce sleep.

After establishing a baseline for butalbital use, convert the dose to a replacement equivalent dose of phenobarbital and have the patient take it at bedtime. Decrease the dose by 30 mg weekly until 15 mg is reached. Once the 15-mg dose is achieved at bedtime, the patient may discontinue the phenobarbital, as it will gradually taper off without a problem. The suggested reading by Loder and Biondi (2003) goes into butalbital withdrawal in more depth and is recommended.

A few additional words and warnings on butalbital and barbiturate weaning are in order. For patients who admit to consumption of large numbers of barbiturate headache pills (ten or more a day), it is best to admit and taper under careful observation. A butalbital level can be drawn, but the result will most likely not be back from the laboratory before the onset of withdrawal symptoms if the patient has stopped the medication abruptly.

Acute barbiturate withdrawal can lead to seizures, status epilepticus, dysautonomia, and death. Therefore, err in favor of utmost caution. Intensive care observation with continuous electroencephalography (EEG) monitoring may be necessary! And, as stated above and worth repeating, never discount the possibility of polysub-

Table 16.5 Clinical pearls on barbiturate withdrawal

○ For patients who admit to consumption of large numbers of combination barbiturate headache pills (ten or more a day), it is best to admit and taper under careful observation
○ A butalbital level can be drawn, but the result will most likely not be back from the laboratory before the onset of withdrawal symptoms if the patient has stopped the medication abruptly
○ Acute barbiturate withdrawal can lead to seizures, status epilepticus, dysautonomia, and death. Therefore, err in favor of utmost caution. Intensive care observation with continuous EEG monitoring may be necessary
○ Never discount the possibility of polysubstance abuse

EEG electroencephalography

stance abuse when planning the wean (see Table 16.5). Please see the references at the end of this chapter by Loder and Biondi, Romero and colleagues, and Deborah Tepper for sobering reading when contemplating butalbital weans.

Other Sedatives and Benzodiazepines

Many patients will present using large amounts of long- or short-acting benzodiazepines. Anticonvulsants will attenuate the withdrawal symptoms of these sedatives, and commonly used antiepileptic agents include carbamazepine, valproate, gabapentin, and pregabalin.

Initiate generous quantities of the antiepilepsy drug (AED) to prevent the need for as-necessary benzodiazepines to limit withdrawal symptoms. Do not use beta blockers when weaning from sedatives, as they can block hypertension, tachycardia, and tremor but do not prevent delirium or seizures.

When in doubt about the baseline use of sedative medications, assume that the patient is using more, since giving too little medication can be hazardous, and the anticonvulsants are benign, in comparison. Some clinicians like to use gabapentin for weaning patients from the benzodiazepines. It is inexpensive and comes in many dosages.

Gabapentin can be used to rapidly taper the patient off agents such as lorazepam or clonazepam and can be maintained, generally in lower daily doses, as a migraine prophylactic agent, although a Cochrane report in 2013 suggested that it is probably ineffective in episodic migraine prevention (see Chapter 11). Immediate-release gabapentin can effectively blunt the agitation of benzodiazepine withdrawal, including seizures.

Replace each 0.5 mg of clonazepam or lorazepam with gabapentin 600 mg (either in one dose or in divided doses over the day). Replace 0.5 mg of benzodiazepine per day this way until the patient is off, and then taper the gabapentin dose either down by 600 mg a day until the patient is off or at the desired dose for migraine prevention (generally 2,400 mg or more; see Table 16.6).

Table 16.6 Clinical pearls on the use of gabapentin to blunt benzodiazepine withdrawal

- Immediate-release gabapentin can effectively blunt the agitation of benzodiazepine withdrawal, including seizures
- Replace each 0.5 mg of clonazepam or lorazepam with gabapentin 600 mg (either in one dose or in divided doses over the day)
- Replace 0.5 mg of benzodiazepine per day this way until the patient is off, and then taper the gabapentin dose either down by 600 mg per day until the patient is off or at the desired dose for migraine prevention (usually at least 2,400 mg)

Relapse and Recidivism

The greatest risk for relapse after opioid or sedative detoxification is within the first 3 months. Post-acute protracted withdrawal symptoms can last up to 18 months, especially for opioids, and may include insomnia, dysphoria, irritability, and decreased ability to concentrate.

Conclusions

The issue of chronic daily headache due to simple analgesic use (MOH) is a large enough problem in medicine today. Compounding this problem is the use of analgesic agents now considered by many experts to be inappropriate to the task and even deleterious to the well-being of the patient, that is, opioids.

In the consideration of migraine and tension-type headaches, opioid analgesics and sedative hypnotics not only appear to disable the body's own analgesic ability but also come with the added risks of inducing physical and psychological dependence. In this day and age, the practitioner must be able to recognize this problem and address its full impact, including the medical and psychological aspects, if there can be any chance for improvement. This is, and will continue to be, a very heavy burden to bear.

The above guidance on the weans of these habituating medications should serve as a start for clinicians contemplating detoxification. The wean is the crucial step in the reversal of MOH.

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Part VIII
Treatment of Secondary Headaches

Chapter 17
Treatment of Major Secondary Headaches

MaryAnn Mays

Introduction

There are a number of disorders and disease states which can produce headache as a symptom. Successful management is dependent on the clinician first correctly diagnosing the underlying condition and secondly determining the appropriate treatment. Which treatment the clinician chooses is largely based upon the treatment guidelines for the primary medical condition, which are evidence-based as much as possible. The clinical presentations and diagnostic evaluations of secondary disorders were outlined previously in Chaps. 6 and 7. Treatment of the underlying disease state is necessary if the head pain is to resolve. In some instances, headache pain persists despite resolution of the condition.

There are a variety of medications used to treat secondary headaches, although evidence to support their use is often limited. Commonly used medications are the same as those used to treat primary headache disorders such as migraine and tension-type headache. Clinicians must use caution when prescribing medications that may worsen an underlying condition or cause a recurrence of symptoms. Because secondary headaches are often daily and constant in nature, the patient is at risk for medication overuse headache. Use of opioid analgesics should be limited to the acute setting or in those patients using opioids within the context of palliative care.

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Table 17.1 Clinical pearls in the management of posttraumatic headache

PTHA type	Abortive therapies	Preventative therapies
Tension-type	NSAIDs	TCAs
	Muscle relaxants	SNRIs
		SSRIs
		Physical therapy
		Prazosin
Migraine	NSAIDs	Beta-blockers
	Triptans	TCAs
	Dihydroergotamine	AEDs: topiramate, valproic acid
	Antiemetics	Riboflavin
		Magnesium
		Butterbur
		Botulinum toxin
		Physical therapy
Cluster	Sumatriptan SQ	Steroids
	Sumatriptan NS	Verapamil
	Zolmitriptan NS	Lithium
	Oxygen	Valproic acid
		Melatonin
		Nerve blocks—sphenopalatine ganglion, greater occipital nerve
		Stimulator placement

PTHA posttraumatic headache, *NSAIDs* nonsteroidal anti-inflammatories, *TCAs* tricyclic antidepressants, *SNRIs* serotonin norepinephrine reuptake inhibitors, *SSRIs* selective serotonin reuptake inhibitors, *AEDs* antiepilepsy drugs

Headache Attributed to Trauma or Injury to the Head and/or Neck

Headache attributed to trauma or injury to the head and/or neck, commonly referred to as posttraumatic headache (PTHA), occurs within 7 days following head injury or whiplash injury. PTHA may be acute, with resolution within 3 months following injury or persistent, with symptoms persisting for greater than 3 months.

The symptoms of PTHA are nonspecific, often resembling those of the primary headache disorders, and treatment follows the recommended guidelines for those disorders (Table 17.1). Opioid analgesics should be avoided due to the risk of dependency and overuse. Physical therapy is useful to treat underlying muscle spasms and to improve restricted cervical range of motion.

Posttraumatic or post-concussion syndrome is a condition seen in patients following head or neck trauma. Headache is the cardinal feature along with other somatic, psychological, and cognitive symptoms. These symptoms may be noted soon after injury or may be delayed in onset.

Treatment of this condition focuses on the various commonly reported symptoms of mood changes, memory loss, dizziness, and insomnia, in conjunction with man-

Table 17.2 Symptomatic management of post-concussion syndrome

Symptom	Therapy
Headache	TCAs: amitriptyline, doxepin, nortriptyline, imipramine
	SNRIs: venlafaxine, duloxetine, desvenlafaxine
	SSRIs: fluoxetine, paroxetine, sertraline, escitalopram, citalopram
	Occipital nerve block
	Prazosin
Psychological complaints: anxiety, depression, irritability, personality change	Antidepressants
	Behavioral therapy/psychotherapy
	Relaxation
Memory loss	Cognitive therapy
	Donepezil, memantine
Seizure	Valproic acid, topiramate
Neck pain	Physical therapy
	Massage/craniosacral therapy
	Acupuncture
	Cervical epidural or facet blocks
	Avoid: immobilization/soft cervical collars
Disability from work	Vocational rehabilitation

TCAs tricyclic antidepressants, *SNRIs* serotonin norepinephrine reuptake inhibitors, *SSRIs* selective serotonin reuptake inhibitors

agement of the headache pain. Neuropsychiatric testing may be useful in documenting the degree of neurocognitive impairment and to monitor success of treatment.

Significant recovery from PTHA and concussion can occur but may require a multidisciplinary approach with use of medications, physical therapy, and behavioral therapy including biofeedback and relaxation techniques (Table 17.2). Although the majority of individuals will have significant improvement over time, as many as 25 % will experience long-term disability despite treatment.

An entire chapter in this manual is devoted to issues of traumatic brain injury and concussion (Chap. 24).

Headaches Associated with Vascular Disease

Headache may occur within the context of cerebrovascular disease, including ischemic stroke and intracranial hemorrhages. Onset of head pain is typically sudden with associated neurological deficits. The headache pain gradually diminishes with time, usually lasting only days in duration. In a small subset of patients, the pain may persist. Therapies are aimed at the specific headache type following the cerebrovascular event. Medications that can worsen the underlying condition or increase the risk for subsequent occurrences are to be avoided (Table 17.3).

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been show to increase the chance of stroke and myocardial infarction (MI). Naproxen has been reported to

Table 17.3 Clinical pearls on medications to avoid following cerebrovascular event

Cerebrovascular disease	Headache medications to avoid	
Ischemic stroke	• Beta-blockers—use with caution	
	• Triptans	
	• Ergots	
	• Isometheptene	
	• NSAIDs—use with caution, short term, and at low dose	
	Risk of stroke with various NSAIDs	
	NSAID	*HR (95 % CI) for risk of stroke*
	Ibuprofen	1.28 (1.14–1.44)
	Diclofenac	1.86 (1.58–2.19)
	Rofecoxib	1.61 (1.14–2.29)
	Celecoxib	1.69 (1.11–2.26)
	Naproxen	1.35 (1.01–1.79)
Intracranial hemorrhage	• Aspirin	
	• NSAIDs	
Subarachnoid hemorrhage	Acute	
	• Aspirin	
	• NSAIDs	
	• Triptans	
	• Ergots	
	Remote (post coiling or clipping)	
	• None	

NSAIDs nonsteroidal anti-inflammatories

have the lowest risk; some meta-analyses raise the question as to whether there is any risk at all with naproxen, and in 2014 an FDA review concluded that naproxen was the safest of the NSAIDs from a cardiovascular standpoint. If NSAIDs are to be used for acute headache management in individuals at increased risk for cerebrovascular or cardiovascular disease, they should be used only intermittently at the lowest effective dose. There is additional detail on this issue in Chap. 10.

Low-dose (81 mg) aspirin is used to prevent cardiovascular and cerebrovascular disease. NSAIDs can block the protective effect of aspirin when the two drugs are taken at the same time. To avoid losing the antiplatelet benefit of aspirin, it should be taken at least 30 min prior to or at least 8 h after taking a dose of any NSAID (Table 17.4).

Giant Cell Arteritis

There should always be a high degree of clinical suspicion for giant cell arteritis (GCA) in individuals who present with new onset of headache over the age of 50. The headache of GCA is the result of a granulomatous inflammation of the blood vessel walls.

Table 17.4 Tiered approach for treatment of pain in patients at risk for cerebrovascular disease, from lowest to highest risk

Lowest risk
Acetaminophen, aspirin, short term only: tramadol or narcotic
↓
Aspirin-like drugs (nonacetylated salicylates)
↓
Non-COX-2 selective NSAIDs
↓
NSAIDs with some COX-2 activity
↓
COX-2 selective NSAIDs
Highest risk

Abbreviation: NSAIDs= Non-steroidal anti-inflammatories; COX: cyclo-oxygenase

Prompt treatment is necessary to avoid secondary ischemic complications, in particular visual loss due to anterior ischemic optic neuropathy. Once loss of vision occurs, it is often permanent.

Therefore, if the clinical picture is suggestive of GCA or if the erythrocyte sedimentation rate (ESR) is elevated, initiation of therapy with corticosteroids is recommended, even if awaiting temporal artery biopsy. GCA is a widespread vasculitis of medium- to large-size vessels, and thus the patient is at risk for significant cardiovascular, neurological, and gastrointestinal complications including MI, aortic aneurysm dissection, stroke, or ischemic bowel necrosis.

Glucocorticoid-sparing agents such as methotrexate have had modest therapeutic benefit, but tumor necrosis factor α (TNFα) blockers have not been shown to demonstrate efficacy. Clinical response has been demonstrated with tocilizumab, a humanized monoclonal anti-IL-6 receptor (IL-6R) antibody (Table 17.5).

Primary Angiitis of the Central Nervous System

Primary angiitis of the central nervous system (PACNS) is an uncommon disease which can present with headache and other focal neurological deficits. It is a granulomatous vasculitis of the central nervous system and immunosuppressive therapies are required to prevent permanent neurological residua (Table 17.6).

Reversible Cerebral Vasoconstriction Syndrome

Reversible cerebral vasoconstriction syndrome (RCVS) often mimics primary CNS angiitis clinically, but the vasoconstriction seen on cerebral angiogram is related to vasospasm which typically resolves spontaneously within 4–12 weeks. RCVS is not a vasculitis, even though it was previously called benign angiitis of the CNS. The treatment for RCVS thus differs from that of PACNS (Table 17.7).

Table 17.5 Clinical pearls in the management of giant cell arteritis

- Initiate prednisone: 40–60 mg per day
- Alternate-day therapy is not effective in preventing vision loss
- Rapid resolution of headache symptoms (1–3 days) following corticosteroid therapy is the rule
- Presence of visual symptoms/loss: methylprednisolone 1 g IV × 3 days followed by daily oral prednisone dosing
- Vision loss is usually irreversible
- Temporal artery biopsy: corticosteroid treatment can be used for up to 10 days without affecting pathology results
- Steroids can begin to be tapered after 1 month of treatment and then gradually over 12 months guided by clinical symptoms and ESR
- The rate of steroid taper is in general 10–20% every 2 weeks or:
  - Initial: 10 mg/month until 20–30 mg/day
  - 5 mg/month until 10–15 mg/day dose
  - Remaining taper of 1 mg/month
- Average duration of corticosteroid therapy: 1–2 years
- Relapse common in the first 18 months after cessation of glucocorticoid therapy
- Aspirin 81 mg per day also recommended
- Osteoporosis prevention: calcium supplementation with vitamin D, bisphosphonates
- Initiate peptic ulcer prophylaxis
- Consultation with rheumatologist, neurologist, and ophthalmologist

Table 17.6 Treatment recommendations in primary angiitis of the central nervous system (PACNS)

- Prednisone is initiated at a dose of 1 mg/kg/day (max 80 mg/day), gradually tapering to a small daily dose over 8–12 weeks
- If disease is aggressive:
  - Pulse steroids: IV methylprednisolone 1 g/day × 3 days
  - Cyclophosphamide: 3–6 months of treatment
- Following cyclophosphamide treatment, long-term immunosuppressive treatments options which have limited evidence include: azathioprine, mycophenolate mofetil, methotrexate, infliximab, etanercept, and possibly rituximab
- Prevention of secondary complications of immunosuppression: pneumocystis pneumonia (*PCP*) prophylaxis, calcium with vitamin D, bisphosphonates, and peptic ulcer disease prevention
- Monitor disease response to therapy: follow-up MRI in 4–6 weeks and then every 3–4 months

Idiopathic Intracranial Hypertension (Pseudotumor Cerebri)

Patients with idiopathic intracranial hypertension (IIH, pseudotumor cerebri) present with severe headache and have papilledema on examination. These patients are at risk for visual loss and other cranial nerve dysfunction due to elevated intracranial pressures. The diagnosis is confirmed by measuring the opening CSF pressure during lumbar puncture.

The removal of CSF is also therapeutic, as it results in an immediate reduction in the intracranial pressure. Unfortunately, the relief is only short lived. Repeated lumbar punctures are not recommended due to risk of complications as well as discomfort to the patient. There are a number of medical as well as surgical treatment options (Table 17.8).

Table 17.7 Management of reversible cerebral vasoconstriction syndrome (RCVS)

- Pain:
  - Simple analgesics
  - Opioids
  - Avoid vasoconstrictive agents (i.e., triptans, ergots)
- Seizures: antiepileptic drugs
- Avoid triggers
- BP control
- Calcium channel blockers:
  - IV nimodipine IV (1–2 mg/kg/h with monitoring of blood pressure—rarely used)
- Oral nimodipine: 60 mg every 4–8 h, for 4–8 weeks, although adequate dose and duration are not fully established

Or

  - Verapamil SR 240 mg a day, for 4–8 weeks, although adequate formulation, dose and duration are not fully established
- Steroids are not helpful and may be harmful in this setting
- IV magnesium

Table 17.8 Clinical pearls in the management of idiopathic intracranial hypertension (IIH, pseudotumor cerebri)

- *Weight loss*
  - Evidence is increasing that this is useful
  - Low salt, low calorie diet
  - Consider bariatric surgery
- *Acetazolamide*
  - 1–4 g/day in 3–4 divided doses
  - Higher doses not well tolerated
  - Reduces intracranial pressure via carbonic anhydrase inhibition
- *Topiramate*
  - 100–200 mg/day
  - Weak carbonic anhydrase inhibition
- *Furosemide*
  - 40–120 mg/day
  - Used alone or in combination with acetazolamide
  - Potassium monitoring is necessary, usually with supplementation
- *Optic nerve sheath fenestration*
  - Preserves vision by reducing pressure on the optic nerve thereby decreasing risk for optic atrophy
  - No effect on headache
- *Ventriculoperitoneal shunt*
  - Reduces pressure, headache pain, and risk for loss of vision
  - Risk of complications with need for revisions is high
- *Lumboperitoneal shunt*
  - Frequent complications with need for revisions
  - Risk of developing acquired Chiari I malformation

Treatment of IIH should be a team approach, combining the skills of neurology, neuro-ophthalmology, and, if necessary, neurosurgery. Therapy should be targeted at three specific goals: (1) reduced intracranial pressure, (2) reduced headache, and (3) preservation of eyesight.

Simple analgesics and preventive headache medications are often used in management, but avoidance of drugs that cause weight gain is recommended. The mainstay of oral treatment remains acetazolamide, which can help with both lowering the pressure and reducing the headaches. Of note, corticosteroids are no longer used to treat IIH.

Surgical options with shunting of CSF can be helpful but are not without significant risks of complications such as back pain, meningitis, intracranial hypotension with cerebellar tonsillar herniation, and subdural hematomas. It is not unusual for patients to undergo multiple shunt revisions. Shunting is therefore reserved only after failure of maximal medical therapy or in patients who are experiencing visual loss and continuing headache.

Shunting is used when medical management is maximized, but headache persists. Shunting can help with all three clinical goals. However, despite the many shunting options that are available, patients can be difficult to treat, and results obtained may not be satisfactory in a subset of patients.

Optic nerve fenestration does not help with either pressure or headache, but does preserve vision. Thus, in the rare case of a patient without significant headache but whose vision is threatened, this approach can be useful and is less invasive than a shunt.

Low Cerebrospinal Fluid Pressure Headache

Headache that is present when the patient is upright but resolves in the supine position is often related to low cerebrospinal fluid (CSF) pressure. This may occur spontaneously but is most often the result of prior lumbar puncture resulting in persistent leak of CSF. The headache pain and other clinical manifestations can be quite debilitating.

Some low CSF pressure headaches will resolve within a week of onset with conservative management of pain. Epidural blood patch is the treatment of choice in those who fail those measures. Evidence supporting the use of different treatments other than epidural blood patch is weak, and recommendations are often based on limited case experience.

A Cochrane review in 2013 investigating effective treatment of headache post-lumbar puncture found only inconclusive results for conventional caffeine treatment, as well as dexamethasone, fentanyl, and indomethacin. Morphine and cosyntropin were found to be effective. The efficacy of fluids and bed rest is without clear evidence, although this is conventionally done both preventively and as treatment (Table 17.9).

Table 17.9 Treatment of low CSF pressure headache

	Dural puncture (LP) or spontaneous low CSF pressure
Treatment conservative	
	• Analgesics • Theophylline: 282 mg tid • Cosyntropin • Bed rest • Hydration • Caffeine IV: 0.5 mg IV Oral: 300 mg
Unproven conventional treatment	• Corticosteroids
Advanced and most likely effective	• Epidural blood patch (lumbar) • Epidural saline injection *Treatments specific to spontaneous CSF leaks* • Epidural blood patch (thoracic or cervical) • Continuous epidural saline or dextran infusion • Epidural fibrin glue • Intrathecal fluid infusion • Surgical repair of defect

Spontaneous CSF leaks are much more challenging to manage, particularly if the source of the leak cannot be identified. A fat-suppression MRI of the entire spine can sometimes show a cryptogenic leak.

Cervicogenic Headache

Headache pain that is referred from the bony structures or soft tissues of the neck can be treated with mild analgesics or muscle relaxers but may require additional preventive therapies, non-pharmacological therapy, or invasive procedures if persistent (Table 17.10). Use of a combination of available therapies seems to provide the greatest pain relief. Since the diagnosis often involves median branch blocks, procedures are frequently called upon in true cervicogenic headache.

Headache associated with Chiari Malformation Type I

A Chiari I malformation is a congenital malformation characterized by herniation of the cerebellar tonsils below the foramen magnum. Some cases may have associated syringomyelia or may have obstruction of CSF flow as documented by a CINE MRI study. Common presenting symptoms are listed in Table 17.11; they are reproduced here to remind the clinician that without these cardinal clinical manifestations, sur-

Table 17.10 Management options for cervicogenic headache

Analgesics	Muscle relaxers	Preventative medications	Non-pharmacological treatments	Interventional therapies
NSAIDs	Tizanidine	*TCAs*	Physical therapy	Anesthetic nerve blocks
– Diclofenac	Baclofen	– Amitriptyline	Massage or manual manipulation	Trigger points
– Flurbiprofen	Cyclobenzaprine	– Doxepin	TENS	Radiofrequency neurotomy
– Ibuprofen	Metaxalone	– Nortriptyline	Biofeedback/relaxation therapy	Botulinum toxin injections
– Indomethacin	Methocarbamol	*AEDs*	Behavioral therapy	Acupuncture
– Naproxen		– Gabapentin		Occipital nerve stimulator
COX-2-selective inhibitor		– Topiramate		Neurectomy
– Celecoxib		– Valproic acid		Dorsal rhizotomy
Acetaminophen				

NSAIDs nonsteroidal anti-inflammatories, *TCAs* tricyclic antidepressants, *AEDs* antiepilepsy drugs, *COX* cyclooxygenase, *TENS* transcutaneous electrical nerve stimulator

Table 17.11 Clinical manifestations of Chiari malformation type I, a reminder on the basics

- Headache
  - Cough headache
  - Suboccipital headache
- Neck pain
- Dizziness
- Vertigo
- Imbalance
- Syncope
- Tinnitus
- Lower cranial nerve symptoms
- Dysphagia
- Paresthesias
- Weakness

gery should not be considered. The ICHD-3 criteria for Chiari 1 are included in Chap. 7, Table 7.9.

