Headache is the fourth most common reason for adult patients to present to the emergency department. Approximately two-thirds of these visits are for primary headache disorders, such as migraine, cluster, and tension-type headache. When evaluating a patient with headache in the emergency department, the physician must first decide if the headache represents a primary headache disorder or whether there is some other underlying etiology. Once a serious cause for headache has been excluded, the physician can focus on pain management. The first half of this chapter discusses the differential and diagnostic work-up of headaches with potentially dangerous etiologies. The last half addresses management strategies for primary headache disorders, with special focus on prolonged and intractable migraine headaches.

Keywords

Emergency department • Emergency room • Headache • Migraine • Migraine management • Pregnancy headache • Primary headache • Reversible cerebral vasoconstriction • Secondary headache • Status migrainosus • Subarachnoid hemorrhage • Thunderclap headache

Introduction

Headache is an extremely common malady that causes numerous sufferers to present to the emergency department for relief and diagnosis. While some headaches are symptomatic of a serious underlying disorder, fortunately, most are of benign origin. Headaches can be classified within two major categories as outlined by the International Headache Society Headache...
Classification of Headache Disorders (ICHD-II) [1]: (1) primary headache disorders, and (2) secondary headache disorders. Primary headache disorders include such diagnoses as migraine, cluster headache, and tension-type headache. These are thought to represent an abnormal activation of the intrinsic pain system that may include both central and/or peripheral mechanisms. The predisposition to such disorders depends on both genetic and environmental factors.

A primary headache is diagnosed based on the patient’s history and the absence of an identifiable underlying etiology. Imaging and laboratory investigations are most often used to help exclude secondary causes for headache. There is an extensive and varied list of possible sources of secondary headache, some of which include intracranial neoplasms, infections, hemorrhage, homeostatic derangements such as hypothyroidism, toxic exposure such as carbon monoxide poisoning, and many others.

This chapter will address the differential diagnosis of headache disorders likely to be seen in the emergency department as well as various diagnostic approaches utilized in the evaluation of secondary causes of headache. It will also outline several treatments for primary headache disorders. Therapeutic options for many secondary headache disorders are covered in other chapters of this book and are beyond the scope of this chapter. For an exhaustive list of all headache disorders and their diagnoses, the reader should see the ICHD-II [1] classification.

Epidemiology

The symptom of headache is a frequent reason for visits to the emergency department (ED). In the National Hospital Ambulatory Medical Care Survey in 2006, headache was the fourth most common reason that adults (patients 15 years and older) sought care in an emergency department. It was the third most common reason among women and the seventh most common reason among men. Overall, headache accounted for over 3.3 million emergency department visits which represented 2.8% of a total of over 119 million visits [2].

In the largest study of its kind, Goldstein and colleagues evaluated a representative sample of all of the adult ED visits for headache between 1992 and 2001, and found that approximately two-thirds of the visits were for a primary headache disorder [3]. Of those that presented with a secondary headache disorder, the vast majority were benign. In fact, only 2% of visits were found to be due to a serious pathologic etiology [3]. Previous studies also found that the majority of patients presenting to the emergency department with headache had primary headaches, with rates of secondary causes as low as 4% [3]. Certain clinical characteristics such as sudden onset, older age, and marked severity increase the probability of finding an underlying cause [3, 4].

Pathophysiology

A detailed discussion of the pathophysiology of all primary headache disorders is beyond the scope of this chapter; nevertheless, a brief overview of the pathophysiology of migraine is appropriate. Migraine headache likely is a result of alterations in central pain nociception regulation with consequential activation of meningeal and blood vessel nociceptors. Headache and its related neurovascular changes occur as a result of activation of the trigeminal system. Reflex links to the cranial parasympathetics comprise the trigeminoautonomic reflex. Activation leads to vasoactive intestinal polypeptide release and vasodilation [5].

Substance P, calcitonin gene-related peptide (CGRP), and neurokinin A are contained in trigeminal sensory neurons [6]. Excitation leads to release of substance P and CGRP from sensory C-fiber terminals [7], which contribute to neurogenic inflammation [8]. These substances interplay with blood vessels, causing dilation, plasma protein extravasation, and platelet activation [9]. Neurogenic inflammation is thought to sensitize nerve fibers (peripheral sensitization) resulting in
responses to formerly innoxious stimuli, like blood vessel pulsations [10], leading to, in part, the pain of migraine [11]. Central sensitization can also take place. After meningeal receptors are activated, neuronal activation takes place in the trigeminal nucleus caudalis [12] and in the dorsal horn in the upper cervical spinal cord [13, 14]. Positron emission tomography has demonstrated brainstem activation during migraine headache in areas approximating nociceptive pathways as well as in systems that modulate pain [15].

Clinical Features

Primary headaches are defined by their onset, duration, and associated features such as nausea/vomiting, visual aura, conjunctival tearing, rhinorrhea, etc. These discriminating features are broken down in detail under the differential diagnosis section. Some secondary headaches have classic presentations as well. The following is a list of clinical features on the history and exam that may be seen with particular headache etiologies.

History of Trauma

A history of trauma increases the chance of intracranial hemorrhage (subarachnoid, subdural, epidural, intraparenchymal), and may also precede a carotid or vertebral dissection. Cerebral venous thromboses are another uncommon but serious complication of closed head injury [16]. Trauma to the cribriform plate or dural sleeve could result in a cerebrospinal fluid (CSF) leak causing a low-pressure headache. Trauma resulting in fractures to the skull base or cervical vertebra can contribute to severe posterior head and neck pain. Minor head injuries can trigger a migraine in patients with a migraine history. Postconcussive headaches following closed head injury may mimic migraine or tension headaches and may have associated symptoms such as cervical pain, dizziness, cognitive impairment, and psychologic/somatic complaints such as irritability, anxiety, depression, fatigue, and sleep disturbance [17].

Fever or Known Infection

The presence of an infection elsewhere in the body should raise suspicion that the infection could have spread to the central nervous system. Patients should be assessed for the presence of neck stiffness/meningismus (resistance to passive movement of the neck), fever, or altered mentation. Recent medications for headache should be noted, as nonsteroidal anti-inflammatory drugs and acetaminophen may mask fever. Fever may also occur in the setting of vasculitis, malignancy, thrombosis, and subarachnoid hemorrhage. In subarachnoid hemorrhage, however, the fever tends to be delayed and is therefore less likely to be present on assessment in the ED.

Immunocompromise (HIV or Immunosuppression)

Patients with compromised immune defenses are at increased risk for possible CNS infections, including meningitis, encephalitis, or abscess. In addition, patients with AIDS are at increased risk of opportunistic CNS neoplasms, such as lymphoma. Certain immunosuppressants, such as cyclosporine, tacrolimus, and gemcitabine, are associated with an increased risk of posterior-reversible leukoencephalopathy. Other immunosuppressive agents, such as liposomal cytarabine, IVIG, intrathecal methotrexate, and azathioprine, can present with headache in the context of aseptic meningitis.

Concurrent Headache in Close Friends, Family, or Coworkers

If people with whom the patient has had contact have also developed new headaches, this should raise suspicion for an infectious or toxic exposure.
Infectious meningitis may present with isolated headache, or may have associated neck stiffness, meningismus, photophobia, nausea/vomiting, fever, or rash. If the symptomatic group of people have been in an enclosed environment (especially in winter), consider carbon monoxide poisoning. Carbon monoxide poisoning may have associated confusion, nausea/vomiting, chest pain, weakness, or dizziness. Tachypnea and tachycardia are the most frequent physical findings [18]. At carboxyhemoglobin levels greater than 31%, a cherry-pink coloring of skin is almost always seen [19]. However, a patient presenting mainly with headache would be expected to have milder levels, and would only rarely present with this classic coloring [20].

History of Cancer

A history of malignancy should raise concern regarding possible metastases to brain parenchyma or meninges. The most common metastases to the adult brain include lung (36–46%), breast (15–25%), and skin (melanoma) (5–20%). Almost any systemic tumor can metastasize to the brain, however, including kidney, colon, testes, and ovaries [21]. Headache in the setting of metastases may be nonspecific, but may be associated with nausea/vomiting, focal neurologic deficits, or seizures. They may be described as getting progressively worse in frequency or intensity, and may worsen in the supine position, with straining, or with cough. A malignancy-associated hypercoagulable state may place the patient at an increased risk of cerebral infarction and cerebral venous thrombosis (CVT). Headache may also occur as a side effect of chemotherapy (such as fluorouracil, procarbazine, or temozolomide). Associated anemia, hypercalcemia, or dehydration may also precipitate headaches.

Pregnancy

Primary headaches, such as tension-type headaches and migraine, often improve or remain unchanged during pregnancy [22–24]. Therefore, if a pregnant patient presents to the emergency department with her first-ever headache or a change in her headaches, the physician should be aggressive in his search for secondary causes.

