Headache and Pain Disorders

Christopher Tarolli, MD
University of Rochester
Rochester, New York

Headache Disorders

Headache disorders are pain syndromes producing pain in the head or neck. While the brain parenchyma itself does not sense pain, various structures within the head and neck (the meninges, skull, blood vessels, skin, facial musculature, and nerves themselves) are innervated by the trigeminal sensory system, upper cervical nerve roots, and, to a lesser extent, other cranial nerves, mediating the pain felt in these diverse disorders.

Headache disorders can be broadly subdivided into primary and secondary etiologies. Primary headache disorders are significantly more common than secondary headache syndromes, which can be due to any number of underlying disease processes. The history and neurologic examination are frequently sufficient to differentiate primary from secondary headache disorders, although further testing may be necessary to confirm the diagnoses.

Primary Headache Disorders

Primary headache disorders are idiopathic pain syndromes resulting in head pain without an underlying structural cause. The group is heterogeneous and includes the two most common headache syndromes, migraine and tension-type headache, and the less common trigeminal autonomic cephalalgias.
**Migraine.** Migraine is one of the most common headache syndromes and is broadly subdivided into two categories: migraine with associated neurologic symptoms, termed *migraine with aura*, and migraine without aura. Migraine is common, affecting 12% to 20% of the population, with women affected around twice as often as men. While some migraine syndromes have a specific genetic association, current data support a polygenic inheritance pattern in the majority of patients. Although the pathophysiologic triggers for migraine are not well understood, pain is mediated by the release of inflammatory neurotransmitters that activate the trigeminal sensory system, causing referred pain, most commonly starting in the distribution of the ophthalmic division. As the attack continues, thalamic networks and pain pathways in the upper cervical spine are activated, resulting in more diffuse pain and central pain sensitization, with reduced response to treatment experienced later in migraine attacks.

Migraine without aura is characterized by headache lasting 4 to 72 hours with either nausea and vomiting or photophobia/phonophobia and at least two of the following criteria: unilateral pain, pounding or pulsating pain quality, moderate or severe pain intensity, or some degree of disability or avoidance of routine activity.

Migraine with aura, according to the *International Classification of Headache Disorders 3 (ICHD-3)*, is now an umbrella term that encompasses migraine with associated neurologic deficits. Former terms, including *complicated migraine, ophthalmic migraine, basilar migraine,* or *migraine accompaniment,* now fall into the broad category of migraine with aura. Around 20% of all patients with migraine will experience aura with at least one headache, with visual aura most common, followed by sensory, aphasic, and brainstem auras. The pathophysiology of migraine aura is not well understood, but focal cortical dysfunction, termed *cortical spreading depression,* characteristically spreading across the cortex at a rate of 3 mm/s is thought to
mediate the deficits. Changes in cortical function, documented by focal slowing on EEG and decreased cortical metabolism on positron emission tomography, have been shown to correlate with the area of cortical spreading depression. Although by definition the aura of migraine lasts between 5 and 60 minutes, prolonged aura is common, most frequently in patients with aphasic or hemiplegic aura.

While weakness falls under the broad category of aura, hemiplegic migraine remains fully subcategorized given the unique clinical and genetic features of this condition. Familial hemiplegic migraine is a well-recognized phenomenon, with autosomal dominant mutations in \textit{CACNA1A}, \textit{ATP1A2}, and \textit{SCN1A} accounting for the majority of cases. Weakness is the defining feature of hemiplegic migraine, although many patients will have other aura symptoms as well. Imaging is typically normal in this condition, although nonspecific changes contralateral to the weakness may be seen; imaging changes suggesting ischemia should be absent.

Treatment of migraine is broadly subdivided into abortive therapy for the acute treatment of migraine attacks and preventive therapy to reduce the frequency and intensity of attacks. Guidelines to dictate which preventive or abortive agent to select first for the treatment of migraine are limited. Comorbid conditions, side effect profiles, and patient preference, however, can aid in the consideration and selection of appropriate pharmacotherapy.

The goal of abortive therapy in migraine is to acutely reduce attack severity, duration, and intensity as well as associated disability. Effective abortive therapy for migraine is dependent on appropriate medication use (including the avoidance of overuse) and treatment early in the course of an attack. In general, over-the-counter analgesic medications, including acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), are recommended for
abortive therapy for migraine attacks of mild severity, while prescription NSAIDs, triptans, and parenteral medications are reserved for migraine attacks of moderate to severe intensity.

NSAIDs, specifically aspirin and naproxen, have long been recognized as effective abortive agents for the treatment of migraine; recent evidence-based guidelines also support the use of diclofenac and ibuprofen (Level A evidence) as well as ketoprofen and ketorolac (Level B evidence). The use of other over-the-counter agents, including acetaminophen and acetaminophen/ aspirin/caffeine, is also supported by Level A evidence; these are frequently used as first-line agents for abortive therapy for mild migraine.