Because many symptoms of Chiari are nonspecific and can also be seen with other disorders, it is important to determine before proceeding to surgical intervention, that concerns are indeed a result of the tonsillar descent and not from another condition. The need for surgical intervention must be carefully considered, especially with borderline findings on imaging.

MRI is used to measure the degree of tonsillar ectopia in Chiari I malformation. Tonsillar tips that extend 5 mm below a line connecting the basion with the opisthion are consistent with the diagnosis. Less than 3 mm of descent is considered normal, unless crowding of the subarachnoid space at the craniocervical junction is seen at the same time.

Patients may be treated conservatively with indomethacin, topiramate, or acetazolamide. However, if headache is severe and unremitting, or clinical signs of significant cerebellar dysfunction or myelopathy are present, patients should be referred to a neurosurgeon for consideration of posterior fossa craniocervical decompression surgery.

Conclusions

- In secondary headache disorders, especially posttraumatic headache, use the same medications as those used to treat primary headache disorders such as migraine and tension-type headache, and select based on whether the secondary headache has those features. Alternatively, treat with the proper medication for the underlying secondary disorder
- In headaches associated with vascular disease, avoid medications that increase the risk of vascular complications, such as vasoconstrictors, and in headaches

with hemorrhage, avoid medications with antiplatelet effect. Certain NSAIDs are more associated with thrombotic risk than others
- Treatment of IIH is targeted at three clinical goals: (1) reduction of intracranial hypertension, (2) reduction of headache, and (3) preservation of vision
- This chapter also provides guidance above on the treatment of primary angiitis of the center nervous system, RCVS, cervicogenic headache, and Chiari malformation type 1

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Part IX
Treatment of Pediatric Headaches

Chapter 18
Treatment of Pediatric and Adolescent Headaches

A. David Rothner and Catalina Cleves-Bayon

Introduction: A Model for Pediatric Headache Treatment

The treatment of headaches in children and adolescents is a combination of art and science. Take into consideration both the diagnosis and the temperament of the family, as well as the personality of the child.

A model or overall paradigm for treatment of headaches in children and adolescents is outlined in Table 18.1.

The above approach varies somewhat when dealing with chronic pediatric headache as opposed to an acute headache syndrome. The patient's headache frequency, its severity, its duration, and its temporal pattern must be taken into consideration. In addition, take into account the degree of disability when considering treatment.

Making a diagnosis is key. Do not begin treatment of a child's headache without a diagnosis. Either a tentative or a definite diagnosis is necessary for initiation of therapy, as different therapies are available depending on the specific diagnosis.

Therapy can still be initiated if the treating physician has only a tentative diagnosis. The patient and parent should be informed that the treatment may change if the diagnosis changes.

This chapter reviews the treatment paradigm for pediatric patients with either recurrent or chronic headaches. The approach to children and adolescents with a variety of other headaches is also presented.

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Table 18.1 Overall model for pediatric headache treatment

1. Confirm the diagnosis
2. Provide confident reassurance
3. Patient education
4. Discuss the role of stress
5. Review lifestyle issues
6. Dietary considerations
7. Rescue medication
8. Preventive medications
9. Alternative approaches
10. Follow-up

Confident Reassurance

When the treating healthcare provider is confident that no life-threatening or serious problem is present, the patient and parent should be so reassured. Emphasize that since no neurological symptoms are present, that the neurological exam is normal, that the course of the headache is not progressive, and the scans and other tests are normal, there is no serious underlying problem!

At this point, it is useful to explain any abnormalities on tests or scans that are present but not relevant. These include arachnoid cysts, pineal cysts, Chiari I malformation, white matter changes, developmental venous abnormalities, and abnormalities of the sinuses. Still, acknowledge the patients' and parents' concerns and tailor therapy accordingly.

Parents know their children best and should be given the opportunity to verbalize concerns. The same principle applies to children themselves. It is useful at times, especially with adolescents, to obtain separate interviews so that they are provided with an opportunity to open up to the health-care provider and take part in the decisions made regarding their own treatment.

Patient Education

Both verbal and written information should be provided to the patient and parent. This will allow them to study the brochures over time and in a less anxiety-provoking situation. Lists of additional readings, organizational contacts, and reputable websites are valuable (See Chap. 23).

Stress

"Stress" is an all-encompassing term for psychosocial issues that may precipitate or aggravate headache. This includes depression and anxiety. Emphasize that all patients experience stress. The most frequent sources of stress in pediatrics include

family and school related issues, difficulty with friends, and excessive extracurricular activities.

Problems regarding divorce, blended families, joint custody, substance abuse, and physical and sexual abuse, frequently play important roles as headache triggers and should be addressed. Otherwise, treatment failure will occur. In patients with chronic daily headache (CDH), stress regarding overachievement is often unrecognized.

Frequent school absences are a barometer of stress. Measures to return patients to full attendance are important; even partial attendance is critical in care. Home schooling should be discouraged. "Normalization" should be the rule.

Isolation from peers and exclusion from family activities will only exacerbate anxiety and depression. Patients with academic struggles are also more prone to headache, and tutoring or providing additional resources can be useful in this setting.

Relationships with fellow students and physical and emotional bullying are being recognized with increased frequency as bringing on or aggravating headache. In addition, many of our patients are overcommitted. Sports, cheerleading, band, debating clubs, and a part-time job not only cause stress but also, when combined with excessive homework, adversely impact sleep. Many adolescents are also now responsible for looking after siblings or ill parents, leaving them in overwhelming situations.

If stressful issues are identified, refer the patient for psychological evaluation. Use adolescent behavioral specialists trained in pain management. Recommendations regarding counseling, biofeedback, or other behavioral methodologies are often very helpful.

Emphasize that these factors require their own treatment, and pharmacological treatment alone is not enough. Adolescents in particular are searching for independence during this important stage of development. A non-pharmacological approach will be more appealing knowing that these techniques empower them to take control over their symptoms and assume a more active role in their own treatment.

Lifestyle

Improving aspects of a patient's lifestyle choices may significantly decrease headache frequency. A regular schedule is needed.

Patients often experience poor sleep quality which contributes to ongoing headache. Many have difficulty falling asleep and experience multiple awakenings. Offer suggestions to improve the quality of sleep (see Table 18.2).

A regular bedtime must be established. Restorative sleep is needed.

The use of melatonin can be helpful. In an adolescent, begin with 3 mg of melatonin 2 h before bedtime. If after 2 weeks there is no improvement, the patient can be instructed to increase the dose to 6 mg. If after 2 weeks, there is still no improvement, increase the dose to 9 mg.

If difficulty persists, a sleep consultation may be indicated. Loud snoring or apneic pauses during sleep must be further investigated.

Table 18.2 Clinical pearls and suggestions for improved sleep

- No TV, computers, or cell phones in the bedroom, no texting!
- Establish a routine (same time to bed/awaken)
- Relax 30–60 min before bedtime
- Your room should be quiet, dark, and cool
- Exercise earlier in the day, not before bedtime
- Do not eat heavily before bedtime
- Avoid caffeine
- Avoid afternoon and evening naps
- Do not take sleep aids without discussing them with your parents and doctor
- Discuss problems falling asleep and awakening at night with your physician or healthcare provider

The treating physician should question the patient about analgesic use, barbiturates, narcotics, aspirin, and caffeine, both by prescription and over-the-counter (OTC) medications. We inform patients and parents that using these medications more than 2 days per week may cause rebound or medication overuse headache and may interfere with the effectiveness of preventive medications. Narcotics and combination products containing barbiturates, aspirin, and caffeine have no place in the treatment of pediatric headache.

The adolescent should be questioned about smoking and alcohol use. In addition to health related issues, they may actually increase headache frequency.

Regular, vigorous exercise decreases headache frequency. Many patients with CDH are deconditioned. In these patients, a stepwise approach using strategies beginning with physical therapy will provide structure in a more controlled setting. Patients with chronic pain who are deconditioned are often afraid that exercise will lead to more pain. Physical therapy can provide a safe reconditioning regimen in a less threatening environment.

Current recommendations include 30 min of vigorous exercise per day or 1 h of vigorous exercise three times weekly. Explain the role of the body mass index (BMI). It is likely that a BMI > 25 and definitely > 30 is associated with an increased frequency of headache. Structured exercise and weight reduction efforts help increase self-esteem and decrease disability due to headache.

Diet

The role of diet in a comprehensive headache treatment program is controversial. We feel that eliminating certain foods and additives can be helpful. Use an 8-week period during which there is elimination of a variety of substances (see Table 18.3).

Foods that the patient or family feels adversely impact the patient's headaches should also be eliminated. At the 8-week follow-up visit, the patient and parents are queried about their experiences with the diet. Foods not implicated are put back into the diet one by one every 2 weeks. Implicated foods should continue to be restricted or offered in limited amounts.

Table 18.3 Dietary considerations: elimination for treating pediatric headache

• No caffeine
• No chocolate
• No luncheon meats
• No aged cheese
• No monosodium glutamate (MSG)
• No foods implicated by the patient/family

Table 18.4 Pediatric acute and rescue medications

Sedatives
Diphenhydramine
Antiemetics
Metoclopramide (0.1 mg/kg, max single dose 10 mg)
Prochlorperazine (0.1–0.15 mg/kg/dose; max. single dose: 10 mg)
Ondansetron (4–8 mg)
Analgesics
NSAIDs: Ibuprofen or Naproxen (10 mg/kg)
Acetaminophen (15 mg/kg)
Abortives/Migraine Specific/Triptans
Sumatriptan (Nasal spray approved for adolescents in Europe)
Rizatriptan (FDA-approved in patients 7 years and older)
Zolmitriptan (Nasal spray approved for adolescents in Europe)
Almotriptan (FDA-approved for adolescent migraine)
Eletriptan
Naratriptan
Frovatriptan

Rescue or Acute Medications

Rescue medication should be limited to 2 days of use per week. When possible, acute medications should be combined with nonpharmacologic measures.

As soon as the headache begins, the patient should retire to a cool, quiet, dark environment. Previously learned relaxation skills should be initiated. A cold compress with a headband is useful for some patients.

It is useful to divide pediatric acute and rescue medications into four categories. (see Table 18.4). The patient and healthcare provider together can decide in what combinations they should be used. Sedation should not be used at school.

Sleep frequently relieves pediatric headache and can even abort it completely. A preferred pediatric sedative is diphenhydramine. Side effects are infrequent.

If nausea and vomiting are prominent and antiemetics are indicated, the orally dissolvable form of ondansetron is effective and very well tolerated. Neuroleptics, such as metoclopramide or prochloperazine, must be used with caution as they can result in dystonic reactions.

Nonsteroidal anti-inflammatory medications are more effective than acetaminophen. A dose of 10 mg per kilogram that does not exceed 660 mg per dose of naproxen sodium is suggested.

Triptans have been studied in adolescents and to a lesser extent in children. They are available as orally dissolvable tablets (rizatriptan and zolmitriptan), nasal sprays (sumatriptan and zolmitriptan), tablets, and by injection with and without a needle (sumatriptan). Most are not approved for pediatric use by the Food and Drug Administration (FDA). Parents should be informed that, with the exception of almotriptan for adolescents, and rizatriptan now approved for ages 7 and older, they are not FDA approved but have been well studied and are safe. Many of the other triptans are approved for pediatric use in Europe.

Start with a combination of anti-emetics (if needed), sedation, and analgesics. If in 2 h the patient is no better, the sedation is repeated, and acetaminophen is substituted for the nonsteroidal anti-inflammatory drug (NSAID). However, sedatives should be avoided in the school setting as they may impair function even if the headache has resolved.

If these medicines are unsuccessful after 2–3 migraine attacks, a triptan is added. In most episodic migraine attacks, these measures combined with stress management, lifestyle change, and diet restrictions are effective. However, if the diagnosis is not clear and the patient has CDH with superimposed acute worsening, rescue medications are less effective.

The route of administration should also be taken into account. For example, in patients with significant nausea or vomiting, a nasal spray or injectable rescue medication should be considered.

Preventive Medications

When the patient presents with more than three attacks of migraine per week or more than 3–4 headache days per week and has failed to respond to lifestyle changes, diet, stress management, and rescue measures, daily preventive medications should be considered. This decision must be made together with the patient and parents.

Other considerations for the use of preventive medications include excessive school absences and analgesic medication overuse. If the attacks are few but extremely severe and/or prolonged, as is often the case in cyclical vomiting, consideration can also be given to the use of preventive medications.

A list of frequently used pediatric preventive headache medications is contained in Table 18.5. None of these medications is FDA-approved for pediatric prophylaxis. Valproate, topiramate, and propranolol are FDA-approved for adults.

Comorbidities are important and play a major role in the selection of prophylactic medication. When possible, choose prevention that treats a comorbid condition, and avoid those that worsen existing problems (see Tables 18.6, and 18.7).

Table 18.5 Pediatric preventive headache medication

Antihistamines
- Cyproheptadine

Antidepressants
- Amitriptyline (1 mg/kg/day)

Anticonvulsants
- Topiramate (50–150 mg/day)
- Gabapentin (600–2,400 mg/day)
- Valproic acid (avoid in girls due to teratogenicity, and other adverse side effects)

Others
- Beta blockers
  - Propranolol
- Calcium channel blockers

Table 18.6 Pediatric headache comorbidities for consideration in choosing prophylaxis

- School absences
- Medication overuse
- Sleep disorders
- Obesity
- Anxiety
- Depression
- Epilepsy

Table 18.7 Clinical pearls on use of comorbidities in choosing prophylaxis

- In a very thin patient, even if that patient is an adolescent, a medication that increases appetite, such as cyproheptadine or amitriptyline, may be desirable
- In patients with problems falling asleep and/or staying asleep, a medication that aids sleep is desirable, such as cyproheptadine and amitriptyline
- If the patient is obese, giving them a medication that increases weight is inappropriate (e.g., tricyclics, [TCAs] or cyproheptadine), but a medication that aids weight loss such as topiramate is desirable
- If the patient is depressed, a preventive such as amitriptyline which has antidepressant properties is desirable
- If the patient is suicidal, or depressed, extreme caution is indicated. The medication must be supervised closely, optimally with a psychiatrist, and administered by the parents. At the first sign of a change in personality or worsening depression, psychiatric consultation is mandatory
- If the patient has comorbid epilepsy, a preventive medication that has antiepileptic properties, such as topiramate, or valproic acid (not in girls), should be considered

How to Administer Preventive Medication

Initiate these medications in sub-therapeutic dosages and increase them slowly every 2 weeks in 2 divided doses. By going slow and limiting daytime dosing, side effects are minimized or recognized early. Beneficial effects are recognized at lower dosages, and excessive medication dosages can be avoided with this approach.

Patients and their parents are encouraged to contact the physician or provider between the initial visit and the 8-week follow-up visit if problems occur. Parents are told not to simply stop medication without talking to the provider's office. Preventive medications are always used in conjunction with lifestyle and dietary changes, as well as stress management as described above.

Set realistic expectations! Most preventive medications may take several weeks to months for clinical benefit to be achieved.

If one medication used in therapeutic dosages is unsuccessful, a second medication with a different mode of action should be added slowly. When the patient has been responsive to these medications, maintain them for approximately 4 months. Never discontinue medication at the start of the school year, as that seems to be a time when headaches exacerbate.

As noted above, all preventive medication should be withdrawn slowly. Other measures, such as lifestyle changes, diet, and counseling, should be continued after preventive medications are tapered. Clinical pearls in administering pediatric prevention are summarized in Table 18.8.

Table 18.8 Clinical pearls in administering pediatric prevention

- Initiate these medications at night in subtherapeutic dosages and increase them slowly every 1–2 weeks
- Certain preventive medications (e.g., TCAs) are given at night only; others are given in two divided doses (e.g., topiramate). Topiramate may be given either nightly or twice per day
- By going slow and limiting daytime dosing, side effects are minimized or recognized early Beneficial effects are recognized at lower dosages, and excessive medication dosages can be avoided
- Patients and their parents are encouraged to contact the healthcare provider between the initial visit and the 8-week follow-up visit if problems occur
- Tell parents not to simply stop medication first without talking to provider
- Preventive medications are always used in conjunction with lifestyle and dietary changes, as well as stress management
- If one medication used in therapeutic dosages is unsuccessful, a second medication with a different mode of action should be added slowly
- When the patient has been responsive to these medications, maintain them for at least 4 months
- Never discontinue medication at the start of the school year, as that seems to be a time when headaches exacerbate
- All preventive medication should be withdrawn slowly
- Other measures such as lifestyle changes, diet, and counseling should be continued after preventive medications are tapered
- It is important to address overuse of rescue medications, as patients who are experiencing analgesic rebound may be more refractory to preventive medications unless the offending agent is discontinued

Table 18.9 Alternative approaches for pediatric headache

A	B
Magnesium	Acupuncture
Riboflavin (vitamin B2)	Yoga
Coenzyme Q10	Massage
Butterbur root	Hypnosis
Feverfew	
Physical therapy	
Biofeedback	
OnabotulinumtoxinA	

Alternative Approaches in the Treatment of Pediatric Headache

Many patients and families wish to avoid medication and explore nonpharmacologic measures to treat their headaches. Table 18.9 lists some of these approaches. Column A includes those with data support for use, although not always in pediatrics. Column B lists those with less data but potential usefulness. Any of these approaches should be combined with lifestyle changes, diet, and stress management.

The use of onabotulinumtoxinA (Botox) has recently been approved in adults for treatment of chronic migraine, defined in the prescribing information as headaches that occur at least 15 days per month, for at least 4 h per day. Data concerning Botox onabotulinumtoxinA in pediatric CDH are sparse. At the time of this writing, it should be used only if the standard measures of medication, lifestyle changes, diet, and counseling for CDH have been unsuccessful. It is not a first-line pediatric therapy.

Multidisciplinary Rehabilitation Treatment of Refractory Pediatric Headache

A mixed inpatient and outpatient rehabilitation program for the treatment of refractory pain in pediatrics can be very useful. At the Cleveland Clinic, four forms of chronic pediatric pain are treated using a rehabilitation model in the Pediatric Pain Rehabilitation Program (also referred to as the Shaker Pain Program). They are complex regional pain syndrome, fibromyalgia, chronic recurrent abdominal pain, and CDH, especially those associated with frequent school absences and medication overuse.

A limited medication/true rehabilitation model is used, stressing psychological and physical rehabilitation modalities. Follow-up data over a period of 3 years indicate a decrease in headache severity, school absences, and work time lost by the parents due to their children's headaches.

When considering participation in this type of intensive approach, take the time to review the diagnosis with family and patient and reassure both. Again, discuss the

need for stress evaluation, and rediscuss the roles of lifestyle, diet, rescue medication, preventive medication, and alternative medication.

A treatment plan should be presented to the patient and parents in writing, along with educational materials. The patient is then asked if they have questions, comments, or criticisms. Once they feel they understand the program and are willing to participate, compliance is discussed. Emphasis is placed on the importance of 8 weeks of strict adherence to the regimen.

Follow-up

Emphasize the opportunity for the patient and/or parent to call with questions and/or comments between the first visit and the 8-week follow-up. Adherence is increased by encouraging communication.

The follow-up visit is the time to revisit the diagnosis and modify it based on new information, new symptoms, or new findings on the examination, and lack of response or side effects to the treatment program. Additional testing may be indicated. This is the ideal time to reassess disability, medication-related side effects, adherence, and the patient's and parents' feelings concerning progress.

Often, in patients with CDH, there is no change in the headache frequency and severity, but the patient is noted to be more involved, with more social contacts, less medication overuse, and less missed school. These are definite signs of progress.

Consideration can be given, in the absence of side effects, to increasing the dose of medication or, if necessary, to starting a second medication. Dietary restrictions can be modified if they are not helpful. Weight loss can be noted and encouraged. At the end of the visit, another visit should be scheduled. Follow-up is crucial for progress and to prevent recidivism.

Special Circumstances

A variety of special circumstances may need to be addressed. These are listed in Table 18.10, and will be covered below.

Acute Pediatric Headache

Children and adolescents are often seen in the emergency room and in their primary care physician's office for the evaluation of an acute headache with no previous history of recurrent headache. The overwhelming majority of patients with acute headache do not have any underlying structural or neurological abnormalities.

Table 18.10 Special situations in treating pediatric headache

1. Acute pediatric headache
2. Migraine: acute, urgent treatment
3. Migraine with neurologic features
4. Menstrual Migraine
5. Cyclical Vomiting
6. CDH
7. Posttraumatic HA (PTH)
8. New daily persistent headache (NDPH)
9. Exertional HA
10. Trigeminal autonomic cephalalgias (TACs)

Often, the patients have a headache related to fever or upper respiratory infection. Some are seen for a primary headache, such as a migraine or tension-type headache. The most important aspect in the evaluation of these patients is to rule out a major secondary cause and to treat the associated illness when present.

If the healthcare provider feels that this is a primary headache, sedation and analgesia should be effective. If the patient has any neurologic symptoms and/or any abnormality on the neurologic examination, immediate, more complete evaluation is necessary prior to treatment. Imaging may be necessary.

Until a diagnosis is secure, children and adolescents should not be given highly sedating medications, which may mask neurological symptoms or signs. The routine use of narcotics is not in the best interest of the patient. Follow-up after office or emergency room discharge is strongly recommended.

Pediatric Migraine Headache: Acute/Urgent Treatment

Migraine headaches are among the most common headaches seen in pediatrics, and healthcare providers are often called upon to treat urgently in the office or ER.

Principles of treatment, acutely, as noted above, include sedation, antiemetics, analgesics, and abortives (see Table 18.11). For the average-size teenager, begin with 25 mg of diphenhydramine and 10 mg per kilogram of naproxen sodium. If they are not better 2 h later, repeat the diphenhydramine and use 15 mg per kilogram of acetaminophen. If the IV route is preferred, ketorolac may be used. If this is unsuccessful, triptans can be used in future attacks.

In younger children aged 7–12, use the 5 mg sumatriptan nasal spray or 2.5 mg zolmitriptan orally dissolvable tablet. Rizatriptan (5 mg in patients <40 kg and 10 mg in patients >40 kg) is also available. If nausea and vomiting are important components of a patient's migraine syndrome, use 4–8 mg of ondansetron orally dissolvable tablet prior to initiating the diphenhydramine and analgesic abortive combination (see Table 18.12).