For pregnant women after 20 weeks gestation, it is necessary to exclude preeclampsia/eclampsia. The presentation may be similar to migraine, and may even be accompanied by a visual aura. Associated altered mental status and seizures are concerning for eclampsia. CVT and reversible cerebral vasoconstriction may occur both during pregnancy and in the first few weeks after delivery [25]. Both carotid and vertebral dissections have been reported during pregnancy and following prolonged delivery [26–29]. Furthermore, the risk for ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage appears to be most elevated during the 2 days prior to, and the 1 day following, delivery. This risk remains somewhat elevated for 6 weeks postpartum [30, 31].

Visual Loss

There is a large differential for headaches presenting with associated visual loss. Bilateral visual loss may occur in the setting of papilledema with increased intracranial pressure from a mass or CVT. A pituitary mass can compress the optic chiasm and cause varying degrees of bilateral visual loss, especially in peripheral vision. Posterior reversible leukoencephalopathy syndrome (PRES) may present with both headache and bilateral visual loss, possibly associated with hypertension, and sometimes seizures. An ischemic stroke or mass in one hemisphere may present with headache and associated visual loss in one visual field (homonomous hemianopsia).

Monocular visual loss (amaurosis) with headache in a patient over age 50 is immediately concerning for temporal arteritis. Associated features may include temple tenderness, reduced temporal artery pulse, jaw claudication, increased erythrocyte sedimentation rate, fever, weight loss, or shoulder aching (polymyalgia rheumatica). Idiopathic intracranial hypertension
is often accompanied by transient visual obscurations which are episodes of visual loss lasting seconds; these are often monocular. Acute angle-closure glaucoma can present with rapidly progressive visual loss and associated eye pain or headache.

**Headache Induced by Valsalva Maneuver**

Exertion, cough, strain (Valsalva), bending over, or lifting heavy objects all tend to increase intracranial pressure. If a headache is precipitated by these maneuvers, consider structural processes affecting the posterior fossa, such as a Chiari malformation [32]. Patients with increased intracranial pressure may also have papilledema, nausea/vomiting, and worsening of their headache in a supine position. Disorders associated with intracranial hypertension such as CNS infection, masses, and hematomas may also worsen with these maneuvers. CVT can be associated with increased intracranial pressure due to venous hypertension. Idiopathic intracranial hypertension (pseudotumor cerebri) may present similarly, although this is a diagnosis of exclusion. It is important to note that there are benign headaches, such as cough headache, that may be triggered by cough or strain. Furthermore, migraineurs most often describe their headaches as worsening with activity in general, frequently including Valsalva maneuvers.

**Pupillary Abnormalities**

Patients presenting with a headache in the ED should routinely be examined for a Horner’s syndrome (small pupil that does not dilate well in the dark with associated mild eyelid ptosis). Though a Horner’s syndrome may occur in primary headaches such as trigeminal autonomic cephalalgias (TACs) and rarely migraine headaches, the presence of a Horner’s syndrome should alert the clinician to the possibility of a carotid or vertebral dissection. A lung/neck malignancy can also cause a Horner’s syndrome, and could be associated with headache in the setting of brain metastases. A larger pupil that reacts sluggishly to light may be seen with acute-angle glaucoma, or a lesion along the pupillary pathway (including optic neuropathy, cranial nerve III palsy, or a brainstem lesion).

**Red Flags**

A helpful mnemonic to remember the clinical “red flags” during evaluation of headache was developed by Dr. David Dodick [33]. He suggested using SNOOP, which stands for:

- **S**ystemic signs/symptoms/disease (fever, myalgias, weight loss, history of malignancy, or AIDS)
- **N**eurologic signs or symptoms (altered mentation, seizure, papilledema, focal neurologic findings)
- **O**nset sudden (thunderclap headache)
- **N**ew onset (headache after age 50)
- **P**attern change from previous headaches (especially if rapidly progressive in severity or frequency)

When any of these are present, further labs, imaging, and/or spinal fluid analysis should be considered to investigate for a secondary cause of headache.

**Approach to Diagnosis**

The clinical history is the most valuable tool the clinician has to efficiently and accurately diagnose and treat a patient suffering from headache in the emergency department. The suddenness of onset and whether the patient has had similar headaches in the past can help guide differential diagnoses and management. A severe and unexpected headache that reaches peak intensity within seconds, often referred to as a “thunderclap headache,” should be considered a neurologic emergency, and requires a systematic work-up (Fig. 1.1). It is tempting to assume that patients with a chronic history of headaches are
presenting to the emergency department for treatment only. However, if the headache has changed dramatically in pattern, a more thorough diagnostic evaluation should be performed. Answers to the following questions should be sought:

- Previous headache history/pattern? How does this headache compare with previous experiences?
- Onset and progression of this headache?
- Location and quality of pain?
- Radiation?
- Severity?
- Duration?
- Any fluctuation in intensity? If so, what makes it better or worse? Specifically, is the severity affected by certain positions, times of day, cough, Valsalva, or sleep?
- Any associated symptoms such as:
  - Nausea/vomiting
  - Photophobia/phonophobia
  - Visual changes (blurring, diplopia, flashing/colorful lights)
  - Whooshing/roaring tinnitus
  - Weakness, numbness, or difficulty walking
  - Autonomic features (tearing, conjunctival injection, rhinorrhea, flushing/sweating)
  - Seizures
- Current pregnancy, infection/fever, immunocompromised state?
- Current medications (anticoagulants, nitrates) and any recent medication changes?
- Past medical history of recent trauma, cancer, previous blood clots/miscarriages, or

**If headache has resolved, consider observation. If headache persists or if suspicion for secondary headache is high, can proceed with further work up**

Fig. 1.1 Proposed work-up for sudden-onset headache
polycystic kidney or connective tissue disease
(last two may increase chance of aneurysm and therefore subarachnoid hemorrhage)?
• Family history of migraines, clots, bleeding?
• Any family members, friends, or coworkers also suffering from new headache?

A general examination with special attention to vital signs is necessary, followed by a careful examination for any focal neurologic findings. This should include:
• Detailed eye exam (for papilledema, pupillary abnormalities, and visual field abnormalities)
• Auscultation for carotid, temple, or orbital bruits
• Palpation of bilateral temple regions to assess for prominent superficial temporal arteries with reduced pulsation
• Identification of any reported areas that increase or cause pain such as the “trigger zones” in trigeminal neuralgia
• Examination of cranial nerves, strength, and sensation, with special attention to symmetry
• Deep tendon reflexes and plantar reflexes (Babinski sign)
• Unless impossible, the gait should be observed for subtle ataxia/weakness. This may also help elicit positional changes in headache severity

Labs and Imaging

Given the wide variability of secondary headache presentations, it is often difficult to identify which patients require more evaluation than just a history and physical examination. As mentioned previously, if there are any associated red flags such as immunocompromised state, older age, or a change in the pattern of headache, further work-up should be considered. A sudden onset, extremely severe, “worst headache of my life” presentation should be treated as a medical emergency and be evaluated in a systematic fashion for subarachnoid hemorrhage or alternative etiologies (see Fig. 1.1).

Serologic Testing

Initial blood tests for headache might include a CBC to look for metabolic derangements and any evidence of dehydration (especially if vomiting). Sedimentation rate should be considered in any patient older than age 50 with a new type of headache, to screen for giant-cell (temporal) arteritis. Coagulation factors (PT and PTT) should be considered if there is concern for hemorrhage, such as with a thunderclap presentation or if the patient is on anticoagulants. If the headache has associated altered mentation, consider liver function tests and a drug/toxicology screen. If carbon monoxide poisoning is suspected, testing for carboxyhemoglobin may also be useful.

ECG

Although rare, cardiac ischemia may present with isolated headache, and is referred to as “cardiac cephalalgia.” If a patient has cardiac risk factors, associated shortness of breath, or a new headache that is precipitated by exertion, consider an ECG and/or stress testing to look for ischemia [34].

Computed Tomography of the Head

Computed tomography (CT) is the most widely available brain imaging technique in the emergency department, and in most cases is adequate to rule out mass effect (from a tumor, abscess, stroke, or other lesion) and acute blood (subarachnoid, epidural, subdural, or intraparenchymal). It is important, however, to understand that CT has its limitations. CT of the head will miss subtle, early, or small infarcts, and may also miss small subarachnoid and subdural hemorrhages. With a well-read head CT, the sensitivity for subarachnoid hemorrhage in the first 12 h is around 90–98% [35–37]. CT becomes less sensitive with increasing time from the onset of headache, with a sensitivity of about 58% at 5 days and about 50% at 1 week [35]. Sensitivity for any type of hemorrhage is reduced if the hematocrit is less than 30% [38]. Lesions and mass effect in the posterior fossa can also be difficult to visualize, especially with a poor-quality CT, given the artifact from surrounding bone structures.