The triptans are a group of serotonin receptor agonists that have a long record of efficacy in the treatment of migraine. Triptans are often used in patients who are incompletely treated with NSAIDs or other over-the-counter agents since this class of drugs has a favorable side effect profile. Seven triptans are available in the United States, with Level A evidence supporting the use of each. Frovatriptan and zolmitriptan have evidence specifically supporting their use in the prevention of menstrual migraine, and both zolmitriptan and sumatriptan have parenteral formulations available. While triptans are considered safe in the majority of patients, their serotonergic agonism poses a theoretical risk of inducing vasospasm. Their use is contraindicated in patients with known pregnancy or cerebrovascular or cardiovascular disease and in patients with migraine with hemiplegic or brainstem aura; women should be advised to stop smoking and avoid oral contraceptive use before triptan initiation given the heightened risk of stroke in this population.

A number of other medications have evidence supporting their use as abortive agents, including ergots (dihydroergotamine, ergotamine caffeine), intravenous (IV) magnesium, IV valproic acid, and corticosteroids. Antidopaminergic antiemetics (metoclopramide, droperidol,
prochlorperazine, and chlorpromazine) are also effective for the treatment of both nausea and pain associated with migraine; they are frequently used in conjunction with other abortive agents.

Evidence exists for the use of opiates in the acute treatment of migraine, with Level A evidence for butorphanol nasal spray. However, given their side effects and risk of addiction, the efficacy of other medications, and changes in pain circuitry with use, opiate use is not supported by the American Academy of Neurology or the American Headache Society for the treatment of migraine.

Data-driven guidelines and consensus statements on the treatment of refractory migraine not responsive to first-line therapy are limited. However, frequently used strategies include IV hydration, IV NSAID administration, short-term oral or IV steroids, or IV dihydroergotamine, each often paired with oral or parenteral antiemetics.

Preventive therapy for migraine is used with the goal to reduce attack frequency and intensity by at least 50%, improve response to abortive therapy, and improve overall function. Current American Academy of Neurology guidelines recommend consideration of preventive therapy in patients with recurring attacks that interfere with quality of life or daily routine, frequent headaches (four or more migraine attacks per month), failure of or contraindication to abortive therapy, or the presence of certain migraine syndromes (migraine with brainstem aura, hemiplegic migraine, or migraine with prolonged aura). Since no strict guidelines exist that dictate first-line preventive therapy for migraine, selection is often based on the presence of comorbidities, with a goal to treat multiple symptoms or conditions with a single agent.

A number of classes of medications have evidence supporting their use as migraine preventives. Level A evidence exists for the use of the beta-blockers metoprolol, timolol, and propranolol and the antiepileptic drugs divalproex sodium, sodium valproate, and topiramate,
with Level B evidence for the antidepressants amitriptyline and venlafaxine. Other agents with relatively favorable side effect profiles but lower levels of evidence supporting their use include the antihypertensives lisinopril and candesartan as well as carbamazepine, cyproheptadine, clonidine, and guanfacine. Verapamil is at least as effective as other prophylactic agents in the prevention of migraine with aura, although its use is not supported in patients without aura. Over-the-counter medications, including riboflavin, magnesium, feverfew, and coenzyme Q10, are relatively safe with some limited evidence supporting each for migraine prevention.

While the purpose of this section is not to outline all agents ineffective for the treatment of migraine, of particular note given its historical use for migraine prevention is lamotrigine, which has strong evidence establishing this medication as ineffective in migraine prevention.

OnabotulinumtoxinA has proven efficacy for the treatment of chronic migraine (more than 15 headache days per month), but data do not support its use in the prevention of episodic migraine. Injections at targeted sites over the head and neck are given every 12 weeks.

Pregnancy represents a unique clinical scenario for the treatment of migraine, since the majority of preventive and abortive agents are unstudied or known to cause harm to the fetus. However, a majority of women experience an improvement in headache frequency during pregnancy, and lifestyle changes are sufficient for prevention in many. Acetaminophen and metoclopramide are the abortive agents of choice in pregnancy, with most other agents listed as Category C or worse. Preventive medication use also should be approached cautiously during pregnancy, with Category C recommendations for propranolol, amitriptyline, and gabapentin. Currently, memantine is the only preventive medication recommended in pregnancy, with a Category B recommendation. Although magnesium was formerly used in the prevention of
migraine in pregnancy, current recommendations argue against using this drug because of the potential risk of fetal osteopenia.

Migraine has been shown to be comorbid with or an independent risk factor for other conditions, including mitral valve prolapse, patent foramen ovale, fibromyalgia, mood and anxiety disorders, obesity, motion sickness, epilepsy, and stroke. Stroke risk is highest in patients with migraine with aura, in women (especially smokers or those taking oral contraceptives), and in patients with patent foramen ovale. Currently, the American Heart Association does not recommend the routine use of aspirin for primary prevention of stroke in any population with migraine.