Table 18.11 Clinical pearl: the principles of treatment of an acute pediatric migraine

• Principles of treatment of acute pediatric migraine: sedation, antiemetics, analgesics, and triptans

Table 18.12 Treatment of an acute pediatric migraine

○ Begin with 25 mg of diphenhydramine and 10 mg per kilogram of naproxen sodium
○ If not better in 2 h, repeat diphenhydramine and use 15 mg per kilogram of acetaminophen
○ If unsuccessful, triptans can be used in future attacks
○ 5 mg sumatriptan nasal spray or 2.5 mg of zolmitriptan orally dissolvable tablet
○ Rizatriptan mg in patients less than 40 kg and 10 mg in patients >40 kg
• For nausea and vomiting
○ Use ondansetron orally dissolvable tablet prior to diphenhydramine and analgesic abortive combination

Tension-type Headache

Many children and adolescents will have an occasional headache of mild to moderate severity without associated nausea and vomiting. These patients can be treated with 10 mg per kilogram of naproxen sodium, and the problem will usually resolve. If the parents find them using these medications more than 2 times per week on a regular basis, further evaluation and use of other treatment options, lifestyle changes, stress reduction, and diet are indicated.

Migraine with Neurologic Features

At times, patients presenting with migraine will have associated neurological features. This can be seen in migraine without aura, migraine with aura (including brainstem aura), and hemiplegic migraine. If symptoms or signs of increased intracranial pressure are present, a workup for underlying structural abnormality is indicated. Migraine with neurologic features requires close follow-up. Specialized testing for hemiplegic migraine may be needed. Triptans should be avoided in patients with brainstem aura and hemiplegic attacks.

Menstrual Migraine

Some adolescent girls experience increased numbers of migraine attacks during their menstrual periods. Most begin their headache the night before the menstrual flow begins.

The patient should keep calendars of both their headaches and their menstrual periods. If there appears to be a predictable pattern, the patient can be started on a course of nonsteroidals, given every 6–8 h for 3–4 days prior to menstrual cycle. This frequently modifies the attacks.

Other considerations, if the attacks are unresponsive to nonsteroidals, would include the use of twice-daily long-acting triptans, such as frovatriptan or naratriptan. The routine use of birth control pills as the first option in the treatment of this disorder is discouraged.

Cyclic Vomiting

Cyclic vomiting is considered a migraine precursor (see Chap. 9). Many patients have a positive family history of migraine and go on to develop typical migraine. The usual patient is a preschool child who periodically begins to vomit repeatedly, averaging 5–8 emeses per hour for several hours every 20–40 days, usually early in the morning. Many have these recurrent episodes with a predictable pattern. Patients should be evaluated to rule out underlying intracranial, abdominal, or metabolic disorders.

Acute treatment includes sedation and antiemetics, and in some cases judicious use of triptans while keeping in mind the patient's age and weight. Some require intravenous therapy. If spells are severe and recurrent, prophylaxis with cyproheptadine or amitriptyline can be useful.

Chronic Daily Headache

CDH in adolescents is very difficult to treat. It may in fact be the most difficult pediatric headache type to treat, and it causes the greatest family disruption. If CDH is complicated by excessive school absences and medication overuse, it is even more difficult to remediate.

The medical model for the treatment of pediatric headache is followed. We emphasize patient education, stress management, lifestyle changes especially sleep, hydration, and exercise, diet modification, and prophylactic medication. The latter is chosen bearing in mind the patient's comorbidities.

If depression or anxiety is present, psychiatric consultation and ongoing counseling are needed. This group of patients is most appropriate for a multidisciplinary rehabilitation program.

New Daily Persistent Headache

New daily persistent headache (NDPH) begins acutely. The patient often has no significant past history of migraine or frequent daily headache. In 40 % of patients, NDPH is preceded by a viral illness, injury, or an emotional event. From that day on, the patient has daily, continuous headache. NDPH is a variant of CDH and should be treated in the same way.

Posttraumatic Headache

Many patients are seen with daily or almost daily headache following a head injury or concussion, usually in the absence of serious intracranial pathology. Patients frequently have associated symptoms such as lethargy, personality change, irritability, and dizziness.

Once secondary causes have been excluded (infections such as meningitis, structural lesions, or IIH), these patients should be treated as if they have CDH. This, too, is a difficult group of patients to treat, and often stress management is indicated. Chapter 24 is entirely devoted to traumatic brain injury and concussion.

Exertional Headache

Many adolescents, but fewer younger children, experience headache during intense exertion. The story one generally hears is that the patient starts an activity without headache, and when they exert themselves, develops either a severe generalized headache or a true migraine with associated phonophobia, photophobia, nausea, and vomiting.

If these attacks are predictable and occur less than 2–3 times per week, treatment with 10 mg per kilogram of naproxen sodium 2 h before the event can be helpful. Indomethacin has been recommended but given the availability and safety of naproxen, try naproxen first.

Pediatric Trigeminal Autonomic Cephalalgias

The trigeminal autonomic cephalalgias (TACs) are a group of disorders which are very uncommon in children and adolescents. TACs generally present with multiple short headaches on a daily basis with autonomic symptoms, except for the continuous hemicrania continua (HC).

The short paroxysmal TACs are cluster, paroxysmal hemicrania (PH), and short-lasting unilateral neuralgiform headache attacks (SUNHA). As noted, HC is classified as a TAC in ICHD-3, but it is continuous with exacerbations that can include autonomic features.

Cluster headache is the most common TAC. PH and HC are indomethacin responsive. TACs are reviewed in detail in Chaps. 2 and 12.

TACs frequently go unrecognized for months to years, but should be suspected if the patient presents with multiple headaches per day. After a thorough evaluation, the use of indomethacin can been very helpful, therapeutically and diagnostically. Cluster and SUNHA, not indomethacin responsive, have more specialized treatments (see Chap. 12).

Healthcare providers not familiar with pediatric TACs may require consultation from a headache medicine specialist. Given their rarity in pediatrics, a careful search for secondary causes is in order when a TAC is suspected.

Conclusions

- The treatment of pediatric headache requires the correct diagnosis and making sure underlying medical or neurological issues have been ruled out
- Provide patients and parents with background information and a treatment plan
- Stress management, lifestyle changes, and diet are the mainstays of pediatric headache management
- Judicious use of rescue and preventive medications in moderation is also of great importance
- Continued communication and follow-up is necessary
- Consultation with a pediatric headache medicine specialist can be sought if initial approaches are not successful

Suggested Reading

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Part X
Special Topics in Headache

Chapter 19
Behavioral Treatment of Headaches

Steven J. Krause

Introduction

Literature examining the connection between headaches and psychological conditions suggests that mental health and emotional well-being play a significant role in course of primary headache disorders. There appears to be an integral relationship between psychological variables, functional status, and the experience of headache itself, with each of these strongly influencing the others.

Stress and Headache

The role of stress in the genesis and maintenance of headaches has been studied for several decades, and is summarized in Tables 19.1 and 19.2.

Adaptive and maladaptive coping strategies are represented in Figs. 19.1 and 19.2.

Reinforcement Processes

Multiple studies have indicated that remarks about pain and pain behaviors such as moaning, groaning, holding or rubbing painful areas of the body, altered posture, witnessed medication use, extensive resting time, frequent position shifts, altered posture, or the use of equipment such as sunglasses and baseball caps to avoid exposure to light, all serve to communicate the presence of headaches to an observer. Over time, such pain displays lead to lowering of both sensory and pain thresholds and increase the frequency and severity with which pain is experienced. Therefore,

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Table 19.1 Stress and headache

- Stress is the discrepancy between the psychological demands placed upon an individual and that person's perceived capacity to deal with these demands. It is therefore highly dependent on the individual's appraisal of both the risks of a situation as well as the ability to cope effectively with those risks
- Stress triggers physiological consequences, including increased cerebral blood flow and muscle contraction that may contribute to headache exacerbation
- Psychological stress mobilizes the body to face external threats, but can be triggered by emotional issues also, and leads to increased headache, largely by increasing attention to headache
- Pain and stress are mutually reinforcing
- Relaxation training is useful to reduce autonomic over-arousal and attention to pain during headache episodes. Multiple therapeutic strategies exist, including progressive muscle relaxation, autogenic relaxation, guided imagery, and diaphragmatic breathing
- Relaxation training is sometimes accompanied by biofeedback, a procedure in which patients' physiological responses, such as respiratory rate, pulse, surface EMG, skin conductivity, or peripheral temperature are monitored during relaxation training. The repetitive pairing of physiological feedback with subjective relaxation enables the patient to more clearly distinguish the states of high and low arousal and to become more adept at cultivating lower arousal states

EMG, electromyography

Table 19.2 Guidelines for assisting patients in reducing headache reactivity to stress

- Health-care providers should not promote excessive attention to headache, but focus instead on the ability to perform ordinary activities
- Remind the patient that primary headache pain is unwelcome, but does not indicate tissue damage, and is not a medical emergency. Pain is an ordinary part of living
- Encourage patients to use self-directed strategies, such as relaxation, biofeedback, and activity pacing, to reduce headache risk *without curtailing activities*

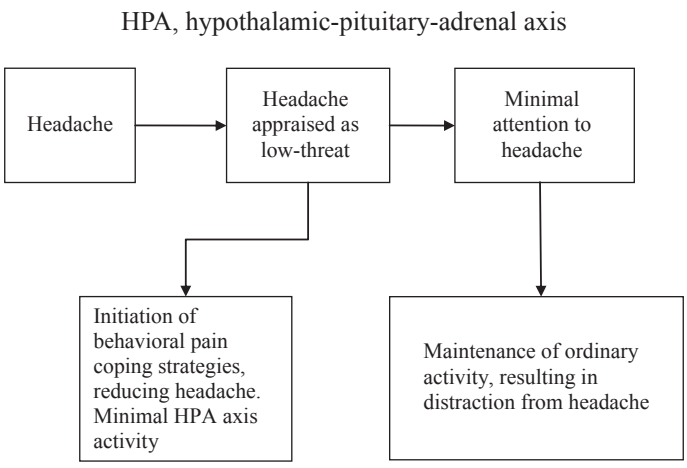

Fig. 19.1 Adaptive headache coping

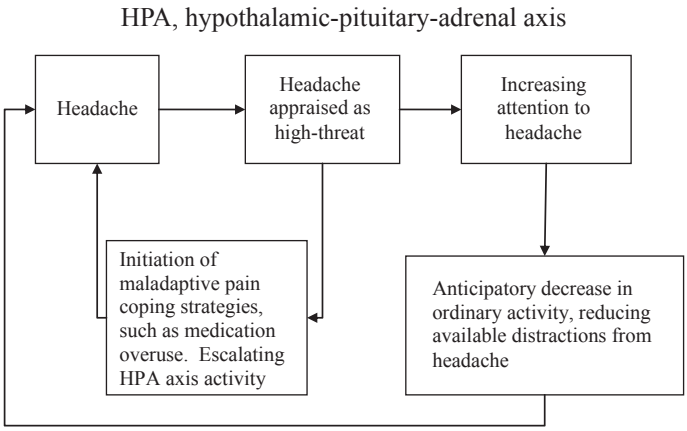

Fig. 19.2 Maladaptive headache coping

since the display of pain is itself associated with increased pain on a long-term basis, factors which tend to increase pain display will indirectly create increased pain experience as well.

Because of physicians' expertise and control over treatment, their responses to patients' pain behaviors strongly shape the outcomes of care. Behavioral guidelines for the management of headache patients are presented in Tables 19.3, 19.4 and 19.5. These are intended to strike an appropriate balance between legitimate gathering of diagnostic and treatment information, compassion for suffering patients, and the need to avoid reinforcement of inappropriate and maladaptive attention to pain.

Maladaptive Activity Patterns

Headache patients frequently struggle with the need to regulate their activity appropriately. The two most common maladaptive strategies involve persistent underactivity to avoid headache and a refusal to make any activity changes in response to the illness.

The health-care provider, as a key part of behavioral treatment, needs to encourage the patient to engage in normal or vigorous activity. Shifting the locus of control to the patient is important. Understanding the underpinnings of the inactivity helps encourage mobilization (Table 19.6).

An alternative but equally maladaptive activity pattern occurs when patients refuse to make any concessions to their headache, instead insisting that they can and must pursue high levels of activity regardless of the consequences (Table 19.7).

It is often useful for clinicians to openly address these issues with their patients and to provide guidance regarding proper activity pacing. Patients can be given blank forms of the type displayed in Form 19.1. Guidelines for using this form are described in Table 19.8.

Table 19.3 Behavioral guidelines for evaluation and initial treatment planning

- *Take a thorough history of the patient's pain complaint, current symptomatology, and other relevant medical information*. Once this is accomplished, however, further attention to minor fluctuations in pain experience may not yield additional useful diagnostic information, but will certainly increase the patient's sensitivity to these variations
- *Help the patient to be goal oriented*. Develop mutually agreed upon goals with each patient, write these in their treatment plan, and then refer to these goals at *every single visit*. Goals must be expressed in terms of activity, role functioning, or behavior, rather than focusing on pain relief
- *Help the patient get specific about each goal*. For example, if the patient says they want to "get better," staff can reply "*Good! Let's identify some things you could do differently which would be meaningful to you.*" If the patient remarks they want pain relief, staff can reply, "*Well, we can't promise how much that will happen. But we can certainly help you regain control of your life, so you can get back to being the person you want to be*"
- *Get the treatment plan in writing whenever possible*. Include patient goals and share a copy of the plan with the patient. Refer back to these goals often with the patient
- *Emphasize measurement*. Ask patients to measure hours of sleep, hours of "up-time," repetitions of exercise, number of social contacts, and hours of work completed

Table 19.4 Behavioral guidelines during treatment

- *Focus on healthy behaviors of patient*. Deliberately seek evidence of good functioning and treatment progress and praise the patient for this. For example, comment on improved posture and gait, non-pain talk, increasing endurance, etc
  - *"You certainly seem to be walking better today"*
  - *"It's nice to hear you talking about your family"*
  - *"I'm glad you were able to drive yourself in today. That's an improvement over when we first met"*
- *Ignore pain behaviors*. Do not engage with patients when they whine or complain about pain. Instead, stay focused on the task at hand, neither attending to pain behavior nor criticizing it. Specific pain behaviors to ignore include
  - Unsolicited patient comments about pain
  - Moans, groans, and other nonverbal noises indicating pain
  - Grimacing, frowning, and wincing
  - Abnormal posture
  - Excessive resting
  - Impaired mobility
  - Holding or rubbing painful body parts
  - Use of sunglasses, eye-shading hats, and other equipment
  - Frequent position shifts
- *Do not allow pain to become an excuse for avoidance of ordinary responsibilities*. For example, if the patient states they cannot complete household tasks, encourage them to persevere
  - "I'm sure you can do it, let's give it a try"
  - "Let's just take them one at a time"
  - "Good job, you're halfway there! Keep going!"
- *Clearly state specific behaviors appropriate to pain treatment*. These may include medication regimens, exercise quotas, attendance at appointments, scheduling of ancillary services, reading educational information, etc

Table 19.4 (continued)

- *Avoid patient "splitting" of staff*. For example, if a patient tells you "The other nurses (PTs, staff, doctors, etc.) are so harsh, but you're so sensitive," you should reply *"If you have a difficulty with other staff members, you need to speak with them about it. Let's stay focused on our work today"*
- *Avoid "enabling"; encourage independence*. If patient requests a glass of water, a tissue, etc., smile and reply, *"I'm sure you can handle that yourself."* Repeat as necessary
- *Avoid inadvertent prompting of pain talk* such as greeting the patient with "How are you?" or worse still "How are you feeling today?"
  - Greet patients with a focus on activity, such as "So, what have you been doing since I last saw you?"
  - If they reply "nothing," staff should look confused and ask "*So where did the day go? How did you spend your time?*"
- *Help patients gain perspective on their problems*. When patients complain that they are not making any progress, return to their stated treatment goals, and ask what they are doing in each area. Comment cheerfully on each evidence of progress, no matter how small
  - "You walked six blocks yesterday. Can you think of any other areas in which you've improved?"
- *Be ultra-generous with specific praise*. Instead of saying the patient is "doing better," comment on his/her, posture, movements, activities, engagement in normal activity, etc. Flood the patient with compliments for every tiny improvement
- *Avoid punishment*. Even negative attention is a form of attention, and isolated people will prefer that over being ignored
  - If you must tell the patient to behave differently, be direct, specific, and matter of fact, and then move on as quickly as you can to something they are doing well
- *Use "earshot reinforcement"* Compliment the patient's progress in front of other staff. *"Dr. Smith, did you know that Mr. Jones has added two extra hours per day at work? He's doing a great job!"*
- *Have patience*. Rehabilitation takes time and cannot happen overnight. Conversely, we expect progress in functional activity as a requirement for continued treatment. Patients can achieve their goals, however slowly, as long as they keep moving forward

Table 19.5 Appropriate responses to patients' headache flare-up phone calls

- Educate patients in how to discriminate between relevant and irrelevant sensory experiences and how to manage a headache appropriately
- Respond promptly to patient contact during flare-ups. Delayed responding merely encourages patients to call more frequently in order to get your attention
- Avoid additional diagnostics or changes in the treatment plan during pain flare-ups, unless clearly indicated by altered pathophysiology
- Express confidence in the original treatment plan, and state clearly that pain fluctuations are normal, expected, and not a reason to alter treatment
- For many patients, simple reassurance may be an effective intervention at such moments, accompanied by reminders about how to use medications and other pain management strategies

Table 19.6 Consequences of insufficient activity

- Self-limiting activity reduces available distractions and increases preoccupation with headache
- Significant decreases in functional activity are associated with reduced production of endogenous endorphins. Over time, this leads to increased rather than diminished pain
- Marked inactivity leads to physical deconditioning, characterized by muscle disuse atrophy, loss of flexibility, and diminished endurance. This loss of physical conditioning often results in frequent provocation of pain by previously painless activities
- Patients frequently misinterpret the cause of their gradually increasing pain, attributing it to disease progression rather than to their own diminished activity. They respond by further diminishing activity

Table 19.7 Consequences of excessive activity

- As pain increases, patients fear that their window of opportunity to remain active is about to close. They then increase activity further in order to "get things done while I still can." This further exacerbates the pain
- The cycle continues until the patients become completely overwhelmed by their headaches. Subsequently, patients endure enforced "down time" during which they ruminate about tasks unfinished, others' impressions of them, and the possibility that their current headache flare-up will become permanent
- This persists until the headache subsides, whereupon patients immediately resume excessive activity. While maladaptive, this abrupt escalation of activity serves to reassure patients that they will not be permanently disabled, signals others that the patients are not merely lazy, and is aimed at helping patients make up for lost productivity during the headache flare-up
- Unfortunately, it also serves to reignite the headache exacerbation, and the cycle continues

Table 19.8 Guidelines for activity pacing

1. Provide the patient with a blank copy of Form 13.1. Instruct them to complete the form each hour, describing their activities of the previous hour briefly on the appropriate line. Discourage the patient from completing the entire form at the end of the day, as their memory is unlikely to adequately recall the details of every earlier hour
2. Ask the patient to complete this form for at least 14 consecutive days
3. Once the forms are completed, tabulate each day's total "up-time." This is calculated as the total number of hours when the patient is not sleeping, lying down, reading, or watching television. Conversation, computer work, self-care, and other productive activities are counted towards the "up-time" total, even if they are not particularly strenuous
4. Calculate the average daily "up-time," and encourage the patient to stabilize their daily activity at this level, avoiding both decreased activities during pain flare-ups as well as increased activity, when pain is low. This will require the patient to regulate activity according to a daily quota, rather than the more typical but maladaptive strategy of regulating it on the basis of pain level
5. Once the patient's activity level has been stabilized for at least a week, the daily activity can be increased in very small increments. For example, the patient can be encouraged to increase daily activity from 10 hours per day to 10.25 hours per day. Such increases are small enough to avoid provoking activity-related pain escalation, but over time will very gradually allow the patient to increase overall activity
6. Increase the daily activity quota by 15-minute increments each week
7. Patients should be discouraged from increasing overall daily activity beyond 15 hours per day. This will allow for 8 hours per night of sleep, as well as another hour during the day to practice relaxation techniques, or for other scheduled "down time"

Form 19.1 Activity and Sleep Log (*Sample*)

	Activity (What were you doing?)
6:00 AM	Brush teeth, shower, dress
7:00 AM	Relaxation, breakfast, drive to work
8:00 AM	Meeting with boss
9:00 AM	Working on report for finance committee
10:00 AM	same
11:00 AM	Staff meeting
12:00 PM	Lunch, relaxation
1:00 PM	Meeting with customers
2:00 PM	same
3:00 PM	same
4:00 PM	Complete paperwork, phone calls
5:00 PM	Relaxation, drive home
6:00 PM	Make dinner
7:00 PM	Eat and clean up after dinner
8:00 PM	Housework
9:00 PM	TV, Relaxation
10:00 PM	To bed
11:00 PM	
12:00 AM	
1:00 AM	
2:00 AM	
3:00 AM	
4:00 AM	
5:00 AM	

Depression

A significant association between headaches and depression has long been observed in both community and clinical samples. Understanding this bi-directional comorbidity will help in directing behavioral headache care (Table 19.9).

The diagnosis of depression in a headache population, however, requires modification of diagnostic criteria that would be appropriate in a strictly psychiatric setting (Table 19.10).

Table 19.9 Comorbidity of headaches and depression

- Depression is 5.2 times more frequent in headache sufferers as compared to the general population
- Among patients with headache and medication overuse, depression is 35 times more likely than in non-headache patients
- Seventy-eight percent of patients with transformed or chronic migraine demonstrated one or several psychiatric comorbidities, with major depression (57%), panic disorder (30%), and dysthymia (11%) the most common
- Among patients with no prior history of headache, a diagnosis of major depression at baseline is associated with a 3.4 times greater likelihood of developing first-onset migraine at the 2-year follow-up, as compared to controls, but no similar relationship has been found for other forms of headache
- Prior diagnosis of migraine is associated with a 5.8 times greater likelihood of developing major depression within 2 years as compared to non-headache controls, although this is not the case for other forms of headache
- Thus, there appears to be a bidirectional relationship between migraine and major depression, through a shared underlying comorbidity, although none exists for other forms of headache

Table 19.10 Diagnosing depression in headache patients

- Carefully distinguish the symptoms of depression from the somatic comorbidities of headache itself
- Place reduced emphasis on the somatic symptoms of depression in favor of a focus on sadness or flat affect and cognitive symptoms such as pessimism, low self-esteem, and inappropriate guilt
- Differentiate between anhedonia and the fear of activity-provoked headache. Only the former is a symptom of depression

Anxiety

Both clinical observation and systematic research converge on the finding that anxiety disorders are substantially more common in headache patients than normal controls. When added to the known comorbidity of depression with headache, anxiety leads to a comorbid triad of migraine, depression, and anxiety (Tables 19.11 and 19.12).

Trauma

Studies have consistently found that self-reported history of childhood sexual abuse predicts increased headache risk in adulthood, especially for chronic daily headache. Self-reported childhood physical abuse had no such effect. This finding has held for multiple ethnic groups, even after controlling for age and education. Prospective studies of patients who self-report a history of childhood abuse indicate a higher risk of developing headaches subsequently. However, studies which assess child abuse status objectively have reached discrepant conclusions.