A CT head is normally performed without contrast in the emergency room. However, it may be reasonable to add contrast if there is suspicion for CVT or metastases.
Lumbar Puncture

When infection is suspected, it is necessary to analyze spinal fluid for inflammatory cells, protein and glucose concentrations, Gram’s stain, and cultures. Ideally the patient should have this procedure in the lateral decubitus position, and opening pressure should be measured. Normal opening pressure is 5–22 cm H$_2$O. Care must be taken to relax the patient with legs extended when measuring the opening pressure, to avoid a spurious elevation of the measurement.

The opening pressure may be elevated with many pathologic processes, including infection or inflammation of the meninges. It may also be elevated with mass effect, increased venous pressure (such as from CVT), idiopathic intracranial hypertension, or metabolic disorders causing cerebral edema (anoxia, hypertensive encephalopathy, hepatic encephalopathy). If there is a concern for a mass lesion, a head CT should be performed prior to lumbar puncture. If a mass lesion is present, the lumbar puncture should be deferred due to the risk of herniation. It may be reasonable to skip the head CT if the following are not present: age greater than 50, immunocompromised state, previous brain injury (stroke, infection, mass), seizures, altered mentation, or focal neurologic findings [39].

If subarachnoid hemorrhage is a consideration and the head CT is negative for blood, a lumbar puncture is required to look for xanthochromia, a yellowish appearance to the CSF. In subarachnoid hemorrhage, xanthochromia is caused by blood breakdown products, such as oxyhemoglobin and bilirubin. Xanthochromia may also be positive if the CSF protein concentration is more than 150 mg/dL, if there are more than 400 red blood cells (RBCs), or with hyperbilirubinemia. Xanthochromia may be undetectable if tested too early (less than 12 h after a hemorrhage) or too late (longer than 2 weeks) [38]. If available, spectrophotometry is significantly more sensitive than visual inspection for xanthochromia [40, 41], though specificity seems to be lower [42].

In the event of a “traumatic spinal tap,” RBCs may be elevated in the CSF. To try and differentiate whether the RBCs are from the lumbar puncture or an acute hemorrhage, it is reasonable to compare the number of RBCs in the first tube to the last tube of CSF. Usually, if the red blood cells are from the procedure, the blood will become progressively dilute and there will be fewer RBCs in the last tube drawn. Keep in mind, however, that if the number of RBCs in the last tube is not zero, it does not necessarily rule out subarachnoid hemorrhage [38].

MRI

MRI is not frequently available in the emergency department for evaluation of headache. Furthermore, there are limited instances where an MRI would be necessary in an emergent situation. One of the cases where a clinician might consider MRI is in a patient with persistent thunderclap headache with a negative head CT and lumbar puncture. If there are no other historical clues to diagnosis, an MRI provides the best visualization of the posterior fossa, and may demonstrate cerebral infarcts or posterior leukoencephalopathy (PRES) missed on CT. Pituitary tumors and colloid cysts that were not evident on CT may also be more conspicuous on MRI. Subdural fluid collections and pachymeningeal enhancement may be noted in spontaneous intracranial hypotension. If an MRI is to be performed in a patient with normal kidney function, it should be with diffusion and contrast imaging to increase sensitivity. If the patient has reduced kidney function, especially in the setting of hemodialysis or prior renal transplant, the benefits of using contrast (gadolinium) should be weighed against the risk of causing the rare, but sometimes fatal, condition of nephrogenic systemic fibrosis (NSF).

Vascular Imaging

If there is suspicion for dissection, the patient should be evaluated with carotid ultrasound, MRA, or CTA (of both the head and neck). If the emergency department is equipped to perform an MRI, MRI with fat saturation sequences will often identify the mural hematoma. An MRA or CTA will help delineate the extent of a dissection. MRA may also help identify unruptured aneurysms or diffuse vasoconstriction. If the patient has a contraindication to MR imaging, such as a pacemaker, then a CTA would be
preferred. An MRV or CTV may be helpful in identifying cerebral venous thromboses that were not identified on CT or MRI.

**Differential Diagnosis**

**Primary Headaches**

As previously described, the majority of patients presenting to the emergency department with headache have a primary headache [3]. Thus, clinicians must have a basic understanding of the various types of primary headaches, their presentations, and their management. The following list is not comprehensive, but covers some of the more common primary headaches. Also listed are some rare, but uniquely presenting headaches that may mimic more serious conditions.

**Migraine**

According to the diagnostic criteria of the International Headache Society (ICHD-2), a diagnosis of migraine without aura requires at least five attacks lasting 4–72 h with nausea/vomiting or photophobia/phonophobia. At least two of the following must also be present: unilateral location, pulsating quality, moderate to severe pain intensity, or worsening of pain with physical activity. Migraine with aura is similar, but is associated with focal neurologic symptoms that typically last for 5–60 min. Aura (when present) typically precedes the headache, but may occur during the headache as well. Visual auras are most common, and tend to occur unilaterally (hemianopia) with a combination of scotomas (blurred or graying visual areas) and positive phenomenon such as sparkling/flash ing lights or colors. Sensory auras also tend to be a combination of negative features (numbness) and positive features (tingling), and may occur in a cheiro-oral (hand and face) distribution [43]. These tend to slowly march over 5–30 min. Unilateral weakness may accompany hemiplegic migraines, while brainstem symptoms, such as dysarthria, vertigo, and diplopia (with or without visual field defect) may be seen in basilar-type migraines. A reduced level of consciousness or transient loss of consciousness may also accompany basilar artery-type migraines.

In the emergency department, neurologic deficits should not be assumed to be related to migraine headache unless the patient has a clear history of the same symptoms with their typical migraine aura. Often the difficulty with migraineurs in the emergency department is not that of diagnosis, but of treatment. This is especially true in patients with status migrainosus, a debilitating attack of an otherwise typical migraine that lasts longer than 72 h. See the treatment section for recommendations on managing migraine in the emergency department.

**Tension-Type Headache**

A tension-type headache is typically described as a bilateral, nonthrob ing pressure or tightness that is mild to moderate in intensity and does not worsen with physical activity. It may last minutes to days and can have associated muscle spasm, especially in the cervical region. There may be photophobia or phonophobia, but usually no nausea or associated aura.

**Cluster Headache and Other Trigeminal Autonomic Cephalalgias**

The TACs are a group of headaches associated with autonomic symptoms, including conjunctival injection, tearing, nasal congestion, rhinorrhea, sweating, ptosis, eyelid edema, and miosis. They are divided into subcategories according to their duration.

**Cluster Headache**

- The longest attack occurs in the most well known of these disorders, cluster headache. These patients present with severe attacks of unilateral pain in the orbital, supraorbital, or temporal areas, with typical autonomic features ipsilateral to the pain. Cluster headaches usually build in intensity, lasting 15 min to 3 h, and may recur up to eight times a day. During an attack, the pain is extremely severe and the patient may seem restless, and may pace back and forth, not wanting to lie down. These may occur at similar times of day, and may recur for weeks or months (clusters), separated by remission periods. Cluster headaches are three
times more prevalent in men and may be inherited in about 5% of cases [1].

**Paroxysmal Hemicrania**
- Episodic paroxysmal hemicrania is similar to cluster headache in that the patient has periods of repeated attacks separated by periods of remission. The attacks tend to be of shorter duration than cluster, lasting 2–30 min, and are described as severe unilateral orbital, supraorbital, or temporal pain accompanied by the autonomic symptoms described earlier. These typically occur more than five times a day from 7 days to 1 year, with pain-free periods of 1 month or longer [1]. In some patients, the attacks may be precipitated mechanically by bending or neck movement. If a patient has attacks for more than 1 year without remission, the headaches are referred to as chronic paroxysmal hemicrania [1]. By definition, attacks are prevented completely by therapeutic doses of indomethacin.

**Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing/cranial autonomic features (SUNCT)**
- Similar to the other TACs, SUNCT headaches are described as unilateral stabbing or pulsating pain in the orbital, supraorbital, or temporal region associated with ipsilateral autonomic symptoms. As evidenced by their names, these headaches are the shortest in the group. They may last 5 sec to 4 min, and occur 3–200 times per day [1]. Similar to trigeminal neuralgia, these paroxysmal pains may be triggered by chewing, smiling, light touch, or a cool breeze.

**Benign Cough Headache**
Benign cough headache is usually bilateral, short lasting (1 sec to 30 min), and only occurs in association with coughing or straining. It occurs more often in men over the age of 40 [1]. Symptomatic cough headache may be caused by Arnold Chiari malformation (Fig. 1.2), posterior fossa mass lesions, cerebral aneurysms, or other carotid/vertebral disease [1].

![Fig. 1.2 Chiari I malformation. Sagittal unenhanced T2-weighted MRI demonstrates descent of the cerebellar tonsils >5 mm below the foramen magnum with an associated syrinx at C6. Note that without gadolinium and clinical screening, a patient with low CSF pressure from a CSF leak may be misdiagnosed as having a Chiari 1 malformation](image)

**Benign Sexual or Orgasmic Headache**
Two types of headache may occur with sexual activity. One is a dull aching pain in the head and neck (similar to tension headache) that intensifies with increasing sexual excitement. The other is an explosive (or thunderclap) type of headache that occurs with orgasm. With an orgasmic headache, it is important to rule out subarachnoid hemorrhage, reversible cerebral vasoconstriction syndrome, and other sources of thunderclap headache [1].