**Tension-type Headache.** Tension-type headache (TTH) is the most common primary headache disorder and likely represents a diverse group of conditions that do not meet criteria for migraine or other headache syndromes. The pain of TTH is of mild to moderate intensity and is characterized by a typically bilateral distribution, a pressing or tightening quality, and, frequently, pericranial tenderness. No nausea, vomiting, or neurologic deficits should be associated with TTH, and the patient may have *either* photophobia or phonophobia, but not both.

Lifestyle factors, including psychosocial stressors, mood and anxiety symptoms, poor hydration or nutrition, and inadequate sleep, have all been linked to worsening of TTH. As such, treatment is directed toward nonpharmacologic interventions, and correction of these lifestyle factors, EMG biofeedback, cognitive-behavioral therapy, acupuncture, and physical therapy are all recommended, although with limited data on efficacy. If pharmacotherapy is required, Level A evidence exists for the use of amitriptyline and Level B evidence for mirtazapine and venlafaxine in the prevention of TTH. NSAIDs are first-line agents for acute treatment of TTH.
with caffeine and combination analgesics recommended as second-line agents. Triptans, muscle relaxants, onabotulinumtoxinA, and opioids have no role in the treatment of TTH.

**Trigeminal Autonomic Cephalalgias.** The trigeminal autonomic cephalalgias (TACs) represent a group of unilateral headache disorders with associated cranial parasympathetic autonomic symptoms ipsilateral to the pain. Autonomic features may include conjunctival injection, nasal congestion/rhinorrhea, lacrimation, eyelid edema, forehead and facial sweating or flushing, fullness in the ear, miosis, or ptosis. This group includes five syndromes: cluster headache, short-lasting unilateral neuralgiform headache attacks with cranial autonomic features (SUNA), short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), paroxysmal hemicrania, and hemicrania continua. These disorders can be differentiated based on epidemiology, clinical features, duration of attack, and response to treatment (Table 1). Although history is sufficient to make a diagnosis of other primary headache syndromes, MRI is appropriate in the evaluation of any patient with a TAC because of an increased prevalence of pituitary pathology among this population.

Cluster headache, while uncommon, represents the most common of the TACs. Headaches are stabbing in quality, last between 15 minutes and 3 hours, and cause significant agitation given their severity, being previously referred to as *suicide headaches*. As implied by the name, cluster headaches tend to occur in groups, frequently following a circadian or circannual schedule, with patients experiencing periods of frequent headaches punctuated by symptom-free periods. While subtler gender differences exist in other TACs, cluster headache has a 3:1 to 4:1 male to female predominance. Given the severity of cluster headache, acute treatment focuses on the use of rapid-acting agents, including subcutaneous, intranasal, or intramuscular triptans and ergots. High-flow 100% oxygen via nonrebreather mask is also first-
line therapy for cluster headache, with response within minutes of initiation. Verapamil is the preventive therapy of choice in cluster headache, and given the somewhat predictable timing of attacks, many patients initiate therapy days or weeks before the onset of a predicted cluster period; lithium and topiramate may be considered in those unresponsive to or unable to tolerate verapamil.

SUNA/SUNCT represent a continuum of short-lived (between 1 and 240 seconds) headache syndromes with the differentiating feature being the presence of both conjunctival injection and tearing in SUNCT and the absence of at least one of these features in SUNA; other autonomic features can be present in either condition. Head pain in SUNA/SUNCT is stabbing in quality, with attacks occurring at least once per day, although sometimes up to 100 times per day. SUNA/SUNCT can be differentiated from trigeminal neuralgia by pain in the ophthalmic division of the trigeminal nerve, a slightly longer attack duration, and the associated autonomic features, all atypical of trigeminal neuralgia. Abortive therapy is not useful for SUNA and SUNCT because of the short duration of the attacks. Data support the use of lamotrigine for prevention of SUNA/SUNCT, and the conditions characteristically are not responsive to indomethacin.

Paroxysmal hemicrania and hemicrania continua are two distinct headache syndromes that differ primarily in duration and headache quality. However, the conditions are similar in their absolute response to preventive therapy with indomethacin, with this response part of the diagnostic criteria for each. The headaches of paroxysmal hemicrania last between 2 and 30 minutes, with differentiating features from cluster headache including an absence of significant agitation and a higher attack frequency of more than five attacks per day. Hemicrania continua has the unique clinical feature of a prolonged baseline headache for longer than 3 months, with
associated attacks with autonomic features that last between 30 minutes and 3 days. While indomethacin is the treatment of choice for both conditions, higher doses are required for the treatment of hemicrania continua. For patients unable to tolerate indomethacin therapy, other NSAIDs, melatonin, and topiramate have some reported benefit.