Table 19.11 Comorbidity of headache and anxiety

• Panic attacks and generalized anxiety are both more than three times more likely in migraine patients than in controls
• Longitudinal studies suggest that prior diagnosis of migraine is associated with an increased risk of developing panic attacks

Table 19.12 Diagnosing anxiety disorders in headache

• Carefully interview patients to determine whether the their anxiety is limited to circumstances in which pain is anticipated or whether it generalizes to circumstances in which pain is not expected
• Even when anxiety is limited to anticipation of a headache, it can exacerbate pain. Treating anxiety is an important part of comprehensive headache management
• Both relaxation training and cognitive–behavioral psychotherapy have demonstrated value in reducing anxiety anticipatory to pain

Table 19.13 Childhood trauma and headache

• A self-reported history of childhood sexual abuse is associated with increased pain, depression, and disability
• The patient's perception of childhood events is more highly predictive than the events themselves
• Mental health intervention is frequently beneficial in patients reporting both headaches and childhood abuse

Inasmuch as the practicing clinician will rarely have access to objective documentation of childhood physical and/or sexual abuse, patient reported history of abuse should be considered a significant risk factor for developing headaches and other chronically painful disorders. Careful and sensitive interviewing is required to elicit patient recollections regarding these matters. Involvement of a mental health professional is likely indicated when headache patients present with symptoms of depression or with any self-reported history of childhood physical or sexual abuse. Thus, this area is one strong reason for referral (Table 19.13).

Family Functioning

Remarkably few studies have addressed the connection between headaches and family functioning, and those studies that are available have largely included pediatric populations. Family responses to headache turn out to be very helpful in predicting behavior and in planning behavioral treatment (Table 19.14).

When patients present with significant depression, anxiety, impaired functional activities, trauma, or family distress accompanying their headaches, referral to a mental health professional can be useful. However, this must be handled sensitively to avoid creating unrealistic expectations or offending the patient (Table 19.15).

Table 19.14 Headaches and family functioning

- The presence of a chronic headache sufferer in a family is associated with substantial psychological distress on the part of the spouse, but this is frequently overlooked by health-care providers
- Among adolescents with primary headache disorders, diminished autonomy and poor family functioning are associated with functional impairment
- Patients with highly solicitous spouses report greater levels of pain in the presence versus absence of their spouse, while no similar effect has been noted for less solicitous spouses
- Both chronic pain patients and their spouses report similar elevated levels of psychological distress
- Children of chronic headache patients, compared to controls, show no differences in self-reported or parent-reported family and psychological functioning
- Behavioral changes coming from the presence of a chronic headache patient in the family can be profound. This often results in unresolved guilt on the part of the headache patient and anger on the part of the caretaking spouse

Table 19.15 Making a mental-health referral for headache patients

- Choose professionals with a background in managing chronic pain. Psychologists with appropriate credentials and an interest in treating chronic pain patients can be located at: www.findapsychologist.org. Use the "advanced search" feature to narrow the search by specialty interests
- Explicitly state that the patient's headaches are the result of a pathophysiological process, and that the referral to a mental health professional is NOT an implication of psychosomatic pain
- Emphasize improved functioning as the purpose of the referral. "Your headaches are caused by a real illness, not a psychological problem. However, I'd suggest you see Dr. Jones because she can help you make the lifestyle changes that will reduce your headache risk and diminish the impact of the headaches on your life"
- Avoid promising that the mental health professional will provide particular techniques, such as biofeedback. Instead, inform the patient that they will initially receive a comprehensive evaluation of the impact of the headaches on their life, followed by treatments to reduce that impact

In summary, practicing physicians and health-care providers need to be aware of the profound influence they can have on their patients, not only through their explicit diagnostic and treatment interventions, but also through their manner in interviewing the patient, the patient behaviors to which they respond, and the treatment goals they endorse. To the extent that physicians emphasize attention to symptoms, they may inadvertently increase symptom reporting.

An emphasis on identifying and pursuing personal goals meaningful to the patient, such as employment or participation in family and social life, improves the likelihood that patients will increase their activity. Much can be learned by direct observation of patients' interactions with family and partners. Their inadvertent reinforcement of a patient's pain and disability will undermine successful treatment.

Unlike traditional "psychosomatic" models of pain, modern psychology assists patients in developing a lifestyle that diminishes headache risk and reduces common comorbidities, such as depression and anxiety. These comorbidities are particularly

Table 19.16 Conclusions: clinical pearls on psychological management of headache patients

- Relaxation, activity pacing without curtailing activities, and biofeedback are useful in lowering stress and preventing headaches
- Help the headache patient become goal oriented with a written treatment plan containing measurable behavioral changes and outcomes
- Focus on healthy behaviors of the patient and ignore pain behaviors
- Avoid splitting and enabling, and help patients gain perspective on their problems. Be specific in expectations and in praise
- Evaluate for comorbid depression and anxiety and for history of self-reported childhood sexual abuse. Actively address these problems when present
- Do not forget family functioning in the patient assessment and plan
- Refer when appropriate to a mental health professional to "make the lifestyle changes that will reduce your headache risk and diminish the impact of the headaches on your life"

common in patients with a self-reported history of prior trauma, and clinicians should gently enquire regarding past victimization. While it is seldom practical for medical professionals to treat these issues directly, an appropriate referral to a trained psychologist or psychiatrist skilled in managing chronic headache or pain patients can be valuable, as long as the referral itself is not introduced in a manner that seems to question the legitimacy of the patient's pain complaint (Table 19.16).

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Chapter 20
Treatment of Facial Pain and Neuralgias

Cynthia C. Bamford and Neil Cherian

Introduction

In this chapter, we discuss the treatment of more common causes of facial pain and cranial neuralgias. Most of these are primary, but a few are secondary. All patients who present with trigeminal neuralgia (TN) symptoms should have a magnetic resonance imaging (MRI) scan with attention to the cerebellopontine angle (CPA) with and without gadolinium to evaluate for secondary causes. Up to 15 % of MRIs will be abnormal, revealing structural lesions including CPA tumor (most commonly epidermoid), arteriovenous malformations of the posterior fossa, or demyelinating disease. The reader should refer to Chapters 6 and 7 for further discussion on the diagnosis of headaches associated with secondary causes.

The International Classification of Headache Disorders, 3rd edition beta (ICHD-3) now refers to the secondary trigeminal neuropathies as painful, as opposed to motor. The causes listed include herpes zoster, post-traumatic, multiple sclerosis (MS) plaque, space-occupying lesion, and other. Treatment will vary according to the diagnosis. The ICHD-3 organization of the secondary or symptomatic TNs is listed in Table 20.1 and was covered extensively in Chap. 7.

Herpes zoster vaccination is the most effective treatment in reducing the incidence of acute herpes zoster infection and post-herpetic pain. There is insufficient evidence that corticosteroids or acyclovir prevent post-herpetic trigeminal neuropathy.

Post-traumatic trigeminal neuropathy is defined as continuous neuropathic pain following complete or partial peripheral nerve injury in the trigeminal nerve distribution.

Treatment with topical therapies such as capsaicin may be of benefit. Neural blockade produces temporary relief only.

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Table 20.1 Painful trigeminal neuropathies as listed by the ICHD-3

Painful trigeminal neuropathies
1. Painful trigeminal neuropathy attributed to acute herpes zoster
2. Post-herpetic trigeminal neuropathy
3. Painful post-traumatic trigeminal neuropathy
4. Painful trigeminal neuropathy attributed to multiple sclerosis (MS) plaque
5. Painful trigeminal neuropathy attributed to space-occupying lesion
6. Painful trigeminal neuropathy attributed to other disorder

Table 20.2 Treatment of painful trigeminal neuropathies

• Amitriptyline	10–150 mg/day at bedtime
• Baclofen	10–80 mg/day divided into 2–3 doses
• Capsaicin, topical	5 times a day for 5 days, then 3 times a day for 3 weeks, which may be applied with topical lidocaine to decrease burning
• Carbamazepine	100–1,200 mg/day divided into 2–3 doses
• Clonazepam	0.5–4 mg in three divided doses
• Desipramine	10–150 mg/day at bedtime
• Doxepin	10–150 mg/day at bedtime
• Duloxetine	20–120 mg/day
• Gabapentin	300–2,700 mg/day divided into two to three doses
• Imipramine	10–150 mg/day at bedtime
• Nortriptyline	10–150 mg/day at bedtime
• Oxcarbazepine	150–1,800 mg/day divided into 2–3 doses
• Phenytoin	100–400 mg/day
• Pregabalin	25–450 mg/day divided into 2–3 doses
• Topiramate	25–400 mg/day
• Trazodone	50–300 mg/day at bedtime
• Valproic acid	125–2,000 mg/day two to three times a day or the ER formulation dosed at bedtime or twice a day
• Venlafaxine	37.5–225 mg/day may be dosed once a day. Doses of 150 mg or greater optimize anti-neuropathic effect
• Zonisamide	50–200 mg/day

Painful trigeminal neuropathy attributed to multiple sclerosis plaque can be unilateral or bilateral. The pain rarely mimics classical TN. Patients tend to benefit less from pharmacotherapy.

Treatment of the Painful Trigeminal Neuropathies

Pharmacotherapy options consist of antidepressants including tricyclic antidepressants (TCAs), serotonin–norepinephrine uptake inhibitors (SNRIs), trazodone, clonazepam, and membrane stabilizers or antiepilepsy drugs (see Table 20.2). Start low and gradually increase medication doses. Side effects of these medications have been discussed in previous treatment chapters. Behavioral strategies include cognitive behavioral therapy, relaxation techniques, and biofeedback.

Table 20.3 Clinical pearls on painful trigeminal neuropathy treatments

- In the absence of an evidence base, try several classes of medications, such as antiepilepsy membrane stabilizers, tricyclics, baclofen, and SNRIs
- Do not forget the potential benefits of behavioral treatments

Table 20.4 Treatment of temporomandibular dysfunction

- Rest
- Avoid chewing or clenching
- Mobility exercise
- Physical therapy
- NSAIDs or mild analgesics
- Oral splints

Clinical pearls summarizing treatment of painful trigeminal neuropathies are included in Table 20.3.

Temporomandibular Joint Dysfunction

The ICHD-3 requires that evidence of causation be present for the diagnosis of temporomandibular joint dysfunction (TMD), including both a temporal relationship to onset and worsening or improvement with the TMD clinical course. The headache must be produced or exacerbated by active or passive jaw movements through jaw range of motion or provocative maneuvers such as temporomandibular jaw or mastication muscle pressure. Finally, the headache must be ipsilateral to the side of the TMD.

Many patients have findings of TMD, but treatment should be reserved for patients with moderate or severe symptoms. Treatment strategies include information and counseling, rest, avoidance of loading, control of contributing factors, mobility exercises, mild analgesics or nonsteroidal anti-inflammatory drugs (NSAIDs) for pain, occlusal splints, and physical therapy (see Table 20.4). Surgical interventions should be considered only after nonsurgical treatments have failed.

Burning Mouth Syndrome

There are few double-blind placebo-controlled randomized trials for treatment of burning mouth syndrome. The ICHD-3 requires daily pain for >2 h/day for >3 months with both a burning quality and a superficial oral mucosa location in the absence of visible abnormalities. Essentially, burning mouth syndrome is characterized by pain or discomfort of the mouth with no known dental or medical cause. It is common, affecting up to 1/3 of postmenopausal women and up to 15% of adults overall.

Table 20.5 Clinical pearls on burning mouth syndrome

- Do not forget to try sucralose first!
- The best evidence for treatment is for clonazepam

Table 20.6 Management of burning mouth syndrome. (Adapted from Speciali and Stuginski-Barbosa, 2008)

- Commercially available granulated sucralose (SPLENDA)[a], 0.5 g
- α-Lipoic acid 200–600 mg daily[b]
- Amitriptyline 25 mg at bedtime[b]
- Systemic capsaicin 0.025 % capsules orally three times a day; adverse effects include epigastric pain[b]
- Clonazepam 1 mg dissolved in mouth for 3 min 3 times a day[b]
- Gabapentin 300–2,400 mg/day divided in three doses[a]
- Nortriptyline 10 mg at bedtime[b]
- Paroxetine 20 mg daily[b]
- Pramipexole 0.125–0.75 mg at bedtime[a]
- Sertraline 50 mg daily[b]
- Topiramate 100–300 mg at bedtime[a]
- Cognitive–behavioral therapy daily[b]

[a] Based on case reports, anecdotal reports, and open label studies
[b] Based on published randomized clinical trials

A systematic review of the literature to assess effectiveness of treatment was published by Buchanan and Zakrzewska in 2010. Oral dissolving clonazepam was the most effective treatment. Some treatments that have been studied and have shown efficacy include clonazepam (best evidence, see Table 20.5), serotonin specific reuptake inhibitors (SSRIs), alpha-lipoic acid, 0.5 mg of commercially available sucralose (SPLENDA), and cognitive–behavioral therapy (see Table 20.6).

There are anecdotal reports and case reports of topiramate and gabapentin reducing symptoms. As alluded to above, in 2011 there was a published report of three patients refractory to all of the previous treatments who responded to 0.5 mg of commercially available sucralose.

The Cranial Neuralgias

A number of cranial neuralgias have been described and are included in the ICHD-3. The most commonly encountered neuralgias in practice are classical TN, occipital neuralgia, and glossopharyngeal neuralgia. The other neuralgias included in the ICHD-3 will be briefly discussed. The successful treatment of a particular neuralgia starts with accurate diagnosis (see Chapter 7).

Table 20.7 Medications to treat classical trigeminal neuralgia

- Carbamazepine
- Oxcarbazepine
- Gabapentin
- Lamotrigine
- Botulinum toxin

Classical Trigeminal Neuralgia

Pharmacological Management

Carbamazepine remains the drug of choice for the treatment of classical (primary) TN. Once the titration period is over, longer acting formulations or related, safer, medications such as oxcarbazepine may be used. Neutropenia and hyponatremia are possible side effects of carbamazepine. During its use, appropriate blood testing is necessary. If the control of symptoms is incomplete, addition of another drug or switching drugs should be considered.

Oxcarbazepine, a prodrug of carbamazepine, as noted, has a better side-effect profile than carbamazepine. Gabapentin has also been shown to be effective in the treatment of TN, particularly in patients with multiple sclerosis.

Some evidence exists to support the use of medications such as lamotrigine or baclofen in the treatment of TN. Botulinum toxin has also been used successfully for the control of symptoms in TN in case reports (see Table 20.7).

Surgical Treatment of Classical Trigeminal Neuralgia

Once medication options have been exhausted due to lack of effect or unacceptable side effects, various surgical procedures may be considered.

The most widely used procedure for TN is the microvascular decompression procedure developed by Dr. Peter Jannetta. This procedure is based on the concept is that a blood vessel (artery or vein) can put pressure on the adjacent trigeminal nerve. Identifying the aberrant vessel and placing a small pad between the nerve and the vessel has been quite successful in abolishing TN symptoms. This procedure tends to be less effective in TN from multiple sclerosis.

Percutaneous approaches to trigeminal nerve destruction can also be effective in symptom management for TN. These procedures include radiofrequency thermorhizotomy, balloon microcompression, and retrogasserian glycerol rhizotomy. These procedures offer less mortality and morbidity than open procedures, although recently microvascular decompression has been described using endoscopic technique.

Stereotactic radiation therapy such as gamma knife is often used for patients failing medical management and those with significant medical comorbidities and/or failed surgical procedures.

Table 20.8 Surgical approaches for classical trigeminal neuralgia

- Microvascular decompression (Jannetta procedure)
- Percutaneous approaches to trigeminal gangliolysis
- Radiofrequency thermorhizotomy
- Balloon microcompression
- Retrogasserian glycerol rhizotomy
- Stereotactic radiosurgery
- Electrical stimulation/neuromodulation

Table 20.9 Clinical pearls on classical trigeminal neuralgia (TN)

- The older the patient, the less likely that the TN is secondary
- The younger the patient, the more likely that the TN is multiple sclerosis
- TN is terribly painful. If the medications are maximized and the patient is still symptomatic, refer to the surgeon or pain anesthesiologist quickly
- The older the patient, the better the response to microvascular decompression, but the greater the operative risk
- The older the patient, the greater the risk of anesthesia dolorosa with trigeminal neurolysis

Table 20.10 Medical approaches to treating occipital neuralgia

- Oral antineuritic medications
- Oral steroids
- Occipital nerve blockade
- Cervical botulinum toxin injection
- Neck physiotherapy
- *Clinical Pearl:* Use nerve blockade first, systemic medicines second

Table 20.11 Surgical approaches to occipital neuralgia (ON)

- Rhizotomy
- Phenol injections
- Occipital cryoneurolysis
- Occipital nerve electrical stimulation

Electrical stimulation in the form of deep brain stimulation has demonstrated some preliminary benefit. Peripheral nerve stimulation has also demonstrated a positive effect (see Table 20.8).

Clinical pearls on treatment of TN are summarized in Table 20.9.

Occipital Neuralgia

Medications that treat TN often benefit occipital neuralgia (ON; see Table 20.10). Surgical approaches for occipital neuralgia are summarized in Table 20.11.

Table 20.12 Treatment of glossopharyngeal neuralgia

- Oral antineuritic medications
- Surgical approaches
  - Stereotactic radiosurgery
  - Microvascular (neurovascular) decompression
  - *Clinical Pearl:* There is increasing evidence for microvascular decompression for glossopharyngeal neuralgia

Table 20.13 Clinical pearls on less commonly encountered neuralgias

- Nervus intermedius neuralgia: Treatment has not been established for this, but medication and surgical approaches to TN management may also be applicable
- Superior laryngeal neuralgia: Local administration of anesthetics and surgical exploration of the nerve can be of benefit. This is no longer included in the ICHD-3 sections on painful cranial neuropathies, other facial pains, and other headaches
- Nasociliary neuralgia: This can be a complication of herpes zoster infection. Thus, typical approaches to this type of infection may be of benefit. This is no longer included in the ICHD-3 sections on painful cranial neuropathies, other facial pains, and other headaches
- Supraorbital neuralgia: Local anesthetic injections may be of benefit. Various antineuritic medications may be used. This is no longer included in the ICHD-3 parts on painful cranial neuropathies, other facial pains and other headaches
- Nummular headache is classified in ICHD-3 under Other Primary Headache disorders and covered in Chap. 11. Nummular headache is rarely responsive to anything, but may be responsive to indomethacin. There are also reports of local anesthetic blockade or botulinum toxin efficacy
- Neck–tongue syndrome: A mechanical disorder of the cervical spine should be considered. Various antineuritic medications may be used. This previously described disorder is no longer included in the ICHD-3

Glossopharyngeal Neuralgia

Once again, with glossopharyngeal neuralgia, a mixture of medical and surgical approaches have been tried, most similar to those used in TN (see Table 20.12).

Other Neuralgias

Table 20.13 summarizes features and treatments of the less commonly encountered neuralgias.

Conclusions on Treatment of Facial Pain and Neuralgias

- Each of the facial pains and neuralgias has slightly different therapeutic approaches
- Generally, medications are tried first, and usually antiepilepsy drugs

- The exception to this is ON where a block is first-line therapy. Nummular headache may also respond to local infiltration of anesthetic
- In classical TN, time is of the essence due to the level of suffering. Refer to a neurosurgeon or pain anesthesiologist quickly if medications provide inadequate relief at reasonable doses

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Chapter 21
Treatment and Consideration of Women's Issues in Headache

Jennifer S. Kriegler

Introduction

Throughout a woman's life, certain events affect headache, and specifically migraine. Prior to approximately age 8, young boys have a higher incidence of migraine than girls. However, at menarche the incidence of migraine in girls increases. Migraine also changes at other key times in a women's life: during menses, with the use of oral contraceptive therapy, pregnancy, lactation, and menopause.

Menstrual Migraine

Menstrual Migraine Diagnosis

The International Classification of Headache Disorders, third edition (ICHD-3) beta, published at the time of this writing, only includes menstrual migraine in the appendix, despite the widespread acceptance of criteria for diagnosis and their extensive, validated use in research. Menstrual migraine is divided into "pure," meaning migraine attacks occur only during flow, and "related," meaning attacks happen both during flow and at other times (see Tables 21.1 and 21.2).

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S. J. Tepper, D. E. Tepper (eds.), *The Cleveland Clinic Manual of Headache Therapy, Second Edition,* DOI 10.1007/978-3-319-04072-1_21,

Table 21.1 Definition of pure menstrual migraine without aura (PMM), ICHD-3 beta appendix

• Meets criteria for migraine, and attacks occur exclusively on days (−2) to (+3) of menstruation in at least two-thirds of menstrual cycles and at no other times
• This is a rare syndrome (~10% of women with migraine)

Table 21.2 Menstrually related migraine without aura (MRM), ICHD-3 beta appendix

• Meets criteria for migraine and attacks occur on days (−2) to (+3) of menstruation in at least two-thirds of menstrual cycles, and additionally at other times during the month
• This is a common syndrome (~66% of women with migraine)

Definitions

Pure Menstrual Migraine Without Aura

- Meets criteria for migraine without aura, and attacks occur exclusively on days (−2) to (+3) of menstruation in at least two-thirds of menstrual cycles *and at no other time*. Note that the first day of flow is considered (+1) and the preceding day is −1; there is no day 0. It is unusual to have migraine only occur with menstruation.

Menstrually Related Migraine Without Aura

- Meets criteria for migraine without aura and attacks occur on days (−2) to (+3) of menstruation in at least two-thirds of menstrual cycles, *and additionally at other times during the month*. This is by far the most common form of menstrual migraine.

Epidemiology: Menstrual Migraine is Very Common

Migraine affects 25% of the female population during the childbearing years (18–49). Migraine is influenced by hormonal changes in the reproductive cycle. Menstrually related migraine (MRM) begins at menarche in approximately one-third of women who get migraines, and climbs, such that between 60 and 70% of women with migraine suffer from MRM during their lifetime. Pure menstrual migraine (PMM) is less frequent and occurs in 7–14% of women with migraine.

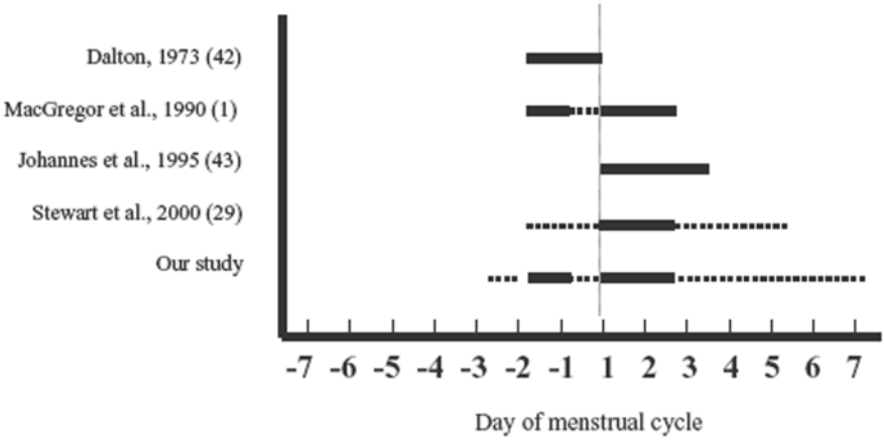
MRM is predictable in some women making them more amenable to planned treatment. However, in the majority of women, migraines around the time of menses are more difficult to treat and longer in duration than migraines at other times of the month. Migraine can occur before, during, and after menstruation, but the greatest likelihood is the day prior to the onset of menses and the first 4 days of the cycle (see Tables 21.3 and 21.4).