**Benign Exertional Headache**
It is not uncommon for headaches, especially migraine, to worsen with exertion. However,
a throbbing headache lasting 5 min to 48 h, brought on by and occurring only with exertion, may represent benign exertional headache [1]. In the emergency department, such a patient should also be evaluated for exertional cardiac ischemia, as headache may sometimes be the only presenting symptom [34].

Secondary Headaches

While primary headaches present more often, the goal in the emergency department is not necessarily to diagnose which primary headache is present, but rather to rule out sources for secondary headache. Amongst the secondary headaches, the most concerning are those that present with an explosive, debilitating, or “thunderclap” presentation. When a patient presents in this way, the first goal is to rule out a subarachnoid hemorrhage. There are many other headaches in which the patient may describe “the worst headache of their life” with acute onset. These are outlined in Table 1.1. More detailed descriptions of some of these are included in the text below.

Subarachnoid Hemorrhage

While the classic thunderclap headache should not be missed, some patients with subarachnoid hemorrhage present with more subtle symptoms (Fig. 1.3). Any headache that is unusual for the patient, especially if there is associated neck pain

Table 1.1 Differential for thunderclap headache

<table>
<thead>
<tr>
<th>Headache type</th>
<th>What to look for</th>
<th>Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>Sudden onset</td>
<td>CT without contrast. If no acute blood, check CSF for xanthochromia</td>
</tr>
<tr>
<td></td>
<td>May have decreased consciousness, possible neck stiffness</td>
<td></td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>Focal neurologic signs, altered mentation, possible seizures</td>
<td>CT without contrast</td>
</tr>
<tr>
<td>Cerebral venous sinus thrombosis</td>
<td>Headache may be postural (worse supine) and may worsen with Valsalva. Check for papilledema</td>
<td>MRV preferred. CT with contrast may reveal Delta sign. CSF may be normal or have increased pressure or elevated protein concentration</td>
</tr>
<tr>
<td>Cervicocephalic arterial dissection (carotid or vertebral)</td>
<td>May have associated neck pain Check for presence of Horner’s sign and other neurologic deficits</td>
<td>MRI and MRA of head and neck. Can start with carotid ultrasound or get CTA if MRI not available</td>
</tr>
<tr>
<td>Pituitary apoplexy</td>
<td>Often have nausea May have change in consciousness, visual loss, or double vision May present with pituitary insufficiency</td>
<td>Start with CT if acute to look for blood. However, MRI may be required</td>
</tr>
<tr>
<td>Acute hypertensive crisis</td>
<td>Presence of hypertension, usually more than 180/110</td>
<td>Need to rule out other causes of headache with high BP ECG Consider CT head for blood, stroke, or PRES MRI is more sensitive for PRES</td>
</tr>
<tr>
<td>Spontaneous intracranial hypotension</td>
<td>Postural headache, better supine, worse upright</td>
<td>MRI to look for pachy meningeal enhancement and low-lying cerebellar tonsils Can check LP for opening pressure</td>
</tr>
<tr>
<td>Reversible cerebral vasocostriction syndrome (RCVS)</td>
<td>May present with recurrent thunderclap headache, occipital or diffuse May have photophobia, nausea</td>
<td>Cerebral angiogram is gold standard; can check MRA or CTA</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>New neurologic deficits, especially in a vascular distribution</td>
<td>MRI with diffusion-weighted imaging; if large or subacute/chronic, may show on CT</td>
</tr>
</tbody>
</table>

(continued)
or stiffness, should raise the possibility of a subarachnoid hemorrhage. Evaluation should include a head CT followed by a lumbar puncture if negative (see approach to diagnosis).

Other Intracranial Hemorrhage
Hemorrhage into brain parenchyma may present similarly to a subarachnoid hemorrhage. If the blood tracks into the CSF, it may cause meningeal irritation and neck stiffness. Focal neurologic symptoms, including seizures and altered mentation, may be present depending on the size and location of the hematoma. Epidural and subdural hematomas may present with headache, often following trauma. A careful history must be taken as the associated trauma may be remote with subdural hematomas. Be concerned about hemorrhage in a patient on anticoagulation therapy with a new-onset headache, especially if they are older.

Cerebral Venous Thrombosis
Presentation depends on the size and location of the thrombosis (Fig. 1.4). The most frequent symptom is headache, which may be subacute
over days or a more sudden “thunderclap” presentation. A large deep venous thrombosis may cause increased intracranial pressure, leading to blurred vision, nausea/vomiting, positional headache, and occasionally a cranial nerve VI palsy. This can progress into subacute mental status changes and coma. A small cortical venous thrombosis may present with focal neurologic findings or seizures [45]. Risk factors for CVT are similar to risk factors for other venous thrombosis, and include infection, malignancy, oral contraceptives, pregnancy/postpartum, and history of a hypercoagulable state.

On a head CT with contrast, the classic appearance of a CVT is the “empty delta sign,” which is the empty-appearing triangle created when the confluens sinuum fails to fill with contrast. This sign is present 25–30% of the time, but more often the CT shows nonspecific focal or generalized edema, gyral enhancement, or enhancement of the falx/tentorium [45]. Diagnosis relies on imaging of the cerebral venous system, with either an MRV or CTV (if MR imaging is contraindicated or difficult to obtain). Anticoagulation appears to be safe in these cases, and may even improve outcome. Even with anticoagulation, the mortality is around 5–10% [46].

Meningitis
The presence of fever, neck stiffness, meningismus, or altered mentation associated with headache is concerning for inflammation of the meninges, or meningitis. Unfortunately, the presentation may be subtle. In one study of bacterial meningitis, only 44% of patients presented with the classic triad of fever, neck stiffness, and change in mental status. However, 95% had at least two of the following four signs and symptoms: headache, fever, neck stiffness, and altered mentation [47]. Some patients present with headache in isolation.

In the emergency department, it is necessary to first rule out infectious etiologies of meningitis, including bacteria, viruses, fungi, and...
mycobacteria. This should be done with a blood culture and a lumbar puncture for CSF (with or without preceding CT, see lumbar puncture section). Meningitis may be due to noninfectious etiologies as well, and present with headache, with or without fever. Etiologies for noninfectious meningitis include leptomeningeal metastases, systemic autoimmune diseases, or medications (NSAIDs, IVIG, intrathecal chemotherapy).

**Cervicocephalic Dissection**

Carotid and vertebral dissections are often associated with head or neck pain. In one study, 8% of 245 patients with cervical dissections presented with head and/or neck pain as their only symptom [48]. In all but one of these cases, the pain was different from their previous headaches. While it is difficult to recommend extensive testing for dissection in every new-onset headache, this should at least be on the differential. Investigations for dissection should be considered in an otherwise unexplained acute or thunderclap headache, or with a new progressive headache associated with neck pain, a Horner’s syndrome, cranial nerve palsies, monocular vision loss (amaurosis fugax), or other focal neurologic signs. A history of preceding trauma to the neck, even minor trauma such as chiropractic neck manipulation or whiplash from a roller coaster ride, increases the suspicion for dissection.

**Ischemic Stroke**

Headache is not uncommon in the setting of ischemic stroke, especially with large strokes. If a patient has a history of migraine headaches, the ischemic stroke may trigger one of their typical headaches. This can make diagnosis quite challenging as migraineurs can have neurologic symptoms as part of a migraine aura (see migraine section). If a migraine patient is presenting in the emergency department with a typical migraine, but has a new or changed neurologic aura, consider the possibility of ischemia or other focal neurologic injury.

**Reversible Cerebral Vasoconstriction Syndrome**

Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by a sudden severe thunderclap headache associated with vascular narrowing in the vessels of the circle of Willis and its branches. The term represents a group of disorders including Call-Fleming syndrome, benign angiopathy of the CNS, postpartum angiopathy, drug-induced vasospasm, migrainous vasospasm, and migrainous angiitis [25, 49]. Headaches tend to last minutes to hours, and may recur over a few days to weeks. Because of the vasoconstriction, most patients also have focal neurologic deficits, and one-third of patients have seizures. CSF is normal or near normal (protein <80 mg/dL, WBC <10 cells mm$^3$), [25] and there may be a slight elevation of ESR [49]. The gold standard for diagnosis is conventional angiography which shows multifocal segmental vasoconstriction, reversible within 12 weeks after onset. MRA or CTA is the recommended first-line imaging procedure, however. MRI and CT may be normal, may show features similar to posterior reversible encephalopathy syndrome (PRES), or may show evidence of intracranial hemorrhage, especially cortical subarachnoid hemorrhage. Patients typically do well even without treatment, although cerebral infarction may occur [50]. There are some case reports suggesting possible benefit with calcium channel blockers such as nimodipine, but there has not been a well-designed trial to explore this further [49].