**Table 1** Trigeminal Autonomic Cephalalgia Comparison

<table>
<thead>
<tr>
<th>Condition</th>
<th>Duration of Attack</th>
<th>Associated Features</th>
<th>Recommended Abortive Medications</th>
<th>Recommended Preventive Medications</th>
</tr>
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<tbody>
<tr>
<td>SUNA/SUNCT</td>
<td>1–240 seconds</td>
<td>SUNA without conjunctival injection and/or tearing Stabbing headache quality Ophthalmic distribution of pain</td>
<td>Often ineffective/unnecessary given short duration of attacks</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>Paroxysmal hemicrania</td>
<td>2–30 minutes</td>
<td>High daily attack frequency (&gt;5 per day) Absence of agitation</td>
<td>Often unnecessary given response to indomethacin</td>
<td>Indomethacin</td>
</tr>
<tr>
<td>Cluster headache</td>
<td>15–180 minutes</td>
<td>More prevalent in males Circadian or circannual recurrence Significant associated agitation Triggered by alcohol</td>
<td>Subcutaneous sumatriptan Intramuscular DHE High-flow oxygen</td>
<td>Verapamil Lithium Topiramate</td>
</tr>
<tr>
<td>Hemicrania continua</td>
<td>30 minutes–3 days</td>
<td>Baseline milder headache for &gt;3 months Attacks with autonomic features</td>
<td>Often unnecessary given response to indomethacin</td>
<td>Indomethacin, typically high dose</td>
</tr>
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DHE = dihydroergotamine; SUNA = short-lasting unilateral neuralgiform headache attacks with cranial autonomic features; SUNCT = short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.

**Secondary Headache Syndromes**
Secondary headache implies underlying neurologic or systemic pathology as a cause of the headache syndrome. Secondary headache should be suspected in patients who develop new headache types, especially in those with no history of a primary headache disorder. While innumerable diverse causes of secondary headaches exist, they can be broadly subdivided into traumatic, vascular, neoplastic, infectious, inflammatory, and psychiatric etiologies. The workup for secondary headache syndromes may include advanced neuroimaging, obtaining CSF, or other specialized tests.

**Headache Secondary to Increased Intracranial Pressure.** Secondary headaches are frequently due to changes in intracranial pressure (ICP), both increased and decreased, exerting noxious stimuli on the meninges and other cranial structures. Characteristic features of headache associated with increased ICP include positional headache (worse while lying down) and, frequently, focal neurologic deficits. In any patient with symptoms suggestive of increased ICP, a detailed neurologic examination and urgent or emergent neuroimaging should be obtained.

The differential diagnosis of headache secondary to increased ICP includes space-occupying lesions (eg tumor, abscess, hemorrhage), obstructive hydrocephalus, cortical venous thrombosis, and idiopathic intracranial hypertension (IIH). The evaluation and management of IIH are discussed in detail here, while evaluation and management of the other conditions above are discussed in the sections on “Neuro-oncology and paraneoplastic syndromes,” “Infectious Disease,” and “Cerebrovascular Disorders.”

IIH, as the name implies, is an idiopathic condition causing headaches characteristic of increased ICP. While IIH is classically associated with young obese women, the condition can be seen in other populations. CSF opening pressure must be at least 25 cm water in the left lateral decubitus position to make a diagnosis, and papilledema should be present on neurologic
examination, although IIH without papilledema has been observed. Other supporting features include pulsatile tinnitus, transient or progressive visual obscurations, and cranial nerve palsies, most frequently involving the abducens nerve and secondary to increased ICP (the false-localizing sign). MRI and, frequently, magnetic resonance venography of the head are a necessary part of the workup for IIH, with characteristic MRI features including an empty sella turcica, flattening of the posterior sclerae, enhancement or protrusion of the optic nerve heads, and tortuous orbital vessels. The most serious complication of IIH is progressive and sometimes permanent vision loss, and treatment is aimed at reducing this risk.

While the pathogenesis of IIH is not fully understood, current theories support impaired CSF outflow from the cranial space. Treatment therefore focuses on reducing CSF production or increasing its removal, with the carbonic anhydrase inhibitor acetazolamide the mainstay of therapy for most patients; as some overlap exists between migraine and IIH, topiramate can be used given its weak carbonic anhydrase activity and its benefit for migraine prophylaxis. Serial lumbar punctures, ventriculoperitoneal shunting, optic nerve sheath fenestration, and bariatric surgery (if a patient is morbidly obese) may be considered for cases refractory to medical management, for patients with contraindications to medical therapy, and for those with rapidly progressive vision loss.

**Orthostatic Headache.** Converse to headache associated with increased ICP, headache secondary to decreased ICP presents with orthostatic worsening of headache symptoms secondary to sagging intracranial structures causing meningeal irritation. The pain is often bilateral and reaches maximal intensity within seconds of sitting/standing, resolving with return to the supine position; Valsalva maneuver or exertion can also relieve discomfort. Lumbar puncture is the most common cause of orthostatic headache, complicating up to 30% of
procedures, but nonprocedural orthostatic headache can be secondary to CSF leaks (traumatic, iatrogenic, or spontaneous), overshunting, or medication effects. Characteristic MRI features include diffuse pachymeningeal enhancement, sagging/flattening of midline structures in the brain, decreased ventricular size, and, occasionally, subdural hematomas or hygromas due to stretching of bridging dural veins. In patients with suggestive symptoms and no clear etiology, spontaneous CSF leak, most frequently in the cervical region, should be considered. Treatment focuses on identification and correction of reversible causes. In patients with recent lumbar puncture or spontaneous CSF leak (suspected or confirmed), lumbar epidural blood patch or IV caffeine can offer rapid improvement in symptoms. If these treatments are unsuccessful, magnetic resonance myelography may be necessary to identify the source of the leak, which can then be repaired.