Many women fail to discuss migraine associated with menses with their doctors, because they believe it is part of the menstrual cycle and premenstrual dysphoric

Table 21.3 Pearls on women with migraine

- One in four women have migraine
- 60–70% of women with migraine have menstrually related migraine
- Critical time: (−2) to (+3) days of menstrual cycle

Table 21.4 Days of menstrual cycle with incidence of migraine. (Granella et al. 2004)



disorder (PMDD). Although MRM may occur in association with PMDD, it is a separate entity and should be treated as such. It is important for physicians to ask about the relationship between a woman's migraines and her menstrual cycle. The relationship may be obscured by frequent headache, such that MRM may only become apparent after reviewing a migraine diary kept for several months.

The Menstrual Migraine Assessment Tool (MMAT) is a simple three-question survey with a high sensitivity (0.94) and specificity (0.74) for MRM that care providers can employ to diagnose MRM quickly in the office (Table 21.5).

Pathophysiology: What you Need to Know to Explain Menstrual Migraine to Your Patients

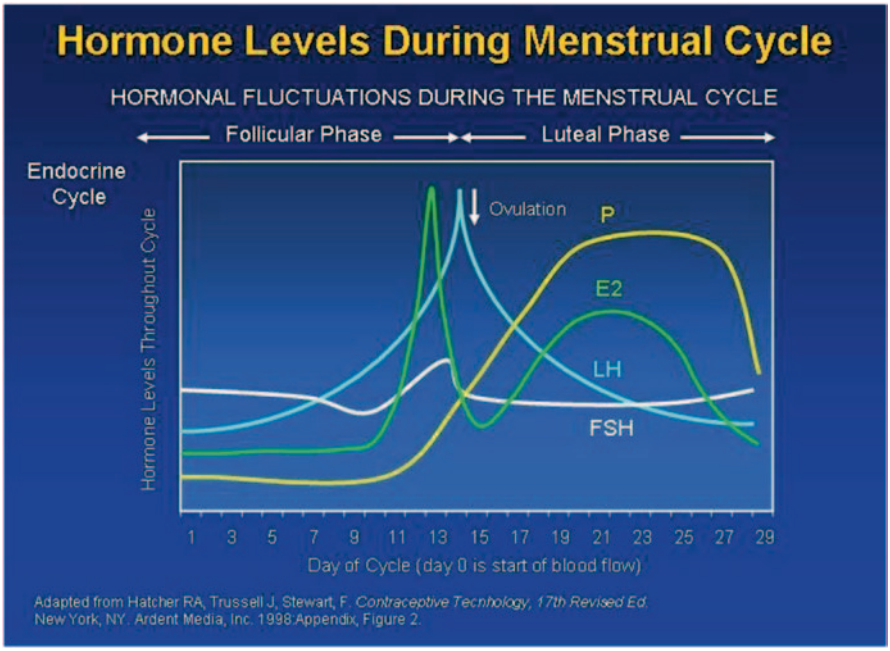
The primary mediator of hormonal migraine is the fall in estrogen which occurs at ovulation and menstruation. It is not the absolute fall, but the relative decrease in hormone which provokes migraine attacks (Table 21.6).

Estrogen is a neuromodulator, and its withdrawal increases the trigeminal mechanoreceptor field and alters central opioid concentration, thereby increasing pain and increasing cerebral vasoreactivity to serotonin. During the menstrual cycle, melatonin, normally increased during the luteal cycle, is decreased in association with MRM. There is alteration of opiate inhibition during MRM, and all of these factors may play a role in genesis of MRM.

Table 21.5 Menstrual migraine assessment tool. (Tepper et al. 2008)

Question 1	Do you have headaches that are related to your period (ie, occur between 2 days before the onset of your period, until the third day of your period) most months?	Answer: yes/no
Question 2	When my headaches are related to my period, they eventually become severe	Answer: yes/no
Question 3	When my headaches are related to my period, light bothers me more than I don't have a headache	Answer: yes/no
With yes to question 1 and at least one other yes		Sensitivity 0.94
With yes to question 1 and at least one other yes		Specificity 0.74

Table 21.6 Hormone levels during menstrual cycle. (Adapted from Hatcher et al. *Contraceptive Technology,* 17th revised Ed., New York, Ardent Media, 1998, Appendix, Fig. 2)



Treatment of Menstrual Migraine

In general, treatment is the same for menstrual as for nonmenstrual migraine. If migraine is infrequent, only abortive or rescue therapy is needed. In general, triptans are the treatment of choice. For many women, nonsteroidal anti-inflammatory drugs (NSAIDs) alone or in combination with a triptan are particularly helpful since they are beneficial in treating menstrual cramps as well.

Table 21.7 Decision tree for menstrually related migraine. (Tepper SJ. 2006)

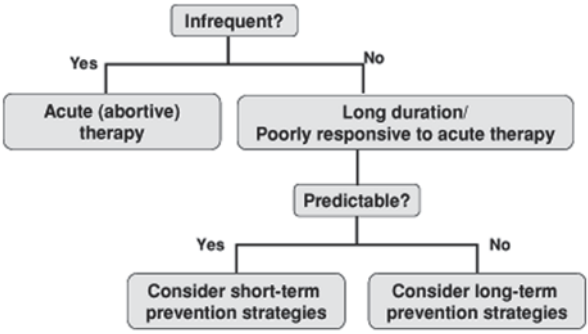


Table 21.8 Prevention of menstrual migraine

- Increase some preventative medications 5 days before and during the menses (limited evidence)
- Add magnesium 500 mg daily or at ovulation and maintain through menses

If migraine is frequent, prolonged, or poorly responsive to therapy, consideration should be given to prophylactic treatment. Use of menstrual migraine mini-prophylaxis can be used for PMM or if headache is predictable (Table 21.7).

Abortive Treatment of Menstrual Migraine

As noted above, triptans are the treatment of choice in patients without vascular disease. NSAIDs may be used alone or in combination with triptans.

Prevention of Menstrual Migraine

Some clinicians increase the dose of certain preventive medications, such as valproic acid or tricyclic antidepressants (TCAs) 5 days before and during the menstrual cycle, although evidence for this being effective is limited and it is not possible with some preventive medications, such as topiramate or beta-blockers. Adding magnesium 500 mg starting around ovulation or day 15 after start of menstrual flow, and maintaining it through menses, or taking it daily may prevent or decrease the severity of migraine attacks (Table 21.8).

Mini-Prophylaxis of Menstrual Migraine

Short-term prevention with either NSAIDs bid (twice daily) or triptans may be useful. Therapy with triptans may be limited by prescription benefits. Mini-prophylaxis with triptans may not contribute to rebound, although generally the use of triptans should be limited to 10 days or less during the month.

NSAID Mini-Prophylaxis

Naproxen sodium 550 mg twice a day beginning 3 days prior to and continuing throughout the menses can be effective.

Triptan Mini-Prophylaxis

Use of triptans in mini-prevention of menstrual migraine is not a Food and Drug Administration (FDA)-approved indication, but multiple randomized controlled trials on triptans used in this way have showed efficacy.

Frovatriptan 2.5 mg bid (double dose 1st day) beginning 2 days before the anticipated onset of MRM, and continued for 6 days, has been shown in two randomized controlled studies to be effective. In addition, no significant adverse events occurred in the 1-year safety trial of this regimen.

Naratriptan, available in generic tablets in the US and most of the world, 1 mg or 2.5 mg bid, beginning 2 days before the expected onset of menstrual headache and continued for 5 days is effective, especially using the lower dose. Naratriptan 2.5 mg tablets can be broken in half, allowing for a ½-tablet bid regimen.

Zolmitriptan, also available generically, 2.5 mg bid, beginning 2 days before expected onset of menses, and continued for 7 days was effective in one randomized controlled trial. Sumatriptan, 25 mg TID beginning 2 days before the expected onset of menstrual headache and continued for 5 days was effective in one open label trial.

Given that four triptans have shown effectiveness in this type of regimen, it is likely that triptan mini-prevention is a triptan class effect.

Continuous Hormone Contraception for Menstrual Migraine

The use of continuous oral contraception will not only prevent the menstrual cycle but may also prevent the migraine or make it easier to treat. Any fixed dose oral contraceptive can be given continuously.

Randomized controlled trials and safety studies on the continuous hormonal approach for menstrual migraine are underway at the time of this writing. For women not on oral contraception, using low-dose estrogen patch for the menstrual cycle to try and prevent the headache will only delay the headache by 5 days, and the delayed headache is more intense, severe, and difficult to treat (Table 21.9).

Migraine and Oral Contraception

The ICHD-3 includes the diagnosis of headache attributed to exogenous hormone, that is, hormone replacement therapy or oral contraception. Because headache can

Table 21.9 Menstrual migraine mini-prophylaxis

- Naproxen sodium 550 mg bid: 3 days before onset of flow or headache and continued throughout menses
- Frovatriptan 2.5 mg: (double dose 1st day) beginning 2 days before the onset of MRM, continued for 6 days
- Naratriptan: 1 mg or 2.5 mg bid, beginning 2 days before expected MRM and continued for 5 days; 1.25 mg bid can be used
- Zolmitriptan: 2.5 mg bid beginning 2 days before expected onset of menses continued for 7 days
- Sumatriptan: 25 mg three times a day (tid) beginning 2 days before the expected MRM and continued for 5 days

Table 21.10 Headache attributed to exogenous hormone, ICHD-3 criteria

1. Regular intake of the exogenous hormone
2. Headache begins with the start of hormone treatment
3. ≥1 of
   a. Headache worsens after increased hormone dose
   b. Headache improves with hormone dose reduction
   c. Headache stops when hormone stops

Table 21.11 Estrogen-withdrawal headache, ICHD-3 criteria

1. Estrogen is taken daily for ≥3 weeks
2. Headache develops in ≤5 days after stopping the estrogen
3. Headache remits in ≤3 days

occur when the administered hormone is stopped, there are also criteria for estrogen-withdrawal headache.

Headache attributed to exogenous hormones must occur with the start of hormone treatment, and correlate with its administration or discontinuation (see Table 21.10). According to the ICHD-3, estrogen-withdrawal headache only occurs after ≥3 weeks of continuous exogenous hormone administration, begins in ≥5 days after stopping it, and then resolves in ≤3 days (see Table 21.11).

There are three types of oral contraception: fixed dose, triphasic, and progesterone only.

The use of triphasic oral contraception may increase migraine due to repeated changes in hormone dosages. In general, triphasic contraceptive pills should be avoided. Use the lowest-dose estrogen pill possible (15 μg or less). There are fewer side effects and the incidence of migraine is lower than with the higher estrogen pills.

Oral progesterone preparations have many side effects including bleeding and weight gain. Progesterone is not associated with menstrual migraine, so for women who cannot use oral estrogens due to headache, these can be an option.

The newer intrauterine devices (IUDs) containing low-dose progesterone may not cause problems. IUDs are difficult to use in nulliparous women due to insertion difficulties, and in women with significant menstrual cramps since IUDs can increase cramping. The NUVARING, a once monthly estrogen- and progesterone-releasing device inserted by the patient vaginally, releases low-dose third-generation estrogen

Table 21.12 Pearls on migraine and hormonal contraception

- Do not use triphasic estrogen preparations
- Use low-dose estrogen (< 15 μg) if possible
- Consider progesterone-only preparations
- Consider other forms of contraception if migraine worsens
- Do not use oral contraceptives in smokers with migraine with aura, as smoking dramatically increases the risk of stroke

Table 21.13 Odds ratios for stroke in women with migraine (approximate)

- Women odds ratio for stroke with migraine without aura: 1
- Women, odds ratio for stroke with migraine with aura non-smoking, not on contraceptive: 1.76-2
- Women, odds ratio for stroke with migraine and oral contraception: 6
- Women odds ratio for stroke with migraine, oral contraception, and smoking: 9

called desogestrel and a progestin. Unfortunately, some research suggests this newer estrogen is associated with an increased risk of blood clots, proving its systemic absorption is significant (Table 21.12).

A woman may have her first migraine when using oral contraception. Many clinicians feel that the "neurological rule of thirds" can be applied to women, migraine, and oral contraception. In one-third of women, there will be no effect of oral contraception on their migraine, one-third of women will get worse, and one-third will improve.

Several menstrually related symptoms presenting after initiation of oral contraception may require reevaluation and/or stopping the pill: a new persistent headache, increased frequency or intensity, new-onset migraine with aura, and unusual or prolonged aura. Some women even develop status aura with oral contraception, which requires immediate discontinuation of oral contraception.

Stroke is an uncommon problem in women under the age of 45 (5–10 per 100,000 women-years), and the use of oral contraception increases a women's risk of stroke. In women under the age of 45, the risk of stroke in migraineurs (odds ratio) is consistently seen as elevated only in those who have aura. In individuals with aura taking oral contraception, the risk jumps to around 6, and in those smoker who have migraine with aura, the risk elevates to about 9 fold. Therefore, it is important to counsel women migraineurs about the small but increased risks of oral contraception and stroke.

In female migraineurs with aura who are smokers, oral contraception should be considered contraindicated. In female migraineurs with typical aura who are nonsmokers, controversy persists, and at the least a discussion on the increased stroke risk accruing with aura and oral contraceptives is in order (Tables 21.13 and 21.14).

Finally, there remains controversy or at least differences of opinion on safety and clinical recommendations for the use of oral contraception in migraine patients. Different organizations have slightly different takes on these issues, including the International Headache Society (IHS), the American College of Obstetrics and Gynecology (ACOG), and the World Health Organization (WHO). Their recommendations are summarized in Table 21.15.

Table 21.14 When to stop oral contraception in migraineurs

Stop oral contraceptives if the following occurs
• Migraine frequency/severity increases
• New-onset migraine with aura
• Unusual or prolonged aura

Table 21.15 IHS/ACOG/WHO task force recommendations for use of combined estrogen progesterone oral contraceptive pill (COCP) in women with headache and migraine. (Adapted from: Edlow and Bartz. Rev Obstet Gynecol. 2010; 3: 55–65)

	IHS	ACOG	WHO
Headache	No contraindication	No contraindication	No contraindication
Migraine wo aura			
Age < 35	Individualized assessment of risk	No contraindication	No contraindication
Age ≥ 35	Individualized assessment of risk, # risk factors[a]	Risk > benefit	Risk > benefit
Smoker	Should quit before starting COCP	Risk > benefit	Risk > benefit
Additional risk factors	Individualized assessment of risk, # risk factorsa Treat risk factors if possible[b]	Risk > benefit	Risk > benefit
Migraine w aura			
Age < 35	Individualized assessment of risk, risk factors[a]	Acceptable risk	Acceptable risk
Age ≥ 35	Individualized assessment of risk, # risk factors[a]	Unacceptable risk	Unacceptable risk
Smoker	Should quit before starting COCP	Unacceptable risk	Unacceptable risk
Additional risk factors	Individualized assessment of risk, # risk factors[a] Treat risk factors if possible[b]	Unacceptable risk	Unacceptable risk

[a] Additional risk factors: ischemic heart disease or heart disease with concern for emboli (atrial fibrillation), DM, FHx of arterial or heart disease at young age < 45, uncontrolled hypertension, obesity, hyperlipidemia, systemic disease associated with stroke (sickle cell, connective tissue disease)

[b] Consider nonestrogen methods in women with ↑risk of ischemic stroke especially those with multiple risk factors

IHS International Headache Society, *ACOG* American College of Obstestrics and Gynecology, *WHO* World Health Organization

Pregnancy and Migraine

There is no evidence of altered fertility rates, toxemia, miscarriage, congenital malformations, or stillbirths in migraineurs versus nonmigraineurs.

Most migraineurs improve during pregnancy, especially in the second and third trimester. However, 4–8 % of women worsen during pregnancy. Ten percent of migraine in women begins during pregnancy. Prepregnancy headache rate returns almost immediately following birth, although some women enjoy reduced migraine during lactation.

Table 21.16 Pearls on migraine and pregnancy

- 50% of pregnancies are unplanned, so use caution when prescribing medication to women of childbearing age
- Always discuss pregnancy as part of initial migraine education
- Most women show improvement in migraine during the second and third trimester of pregnancy
- Migraine generally reverts to the prepregnancy frequency following delivery

Table 21.17 FDA pregnancy categories for medications

A:	Controlled human studies show no risk
B:	There are no adequate and well-controlled studies in pregnant women, but animal reproductive studies *have not shown* a risk to the fetus
C:	There are no adequate and well-controlled studies in humans, but animal reproduction studies *have* shown an adverse effect on the fetus. Potential benefits may warrant the use of the drug in pregnant women despite potential risks
D:	Positive evidence of risk to humans from human studies or post-marketing data
X:	Contraindicated

Table 21.18 Triptans and ergots in pregnancy

- Triptans are category C in pregnancy
- Ergots are category X in pregnancy

Table 21.19 Emergency treatment of pregnancy migraine

- 1 L D5 1/2 normal saline over 1 hour
- Ondansetron 8 mg IV over 20 min OR
- Metoclopramide 10 mg IV over 20 min
- Diphenhydramine 25–50 mg IV

The WHO international survey found that 50% of pregnancies are unplanned, so inadvertent fetal exposure to medications is likely. In one registry, 86% of 14,778 pregnant women took a prescription drug. On average, 2.9 prescription medications were used by women who became pregnant.

It is therefore important to counsel women about pregnancy and prepare for pregnancy by discontinuing unnecessary medications. Women should not panic if they have inadvertently taken medication while pregnant, but should inform their doctors and rapidly stop medications or switch to FDA category B medicines (no evidence of risk in humans) if possible (see Tables 21.16, 21.17, 21.18, 21.19 and 21.20).

Magnesium sulfate received a change in FDA pregnancy safety recommendations in May 2013. It is now rated category D in pregnancy based on studies showing low calcium levels and bone problems in developing fetuses, including thin bones and osteopenia. Magnesium oxide was not mentioned in this safety warning, but since they would likely have similar effects, it can no longer be unequivocally recommended in pregnancy. (see Chapter 11). Vitamin B-2 is only pregnancy Category B if given in doses of 1.6 mg or less, and this would be much less than the usual migraine preventive doses of 200–400 mg. Coenzyme Q10, another supplement used for migraine prevention, does not have sufficient safety data for use in

Table 21.20 FDA pregnancy category for acute migraine medications, including nausea prevention

Pregnancy category	Medication
B	Acetaminophen
	Caffeine
	Metoclopramide
	Ondansetron
	Diphenhydramine
	Cyproheptadine
C	Aspirin not rated, not recommended beyond first trimester because of risk of cerebral hemorrhage
	Codeine and other narcotics
	prednisone/methylprednisolone
	Methocarbamol
	Promethazine
	Prochlorperazine
	Trimethobenzamide
	Quetiapine
	Indomethacin
	Triptans
	Hydroxyzine po, IM
	Butalbital
	Ibuprofen, naproxen, other NSAIDs first and second trimester
D	Aspirin (second and third trimester)
	Butorphanol (third trimester)
	Ibuprofen and other NSAIDs (third trimester)
	po and IV valproic acid
	Benzodiazepines
	Isometheptene
X	Ergots

pregnancy. Other nonmedication options include biofeedback and other pain and stress management techniques. Yoga may also be of benefit in some women.

Acupuncture has not been proven to be useful for migraine prevention in sham-controlled studies thus far. Caution should be used with acupuncture during pregnancy since in the hands of an unskilled practitioner labor can be induced.

Acute Migraine Medications in Pregnancy

Triptans are rated Category C in pregnancy. Although large pregnancy registries have been kept (GlaxoSmithKline has the largest) without demonstration of increased birth defects beyond baseline, there are still little data about ongoing use in pregnancy. If a woman gets pregnant and has used a triptan, she should not panic, but should stop taking the medication.

NSAIDs such as naproxen sodium are FDA category C now after it was discovered that animal studies showed decreased fetal body weight, increased fetal demise, and an increase in fetal anomalies involving heart, bone, and lung development. Studies in humans have been contradictory, but for now NSAIDs remain pregnancy Category C in the first two trimesters and Category D in the third trimes-

Table 21.21 Special cautions for pregnancy migraine

- Some medications may be FDA category B during one trimester and C or D during the other trimesters or breast feeding
- Examples are
  - NSAIDs, category C in first/second trimester; contraindicated third trimester
  - Cyproheptadine, category B in pregnancy; contraindicated in breast feeding
- Valproic acid should not be used in women during the childbearing years

ter since there is a chance of inducing premature closure of the ductus arteriosis. Indomethacin is contraindicated for this reason.

In general, acetaminophen, diphenhydramine, cyproheptadine, and metoclopramide are considered safe in pregnancy. Opioids are pregnancy category C in pregnancy. Additionally, there is evidence that as few as 8 days of narcotic analgesics per month can induce rebound and daily headache, which is a clinical nightmare in pregnancy.

Steroids should not routinely be used to break intractable migraine in a pregnant woman as these are pregnancy category C. Intravenous magnesium sulfate is also now pregnancy category D because of fetal bone thinning and fractures resulting from use beyond 5 days. Even though the studies were done with prolonged use, the entire drug remains now category D, probably because it cannot be defined exactly when these skeletal problems will develop.

Emergency Treatment of Pregnancy Migraine

Aggressive treatment of severe migraine or status migrainosus is imperative, since vomiting and dehydration can put both the mother and fetus at risk. In general, start with 1 L of D5 ½ normal saline and rehydrate the patient. Often, rehydration alone can help the vomiting pregnant woman. Ondansetron (category B) 8 mg IV may be given for nausea. Metoclopramide is also category B and does help to treat the migraine itself (Tables 21.21 and 21.22).

Lactation and Migraine

The American Academy of Pediatrics 2012 position statement on breastfeeding is aligned with the WHO and reaffirms its recommendation of “exclusive breast feeding for about 6 months.” This policy cites the numerous health benefits to both the mother and infant.

Approximately half of women with migraine have a recurrence within 1 month of giving birth. This may be delayed by nursing. Most medications are excreted to some degree into breast milk, so some caution should be used when prescribing preventive medications. In general, those medications used during pregnancy may be used during lactation. An exception to that is diphenhydramine which is a preg-

Table 21.22 FDA pregnancy categories for preventive medications

Pregnancy category	Medication
B	Cyproheptadine
C	Beta blockers: propranolol, atenolol, nadolol, timolol
	Anticonvulsants: gabapentin, lamotrigine, zonisamide
	Bupropion
	SSRIs: fluoxetine, sertraline
	Some SSRIs (citalopram, escitalopram)
	Some tricyclics (doxepin, protriptyline, amitriptyline)
	SNRIs: venlafaxine, desvenlafaxine, duloxetine, milnacipran
	Tizanidine
	Baclofen
	OnabotulinumtoxinA
D	Some tricyclics (nortriptyline, imipramine, desipramine)
	Magnesium sulfate
	Paroxetine
	Lithium
	Anticonvulsants: divalproex sodium, topiramate

Table 21.23 Clinical pearls on treatment of headaches during nursing

- DO NOT use diphenhydramine or cyproheptadine in nursing mothers
- Sumatriptan is probably safe while nursing

nancy schedule B, but is contraindicated in nursing infants. A second exception is cyproheptadine, category B in pregnancy and contraindicated in lactation.