**Low-Pressure Headache**

When there is a decrease in CSF, patients may develop an orthostatic headache that is worse in the upright position and better while recumbent (Fig. 1.5). Low-pressure headaches are often throbbing (not always) and either bilateral or holoccephalic. These may occur as thunderclap headaches and occasionally present only with exertion. There may be a variety of associated symptoms, many of which are also orthostatic in nature. These include dizziness, hearing changes with a sense that sounds are muffled (from stretching of cranial nerve VIII or changes in perilymphatic pressure), visual blurring, reduced consciousness (from compression of the diencephalon), and ataxia or other gait disorders (from compression on the posterior fossa and spinal cord) [51]. The depletion of CSF may be from hypovolemia, overshunting of CSF, or a CSF
leak. A history of recent lumbar puncture, epidural, spinal surgery, or motor vehicle accident suggests a persistent traumatic CSF leak. Spontaneous CSF leaks may occur through weak meningeal diverticula or weak dura, and may be associated with connective tissue disorders [51]. A head CT is usually unremarkable, although subdural fluid collections are sometimes appreciated. On MRI, typical findings include pachymeningeal enhancement, descent of the cerebellar tonsils (resembling Chiari I malformation), crowding of the posterior fossa, decreased ventricle size, and subdural fluid collections (typically bilateral). Lumbar puncture is not necessary for diagnosis, but when it is performed, the opening pressure may be normal to low and CSF protein concentration may be normal to high. Pleocytosis (WBC in the 10–50 cells/mm³ range, rarely up to 220 cells/mm³) may also occur [52, 53]. Most of these are self-limited and respond well to bed rest, caffeine, and increased fluid intake. However, a persistent headache may require an epidural blood patch by anesthesiology. Severe or persistent cases may need to be further evaluated with CT myelography to identify the leak for possible surgical repair.

**Hypertensive Crisis and PRES**

In a study of 50 patients presenting with hypertensive urgency (blood pressure greater than 180/110), the two most common presenting complaints were headache (42%) and dizziness (30%) [54] (Fig. 1.6). With hypertensive crisis, there is also evidence of end-organ damage such as stroke, hypertensive encephalopathy, or acute pulmonary edema. A patient presenting with headache and marked elevation of blood pressure presents a diagnostic dilemma. Severe hypertension may be a source for headache, but severe headache pain may also result in secondary elevation of blood pressure. Furthermore, a patient may have an underlying process, such as a hemorrhagic or ischemic stroke, that is associated with both. The possibility of ischemic stroke is particularly worrisome because lowering blood pressure could potentially exacerbate cerebral ischemia. Before attempting to lower blood pressure, a careful neurologic examination should be performed to look for signs of ischemic stroke.

Posterior reversible leukoencephalopathy, also termed posterior reversible encephalopathy syndrome (PRES), is a syndrome involving vasogenic edema preferentially affecting the white matter of
the posterior brain, including the occipital lobes and cerebellum. Symptoms may include headache, nausea/vomiting, seizures, altered mentation, and sometimes other focal neurologic signs, such as bilateral visual loss. The name is somewhat misleading because PRES does not necessarily have to be posterior, reversible, or limited to white matter.

PRES may occur with hypertensive encephalopathy, as well as preeclampsia/eclampsia, and some immunosuppressive agents such as cyclosporin, tacrolimus, and IVIG. When diagnosing PRES, MRI is more sensitive than CT and demonstrates an increased T2 signal abnormality. Posterior reversible leukoencephalopathy may sometimes be noted as hypodense regions on a head CT.

**Pituitary Apoplexy**

Pituitary apoplexy occurs when a pituitary tumor (typically a benign adenoma) spontaneously hemorrhages or when it outgrows its blood supply (causing pituitary infarct) (Fig. 1.7). Patients may present with a sudden-onset severe headache, mimicking subarachnoid hemorrhage. They may have associated nausea, visual loss, or double vision. On occasion, they may present with a change in consciousness or adrenal failure. A head CT may show changes consistent with acute hemorrhage, but may miss subtle hemorrhage or infarct. If pituitary apoplexy is suspected and the CT is negative, consider MRI.

In addition to neurosurgery (for possible urgent transsphenoidal resection), an endocrinologist is often involved acutely and in recovery to help manage high-dose corticosteroids and other hormonal replacements.

**Idiopathic Intracranial Hypertension**

The typical patient is an obese female presenting with headache that is daily, severe, throbbing, lasts hours, and may wake the patient from sleep. Patients may have associated nausea/vomiting, transient visual obscurations or loss of vision (from papilledema), sparks/flashes in their vision, or horizontal diplopia. They may have...
associated tinnitus that is synchronized with their pulse [58]. Most work-up for idiopathic intracranial hypertension is performed as an outpatient. However, if the patient presents to the emergency department for evaluation, a head CT would need to be performed to exclude a mass lesion. A lumbar puncture should show normal composition and an elevated CSF pressure (>20 cm H\textsubscript{2}O in the nonobese, >25 cm H\textsubscript{2}O in the obese). As this is a diagnosis of exclusion, at some point the patient should have further testing such as an MRI and MRV to exclude sources for venous hypertension (from a dural venous thrombosis, AVM, or AV fistula) [59, 60]. In one study, 9.4% of 106 patients with presumed idiopathic intracranial hypertension had a CVT [61].

Management generally begins with treatment of obesity and discontinuing any medications associated with intracranial hypertension, such as nitrofurantoin, retinoic acid, excessive vitamin A, anabolic steroids, tetracycline, etc. [58]. Medical therapy with acetazolamide or furosemide may be attempted. If the patient fails therapy or has progressive visual loss, a surgical procedure such as optic nerve sheath fenestration or shunting may be required [59, 60].

**Postconcussive**

Postconcussive headaches following closed head injury may mimic migraine or tension headaches. Furthermore, trauma may trigger a typical migraine in a migraineur. Sometimes postconcussive headaches are part of a syndrome of symptoms including cervical pain, dizziness, cognitive impairment, and psychologic/somatic complaints such as irritability, anxiety, depression, fatigue, or sleep disturbance [17]. Imaging performed on a patient with a headache following trauma is primarily done to rule out traumatic lesions such as intracranial hematomas. While subtle MRI changes may be seen later, there are no specific imaging findings to help diagnose a postconcussive headache [62]. As mentioned previously, dissection, cerebral venous thromboses, and CSF leaks with resulting intracranial hypotension should be considered in the differential for a headache following closed head injury and trauma.

**Third Ventricular Colloid Cyst**

Colloid cysts are benign congenital cysts that arise in the anterior third ventricle (Fig. 1.8). They are usually asymptomatic, and found
incidentally on imaging in adulthood. However, if the cyst obstructs the foramen of Monro it can disrupt CSF flow and lead to hydrocephalus. If both foramen of Monro are obstructed, this may lead to syncope, coma, or death. Occasionally, the tumor will act as a ball valve and only intermittently obstruct CSF flow. When this happens, the patient may complain of a severe positional headache, relieved in recumbency, sometimes associated with nausea and vomiting [63, 64].

**Trigeminal Neuralgia**

Classic trigeminal neuralgia presents as paroxysmal attacks of intense, sharp, and stabbing pain along one or more divisions of the trigeminal nerve. These attacks last from less than 1 s to 2 min, and are often precipitated by stimulating certain “trigger zones.” Chewing, talking, brushing teeth, cold air, or the slightest touch may trigger the paroxysmal pain [1]. Trigeminal neuralgia is most commonly due to compression of the trigeminal nerve by a blood vessel near its origin where it exits the brainstem. A demyelinating lesion or infarct at this so-called dorsal root entry zone may also cause trigeminal neuralgia, and should be suspected in younger patients presenting with these symptoms. Much less commonly trigeminal neuralgia is due to compression by a mass lesion such as a meningioma or schwannoma, or is idiopathic. Imaging is frequently performed to rule out a secondary etiology, but usually in an outpatient, rather than emergent, setting.

**Glaucoma**

Acute-angle glaucoma may present with headache and associated eye discomfort, and there are also reports of subacute angle-closure glaucoma presenting with headache as the main presenting complaint [65]. If not identified and managed properly, either of these can result in permanent vision loss in the affected eye. Be concerned about glaucoma if the patient’s headache pain came on suddenly when exposed to the dark. When going from light to dark, the sudden dilation of the pupil
may block the outflow channels in the anterior chamber, leading to sudden increased intraocular pressure. The patient may complain of sudden severe unilateral headache and eye discomfort, associated with blurred vision in the affected eye and “halos” around lights. The affected eye is often red with a middilated, sluggishly reactive pupil (may be irregularly shaped) and a hazy cornea [66]. Nausea and vomiting may be present. This is best evaluated by an emergent ophthalmology consult.