**Thunderclap Headache.** A thunderclap headache is a headache with abrupt onset, reaching maximal intensity within 1 minute. Thunderclap headaches can be secondary to a range of causes, although the most common etiologies are subarachnoid hemorrhage and reversible cerebral vasoconstriction syndrome. For more information on the clinical criteria, evaluation, and management of subarachnoid hemorrhage and reversible cerebral vasoconstriction syndrome, refer to the section “Cerebrovascular Disorders.” Emergent neuroimaging is necessary in any patient with new-onset thunderclap headache, with noncontrast head CT the initial study of choice. This study is 95% sensitive in the identification of subarachnoid hemorrhage. However, in patients without an identified etiology on initial imaging, lumbar puncture should be performed to evaluate for xanthochromia, given the potential morbidity associated with subarachnoid hemorrhage and the potential for repeat bleeding following a sentinel event.
Noninvasive vascular imaging of the head and neck and contrast-enhanced MRI aid in ruling out other secondary causes of thunderclap headache.

Cough headache, exertional headache, and headache associated with sexual activity represent primary headache syndromes frequently manifesting as thunderclap headache immediately following the associated activity. The diagnostic evaluation described remains necessary in these patients given the association of aneurysmal rupture with Valsalva maneuver common to these clinical scenarios. Once more concerning etiologies have been ruled out, indomethacin premedication is the therapy of choice for prevention of these entities.

**Medication-Overuse Headache.** Medication-overuse headache (MOH), also termed *rebound headache*, represents a common cause of chronic daily headache in patients with a primary headache diagnosis who overuse abortive therapies. This results in the development of a new headache type or a marked worsening of the preexisting condition. According to *ICHD-3*, abortive use must exceed 10 to 15 days per month over a period of 3 months or more, although some medications may induce MOH with as few as five uses per month. While all abortive medications have the potential to cause MOH, the most common culprit medications include caffeine, barbiturate-containing analgesics (butalbital-caffeine-acetaminophen, butalbital-caffeine-aspirin), opiates, and acetaminophen. Management of MOH begins with prevention, avoiding typical causative medications and educating patients about the risk of overuse. Treatment focuses on complete cessation of abortive medications, although care must be given to avoid withdrawal syndromes in patients who are overusing opiates or barbiturates. While the speed and duration of discontinuation is debated, initiation of appropriate preventive therapy is indicated in conjunction with the wean to improve the likelihood of success. Any of the typical migraine preventives, including onabotulinumtoxinA, can be used in bridging patients with
MOH. While abortive medications can be added back to a patient’s regimen, strict limits on their use must be established when starting any new treatments.

**Giant Cell Arteritis.** Giant cell arteritis (GCA), also termed *temporal arteritis,* is an inflammatory vasculitic secondary headache syndrome that should be considered in adults older than 50 years of age with new or changing headaches. Granulomatous inflammation of intracranial and extracranial arteries results in headache, frequently with temporal tenderness, jaw claudication, scalp allodynia, and throat discomfort. Vision loss secondary to an arteritic anterior ischemic optic neuropathy is a concerning complication and dictates rapid evaluation and treatment. Initial evaluation focuses on systemic inflammatory markers (erythrocyte sedimentation rate and C-reactive protein) with temporal artery biopsy required for confirmation. Urgent initiation of steroid treatment is necessary for visual protection in any patient with suspected GCA. For a discussion of the evaluation and management of GCA, refer to the section “Neuro-ophthalmologic and Neuro-otologic Disorders.”

**Painful Cranial Neuropathies**

Headaches secondary to irritation of nociceptive cranial and upper cervical nerves constitute a unique group of disorders with specific symptomatology and, frequently, significant disability. While irritation of any of the cranial or cervical nerves has the potential to produce somatosensory pain, typically through the trigeminal system, this section focuses on syndromes related to direct irritation of the trigeminal, glossopharyngeal, and occipital nerves.

**Trigeminal Neuralgia.** Trigeminal neuralgia is the most common painful cranial neuropathy, typically affecting adults older than 50 years of age. The pain of trigeminal neuralgia is characterized by brief unilateral episodes of lancinating shock-like pain, most commonly in the
maxillary (V2) and mandibular (V3) divisions of the trigeminal nerve. Attacks can be spontaneous, but diagnostic criteria require triggering of painful episodes by apparently innocuous stimuli, including brushing the teeth or hair, eating, speaking, or a breeze on the face. While these symptoms can be similar to the trigeminal autonomic cephalalgias SUNA and SUNCT, the innocuous triggers, V2 and V3 distribution, and absence of autonomic features favor the diagnosis of trigeminal neuralgia.