The prescribing information still recommends "pump and dump" for triptans during nursing. However, the American Academy of Pediatrics position is that this is no longer necessary for sumatriptan during nursing.

A comprehensive manual *Medications and Mother's Milk* written by Thomas Hale, PhD, is available online at http://www.iBreastfeeding.com and in paperback. The LactMed database is peer reviewed and referenced and is free to download at http://toxnet.nlm.nih.gov (Table 21.23).

Perimenopause, Menopause, and Migraine

Perimenopause is described as the decade preceding menopause when hormonal fluctuations may begin. Menopause is defined as the absence of menstruation for 1 year.

The average age of menopause is approximately 53, and an increase in migraine due to the fluctuating hormones of perimenopause may present a challenge to both the patient and physician. Following a natural menopause, approximately 60–70% of women have an improvement in their migraine. In contrast, 40–70% of women who undergo a surgical menopause causing an abrupt cessation of female hormones may actually experience a worsening of their migraine.

Table 21.24 Menopause and migraine, the prognosis

• 60–70 % of women improve following natural menopause
• 40–70 % of women worsen with a surgical menopause

Table 21.25 Hormone replacement therapy and migraine

• Transdermal preparations may be preferable to oral HRT due to more complete and less variable absorption

Hormone replacement therapy (HRT) has a variable effect on migraine. The Women's Health Study, a population-based study of 17,107 postmenopausal women, reported that those using HRT were 1.42 times more likely to report migraine than nonusers. Other studies have shown a variable response, with approximately 50 % of women demonstrating no change and approximately 25 % who worsen and 25 % who improve with HRT.

If HRT is necessary, using a transdermal formulation of hormones may be preferable to oral medications, because there is more complete and less variable absorption. Migraine may be less frequent and easier to manage (Tables 21.24 and 21.25).

Conclusions: Key Points on Women and Migraine

- Migraine is more common in women due to fluctuating hormone levels
- MRM is longer in duration and may be more difficult to treat
- Treatment during pregnancy can pose risks to the fetus
- Many preventive medications (especially anticonvulsants) require close monitoring in pregnancy because of increased clearance through the liver
- Oral contraceptives should not be used in smoking women with migraine with aura
- Discuss risk of strokes with nonsmoking women with migraine with aura seeking or currently taking oral contraceptives
- Perimenopause results in increased migraine
- Natural menopause may improve migraine, whereas surgical menopause may worsen migraine
- Use triptans as abortive treatment when possible
- Mini-prophylaxis with NSAIDs may prevent migraine and menstrual cramps

Suggested Reading

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Chapter 22
Diagnosis and Treatment of Dizziness and Headache

Neil Cherian

Introduction

Dizziness is a complex symptom with a myriad of etiologies. This chapter discusses three main areas in which dizziness and headache overlap, including vestibular migraine (VM), migraine with orthostatic intolerance (OI), and cervicogenic headache with cervically mediated dizziness. Other phenomena attributable to the overlap of dizziness and headache are also addressed.

First and foremost, dizziness is a symptom and not a disease unto itself. It is similar to pain in that it is a reflection of dysfunction. Dizziness is commonly accompanied by other symptoms, including nausea, vomiting, and motion sensitivity. The severity of the dizziness, presence of auditory symptoms, associated neurologic symptoms (weakness, numbness, tingling), and rate of compensation help to evaluate whether the etiology is peripheral or central in nature.

Common peripheral vestibular etiologies of dizziness include labyrinthitis (also referred to as vestibular neuritis or vestibular neuronitis), benign paroxysmal positional vertigo (BPPV), and Meniere's disease. Common central vestibular etiologies include cerebrovascular, neurocardiac, metabolic, medication-induced, and migraine-related etiologies. A cerebrovascular etiology often tops the differential for many clinicians even though further investigation does not always support this. Evaluation of dizziness may include imaging and special testing. These are listed in Table 22.1.

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Table 22.1 Clinical pearls: evaluations for testing dizziness

- Head imaging
- Vestibular testing (Dix–Hallpike, caloric and rotation chair testing, videonystagmography)
- Audiometry
- Vestibular evoked myogenic potential testing (VEMP)

Diagnosis of Dizziness

Dizziness is a complex symptom. As there are so many clinical entities, and headache disorders are also quite numerous and complex, when discussing dizziness it may be helpful to evaluate associated findings, aggravating and alleviating factors, and temporal evolution.

Associated Findings of Dizziness

Duration of Dizziness

Duration of dizziness can be a helpful clue in diagnosis. BPPV tends to have a short duration of seconds to minutes. Meniere's lasts a minimum of 20 minutes to many hours, and vertigo that lasts many hours to days suggests VM (see Table 22.2).

Nausea and Dizziness

Nausea is intrinsic to the diagnosis of migraine and is the most sensitive and specific criterion for migraine diagnosis (see Chapter 1). Obviously, nausea is not unique to migraine and may accompany many other phenomena, including gastrointestinal problems, anxiety, and sensitivity to motion.

There is, however, much evidence to suggest that motion sickness may also have its roots in migraine. Furman and Marcus demonstrated that VM responded to rizatriptan. Therefore, factors that aggravate migraine may also increase sensitivity to motion and associated dizziness in susceptible individuals.

Aura and Dizziness

International Classification of Headache Disorders, third edition, beta (ICHD-3) migraine with brainstem aura (previously referred to as basilar-type migraine in ICHD-2) may include vertigo as part of the aura. In this situation, it is important to

Table 22.2 Clinical pearls on duration of dizziness

- *Benign paroxysmal positional vertigo (BPPV)*
  - Seconds to minutes, with recurrence over days to weeks to months
- *Meniere's disease*
  - At least 20 min, up to days at a time
- *Vestibular migraine (VM)*
  - Seconds to hours to days

understand the relationship of the dizziness to the migraine episode. The diagnosis of migraine with brainstem aura is discussed in Chapter 1. When contemplating this diagnosis, appropriate measures should be taken to exclude other sources of vertigo, including peripheral vestibular disorders.

Dizziness in Childhood

ICHD-3 benign paroxysmal vertigo (previously referred to as benign paroxysmal vertigo of childhood in ICHD-2), different from BPPV, is a disorder that occurs generally in otherwise healthy children. It is characterized by recurrent brief attacks of vertigo coming on without warning and resolving spontaneously. It is thought to be a precursor of migraine and is covered in Chapter 9.

Vestibular Migraine

The concept of VM has been around for many years but it has been discussed more frequently in recent years. There are a variety of similar terms used for VM including migraine-associated dizziness, migrainous vertigo, and migraine-associated vertigo. This disorder can occur with or separate from typical migraine episodes.

The ICHD-3 marks the first time that the International Headache Society has acknowledged the existence of this disease entity. Essentially, the definition of VM is moderate-to-severe vestibular symptoms from 5 min to <72 h with a link to migraine. The link to migraine requires a previous history of migraine and symptoms of migraine without aura or of typical visual aura. These diagnostic criteria are included in the appendix (A1.6.5) of the ICHD-3 (see Table 22.3).

In 2001, Neuhauser set forth criteria for "migrainous vertigo" which predated the ICHD-3 criteria for VM. Neuhaser's requirements also included an established history of migraine headaches. Furman developed subsequent criteria discussing definite versus probable migrainous vertigo, with inclusion of vertiginous symptoms triggered by typical migraine precipitants.

Table 22.3 VM, ICHD-3 appendix criteria

A. ≥ 5 episodes in a patient with previous ICHD-3 migraine
B. Moderate-to-severe vestibular symptoms of 5 min to < 72 h duration
C. ≥ 50 % of attacks have ≥ one of the following three features,
1. Headache with at least two of the following four characteristics
a) One-sided
b) Throbbing
c) Moderate or severe intensity
d) Worse with routine physical activity
2. Photophobia and phonophobia
3. Typical visual aura
D. Not better accounted for by another ICHD-3 diagnosis or by another vestibular disorder

Pitfalls in the Diagnosis of VM

The VM criteria are sufficiently limited as to make it difficult to definitely pinpoint a syndrome. It is possible to have a person with a history of migraine, with vertigo and phonophobia but no headache, and meet criteria for VM.

The issue becomes whether one can fully rule out other central or peripheral vestibular disorders causing vertiginous symptoms that are not related to migraine. Vertigo and phonophobia together can coexist in an otogenic (inner ear) disorder even with normal audiometric and vestibular testing, particularly in early cases of Meniere's disease. Furthermore, the lifetime history of migraine does not preclude a non-migraine etiology of dizziness.

To address these diagnostic problems, some authors use the terms migrainous vertigo and migraine-associated vertigo differently, in which the former refers to episodic vertigo spells that occur concurrently with other migraine features, and the latter refers to episodic vertigo in an individual with a history of migraine, not requiring that the vertigo and headache occur together. The complexities of migraine and vestibular symptoms have made it challenging to develop a validated descriptive classification system which is not based on a physiologic parameter.

Treatment of VM

Treatments that may be helpful to treat VM include trigger avoidance, conventional acute and preventive migraine pharmacotherapy, acetazolamide, and vestibular physical therapy. These are listed in Table 22.4.

Table 22.4 Clinical pearls on treatment of VM

- Avoidance of triggers
- Typical migraine treatments should be considered, e.g.
  - Preventive migraine treatment such as topiramate (has been demonstrated in randomized, controlled trials)
  - Acute migraine treatment such as triptans
- Acetazolamide (commonly used in patients with episodic ataxia type 2)
- Vestibular rehabilitation physical therapy

Table 22.5 The orthostatic intolerance (OI) disorders

OI disorders	Diagnosis characteristics
Vasovagal response (neurocardiogenic)	Decreased BP and decreased HR/bradycardia
Cardioinhibitory syncope	Inhibition of sinus and AV node activity Vasodilatory response
Postural Orthostatic Tachycardia Syndrome (POTS)	Increased heart rate 1. Increased heart rate 30 bpm in first 10 min of tilting 2. Heart rate 120 bpm in first 10 min of tilting 3. Increased heart rate of 30 bpm when isoprenaline is infused at a rate of 1 mg/ml

AV atrioventricular; *BP* blood pressure; *HR* heart rate

Migraine, Dizziness, and Orthostatic Intolerance

OI covers a spectrum of symptoms including pre-syncope and syncope, weakness and fatigue, tachycardia or palpitations, nausea, and difficulty concentrating. Symptoms can be aggravated by prolonged standing, physical exertion, environmental warming, postprandial states, and menses. Diagnosis is based on history and results of heads-up tilt table testing.

OI is a subset of dysautonomia. Common OI disorders include vasovagal response, cardioinhibitory syncope, and postural orthostatic tachycardia syndrome (POTS) (see Table 22.5).

A vasovagal response (VVR) occurs when the blood pressure and heart rate decrease to a threshold, precipitating syncope. In general, the VVR slows the heart rate, decreases the blood pressure, contracts the pupils, and increases gastrointestinal activity. Factors provoking VVR include dehydration, sleep deprivation, stress and anxiety, and even pain. These triggers are usually added to an innate tendency towards VVR in susceptible individuals and in certain pathologic states.

Stimulation of the vagus causes slowing of the heart rate, which if sufficient, can cause fainting or even cardiac arrest. Usually when this happens, the ventricles start to beat on their own accord despite continued vagal stimulation.

Hypotension is generally associated with increased nervous system activation and reflex tachycardia, although one type of hypovolemic hypotension, occurring after hemorrhage or certain drugs, induces a decrease in heart rate. Both types of

Table 22.6 Diagnostic steps for establishing orthostatic intolerance, the basics

• History
• Head-up tilt table testing (70°): diagnostic testing to identify patterns of blood pressure and pulse fluctuation in relation to upright posture
• Quantitative Sudomotor Axon Reflex Testing (QSART): a measure of the autonomic nerves that control sweating
• Blood volume studies, radionuclide hemodynamic studies: method to evaluate blood volume, velocity of systemic blood movement in the areas of blood pooling
• Blood volume studies, radionuclide hemodynamic studies: these are methods to evaluate blood volume and velocity of systemic blood movement in the areas of blood pooling

VVR result from abnormal excitation of the vagus nerve, and hence the term used to describe the resulting loss of consciousness that may result is vasovagal syncope.

Cardioinhibitory syncope is the response of the inhibition of sinus and atrioventricular node activity. It is associated with a vasodilatory response (arterial dilation), decreased blood pressure, nausea, salivation, and diaphoresis. The symptoms are common after an increase of parasympathetic output. This increased output can occur after direct stimulation of the vagal nerve or as a response to cessation of sympathetic activity.

POTS is the most common OI diagnosis for adults seeking referral. This syndrome not only causes daily symptoms, but it can also disrupt the patient's ability to work or do daily tasks. POTS is diagnosed when symptoms of OI are present, and the heart rate increases above 120 beats per minute within 10 minutes of head-up tilt, or an increase by at least 30 beats per minute when transitioning from a supine position to an upright position.

Most commonly, POTS affects female patients aged 12–50 years and usually presents after a virus or inflammatory condition. The frequency of children and adolescents experiencing POTS is on the rise, but the pathophysiology of this disorder remains incompletely understood.

POTS is thought to be associated with abnormal venous pooling and fluid collection in the lower extremities. Symptoms that often accompany POTS are tachycardia, hypotension, dizziness, fatigue, palpitations, and nausea.

Diagnosis of OI requires a good history as well as a tilt table test, and, often additional workup (listed in Table 22.6).

Episodes of syncope and near-syncope are not uncommon in individuals with migraine, occurring more commonly in migraineurs than in the general population. Migrainous syncope and near-syncope can be ictal or interictal.

Migraineurs often have lower blood pressure than non-migraine individuals. The basis for this is not fully understood, however problems in the neurocardiac axis, as manifested by these higher rates of syncope and near-syncope, may reflect certain genetic subforms of migraine.

OI can occur without migraine, but it is common to have both disorders. It is difficult to discern whether they are comorbid and separate or whether one disorder provokes the other.

Table 22.7 Clinical pearls on treatments for orthostatic intolerance

- Make changes to your lifestyle: eat small frequent meals, sit at the side of the bed before arising
- Increase dietary sodium intake
- Use compression stockings (Jobst)
- Medications such as beta-blockers, fludrocortisone, midodrine, and pyridostigmine
- Perform lower-extremity/core strengthening exercise

A case series by Stillman in 2013 reviewed patients with headache (all meeting the ICHD criteria for migraine) and symptoms of pre-syncope or frank syncope, and revealed significant abnormalities frequently occurred on head-up tilt table testing. It is not uncommon to see a woman with an acute migraine around her period with blood loss and faint feeling without a true disorder of OI.

Treatment of Orthostatic Intolerance

Treatments for OI can be pharmacologic or non-pharmacologic. One theory for the genesis of migrainous OI is an abnormal reflex tachycardia occurring after the postural hypotension.

It is counterintuitive to use beta-blockers in a patient with hypotension and syncope, but they work by blocking reflex tachycardia, and they help prevent migraine. Other commonly used medications for preventing the hypotension include midodrine and fludrocortisone.

Some clinical pearls on the treatment of OI are listed in Table 22.7.

Cervicogenic Headache and Cervically Mediated Dizziness

Cervicogenic headache is classified in the ICHD-3 under "Headache or facial pain attributed to disorder of the…neck," Section 11 and was discussed in Chapters 7 and 17. Because of its relations to dizziness, it is reviewed again here.

Cervicogenic headache is generally a unilateral headache syndrome referred from a source in the neck and perceived in the head and/or face. There is no one etiology of cervicogenic headache. A number of cervical spine disorders are possible causes, although cervical abnormalities alone do not establish the cervicogenic diagnosis.

For diagnosis of cervicogenic headache, it is necessary to identify a lesion in the cervical spine or neck soft tissues known to be a valid cause of headache. Establishing a cervical etiology may include the abolition of the headache following diagnostic blockade of a cervical structure or its nerve supply, or the demonstration of clinical signs that establish a source in the neck. The pain must also resolve within

Table 22.8 Cervicogenic headache, ICHD-3 criteria

A. Clinical, laboratory, or imaging evidence for a lesion of the cervical spine or cervical neck tissues known to cause headache
B. Proof of causation with ≥2 of:
a. Headache developed with the onset of the neck lesion
b. Headache improved with treatment of the neck lesion
c. Headache is make worse by provocative neck maneuvers and neck range of motion is reduced
d. Headache is abolished by diagnostic cervical blocks

Table 22.9 Clinical pearls in diagnosis of cervicogenic headache

• Pain should always originate from the neck and be triggered by neck movements, even as it radiates forward
• Although it may start bilaterally, the pain should end up primarily unilateral
• As noted in the ICHD-3 criteria, the headache should *not* meet ICHD criteria for a primary headache disorder such as migraine

3 months after successful treatment of the causative disorder or lesion. The ICHD-3 criteria for diagnosing cervicogenic headache are listed in Table 22.8.

As discussed in Chapter 6, the late Dr. John Edmeads noted several features or clinical pearls that may aid in the diagnosis of cervicogenic headache. These are summarized in Table 22.9.

Cervicogenic Dizziness

A controversial disorder referred to as "cervicogenic dizziness" may overlap with cervicogenic headache. Symptoms include a vague non-vertiginous dizziness, often worse with activity, and may or may not be associated with neck pain or with obvious vestibular pathology.

The term cervicogenic dizziness is actually a misnomer in that the neck is not the genesis of the vestibular symptoms, although it plays a vital role. A more descriptive name for this disorder would be "cervically mediated dizziness." This disorder may also occur without headache. Formal vestibular testing may be normal or nonspecifically abnormal.

Treatment of Cervicogenic Headache

Treatment for cervicogenic headache includes occipital nerve blocks, cervical botulinum toxin injections, neck physiotherapy, and oral neuropathic pain medications such as gabapentin. If a cervical lesion is proven by a placebo-controlled block or a differential block, neurosurgical procedures or pain anesthesia ablations can be curative.

Table 22.10 Factors linking headache and dizziness

- Head trauma/whiplash
- Chiari malformation type 1
- High altitude
- Carbon monoxide poisoning
- Anxiety/ panic disorder
- Hypoglycemia
- Medications
- Hypotension
- Chronic post-bacterial meningitis

Treatment of Cervically Mediated Dizziness

Cervically mediated dizziness can be successfully treated with a combination of neck physiotherapy, occipital nerve blocks, and oral antineuritic pain medications such as gabapentin or amitriptyline. Thus, nonsurgical treatments for both cervicogenic headache and dizziness overlap.

Further understanding of cervically mediated dizziness comes from treating dizzy patients without headache and cervicogenic headache patients without dizziness. The disorder is suggested by not meeting ICHD criteria for either cervicogenic headache or migraine. A spectrum of improvement was observed in one clinical study with greater occipital nerve injections for patients with dizziness and headache, including relief of symptoms of ear discomfort, tinnitus, and neck pain, along with improvements in the headache and dizziness.

The upper cervical spine may play an important role in various headache and vestibular disorders, and an underlying mechanism may connect the trigeminal nucleus caudalis and trigeminocervical pathways. Due to the intricate pathophysiology of headache and dizziness separately, it is plausible to also conceptualize situations in which a vestibular syndrome (peripheral or central) can provoke a headache syndrome and vice versa.

Certain common factors can provoke both headache and dizziness, suggesting this potential anatomic relationship. These include trauma, congenital abnormalities, comorbid illnesses, infections, and medications, and they are listed in Table 22.10.

Conclusions on Diagnosis and Treatment of Dizziness and Headache

Dizziness and headache are separately quite common. There are, however, a number of scenarios where the two can be interconnected. An area of significant clinical interest at this time is VM in which the migraine generator produces the vestibular symptoms.

- VM should only be diagnosed in an individual with an established history of migraine.
- There can be an overlap between OI and migraine, with a spectrum of symptoms from palpitations and tachycardia to pre-syncope to actual syncope.
- Cervicogenic headache may overlap with vestibular symptoms.
- Treatment of cervicogenic headache with subsequent resolution of the vestibular symptoms may suggest cervically mediated dizziness.
- For any of these entities, a discrete peripheral vestibular syndrome must be appropriately excluded.
- There are also a number of systemic entities that can cause both dizziness and headache (see Table 22.10).

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Chapter 23
Nursing Issues in the Diagnosis and Treatment of Migraines

Deborah Zajac

Introduction

Our current health-care model is placing greater demands on physicians to see more patients, treat increasingly complex diseases, document efficiently, and do this all in a timely and cost-effective manner. Tapping into the knowledge, energy, level of trust, and respect that nurses have should be an essential part of comprehensive health care for all headache patients. It only seems natural to use the talents of the nursing profession to augment ongoing care of patients diagnosed with headaches.

A formal introduction to the nurse by the physician at the initial medical appointment will highlight the team approach for headache management. This provides a level of comfort to the patient when a nurse intercedes with follow-up telephone calls, visits for continuing disease education, testing procedures, medication instructions, symptom management, and functional goal setting.

The nurses can provide advice to patients who "don't want to bother the doctor." Additionally, the risk of problems with patient adherence can jeopardize medical outcomes; therefore, nurses play a key role in monitoring a patient's commitment to the care plan.

Nurses provide frequent contacts and updates to both the patient and physician on treatment progress and any changes that are necessary. This connection to the nurse can save money and time, while enhancing patient satisfaction and outcomes. It is because of the enormous benefit to physician and patient alike that the authors of this text felt it would be vital to include a practical guide to nursing participation in headache care.

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Table 23.1 Nursing roles in headache treatment

- Documentation of history
- Education
  - Disease overview
  - Medication instructions for use/side effects
  - Adherence
  - Symptom management
  - Triggers
  - Diet/exercise
  - Medical communication skills
  - Behavioral and emotional support

Nursing diagnosis

- Follow-up visits/calls
- Educational sessions/support groups
- Headache organizations/web site resources

Nurse Roles

The nurse should play five key roles in headache management. The first is documentation of the history. The second is an integrated role in patient education. The third is participation in follow-up visits and phone calls. The fourth can be leading groups. Finally, the nurse can direct patients to headache resources (Table 23.1).

Documentation of History

The use of nurses for history documentation aids physicians in many ways. History taking establishes a trusting relationship with the nurse useful for further interactions. In addition, nurses skilled in headache medicine provide insights helpful to physicians in diagnosis and management.

Training the nurse in detailed history taking is essential. This includes onset of headaches, location, duration, frequency, severity and quality, associated features, aggravating factors or triggers, and improving factors. In addition, the nurse can obtain the usual and mandatory parts of any medical history, that is, allergies, meds, past medical and surgical history, social history, habits, sleep, family history, quality of life, disability information, review of symptoms, and, perhaps most importantly, what the patient hopes to gain from the visit (Table 23.2).

Education

Without providing patient education, we cannot expect to run a successful headache clinic. The learning process begins with the first patient interaction and should continue throughout that patient's initial medical evaluation.