**General Approach to the Management of Primary Headache in the Emergency Department**

Once secondary headache disorders are excluded, the primary goal of the treating physician is to provide relief of headache pain and the accompanying symptoms such as nausea and vomiting. The majority of patients who present to the ED with headache will be diagnosed with a severe and/or prolonged migraine attack. Occasionally, patients with other diagnoses such as tension-type or cluster headache will present to the emergency department. Often the individual will have utilized her/his usual headache remedies without success. If the attack has lasted hours or longer and has been accompanied by poor oral intake of fluids with or without vomiting, the patient will likely be fluid depleted. If the patient is dehydrated, intravenous fluids need to be administered along with pharmacologic agents that treat the pain and other manifestations that accompany the pain. Often patients are quite distressed and anxious due to the duration and/or severity of the attack. The following general principles should be utilized:

- Place the patient in a darkened, quiet room.
- Provide reassurance.
- Provide IV rehydration.
- Treat nausea and vomiting quickly.
- Implement treatment with non-oral medication as soon as possible.
- Do not restrict antiemetics in patients with nausea, as many of the agents in this class are dopaminergic antagonists which have an antimigraine action in addition to their antiemetic effect.
- Avoid drug-dependency-producing agents when possible (avoid butalbital and limit opioids, or at least use opioids with care).
- Rather than minimal dosing, use medication doses that are likely to be most effective.
- Use “migraine-specific” therapy when possible.
- Educate the patient regarding his condition.
- The patient should be counseled to make arrangements for follow-up as an outpatient for consideration of approaches that will optimally manage headaches.

**Protocols for Acute Treatment of Migraine in the Emergency Department**

There are several protocols employing a variety of agents that can be utilized for management of primary headache disorders in the emergency department. Again, most patients will be presenting with migraine and most of the protocols have been developed specifically for this disorder. Several of these have been shown to be effective in small prospective, controlled trials. To address the severe headaches that lead patients to seek care in the emergency department, many of these protocols focus on parenteral agents. Obviously, the treating care provider may elect to use an oral agent for management that can be self-administered by the patient.

The medications fall into relatively few categories of agents: (1) migraine-specific drugs (dihydroergotamine and sumatriptan); (2) dopamine (D₂)-blocking agents, such as neuroleptic drugs and metoclopramide; (3) other non-dependency-producing medications; and (4) opioid drugs.

It is important to note that drugs from different classes are often used together. This is done to maximize efficacy, to treat symptoms other than pain (e.g., nausea and vomiting), and, in some cases, to reduce the likelihood of side effects of another agent. For example, D₂ antagonists are always administered with intravenous dihydroergotamine to minimize its side effects of nausea and vomiting.
Migraine-Specific Agents

Sumatriptan (5HT 1B/D Receptor Agonist)

Sumatriptan, 4 or 6 mg injected subcutaneously, has been shown to be both efficacious for treatment of acute migraine headache and for associated symptoms [67]. The dose can be repeated after an hour. Response rate at 1 h after a single dose of 6 mg is 70% [68]. Side effects include chest tightness, tingling, flushing, dizziness, and limb heaviness. Sumatriptan is the triptan of choice in the emergency department because it is the only triptan available in a subcutaneous formulation, which provides a rapid serum concentration and bypasses nausea, vomiting, and gastroparesis. Sumatriptan is at this time the only triptan to be considered “compatible” with breastfeeding by the American Academy of Pediatrics.

Contraindications for sumatriptan include:
- Pregnancy (relative contraindication)
- History or suspicion of ischemic heart disease
- History of coronary artery disease or Prinzmetal’s angina
- Severe peripheral vascular disease
- Use of an ergot alkaloid (i.e. DHE, ergotamine) or other 5HT 1 agonist (i.e. another triptan) within 24 h
- Uncontrolled hypertension
- Previous adverse reaction
- Basilar or hemiplegic migraine
- Ischemic cerebrovascular disease

Dihydroergotamine

Dihydroergotamine mesylate (DHE) is an effective parenteral treatment for migraine attacks. The beneficial effects of DHE were initially attributed to vasoconstriction, but other mechanisms involving neurogenic inflammation and activity within central serotonergic systems provide a better explanation [69, 70]. It is important to note that headache resolution after treatment with IV DHE and metoclopramide has been reported in patients suffering headaches secondary to viral or carcinomatous meningitis; thus, response does not imply the diagnosis of a primary headache such as migraine or cluster headache [71]. Common side effects of DHE are nausea, vomiting, diarrhea, abdominal cramps, and leg pain.

DHE may be administered subcutaneously, intramuscularly, or intravenously. The intravenous route is the most rapidly effective. Unfortunately, the side effects of nausea and vomiting seem to be more prominent with intravenous administration.

The usual dose when administered subcutaneously or intramuscularly is 1.0 mg [72, 73]. In order to help prevent nausea, give an antiemetic such as 10 mg IV metoclopramide or 10 mg IV prochlorperazine approximately 10 minutes before giving DHE intravenously. The side-effects and the utility of these D2 blocking agents are outlined elsewhere in this chapter. DHE, 0.5 mg, is then slowly administered over a few minutes [74–76]. An additional 0.5 mg dose may be administered a few minutes later if no significant nausea or chest pain has developed. A one mg dose via subcutaneous, intramuscular, or intravenous routes may be repeated after one hour. In the case of status migrainosus or truly intractable migraine, the patient may require hospital admission, and could be treated with repetitive or continuous DHE, using published protocols such as those of Raskin or Ford [77–79]. For instance, if the patient tolerates the medicine, IV DHE could be given as 0.5, 0.75, or 1.0 mg every 8 hrs for 2–5 days along with an antiemetic such as metoclopramide 10 mg IV every 8 hours. Please see (Fig. 1.9) for an example protocol. If extrapyramidal symptoms such as dystonia, akathisia, or oculogyric crisis develop from the metoclopramide, these could be addressed using parenteral benztrapine mesylate or diphenhydramine. Alternatively, parenteral benztrapine mesylate or diphenhydramine could be given with as a pretreatment with each dose of DHE/metoclopramide to prevent these extrapyramidal side effects.

Contraindications for DHE include:
- Uncontrolled hypertension
- Ischemic heart disease
- Vasospastic angina
- Severe peripheral vascular disease
- MAO inhibitors within the last 2 weeks
- Prior use of a triptan within the last 24 h
- Significant hepatic disease
- Pregnancy
- Hemiplegic or basilar artery-type migraine

Antidopaminergic Agents

Antidopaminergic agents have well-recognized antiemetic and sedative effects which prove useful
in the treatment of acute headache. In addition, there is significant clinical and experimental data suggesting that there is relative hyperactivity of dopaminergic neurotransmission in at least some migraineurs. These agents may have a specific antimigraine effect via blockade of D₂ dopamine receptors [80].

Common acute side effects of these agents include akathisia, acute dystonia, dizziness, and somnolence. Prolonged exposure (which is not an issue in the emergency department setting) may result in drug-induced tardive dystonia, parkinsonism, and tardive dyskinesia. The dizziness may be due to hypotension; therefore, carefully monitoring of vital signs, including a standing blood pressure prior to discharge, should be routine after administration of these agents.

The acute extrapyramidal side effects can be ameliorated by diphenhydramine, 25 mg, (intravenously or intramuscularly) or benztrapine, 1 mg (intravenously or intramuscularly).

Rare but potentially fatal complications of these drugs include prolonged QT syndrome and torsades de pointes. Some individuals have an underlying genetic predisposition to the disorder, but it can also be acquired secondary to pharmacologic

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**Fig. 1.9** Repetitive (every 8 hours) intravenous (IV) dihydroergotamine mesylate (DHE)–Raskin protocol. PO, Orally; IM, intramuscular; BP, blood pressure; PRN, as needed; q, every. (Used with permission from Seminars of Neurology….blah blah blah…. Adapted from Raskin31; presented at: Headaches in the ED; AAN Annual Meeting; May 4, 2007; Boston, MA.)
agents. For a list of agents which may produce a prolonged QT interval, see the online resource at Arizona Center for Education and Research on Therapeutics [79]. If a patient is taking one of these agents, treatment with a $D_2$ agent should be used with care. Prior to the parenteral administration of any of these agents, it is suggested that an ECG be obtained and the QT interval be carefully measured. If there is evidence of a prolonged QT interval, these agents should not be used.

Controlled trials show that a number of these drugs are effective in the acute management of migraine headache.

**Prochlorperazine**

Prochlorperazine has been shown to be an effective pain-abortive agent that can be used in repeated intravenous doses in a hospital or emergency department setting [80, 81]. Prochlorperazine, 10 mg per cc, can be diluted with 4 cc of normal saline to the concentration of 2 mg per cc. This is injected at a rate of 1 mg/min until the headache is relieved, or a maximum of 10 mg is administered [82, 83]. Most often, a dose of 10 mg of intravenous prochlorperazine is injected over 2–5 min and this is repeated every 20 min, up to a maximum dose of 30 mg. Prochlorperazine, administered as a 25-mg rectal suppository, is also effective for acute migraine therapy [84]. Its onset of action, however, is substantially slower than when administered intravenously.