The neurologic examination in patients with trigeminal neuralgia is frequently normal, although trigeminal distribution sensory loss is described and should raise concern for a structural cause. While a number of etiologies have been described, vascular compression of cranial nerve V by a redundant vascular loop is the most commonly found. In younger patients or those with bilateral trigeminal neuralgia, multiple sclerosis or other demyelinating conditions should be considered. Gadolinium-enhanced MRI with attention to the entire course of the nerve is a necessary part of the diagnostic workup of any patient with new-onset trigeminal neuralgia to evaluate for these possibilities, although it may not be sensitive enough to visualize vascular compression.

Carbamazepine is the mainstay of therapy for trigeminal neuralgia with lower levels of evidence for oxcarbazepine, baclofen, lamotrigine, and gabapentin. In patients with vascular compression and symptoms refractory to medical therapy, decompression may be effective, although responses are variable. Surgical alternatives include deafferentation of the trigeminal nerve via gasserian ganglion blockade or gamma knife therapy. Although direct comparisons have not been performed, these are generally thought to offer less permanent relief than decompression.
Glossopharyngeal Neuralgia. Glossopharyngeal neuralgia is similar in quality to trigeminal neuralgia, although far less common. While the condition is called glossopharyngeal neuralgia, it may affect either the glossopharyngeal or vagus nerve. The distribution of pain is unilateral and located in the pharynx, base of tongue, or ear, with painful paroxysms induced by speaking, swallowing, yawning, or coughing. Treatment is similar to that for trigeminal neuralgia, with carbamazepine the mainstay of therapy. Neurovascular compression of the vagus or glossopharyngeal nerve is less common than in trigeminal neuralgia, and more invasive surgical techniques are typically avoided because of the risk of complications from damage to other branches of the vagus nerve.

Occipital Neuralgia. Occipital neuralgia is a relatively common cause of headache secondary to irritation of the greater or lesser occipital nerve. Pain is typically unilateral and radiates into the scalp and upper neck, with a lancinating or electric quality. Occipital neuralgia is most commonly due to compression of the C2 or C3 nerve roots as they exit the spinal canal, frequently with comorbid cervical spondylosis. Neurologic examination may reveal decreased sensation or dysesthesia in the distribution of these nerves, and percussion over the course of the nerve will often induce an attack. Conservative treatments, including stretching, physical therapy, heat, and NSAIDs, are often sufficient to treat the condition, although occipital nerve blockade with or without corticosteroid injection is considered the most effective therapy. Insufficient evidence currently exists to support surgical decompression for isolated greater occipital neuralgia.

Pain Disorders
Pain disorders are common, disabling, and frequently, difficult to treat conditions resulting in pain in any part of the body. Many pain disorders are mediated by changes in pain processing in the central or peripheral nervous system, though the pathophysiologic mechanism of most pain syndromes remains incompletely understood.

**Neuropathic Pain**

Neuropathic pain is defined as pain initiated or caused by dysfunction in the nervous system. While central and peripheral localizations are possible, neuropathic pain is most commonly associated with peripheral neuropathy. Neuropathy itself is common, with numerous etiologies described and the distribution and symptoms involved dependent on the cause.

While no absolutes exist, neuropathic pain tends to be seen in patients with sensory symptoms, particularly sensory neuropathies, with a relative sparing of those with pure motor variants. Diabetic neuropathy, the most common cause of neuropathy in the United States, is also the most common cause of neuropathic pain. Other typical causes of neuropathic pain include postherpetic neuralgia (PHN), vitamin deficiency neuropathies, lumbosacral radiculopathy, and chemotherapy-induced peripheral neuropathy. Small fiber neuropathies, while significantly less common, are associated with severe pain that is often difficult to treat.

Neuropathic pain is typically described as burning, tingling, or pruritic, often with associated allodynia or dysesthesia. The management of neuropathic pain involves first identifying the underlying etiology, with attempts to correct it. While some symptoms will improve with treatment of the underlying etiology, pain commonly remains. Beyond correction of the cause, pain control involves medications with or without the addition of nonpharmacologic treatments. While limited data exist in the efficacy of a majority of behavioral interventions for
neuropathic pain, graded exercise and cognitive-behavioral therapy or psychotherapy have demonstrated benefit in the treatment of neuropathic pain in conjunction with medical therapy. Identification and treatment of underlying psychiatric disease is also imperative to treatment.