Table 23.2 Nursing headache history

1. Onset: age
2. Location: localized, global, changing
3. Duration: minutes, hours, days
4. Frequency: how many headache days per month, not just how many headache attacks per month
5. Severity: 0–10 scale or 0–3 scale
6. Quality of pain
7. Associated features
   a. Symptoms before, during or after the pain starts, e.g., aura or premonitory symptoms
   b. Response to routine physical activity
   c. Nausea, photophonophobia
   d. Autonomic features
   e. Other neurologic features such as numbness, weakness, vertigo, etc.
8. Aggravating or precipitating factors: triggers, exercise, sexual activity
9. Improving factors: dark, quiet, lying down, pacing, movement, ice, sleep, etc.
10. Allergies/adverse effects from previous medications
11. Current and previous medications
12. Past medical history
13. Past surgical history
14. Social history: marital/family status, education, occupation, outside interests, recent significant life changes, drug or toxin exposure
15. Habits: alcohol, caffeine, street drugs, and tobacco
16. Sleep history
17. Family history: any headaches in family members
18. Past headache history: detailed. Document types of headache described by patient, and how they are viewed as different
19. Quality of life: the impact headaches are having on life
20. Disability and impact can be charted using the Migraine Disability Assessment Scale (MIDAS) or the Headache Impact Test (HIT-6)
21. Define what the patient is hoping to obtain from this office visit

Many patients come to physicians with a long history of headaches and treatment failures. These failures lead to patient frustration, anger, confusion, feelings of being overwhelmed, hopelessness, and a bewildering variety of responses.

In order to provide successful education, care providers must meet the patients at the point at which they are at the visit, emotionally, educationally, and physically. Nurses must teach simply, clearly, and slowly, using nonmedical terminology, and provide time for patients to absorb information without feeling rushed.

Nursing education needs to be both verbal and written, and sometimes entails the need to have the patient demonstrate back to the nurse their understanding of the information they received. This helps to insure that the patient has understood and is comfortable with the information received.

Documentation of education received must be put in the patient's medical record. This helps to ensure that all providers are aware of the educational needs of the patient and facilitates further continuity during future appointments.

Nursing education needs to encourage patients to talk openly about their concerns, and this is best achieved by asking open-ended questions.

Table 23.3 Key points for nursing education of headache patients

- Meet the patients at the point at which they are at the visit, emotionally, educationally, and physically
- Teach simply, clearly, and slowly using nonmedical terminology and provide time for patients to absorb the information provided without feeling rushed
- Provide verbal and written information
- Have the patient demonstrate information received
- Take the history using open-ended questions
- Stick to key points when providing education. Most patients can only absorb so much information at one session
- Provide patients with a take-home sheet of potential questions to ask at the follow-up visit with the physician
- Help the patient set up the follow-up visit

Table 23.4 Nursing education: disease overview

- Provide patients with written information on their specific headache diagnosis
- Review the diagnosis with patients and discuss it in nontechnical language
- Give patients general information about their specific headache
- Give written information on the patient's particular type of headache

Stick to key points when providing education. Most patients can only absorb limited information at one session. If necessary, set up a follow-up nursing appointment to review plan of care compliance and understanding.

Nurses should provide patients with a take-home sheet of potential questions to ask at follow-up visits with the physician. It is crucial to encourage patients to immediately set up a follow-up visit while they are in the office (Table 23.3).

Education of Patients: Disease Overview

Nurses should provide patients with written information about their specific headache diagnosis. Reviewing the diagnosis with patients and discussing it in nontechnical language is crucial. It is important to give patients information about their specific headache type, including why certain medications may not be helpful, e.g., narcotics or caffeine. It is helpful for patients to receive written information on their particular type of headache (Table 23.4). This allows them to go back and explain to family and friends why their headaches are affecting their lives.

Table 23.5 Personal medication profile card

Personal medication profile card	
Medical record no:	
Patient's name:	
Phone:	
Doctor's name(s):	
Phone:	
Patient's current medications (drug, strength)	Directions for use
Notes:	

Education of Patients: Medication Instructions for Use/Side Effects

A very useful role is for the nurse to review the importance of knowing the names of the medications patients are taking (both trade and generic), dose, and directions for use of all prescribed medications. Provide patients with a tool to write down their medications. Encourage them to keep this list with them at all times (Table 23.5).

The following is medical education guidance: Instruct patients on why a medication is ordered and what it does for their headaches. If the patient has a clear understanding of why a certain medication is ordered, they will be more likely to comply with the recommendations for use. Educate patients on the differences between abortive and preventive medications. Continually review when and how to use medication. Insist on the use of the 0–10 pain scale or the 0–3 scale to evaluate both the headache severity and the response to medication (Table 23.6).

Instruct on the importance of early intervention for maximum acute treatment benefit. Teach patients on dose, frequency, and delivery of each of their medications, and encourage having a routine for taking their medications.

Provide marked pillboxes to encourage consistent and predictable use of medication.

Teach patients to use a medication diary/calendar to write down their response to abortive medications, along with any side effects that may occur (Table 23.7).

Instruct patients not to wait until they are completely out of their medication before calling the physician's office or going to the pharmacy for refills. Set clear written instructions and limits on office turnover time for refill requests. Limit *urgent* refill requests. Provide written guidelines before patients leave the office (Table 23.6).

Nurses should continuously monitor patients' use of rescue medication, be ready to reeducate on misuse, and alert the physician with any concerns. Encourage patients to fill/refill their medications at the same pharmacy, keeping pharmacy's and prescribing physician's name and telephone numbers on their medication cards at

Table 23.6 Nursing education, medication, the medicines—1 and prescriptions—2

- Provide patients with a medication card to write their medications down and encourage them to keep it with them at all times
- Instruct patients on why a medication is ordered and what it does for their headaches
- Educate patients on the differences between abortive and preventive medications
- Review frequently when and how to use medication
- Insist on the use of the 0–10 pain scale or the 0–3 scale to evaluate both headache severity and response to medication
- Instruct on the importance of early intervention with abortive medications for maximum benefit
- Teach patients on dose, frequency, and delivery of each of their medications and encourage a routine for taking their scheduled medications
- Provide marked pillboxes to encourage consistent use of medication
- Teach patients to use a medication diary/calendar for type, dose, and number of medications used, effectiveness, side effects, and triggers
- Review the importance of not using over-the counter medications or vitamins/herbal supplements without telling their physician
- Review all common or expected side effects of medications or treatments
- Review "when not to worry"
- Review unexpected side effects of medications or treatments
- Review "when to worry" and who to call if these side effects should occur
- Review contraindications in the use of their prescribed medications
- Instruct patients not to wait until they are completely out of their medication before calling in to the physician's office or going to the pharmacy for refills
- Set clear written instructions and limits on office turnover time for refill requests
- Limit *urgent* refill requests. Provide written guidelines before the patient leaves the office
- Monitor patients' use of rescue medication, be ready to reeducate on misuse, and alert the physician of any concerns
- Advise patients to fill/refill their medications at the same pharmacy, keeping pharmacy's and prescribing physician's telephone numbers on their medication cards at all times
- Encourage patients to know what their insurance prescription benefit coverage is before going to the physician
- Advise patients to bring the printed insurance formulary list with them to their appointments
- Remind patients to pack sufficient medication with them when traveling and to carry abortive medications at all times

all times. Encourage patients to know what their insurance prescription benefit coverage is before going to the physician; advise patients to bring the printed insurance formulary list with them to their appointments.

Remind patients to bring a sufficient supply of medication with them when traveling and to carry abortive medications with them at all times. Review the importance of not using over-the-counter medications or vitamins/herbal supplements without telling their physician.

Review all common or expected side effects of medications or treatments. Review "when not to worry." Review unexpected side effects of medications or treatments; review "when to worry," and who to call if these side effects should occur. Review contraindications to the use of their prescribed medications.

Table 23.7 Headache diary example (Weekly diary)

Day	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
Dates							
Prodrome							
Aura							
Time of pain onset							
Severity of pain							
Treatment 1 (dose)							
Symptoms (nausea, throbbing, disability)							
Treatment 2 (dose)							
Treatment 3 (dose)							
Time to pain relief							
Noted triggers (caffeine, menses, etc.)							
Type of headache (migraine, tension)							
Other comments or questions							

Education of Patients: Adherence

Roger Cady and colleagues wrote: "Patient–provider collaboration in treatment planning tends to increase the patient's investment in a positive outcome, and results in a plan that is more realistic to the patient's particular circumstance." Omitting this collaborative effort is the greatest reason why patients fail their treatment plan. To enhance adherence, it is important to thoroughly educate headache patients on their medications and to monitor their ability to stick to the plan of care. They should be able to identify why they stopped using their medications. Was it because:

1. They thought they were feeling better or worse.
2. They forget to take their medications.
3. They take their medications at the wrong times.

All of these variables can affect the outcome of the treatment plan.

Patients need to understand the purpose of each prescription and be advised about "off-label" indications for these medications. When patients pick up their prescriptions at the pharmacy, they may be educated by the pharmacist or read the drug information sheets provided, which will indicate the intended use of the prescribed medication.

Since headache medications are often used off label in the prevention and acute treatment of headaches, this leads to confusion when the medication is not identified ahead of time as useful for headache treatment. In fact, many prescribing inserts list headaches as a common side effect, leading to poor or no adherence.

In order to avoid this circumstance, it is better to explain the use of a given medication right up-front. Most people are not seeking a lengthy discussion about the prescribed medications, but providing a succinct explanation in nontechnical language relieves misperception and apprehension and improves adherence.

Creating drug information handouts for patients to take with them is a useful educational tool. Nurses can also provide a written explanation of the medication's indication, any off-label use, as well as how to manage expected side effects. Include how long it may take the medication to become effective, especially for preventive treatment.

Nurses should encourage the patient to read the pharmacy handouts, because they go into more detail about the drug's appearance, what to do with missed doses, less frequent side effects, and storage instructions. By keeping handouts short, clear, and to the point, patients will be more comfortable with using the medication.

Trust between the patient and their provider is the most important factor in treatment plan success. The nurse can support this trust by facilitating communication through education and providing easier availability to answer questions that occur after patients leave their scheduled office visit.

The expectations of the patient and the provider need to be balanced and understood upfront. The nurse can be the stabilizing force in this communication, identifying if the patient is ready to make positive changes, assuring they understand why this improvement is needed, and then reinforcing patient confidence that they can accomplish the things that are recommended in the plan of care. Success is directly related to the patient's attitude and motivation to complete the requested treatments. Nurses can provide the education and encouragement that many headache sufferers need in order to make meaningful changes in their lives (Table 23.6).

Education of Patients: Symptom Management

Nurses can develop and use a check-off list to identify the symptoms their patients experience with their particular headaches (see Table 23.9). Verbal and written instructions should be provided regarding the care, both medicinally and non-medicinally, for each of the symptoms identified. Individual physicians may have their own protocols for providing relief from any of the above symptoms, and it is important that these protocols be standardized for their practice.

Using the North American Nursing Diagnosis Association (NANDA) for nursing care plans and goals is the accepted professional standard for the assessment, intervention, and education of individual symptoms each patient may exhibit (see Table 23.10). Nurses are obligated to provide care using these methods.

Table 23.8 Representative medication sheet for sumatriptan

Sumatriptan (*IMITREX*)

Your physician has prescribed sumatriptan to relieve your migraine headache. It has been approved by the Food and Drug Administration for the abortive treatment of acute migraine attacks. The subcutaneous (under the skin) injection has also been used successfully for the treatment of cluster headache attacks as well as migraine. Sumatriptan may work in part by targeting the specific chemicals in the brain that turn on migraine and cluster headaches

Sumatriptan is approved in the USA in four forms; oral tablets in 25-, 50-, and 100-mg dosages; nasal spray in 5- and 20-mg dosages; subcutaneous injection in 4- and 6-mg dosages; and an iontophoretic electric skin patch in a 6.5-mg dose. The injection comes in two forms, with a needle and in a needle-free form. The injection is the most rapid acting form, followed by the nasal spray, then the tablets, and finally the patch. The injection and the nasal spray are most beneficial for people who experience quick onset to vomiting with their headaches, while injection, nasal spray, and patch work best with early nausea

You should not use sumatriptan if you have uncontrolled high blood pressure, a history of a heart attack, heart or vascular disease, cerebrovascular disease, peripheral vascular disease, significant liver or kidney dysfunction, or if you are pregnant. Do not use on the same day if you are taking ergotamine medications, including dihydroergotamine (DHE) or Migranal. Do not use with other triptan medications on the same day, including zolmitriptan (ZOMIG), rizatriptan (MAXALT), almotriptan (AXERT), eletriptan (RELPAX), naratriptan (AMERGE), or frovatriptan (FROVA)

Side effects:

- A feeling of pain or tightness in the chest or throat
- A general feeling of warmth or flushing
- The headache and/or nausea may worsen briefly before the headache is relieved
- A feeling of heaviness in the extremities, especially the arms
- A tingling or burning sensation in the neck, head, or face
- Local irritation at the injection site
- Nasal irritation and bad taste with the nasal spray

Tablets (IMITREX, generic):

Take 100 mg at the onset of your headache. If you have partial or no relief in 2 h, you may repeat one tablet

**Do not take more than 200 mg in a 24-h period*

Nasal spray (IMITREX, generic):

Adults are prescribed the 20-mg dose

Take one spray in either nostril at the onset of your migraine. If partial or no relief, a second dose may be repeated in 2 h

**Do not take more than 40 mg in a 24-h period*

*You may take one spray and 100 mg of tablet in the same 24-h period

Sumatriptan injection (STATDOSE IMITREX, generic, ALSUMA, SUMAVEL):

This comes in a pre-filled package of two injections containing 4 or 6 mg for the Statdose or generic needle injection systems. It also comes in a needle-free injection called Sumavel DosePro, in the 6-mg dose in a package of six

Take one injection at the onset of your migraine or cluster headache

If partial or no relief, you may repeat a second injection in 1 h

**Do not use more than 12 mg in a 24-h period*

*You may take one injection and 100 mg of tablet in the same 24-h period

Additional instructions: ***

Sumatriptan *iontophoretic patch* (*ZECUITY*)

This comes in a box of six patches, each delivering 6.5 mg sumatriptan

Place one patch at the onset of your migraine on the skin

Maximum number of patch applications per day is two

Do not apply a patch to the same exact location for 3 days

NOTE: If you are treating more than two headaches per week with sumatriptan, notify your physician

Table 23.9 Symptoms in migraine

- Nausea
- Vomiting
- Blurry vision
- Nasal congestion
- Anorexia/hunger
- Diarrhea
- Photophobia (dislike of light)
- Phonophobia (dislike of noise)
- Osmophobia (dislike of smells)
- Memory impairment
- Fatigue
- Poor sleep
- Anxiety
- Irritability
- Dizziness

Table 23.10 North American Nursing Diagnosis (NANDA). (Adapted from NANDA)

NANDA-nursing care plan development

NANDA nursing diagnosis: pain

NOC outcomes (nursing outcomes classifications)

1. Comfort level
2. Medication response
3. Pain control

NIC interventions (nursing intervention classification)

1. Pain management

Assessment

1. Assess pain characteristics, location, duration, onset, severity, quality, precipitating factors
2. Observe and monitor signs and symptoms related to pain, monitor blood pressure, heart rate, mental status, skin temperature and color
3. Assess patient's knowledge of pain triggers and pain relief alternatives including medicinal and non-medicinal methods for relief
4. Evaluate patient's response to the techniques used to reduce or eliminate pain
5. Assess cultural, environmental, or psychological variables that can contribute to pain and pain relief, including what pain means to the patient
6. Assess patient's expectations for pain relief and willingness to learn alternative ways to help with pain control
7. Respond to patient's pain complaints immediately
8. Assist in providing decreased stressors or sources of pain when possible
9. Determine the best pain relief method through reports of pain relief and observance
10. Notify physician of relief or non-relief of pain

Education

1. Provide instructions on pain relief measures, including timing of medication use and non-medicinal alternatives
2. Provide education on pain causes
3. Instruct patient on documentation of pain levels and how to report pain levels

Education of Patients: Triggers

Martin states that triggers are "defined as factors that, alone or in combination, induce headache attacks in susceptible individuals. Triggers usually precede the attack by less than 48 h." Lists of potential triggers are described in Table 23.11.

It is essential that nurses become familiar with the primary headache triggers and then provide education on avoidance and management of them (Table 23.12). Promoting cognitive and behavioral techniques helps patients to not only cope with inevitable triggers but also think about them differently. This allows patients to live with their headaches in spite of unavoidable trigger exposures (see Chapters 15 and 19 on behavioral therapies).

Education of Patients: Diet and Exercise

Nurses should emphasize to patients the importance of routine exercise (Table 23.13). Discuss the increase in brain serotonin with exercise as a "natural" form of getting medication.

Physical activity and good dietary guidelines not only help control a patient's headaches but also contribute to an overall healthier body. These suggestions should be introduced to patients as necessary for general good health.

Wellness programs in the community, along with daily routine physical activity, should be expected and encouraged. Nurses can be proactive in helping patients adjust to a healthy lifestyle.

Nurses may provide patients with information on local health clubs, printouts on physical activity, and facilitate a formal referral to a physical therapist to obtain an evaluation of fitness level and development of a home-based fitness plan. This may include ergonomic analysis of the patient's work environment and activities of daily living.

Provide patients with information on supplemental CDs or DVDs to help build up their physical activity, strength, flexibility, endurance, and confidence. This physical activity contributes to decreased stress, improved self-esteem, and provides patients with skills to manage their own health care and maintenance.

Teach patients about activity pacing. Patients who practice moderation in their daily activities are less likely to overdo or revert to sedentary practices. This is covered in greater depth in Chapter 19.

Education of Patients: Medical Communication Skills (Table 23.14)

Some clinical pearls on nursing communication for the patient are summarized in Table 23.14.

Table 23.11 Common migraine triggers

1. *Stress*: The most common triggers in inducing migraines include, but are not limited to, anxiety, worry, anger, depression, crying, poor coping abilities, weekend or vacation activities, and include letdown after these activities
2. *Foods/diet*: Alcohol, MSG, nitrites, chocolate, caffeine, etc. Educate patients that dietary triggers do not mean that a patient is allergic to that food item. This should eliminate the need for patients to seek a consultation with an allergist for expensive allergy testing, when no treatment is beneficial outside of elimination. Assure patients that not every item on a dietary list needs to be eliminated from their diet. Dietary lists are just guidelines for common triggers, but not all-inclusive. Remind patients that regular meals, not skipping meals, and maintaining hydration remain just as important as eliminating triggering potential foods from their diets. Dehydration is often overlooked as a trigger but is one of the easiest tricks to both prevent and abort headaches. Water is the best beverage for hydration, and patients should try for 64 ounces per day on average

Potential diet triggers:

Meat/Fish/Poultry: hot dogs, lunchmeats, pepperoni, salami, ham, smoked meats, bacon, liverwurst, pickled fish, canned meats, cured meats

Dairy: *aged cheeses (blue cheese, mozzarella, swiss, sharp cheddar, feta, parmesan, romano), sour cream yogurt, buttermilk, cream*

Beverages: *coffee, tea, apple juice, colas, alcohol (wine, beer, scotch, vodka), fermented beverages*

Vegetables and fruits: *avocados, bananas, bean pods, cabbage figs, eggplant, lentils, lima beans, navy beans, onions, peas, soybeans, spinach, tomatoes, sauerkraut, pickles, citrus, red plums, raisins, papaya*

Nuts and seeds: *all nuts and seeds including peanut butter, pumpkin seeds, walnuts, sesame seeds, pecans, etc.*

Miscellaneous food ingredients: *MSG, nitrites, meat tenderizers, soy sauce, yeast, seasoned salts, teriyaki sauce, bouillon, salad dressings, highly processed foods such as frozen pizza, macaroni, and cheese and processed packaged dinners*

Chocolate

Caffeine

3. *Menstruation*: Migraine may be induced by ovulation, hormonal replacement, birth control pills, and menstruation irregularities. Educate patients to keep a diary of their menses
4. *Lifestyle*: Irregular sleep habits including too much or too little sleep and napping can all contribute to headaches. Encourage patients to maintain a diary and record the time that they get into bed for the night, the time they get out of bed for the day, and the actual number of hours they slept during that time

Many patients only see a lack of sleep as the potential problem, although oversleeping can be equally critical in triggering migraines. Development of a bedtime routine is essential for good control of this headache trigger. Generally, a lack of sleep as well as an irregular sleep pattern or hours can contribute to headaches. Snoring, sleep apnea, and poor positioning during sleep have all been associated with increasing headache occurrence. These are other potential triggers that should be discussed with the patient

5. *Physical/environmental*: There are many environmental factors associated with triggering migraines, including flashing lights, sunlight, fluorescent lights, and visual stimulation such as rapid movement in a person's visual field, odors, weather changes, high altitudes, loud noise, and crowds. Environmental triggers seem to vary greatly from patient to patient, and nurses should never dismiss what a patient states is their environmental trigger, even if it sounds bizarre
6. *Medication*: Many commonly prescribed medications can precipitate headaches. The patient's medication list should be evaluated thoroughly for any potential offenders. Overuse of common over-the-counter medications, as well as prescription medications, can contribute to headache chronicity and may be considered a trigger. Educate patients on what rebound headaches are and why they occur. Provide patients with a list of potential rebounding medications
7. *Miscellaneous*: Other triggers include smoking, head trauma, sexual activity, physical exertion, and fatigue, *MSG* monosodium glutamate

Table 23.12 Nursing education on triggers of migraine

- Stress
- Foods/diet: alcohol, MSG, nitrites, chocolate, caffeine
- Menstruation
- Lifestyle: irregular sleep habits, such as too much or too little sleep
- Physical/environmental: flashing lights, sunlight, fluorescent lights, and visual stimulation such as rapid movement in a person's visual field, odors, weather changes, high altitudes, loud noise, crowds
- Medication
- Miscellaneous: smoking, head trauma, sexual activity, physical exertion, fatigue

Table 23.13 Nursing education on diet and exercise

- Wellness programs
- Health clubs
- PT referrals
- Ergonomic evaluations
- CDs and DVDs of exercise programs
- Activity pacing teaching

Table 23.14 Nursing education on communication for the patient

- Be assertive: take an active role in your health care
- Keep good records of your health care
- Learn as much as you can about your illness
- Write an agenda before the office visit and prioritize objectives
- Do not withhold information
- Make sure you have paper and pen to write down everything
- Repeat back instructions that the health-care provider has given, and make sure you understand what is expected before leaving the appointment
- At the conclusion of the appointment, you should be able to answer the following questions: What is my main problem? What do I need to do? Why is it important for me to do this?

Education of Patients: Behavioral and Emotional Support

The reason many nurses choose the nursing profession is to provide emotional and psychological support to patients. This should remain the focus of nursing practice.

Nurses can find themselves very busy doing administrative functions in their daily practices, leaving little time to listen and educate patients. There are no licensing constraints prohibiting nurses from providing emotional and behavioral support. This can be the most rewarding and beneficial aspect in a patient's plan of care and make a difference in the success or failure of treatment goals.