**Chlorpromazine**

A number of studies demonstrate that chlorpromazine is an effective parenteral, acute treatment for migraine attacks. Prior to intravenous administration of this agent, the patient is often pretreated with 500 ml of normal saline to reduce the hypotensive side effect; more fluid may be appropriate if the patient has been vomiting or is dehydrated.

One of the most effective and easiest to use protocols is 12.5-mg chlorpromazine IV, which is repeated at 20-min intervals to a maximum of 37.5 mg [85]. Another protocol consists of chlorpromazine 0.1 mg/kg IV, which is repeated every 15 min as needed, up to a total of three doses [86]. Alternatively, chlorpromazine, 25 mg per cc, is diluted with 4 cc of normal saline to a concentration of 5 mg per cc. To reduce the risk of hypotension, chlorpromazine can be administered at a rate of 5 mg (1 cc) every 5 min until the headache is relieved, or the entire 25 mg is administered. An additional 10 mg (for a total of 35 mg) may be given in some cases. Chlorpromazine, 1 mg/kg intramuscularly, is also an effective headache-abortive treatment, but its action is slower in onset and the efficacy is less than by intravenous administration [87, 88]. Bigal et al. performed a double-blind randomized controlled study of 128 tension-type headache sufferers who either received placebo or 0.1 mg/kg of chlorpromazine IV as a one-time dose [89]. At 60 min, effects were statistically different from placebo for pain, nausea, photophobia, phonophobia, and need for rescue medication. Side effects included drowsiness and postural hypotension.

**Haloperidol**

In a small open study, haloperidol, 5 mg IV over a few minutes, resulted in headache relief [90]. A more recent randomized, controlled trial found that 5 mg of haloperidol in 500 cc of normal saline as a 20–30-min one-time infusion resulted in 16/20 (80%) of patients enjoying a marked relief from pain (a drop of greater than three on the visual analog pain scale) versus 15% in the placebo group measured between 1 and 3 h after infusion [91]. Side effects included 53% motor agitation (akathisia) and 53% sedation. Three of 20 patients treated with haloperidol returned to the emergency department with recurrent headache within 2–3 days. Haloperidol seems to cause less sedation and less hypotension than prochlorperazine or chlorpromazine.

**Droperidol**

Droperidol can be administered as 2.5 mg intravenously over 1 min, and may be repeated every 30 min, up to a total of 7.5 mg [92]. Droperidol can also be effective when administered via the intramuscular route in doses ranging from 2.75 to 8.25 mg [93]. Though randomized controlled studies have demonstrated an effect equal to prochlorperazine, there is now a black-box warning for droperidol because it may provoke QT interval prolongation, *torsades de pointes*, or cardiac arrest.
ECG monitoring should occur before, during, and for up to 2–4 h after administration, especially for those with congestive heart failure, bradycardia, cardiac hypertrophy, hypokalemia, hypomagnesemia, or those patients using diuretics or other drugs known to cause QT interval prolongation [94]. As already noted, QT prolongation is a risk of all drugs in this class.

**Metoclopramide**
Metoclopramide, while not a neuroleptic agent, does have D₂ dopamine receptor-blocking properties [78]. It can be administered in a dose of 10 mg intravenously over a few minutes [95, 96]. Metoclopramide is generally less effective than the above neuroleptic agents, but efficacy can be substantially enhanced when used in combination with other antimigraine agents [97].

**Sodium Valproate**
Several preliminary or open-label studies found intravenous sodium valproate to be an effective, well-tolerated, acute abortive agent for migraine in the emergency setting [98, 99]. Sodium valproate, 300–500 mg diluted in 100 cc of normal saline, is infused at a rate of 20 mg/min. Intravenous valproate has several advantages including lack of cardiovascular side effects (no telemetry required), no interaction with triptans or ergot alkaloids, lack of sedation, and absence of dependence or habituation. Trials have used various dosing regimens. The half-life is 9–16 h, bioavailability is approximately 100%, and therapeutic blood levels are reached almost immediately [100].

In an open-label trial, Mathew et al. used 300-mg IV sodium valproate in 61 migraineurs and found that 73% of attacks had significant improvement within 30 min [99].

An open-label comparison between intravenous valproate 500 mg versus 10-mg IM metoclopramide followed by IM DHE 1.0 mg found that both worked equally well and valproate had fewer side effects [98].

A randomized, controlled study comparing intravenous valproate (500 mg) with IV prochlorperazine (10 mg) over 2 min found that prochlorperazine was statistically and clinically superior to IV valproate in reducing pain and nausea in migraine patients [101].

A recent study of 113 migraineurs compared 10-mg intravenous metoclopramide versus 2-g intravenous magnesium sulfate versus placebo. The study measured pain reduction at 30 min and found no difference compared to placebo for either magnesium or metoclopramide [104]. Another study found magnesium to be moderately helpful, but not as effective as prochlorperazine [81]. Yet another study showed that magnesium sulfate (1-g IV) was no better than placebo in pain relief when all patients with migraine were analyzed. However, in migraine with aura, there was significant improvement of pain and of all associated symptoms compared with controls with a therapeutic gain of nearly 37% at 1 h [105].

**Magnesium Sulfate**
The evidence for magnesium sulfate’s efficacy is far from overwhelming, but it can be used safely during pregnancy. One study concluded that 1 g of magnesium sulfate, given intravenously, resolved or improved acute migraine headaches (as well as cluster headaches) [103]. Improvement was more likely if basal serum ionized magnesium levels were low (less than 0.70 mmol/L). These results have not been confirmed in a placebo-controlled study. In this trial, magnesium sulfate had no significant side effects except mild flushing.

A recent study of 113 migraineurs compared 10-mg intravenous metoclopramide versus 2-g intravenous magnesium sulfate versus placebo. The study measured pain reduction at 30 min and found no difference compared to placebo for either magnesium or metoclopramide [104]. Another study found magnesium to be moderately helpful, but not as effective as prochlorperazine [81]. Yet another study showed that magnesium sulfate (1-g IV) was no better than placebo in pain relief when all patients with migraine were analyzed. However, in migraine with aura, there was significant improvement of pain and of all associated symptoms compared with controls with a therapeutic gain of nearly 37% at 1 h [105].

**Nonsteroidal Analgesics**
Analgesics are widely used for acute treatment of headache. Ketorolac, a nonsteroidal anti-inflammatory drug which is available for injection, can be useful for treatment of some migraine attacks. The medication is given in a 30–60-mg IM injection [77]. Intravenous ketorolac (0.4 mg/kg) can
terminate both headache- and migraine-associated allodynia in up to 68% of patients within 1 h of treatment, even in those patients who have failed to respond to sumatriptan [106]. Ketorolac at a dose of 30-mg IV was beneficial but not as effective in reducing pain as 10-mg IV prochlorperazine [107]. Most patients should also be treated with an antiemetic. Drowsiness, dyspepsia, and nausea are potential side effects. Acute renal failure and gastrointestinal hemorrhage have been precipitated rarely by this agent.

In a small study comparing ketorolac 60-mg IM versus IV DHE/metoclopramide in various doses, only six of nine patients had moderate relief with ketorolac versus eight of nine who were given DHE/metoclopramide [77].

Corticosteroids
Corticosteroids are typically given in combination with other antimigraine agents to enhance efficacy. Dexamethasone can be given IV or IM. Doses as high as 10–20-mg IV given over 10 min, followed by 4-mg IV every 6 h as needed, are very effective [108–110]. Alternatively, a one-time IM injection of 8 mg can also be employed [111].

A meta-analysis of studies that evaluated the efficacy of dexamethasone in addition to other therapy for acute migraine was performed. The analysis included studies that used randomized, double-blind, placebo-controlled methodology and that were performed in the emergency department. A pooled analysis of seven trials involving 742 patients suggested a modest but significant benefit when dexamethasone was added to standard antimigraine therapy. The analysis showed the addition of dexamethasone reduced the rate of patients with moderate or severe headache on 24- to 72-h follow-up evaluation (RR of 0.87, 95% CI of 0.80–0.95; absolute risk reduction of 9.7%). The treatment of 1,000 patients with acute migraine headache using dexamethasone in addition to standard antimigraine therapy would be expected to prevent 97 patients from experiencing the outcome of moderate or severe headache at 24–72 h after emergency department evaluation [112].

Opioids
Despite multiple effective regimens of nonopioid medications, opioids continue to be commonly used for acute management of headache in the emergency department. In a nationwide survey of 811,419 adult migraine sufferers who visited an emergency department, 51% were treated with opioids and an alarming 77% of these had not received any nonopioid medications as a first-line attempt [113]. In a Canadian survey of 500 emergency department visits for headache, 59.6% of patients received narcotics as first-line treatment [114]. Opioids are not “migraine specific,” and are generally not as effective as other agents. Further, in the setting of frequent emergency department or outpatient visits, their use raises concern about rebound and tolerance. Nevertheless, there are some patients for whom an opioid is the most effective and best-tolerated agent for acute, severe headaches, and opioids continue to play a role as rescue agents. Meperidine is the most commonly utilized agent in this setting. It may be administered intravenously or intramuscularly, most commonly in a dose of 75–150 mg. It should be accompanied by promethazine, 25–50 mg, or hydroxyzine, 25–100 mg, intramuscularly to treat nausea and vomiting; these also provide sedative and anxiolytic effects [115].