Pharmacotherapy for neuropathic pain is similar regardless of the etiology, although the majority of data evaluate the management of moderate to severe PHN and painful diabetic neuropathy. Three medication classes are approved in the treatment of neuropathic pain: (1) antidepressants, specifically secondary amine tricyclic antidepressants (nortriptyline, desipramine) and serotonin-norepinephrine reuptake inhibitors (duloxetine, venlafaxine); (2) anticonvulsants, specifically calcium channel α2-δ ligands ( gabapentin, pregabalin); and (3) topical lidocaine for localized neuropathic pain. No head-to-head comparison data dictating the best first-line management for neuropathic pain exist; as such, the choice of agent is typically based on side effect profile and medical comorbidities. Opioids are not recommended for long-term management of any chronic pain syndrome except for cancer pain. However, in patients with acute neuropathic pain, neuropathic pain in the setting of cancer, or episodic exacerbations of neuropathic pain, or in those requiring acute relief during titration of a first-line agent, a short course of opioids or tramadol is appropriate.

Since neuropathic pain is often inadequately managed with the medications discussed, alternative nonpharmacologic interventions beyond behavioral changes are often considered. Epidural injection of a local anesthetic combined with steroids has demonstrated benefit in prevention and treatment of PHN and radiculopathy in the setting of a prolapsed lumbar disc; however, given the weak quality of evidence, this is generally reserved for patients unresponsive to oral pharmacotherapy. No data or consensus guidelines that outline optimal frequency, duration, or timing of injections exist. Radiofrequency lesioning for radiculopathy and
sympathetic nerve blocks for PHN are proven ineffective. The majority of other procedures, including intrathecal injections, transcutaneous electrical nerve stimulation, surgical decompression, and deep brain stimulation, have limited data, with no consensus guidelines on efficacy.

**Central Pain Syndromes**

Central pain syndromes are an alternative cause of neuropathic pain due to lesions of sensory structures in the brain or spinal cord; the onset of symptoms is most commonly soon after the return of lost sensation, although it may be delayed by months or years. While the character of the pain may be similar to peripheral neuropathic pain, cramping symptoms, lancinating sensations, and burning allodynia or dysesthesia are most common. Medical management of central pain syndromes is similar to that of neuropathic pain secondary to a peripheral etiology, although few studies exist to guide treatment. The tricyclic antidepressant amitriptyline and anticonvulsant lamotrigine have evidence supporting their use in central pain syndromes specifically related to poststroke pain; amitriptyline is generally considered first-line therapy. Calcium channel α2-δ ligands are second-line agents, with limited data supporting their use. Carbamazepine should be used in patients with episodic facial pain secondary to central lesions as the treatment of choice for trigeminal neuralgia. The use of spinal cord stimulators or deep brain stimulation in the treatment of central pain syndromes is not supported with strong data.

**Complex Regional Pain Syndrome**

Complex regional pain syndrome (CRPS) represents a group of conditions characterized by pain, edema, vasomotor instability, and abnormal sympathetic activity in a limited body region,
typically following, but out of proportion to, a preceding trauma or injury. The condition is now subdivided into CRPS type I (formerly termed reflex sympathetic dystrophy) and CRPS type II (formerly termed causalgia). The majority of cases of CRPS are type I, defined by an absence of associated nerve injury, compared with the associated partial peripheral nerve injury in CRPS type II. Preceding injuries include fracture, soft tissue injury, surgery, or immobilization.

Symptoms of CRPS include pain out of proportion to the degree of injury, allostynia, temperature asymmetry or skin color changes, edema, hyperhidrosis, and, occasionally, loss of limb function or loss of hair, nails, or bone density in the affected region. Affected sites are typically distal to the site of injury, although pain may spread to involve a greater portion of a limb over time; the discomfort is not limited to the distribution of a nerve or dermatome. The pathogenesis is not well understood, although it likely involves a combination of classic and neurogenic inflammation with neuropeptides and pro-inflammatory cytokines, central pain sensitization, and sympathetic hypersensitivity accounting for the excessive sympathetic symptoms.

The treatment of CRPS focuses primarily on functional restoration with a goal to return limb function and reduce symptomatology. The technique focuses on graded reintroduction of stimuli and activity with a goal to return to day-to-day function. Progressive desensitization with initially innocuous textures followed by the gradual introduction of more noxious stimuli also has supporting data. Evidence also exists to support treating underlying psychiatric disease with counseling, cognitive-behavioral therapy, or traditional pharmacotherapy.

Pharmacotherapy is best used when combined with functional restoration in CRPS to increase a patient’s ability to tolerate the graded reintroduction of activity. Limited data exist regarding the specific treatment of pain in CRPS, although similar strategies to those used in
other causes of neuropathic pain are often employed. Gabapentin, pregabalin, tricyclic antidepressants, venlafaxine, duloxetine, and NSAIDs are commonly used; topical lidocaine or capsaicin cream may be considered early in the course of CRPS but are generally not tolerated in patients with long-standing disease. Bisphosphonates are shown to be effective for pain relief and prevention when used early in patients with CRPS who have reduced radioisotope uptake on a bone scan. Oral, epidural, or intrathecal steroid use has been attempted in the treatment of pain secondary to CRPS, although data on efficacy are limited.