Utilization of nurses in the "gatekeeper" role of the patient's plan of care allows other members of the medical team (e.g., the physicians) to do what they do best, diagnose and treat. Leaving the role of education and support to the nursing staff is

an effective and efficient way to provide patients with stress-reduction techniques, emotional support, continuity of care, and ongoing assistance.

Teaching patients relaxation techniques can play a role in stress reduction. They can decrease the severity of headaches and help reduce the need for multiple preventive medications and overly frequent use of acute medications. Some of the more common relaxation techniques used include rhythmic breathing, deep breathing, visualized breathing, progressive muscle relaxation exercises, guided imagery, and autogenics. Providing patients with material to facilitate these practices gives patients a means of self-control over their headaches. There are many wonderful apps available for smart phones. Encourage patients to utilize this technology. There are more than 250 different relaxation programs available, and most of them are free. These applications may incorporate white noise, nature sounds, guided imagery, soundscape patterns, and many other rhythmic applications.

Follow-Up Visits/Calls

Follow-up visits, as well as recurrent phone calls, to the office should be handled in the same manner as the initial visit. A complete inquiry into the patient's concerns should include a comprehensive reassessment of their pain and symptoms that are of concern. Providing the physician with a clear account of the patient's phone call helps them assist the nurse in providing appropriate telephone advice.

It is critical that nurses work within their practice scope. Nurses should not advise changes in medications without prior physician review and documentation. Many patient phone calls, though, are easily handled by the nurse by providing a calm and reassuring voice along with educational support. This may be all that is needed to keep a patient on track with their plan of care.

Education Sessions/Support Groups

Nurses can play a key role in the development and implementation of a headache support group. Support groups give patients the opportunity to share common concerns and facilitate learning within a mutually respectful environment.

It is very important that support groups are well led with a facilitator who can keep the group focused on positive interactions and educational support. Planning needs to be accomplished long before a group is formed. This facilitates a stronger base and leads to a more purposeful and successful outcome. The support groups' initial programming, location, time, and marketing are essential. Topics for meetings will need to be planned in advance of the scheduled dates in order to retain guest speakers and topics that attract patients to attend. Working with local physicians and obtaining funding for headache support groups are necessary for ongoing success.

Table 23.15 Headache organizations/web resources

Headache organizations
American Council for Headache Education (*ACHE*)
19 Mantua Road, Mt. Royal, NJ 08061, (856) 423-0043, Fax: (856) 423-0082 e-mail: amf@talley.com. http://www.achenet.org/
American Headache Society (*AHS*)
19 Mantua Road, Mt. Royal, NJ 08061, (856) 423-0043, Fax: (856) 423-0082 e-mail: ahshq@talley.com. www.ahsnet.org
National Headache Foundation (*NHF*)
820 N. Orleans, Suite 411,Chicago, IL 60614-2750,(888) NHF-5552 or (312-274-2650) e-mail: info@headaches.org. www.headaches.org
MAGNUM (*Migraine Awareness Group A National Understanding for Migraineurs*)
100 North Union Street, Suite B, Alexandria, VA 22314, (703) 739-9384, Fax: (703) 739-2432. www.migraines.org

Publicity can be very useful in the beginning. Use newspapers, radios, TV, cable, individual mailings, and flyers announcing the date, location, time, and brief description of the purpose of the group to attract attendees.

Starting and running a support group is a learned skill, and, therefore, should not be discouraged if it is not perfect the first time. It is helpful to have the support of a professional who has run support groups in the past (Table 23.15).

Suggested Reading

Cady RK, Farmer K, Beach ME, Tarrasch J. Nurse-based education: An office-based comparative model for education of migraine patients. *Headache* 2008;48:564–569.

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Chapter 24
Headaches, Traumatic Brain Injury, and Concussion

Jay Alberts and Neil Cherian

Introduction

Head-trauma-related symptoms are quite common and varied. There are a myriad of common causes of head trauma including battle injury, motor vehicle accidents, falls, domestic violence, recreational cycling, and the world of sports. Due to evolving guidelines, numbers of participants, frequency of injuries, and legal implications, much focus has been turned to the sports world.

The incidence of sport-related concussion in the USA has been estimated to be 1.6–3.8 million annually. Actual incidence may, in fact, be even greater, given that many concussive injuries go undetected or unreported. While 80–90 % of individuals recover neurologic function within 10 days of injury, those who develop chronic symptoms may experience potentially life-altering effects on academic and job-related performance, in addition to diminished quality of life. Timely detection, diagnosis, and clinical management are critical in the safe and efficacious management of individuals with concussion.

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S. J. Tepper, D. E. Tepper (eds.), *The Cleveland Clinic Manual of Headache Therapy, Second Edition,* DOI 10.1007/978-3-319-04072-1_24,

Table 24.1 A simple definition of concussion

• Concussion is a subset of traumatic brain injury (TBI) resulting in a transient disturbance in brain function, due to a direct or indirect blow to the head

Diagnosis of Concussion

While there is no universally accepted definition, concussion is considered a subset of traumatic brain injury (TBI) resulting in a transient disturbance in brain function, due to a direct or indirect blow to the head (Table 24.1). Rotational, angular, or linear biomechanical forces are thought to cause a shearing or rotational effect of the cerebral hemispheres about the upper brain stem. A complex pathophysiological process ensues, resulting in temporary neuronal dysfunction, rather than cell death, causing a wide array of symptoms affecting the cognitive, physical, behavioral, and sleep domains of neurological function.

The diagnosis of concussion remains a clinical one, determined largely by the identification of an appropriate mechanism followed by the onset of symptoms. At present, no biomarker has been identified with sufficient sensitivity to definitively diagnose a concussion, and routine brain imaging is typically normal and not helpful in the diagnostic process or in determining the severity of concussive injuries.

Classification of Concussion

Concussion was previously classified into grades of severity according to loss of consciousness (LOC) and posttraumatic amnesia. Evidence has since indicated that neither LOC (occurring in less than 10% of patients) nor amnesia are hallmarks of concussive injuries, or an indication of concussion severity, predictors of recovery, or influence return-to-play decisions. As a result, concussion grading systems are no longer endorsed, as evidenced by recent position statements published by the International Conference on Concussion in Sport, American Medical Society for Sports Medicine, and the American Academy of Neurology. Instead, all three groups' position statements refer to modifiers or clinical factors that have been shown to predict injury severity, risk for prolonged recovery, and may serve to influence the clinical management of individuals with concussion.

Among the most common modifiers that may result in a protracted recovery are history of prior concussion; symptom prevalence, severity, and duration; female gender; age <18; genetic predisposition; and comorbidities/premorbidities including migraine, depression, learning disability, attention deficit disorder, or sleep disorders. Table 24.2 depicts each of these modifiers in greater detail, and should be considered when conducting a detailed concussion history.

Identifying these modifiers early in the post-injury phase may warrant more aggressive clinical management for those individuals, whether pharmacological, rehabilitative, or behavioral, to improve symptom management and potentially avoid

Table 24.2 Concussion modifiers and risk factors

Factor	Modifier
Prior concussion	Total number and frequency
	Time between previous concussion(s)
	Lower threshold or impact required to sustain subsequent concussion
Symptoms	Total number
	Severity
	Duration
Signs and sequelae	Loss of consciousness (>1 min)
	Amnesia
	Concussive convulsions
Demographic factors	Age <18
	Female gender
Comorbidities and pre-morbid conditions	Migraine
	Depression or other mental health disorders
	Attention deficit disorder or attention deficit hyperactivity disorder
	Learning disabilities
Medication	Psychoactive drugs, anticoagulants
Sport and behavior	High-risk activity or position with contact/collision
	Dangerous or aggressive style of play

long-term consequences associated with protracted recovery including depression, sleep disorders, and declines in academic or work-related performance.

Pathophysiology and Symptom Manifestation

Generally, in this handbook, we have not included extensive discussions of pathogenesis. However, in the setting of TBI and concussion, some understanding of pathophysiology is useful in diagnosis, evaluating prognosis, and treatment, that is, in syndrome management.

There is no known biomechanical impact threshold for the diagnosis of concussion. A given magnitude of linear, angular, rotational, or a combination of these forces of sufficient magnitude, when transmitted to the brain, produces temporary neuronal dysfunction resulting in a neurochemical and neurometabolic cascade that can be categorized into three phases—acute, intermediate, and late. It is during these phases of neurophysiological recovery that the injured brain remains vulnerable to repeat injury (occasionally catastrophic) and long-term disability.

Note that the neuropathological phases describe physiological changes occurring at the cellular level and are not synonymous with clinical phases of concussion. During the acute phase, axonal stretching and the disruption of neural membranes lead to an ionic and metabolic imbalance in the presence of decreased cerebral blood flow.

A widespread release of primarily excitatory neurotransmitters ensues, resulting in an efflux of potassium and an influx of calcium. The excessive extracellular

Table 24.3 Some graded symptom checklists for concussion

- Concussion Symptom Inventory (Randolph et al. *Arch Clin Neuropsychol.* 2009; 24: 219–29)
- Post-Concussion Symptom Scale (Kontos et al. *Am J Sports Med.* 2012; 40: 2375–84)
- Graded Symptom Checklist of the Consensus Statement on Concussion in Sport (McCrory et al. *Br J Sports Med.* 2013; 47: 250–8)

potassium causes further depolarization and additional calcium influx, leading to mitochondrial dysfunction, impaired oxidative metabolism, and decreased adenosine triphosphate (ATP) production.

In attempts to restore the ionic balance, sodium/potassium pumps, which are dependent on ATP, are activated, yet resort to glycolysis in the absence of adequate levels of ATP. Increased utilization of glucose results in extracellular lactate accumulation, leading to neuronal dysfunction due to metabolic acidosis, membrane damage, changes in the permeability of the blood–brain barrier, or cerebral edema. During the intermediate phase, uncoupling of glucose metabolism results in a 50% reduction of cerebral blood flow. Oxidative metabolism recovers initially by day 2 post-injury, diminishes through day 5, and recovers fully by day 10. Excess calcium can persist for 2–4 days, while cerebral glucose metabolism recovers at 10 days, on average. In the absence of full neurometabolic and neurochemical recovery, persistent elevations in intracellular calcium can lead to delayed cell death, characteristic of the late phase of recovery. Persistent alterations in neurotransmitter function can lead to symptoms commonly seen in post-concussive syndrome, including impaired memory, cognition, and learning, in addition to disinhibition and distractibility.

The functional neuronal injury associated with concussions results in a wide array of symptoms unique to each individual. Graded symptom checklists (GSCs) are commonly used to document symptom incidence and severity.

While numerous symptom checklists have been published including the Concussion Symptom Inventory (Randolph, 2009), Post-Concussion Symptom Scale (Kontos, 2012), and the GSC endorsed by the Consensus Statement on Concussion in Sport (McCrory, 2013), none has been found to be superior to others (Table 24.3). As with any tool, the purpose for which the GSC is administered should drive the content (Table 24.4). It has been suggested that the evolution of different symptom checklists has occurred as some clinicians seek to detect the effects of a concussion, while others look to understand the characterization or manifestation of those effects.

Furthermore, some symptoms such as nausea or vomiting are associated with the immediate post-injury phase of concussion, while others such as mood and sleep disturbances typically occur in later phases or with protracted recovery. Efforts have been made to categorize symptoms according to the domains of function they relate to, in part to provide clinicians with a simple method of determining where the individual's greatest self-reported deficits lie and to focus clinical interventions.

While there is some inconsistency with how the domains are classified, the most common ones currently used are affective/emotional, cognitive, sleep, and somatic/physical. A list of common symptoms and their respective domains is included in Table 24.5.

Table 24.4 Clinical pearls on graded symptom checklists (GSC) for concussion

- The purpose for which the GSC is administered should drive the content
- Different symptom checklists are used for different outcomes and in different circumstances:
  - Early or late after injury
  - Effects of a concussion
  - Characterization or manifestation of concussion effects
  - Domains of concussion effects:
    - Affective/emotional
    - Cognitive
    - Sleep
    - Somatic/physical

Table 24.5 Selected concussion symptoms by domain

Affective/emotional	Somatic/physical
Anxiety/nervousness	Headache
Sadness	Dizziness
More emotional	Balance problems
Irritability	Pressure in head
Cognitive	Neck pain
Confusion	Nausea or vomiting
Difficulty concentrating	Blurred vision
Difficulty remembering	Sensitivity to light
Feeling foggy	Sensitivity to noise
Feeling slowed down	"Don't feel right"
Sleep	Fatigue or low energy
Trouble falling asleep	Ringing in the ears
Sleeping more than usual	Numbness or tingling
Sleeping less than usual	
Drowsiness	

Concussion Treatment: The Phases of Return to Activity as Standard of Care

In the immediate aftermath of concussion, Phase 1 of the graduated return-to-activity program entails relative (symptom limited) physical and cognitive rest. Pathophysiologically, the injured brain is in a vulnerable state of disrupted homeostasis during which additional trauma can be catastrophic, leading to *second impact syndrome* with cerebral swelling and dysregulation of blood flow, potentially resulting in death. Additionally, the threshold for repeated and more severe injury appears to be significantly lower in the 7–10-day period following a concussion. The rationale for relative cognitive rest is due to evidence that mental activities tax the recovering brain, often exacerbating symptoms and potentially delaying recovery.

Once the individual is symptom free at rest and can tolerate a routine day of physical and cognitive tasks (i.e., attending work or school), a progressive return to the activity program is recommended. It is recommended that each phase take at least 24 h, and that more than one phase should not be completed in 1 day. Should

Table 24.6 Phases of concussion recovery and return to activity

- Each phase should take ≥24 h
- Return to activity takes a minimum of 7 days
- *Phase 1*:
  - Relative (symptom limited) physical and cognitive rest
  - Avoid second impact syndrome, which can be lethal
  - Threshold for repeated and more severe injury is significantly lower for 7–10 days post-concussion
- *Phase 2*:
  - Light aerobic activity, with:
  - Activity intensity at <70% of maximum heart rate
  - No resistance training
- *Phase 3*:
  - Continued aerobic activity
  - Inclusion of sport-specific drills
  - No drills or activities involving head impact
- *Phase 4*:
  - Complex sport-specific noncontact training drills
  - Resistance training initiated
- *Phase 5*, after medical clearance:
  - Full-contact practice
  - Normal training activities
- *Phase 6*:
  - Return-to-normal-game play

the individual become symptomatic during the program, he/she is instructed to return to the previous asymptomatic phase following a 24-h period of rest.

During Phase 2, light aerobic activity is prescribed, with intensity at <70% of maximum heart rate. Resistance training is avoided during this phase.

Phase 3 is characterized by continued aerobic activity with the inclusion of sport-specific drills. Drills or activities involving head impact are not permitted. During Phase 4, more complex sport-specific noncontact training drills are introduced. The individual may initiate resistance training.

Once medically cleared, full-contact practice and normal training activities occur in Phase 5, followed by return-to-normal-game play in Phase 6. The outlined return-to-activity program takes a minimum of 7 days to complete if the athlete advances daily through the phases and remains asymptomatic at rest and with provocative exercise.

The phases of recovery are listed in Table 24.6. Clinical pearls on return to activity are listed in Table 24.7.

Vestibular Symptoms and TBI

Vestibular symptoms are common with head trauma. They can be fleeting or persistent, with severity ranging anywhere from minimal to debilitating. Symptoms tend to resolve without intervention, similar to many of the other related neurological

Table 24.7 Clinical pearls on return to activity

- Rest is crucial for up to 7–10 days to avoid second impact syndrome
- Each phase should take ≥24 h
- Return to activity takes a minimum of 7 days

Table 24.8 Factors that can influence headache generation after concussion

Physical:
Nature of trauma (sport specific, particular play within the game)
Protective gear (helmets, mouth guard, pads…)
Force of hit (difficult to quantify; direction)
"Location" of trauma (head and/or neck vs. acceleration/deceleration of head)
Individual:
Prior concussion(s)
History of migraine
Family history of migraine

symptoms. Common dizzy entities include benign paroxysmal positional vertigo (BPPV), related to force transmission to the utricle of the inner ear (particle reposition is often of benefit); vestibular migraine; post-concussive syndrome; and neurocardiac presyncope or frank syncope, and possibly cervically mediated dizziness (controversial). Further discussion of this topic is included in Chapter 22.

Headache in Concussion

Headache is the most frequently reported symptom of sport-related concussion, and one of the most common symptoms requiring pharmacological management, with up to 86% of athletes reporting posttraumatic headaches. In addition to its prevalence in the immediate post-injury phase, it is estimated that 15% of individuals will develop chronic posttraumatic headache as a result of mild head injury.

As discussed earlier, the concussion cascade is quite complex. Additional elements that may influence the development of headache include various physical and individual factors (Table 24.8).

The most common recognizable forms of posttraumatic headache in concussion are tension-type headache, cervicogenic headache, migraine, and combined tension-type headache and migraine. The presence and severity of posttraumatic headaches have been linked with declines in neuropsychological test performance, and posttraumatic headache is thought to impair other functions such as energy, sleep, attention, higher-level cognitive function, and emotion. Headaches can also result in decreased activity tolerance and are frequently exacerbated during physical activity tolerance testing as a component of return-to-play rehabilitation programs.

Table 24.9 Mild head injury, ICHD-3 definition

- Head injury with all of the below:
  1) No loss of consciousness for >30 min
  2) Glasgow Coma Scale (GCS) score >13
  3) No posttraumatic amnesia lasting >24 h
  4) No change in level of awareness for >24 h
  5) No positive imaging of hemorrhage, edema, brain contusion, etc.
- Following the head injury ≥1 of:
  1) Temporary confusion, disorientation, or altered consciousness
  2) Amnesia for events around the head injury
  3) ≥2 of two of symptoms of mild traumatic brain injury:
     a) Nausea
     b) Vomiting
     c) Visual disturbances
     d) Dizziness
     e) Vertigo
     f) Altered memory
     g) Altered concentration

Table 24.10 Moderate or severe head injury, ICHD-3 definition

- The patient must have persistent headache attributed to traumatic injury to the head, that is, headache lasting at least 3 months
- Initial head injury was associated with ≥1 of:
  a. Loss of consciousness for >30 min
  b. Glasgow Coma Scale (GCS) score <13
  c. Posttraumatic amnesia lasting >24 h
  d. Change in level of awareness for >24 h
  e. Positive imaging consistent with traumatic brain injury with hemorrhage, edema, brain contusion, etc.

Spectrum of Headache Disorders in Concussion

The ICHD-3 stipulates that headache must be reported to have developed within 7 days of the head trauma for it to be considered as the cause of the headache and thus coded as a secondary headache to the trauma. The headache is considered acute within the first 3 months and is termed persistent when it lasts longer (ICHD-2 referred to this as chronic). Judgment must be used to delineate whether the headache entity is truly new or the provocation of a preexisting disorder.

The ICHD-3 criteria for posttraumatic headache do not list any particular characteristics of headache attributed to head injury; any headache will do. The ICHD-3 criteria do distinguish between mild (Table 24.9) and moderate to severe (Table 24.10) head injury, and as noted, between acute (Table 24.11) and persistent (Table 24.12).

Table 24.11 Acute headache attributed to traumatic injury to the head, ICHD-3 criteria

- Any headache which begins in ≤7 days after ≥1 of:
  1. Head injury
  2. Regaining consciousness after head injury
  3. Stopping any sedating or analgesic drugs after head injury
- Either of the following:
  1. The headache resolves in ≤3 months after the head injury
  2. It is not yet 3 months, and the headache has not yet resolved

Table 24.12 Persistent headache attributed to traumatic injury to the head, ICHD-3 criteria

- Any headache which begins in ≤7 days after ≥1 of
  1. Head injury
  2. Regaining consciousness after head injury
  3. Stopping any sedating or analgesic drugs after head injury
- Headache persists for >3 months after the injury to the head

Headache Associated with Identifiable Structural Damage

With physical trauma playing a role in the generation of the headache in concussion, gross structural damage, when present, may contribute. Potential vascular manifestations include subdural hemorrhage, subarachnoid hemorrhage, carotid dissection, and vertebral dissection.

Involvement of the upper cervical spine and base of the skull can contribute to headache. Diagnoses to consider include headache attributed to whiplash (acute or persistent), cervicogenic headache, and occipital neuralgia. Cervical myofascial pain, even without meeting criteria for cervicogenic headache, can potentially contribute to headache.

Other considerations include headache related to acute glaucoma or related to refractive error as a consequence or orbital trauma, and headache related to temporomandibular joint dysfunction (TMD).

Posttraumatic Headache Management

Once the headache type has been determined, treatment is often consistent with the respective disorder. Experts urge a cautious approach, as the aggressive clinical management of posttraumatic headache and other symptoms of concussion in the immediate post-injury phase with medications may mask unresolved symptoms and lead to the premature return of an athlete to the playing field or a soldier to battle. In addition, this can potentially lead to medication-overuse headache (Table 24.13).

Table 24.13 Clinical pearls in posttraumatic headache treatment

- Match treatment to the form or type of posttraumatic headache in the patient, that is, if it seems migraine-like, treat with anti-migraine medications, etc.
- Treat cautiously and avoid excessive medication use or premature return of an athlete to the playing field or a soldier to theater
- Overuse of acute medications post concussion can lead to medication-overuse headache

Pediatric Populations

The young developing brain is presumably at increased risk of damage from trauma compared to more mature brains. This may be one reason why second impact syndrome appears to occur more frequently in younger TBI patients, although statistics are limited. Additionally, the literature is currently sparse for concussion management in children under the age of 12.

Another additional consideration for a young concussed individual is return to school but not initial return to play. This requires a coordinated effort between the treating physician, the family, and the school (teacher, coach).

For the pediatric population, it must be kept in mind that migraine does commonly appear in this age group. Given this fact, if the first manifestation of migraine headache occurs soon after head trauma, would it have manifested sometime later with no trauma?

In Closing

The Cleveland Clinic recently launched its Concussion Center, a multidisciplinary initiative to diagnose concussion and manage its related symptoms. Core team members include individuals from sports medicine, neurology, neurosurgery, neuropsychology, physical therapy, and biomedical engineering. This runs in collaboration with a network of athletic trainers.

Additional providers include speech and cognitive therapists, rehabilitation doctors, and psychiatrists. The program is integrated through the use of an iPad-based app which integrates the various cognitive tests along with tests of balance function, a GSC, and tests of reaction time and vision.

In this era of cost containment and value-based care, a comprehensive care path is currently being developed to streamline concussion management across the entire Cleveland Clinic health system. An integrated approach to concussion and TBI with their residual effects, including headache, seems well advised.

Conclusions on Headaches, Traumatic Brain Injury, and Concussion

- Concussion is a subset of TBI resulting in a transient disturbance in brain function, due to a direct or indirect blow to the head
- GSC can be useful in assessing concussions, especially in the domains of concussion effects, such as affective/emotional, cognitive, sleep, and somatic/physical
- Rest is crucial for up to 7–10 days to avoid second impact syndrome
- Each phase of recovery, and there are seven phases, should take ≥ 24 h
- Return to activity therefore takes a minimum of 7 days
- ICHD-3 criteria for headache attributed to traumatic injury to the head requires onset within 1 week
- If posttraumatic headache resolves in < 3 months, it is termed "acute"; if it goes longer than 3 months, it is termed "persistent"
- Match medication treatment to the characteristics of the posttraumatic headache

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