Because clinical trials assessing efficacy and side effects of meperidine performed to date have been small and have not arrived at consistent conclusions, Friedman et al. performed a systematic review and meta-analysis to determine the relative efficacy and adverse effect profile of opioids compared with nonopioid active comparators for the treatment of acute migraine [116]. Four trials (involving 254 patients) compared meperidine to dihydroergotamine, four trials (involving 248 patients) compared meperidine to an antiemetic, and three trials (involving 123 patients) compared meperidine to ketorolac. Meperidine was less effective than dihydroergotamine at providing headache relief (OR of 0.30; 95% confidence interval [CI] 0.09–0.97) and trended toward less efficacy than the antiemetics (OR of 0.46; 95% CI 0.19–1.11); however, the efficacy of meperidine was similar to that of
ketorolac (OR of 1.75; 95% CI 0.84–3.61). Compared to dihydroergotamine, meperidine caused more sedation (OR of 3.52; 95% CI 0.87–14.19) and dizziness (OR of 8.67; 95% CI 2.66–28.23). Compared to the antiemetics, meperidine caused less akathisia (OR of 0.10; 95% CI 0.02–0.57). Meperidine and ketorolac use resulted in similar rates of gastrointestinal adverse effects (OR of 1.27; 95% CI 0.31–5.15) and sedation (OR of 1.70; 95% CI 0.23–12.72). The authors appropriately conclude that emergency department physicians should consider alternate parenteral treatments for migraine headaches.

Indeed, meperidine is losing favor among pain specialists for use as an analgesic and many authorities argue that other opioids should be used for acute pain. This is due to meperidine’s poor efficacy, toxicity, and multiple drug interactions [117]. The argument can be made that if a parenteral opioid is needed, then an opioid other than meperidine should be selected and administered in an equipotent dose [118].

**Cluster Headache Treatment**

Therapeutic options for cluster headache vary in some respects from other primary headache disorders and are therefore considered separately. Effective treatments include:

**Oxygen**

A range of 8–12 L/min of 100% oxygen through a closed face mask can abort most cluster headache attacks if the sufferer can begin therapy at the onset of the attack. Sometimes, a flow rate of 15 L/min is effective when lower flow rates are not. Oxygen’s effectiveness in cluster headache has been proven in a double-blind controlled trial [119].

**Sumatriptan**

In one study, 96% of cluster headache sufferers achieved pain relief in 15 min with 6-mg SC sumatriptan [120]. The maximal recommended dose per 24 h is 12 mg. Now that it comes in a 4-mg subcutaneous dosage, a cluster patient may use up to three doses a day. Some may break open the subcutaneous device and dole out only small quantities in order to make their medicine last longer and treat more attacks.

**Dihydroergotamine**

One milligram IV dihydroergotamine preceded by 10-mg metoclopramide can rapidly abort cluster headache attacks in less than 15 min [121]. Subcutaneous or IM injections of 1-mg DHE up to 2–3 times a day can be used outside of the office or emergency department, but onset of relief is slower. Intranasal DHE is difficult to use and too slow to abort individual attacks, but it may lessen attack severity.

**Corticosteroids**

Corticosteroids can provide a temporary reprieve lasting days to weeks in many patients with cluster headache. Corticosteroids have been used to treat cluster headache for over 50 years, and they have been shown to be more effective than placebo [122]. In a large, retrospective series, Kudrow found that 60 mg a day produced a complete remission in up to 77% of patients [123].

In one open-label study, 13 cluster headache patients used 30 mg/kg of IV methylprednisolone as a 3-h infusion in saline on the eighth day of the cluster period [124]. Only 3 of 13 patients had a complete remission of headache, and the mean interval until the next attack was 2–7 days indicating no advantage over prednisone.

In another study using IV methylprednisolone, 250-mg boluses over three consecutive days, followed by 90 mg per day of oral prednisone tapered off over 4 weeks, lowered attack frequency substantially for several weeks [125].

**Special Circumstance: Treatment of Headache in the Pregnant Patient**

Because home treatment options are somewhat limited, the pregnant migraine sufferer may be forced to come to the emergency department for management. There is general agreement that Tylenol, possibly combined with caffeine, is a good first-line choice for the acute migraine attack [23, 24, 126, 127], as both are felt to be...
generally safe during pregnancy. The drawback to Tylenol is that it is a short-acting analgesic and, if taken too frequently, could contribute to a potential rebound, or analgesic overuse, headache. Furthermore, by the time the patient arrives to the emergency department, there is a strong possibility that she has already tried this.

As mentioned early in the section on headache management, the initial approach should include conservative measures, such as making sure the patient is well hydrated. Magnesium sulfate is considered safe for the fetus and may help with the migraine [128]. Ibuprofen and naproxen are generally considered safe during the second trimester, but should be avoided during the third trimester as they may cause premature closure of the ductus arteriosus [24, 129]. Some studies have shown a small risk of increased spontaneous abortion and congenital malformations when these NSAIDs are taken in the first trimester, so one might also be cautious early in pregnancy [130].

For nausea, metoclopramide has been used during all stages of pregnancy with no evidence of embryo, fetal, or newborn harm, and is considered FDA class B (no evidence of risk in humans, but no controlled studies) [130]. Other antiemetics such as prochlorperazine remain class C due to limited information, and therefore should be reserved for when the benefits are thought to outweigh the potential risks [129, 130].

As mentioned previously, narcotic medications should be avoided if at all possible, given the association with drug dependency and rebound headache. With prolonged use in pregnancy, especially in the third trimester, there is a risk of neonatal addiction and respiratory distress. Of the opiate medications, codeine has been associated with more reports of cleft lip/palate, cardiac, and respiratory defects and should therefore probably be avoided, especially during the first trimester [131]. Morphine, oxycodone, and meperidine are probably not teratogenic, but the data is somewhat limited [130]. Given the limited options during pregnancy, these may be considered for very short-term use, during status migrainosus, if necessary.

Sumatriptan was embryolethal in rabbits when given in large doses intravenously, and produced some vascular and skeletal anomalies when given in large doses orally [130]. The data in human fetuses is less clear. In the sumatriptan pregnancy registry, sumatriptan use has been associated with an increased risk of preterm delivery and low birth weight [132]. There have also been a small number of recorded birth defects, with any-trimester exposure proportion of 4.4% (95% CI 2.8–6.8%) as compared to the prevalence of birth defects in migraineurs, which has been estimated at 3.4% [130]. In other retrospective and observational cohort studies, the risk has been even less [130]. Ultimately, there is not enough data on sumatriptan use in human fetuses to detect minor anomalies. Furthermore, some of the existing studies lack the long-term follow-up needed to detect late adverse effects. As there is insufficient data to rule out risk to the fetus, all triptans including sumatriptan remain FDA pregnancy class C.

Corticosteroids have been shown to increase major malformations when used in the first trimester. Therefore for the first trimester, they are FDA class D [130], showing positive risk to humans. One of these risks appears to be a small risk of orofacial defects [130]. For the rest of the pregnancy, animal studies show clear risk to the fetus, but the human studies are less clear. Because of the limited information, they are considered FDA class C during second and third trimesters. Of the corticosteroids, oral prednisone seems to have less risk than prednisolone [130], and has been advocated by some as an option for the short-term management of status migrainosus [23, 129].

Ergotamine/DHE should be avoided during pregnancy (FDA class X) as there have been idiosyncratic responses to treatment that have been associated with fetal toxicity and teratogenicity, possibly due to the disruption of maternal-fetal vascular supply [130]. Valproic acid (FDA class D, human data suggests risk) is also a known teratogen, and should be avoided during pregnancy [130].

Summary of pregnancy list in the acute setting [24, 129, 130]:
• **Probably safe in the acute setting (FDA class B):** Tylenol, caffeine, magnesium, NSAIDs during the second trimester, metoclopramide, morphine, oxycodone, and meperidine
• **Use if the benefit outweighs the risk (FDA class C):** NSAIDs during first trimester, triptans, prochlorperazine, oral prednisone, and codeine
• **Probably avoid (FDA class C but shows risk during first and third semesters):** Aspirin
• **Avoid (FDA class D or X):** NSAIDs or aspirin during third trimester, sodium valproate, and ergotamine/DHE

Because of the difficulty in management, the pregnant patient should receive counseling on how to minimize the frequency of future headaches. This would include avoidance of headache triggers and maintaining regular meals and sleep patterns. Physical therapy, exercise, relaxation, and biofeedback are nonmedication options to try. Thermal biofeedback, in particular, has been associated with headache reduction during pregnancy [129].

**References**