Spinal cord stimulator use in patients with CRPS type I is supported by weak evidence in patients with pain refractory to pharmacotherapy; its use in CRPS type II is not well studied. Other attempted procedures in patients with refractory pain include sympathetic nerve blockade, sympathectomy, ketamine infusions, or intrathecal medication delivery, but insufficient evidence exists to support their use at this time.

**Myofascial Pain Syndromes and Fibromyalgia**

Myofascial pain syndrome (MPS) and fibromyalgia fall into the broad category of functional somatic syndromes characterized by subjective symptoms without underlying objective abnormalities on evaluation. Fibromyalgia is characterized by the presence of chronic generalized aches, pains, or stiffness with multiple *tender* points at 18 characteristic locations throughout the body, compared with a more limited region of pain with associated *trigger* points in MPS. Tender points of fibromyalgia tend to be near joints or muscle insertion points as opposed to the muscle belly location of trigger points in MPS. Commonly associated symptoms with fibromyalgia include impaired sleep, cognitive slowing, generalized fatigue, chronic
headaches, irritable bowel syndrome, and other somatic symptoms; these are less common in MPS.

While the history and examination are often suggestive of the diagnosis, a laboratory evaluation with complete blood count, erythrocyte sedimentation rate, C-reactive protein, thyroid function testing, and creatine kinase should be undertaken to rule out an underlying systemic cause; evaluation for underlying connective tissue disease is recommended if acute phase reactants are elevated or if the history or examination has suggestive features. A sleep study and psychiatric evaluation should be considered to rule out other treatable primary causes.

The pathogenesis of fibromyalgia is poorly understood, although aberrant central pain processing is thought to underlie the condition. Sleep disorders, mood disorders, and autonomic nervous system dysfunction are seen in conjunction with fibromyalgia, although it is not clear if these are premorbid causative conditions, simple associations, or symptoms of the disease itself.

The treatment of fibromyalgia focuses on lifestyle interventions and pharmacotherapy. Patient education, sleep hygiene training, cognitive-behavioral therapy, and graded low-impact exercise have proven benefit in the treatment of fibromyalgia. Currently, three medications are US Food and Drug Administration (FDA) approved for the treatment of fibromyalgia in the United States: pregabalin and the serotonin norepinephrine reuptake inhibitors duloxetine and milnacipran. Multiple meta-analyses have also shown the tricyclic antidepressant amitriptyline to be at least as effective as other antidepressants in treating multiple symptoms of fibromyalgia; any of these medications can be considered as first-line therapy. Cyclobenzaprine and gabapentin are frequently used but have lower levels of evidence supporting their efficacy. No consensus guidelines exist on the treatment of patients unresponsive to initial therapy, although frequently employed strategies include the use of combination pharmacotherapy, analgesics, or NSAIDs.
Annotated Bibliography


This comprehensive update from the International Headache Society provides guidelines on the classification, evaluation, and diagnostic criteria for primary and secondary headache disorders.


This systematic review from the American Academy of Neurology and American Headache Society establishes evidence-based practice guidelines on the use of preventive therapy for migraine with a focus on indications for preventive therapy and level of evidence for the use of each migraine preventive.


This article by the American Headache Society is an excellent resource, with updated guidelines and an evidence-based review of the efficacy of pharmacotherapy for the acute treatment of migraine and its subtypes.

This article by the European Federation of Neurological Societies provides an updated review of the current treatment options for tension-type headache. The article has a particular focus on the level of evidence for both preventive and abortive therapy for tension-type headache.


This article provides an overview of the treatment options available for the trigeminal autonomic cephalalgias, including evidence-based recommendations on first-line therapy for acute and prophylactic treatment of cluster headache, SUNA/SUNCT, paroxysmal hemicrania, and hemicrania continua.


This extensive systematic review provides pooled data on available and studied interventions for the treatment of idiopathic intracranial hypertension.

This article provides an extensive review of the current knowledge base surrounding spontaneous intracranial hypotension with a particular focus on diagnostic criteria, evaluation, and management of the condition.


This article provides an evidence-based review of the current understanding of medication-overuse headache and its management. The article focuses on the most commonly implicated medications and the frequency of use required to cause the condition.


This article provides a retrospective population-based analysis of the features of both trigeminal neuralgia and glossopharyngeal neuralgia. The article highlights the similarities and differences in the clinical presentation of the two conditions.


This excellent article provides updated evidence-based consensus guidelines on the pharmacologic management of neuropathic pain. The authors review the level of evidence for each analgesic in the treatment of numerous neuropathic pain conditions.


Goldenberg DL. Fibromyalgia syndrome: an emerging but controversial condition. JAMA 1987;257(20):2782–2787. doi:10.1001/jama.1987.03390200122026. This landmark article provides a description of the classic clinical features and diagnostic criteria for fibromyalgia. The article also provides a strong argument for the diagnosis as an independent syndrome, rather than a feature of comorbid psychiatric disease or sleep disorder.

This article describes currently approved therapies for fibromyalgia and provides evidence-based treatment guidelines on pharmacologic and nonpharmacologic interventions for management of the condition.